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International Association of Biological Standardization

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INTERNATIONAL SYMPOSIUM ON VACCINATION AGAINST COMMUNICABLE DISEASES

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Sessions held:

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II	Established vaccines for regular programmes
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A 'code of conduct' for clinical trials

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FOREWORD

During the last seventeen years our International Association of Biological Standardization (formerly known as the Permanent Section of Microbiological Standardization of the International Association of Microbiological Societies) has been concerned with the technical developments in the manufacture and control of vaccines. When the suggestion was made that we should now consider every facet concerning immunization of large communities against communicable diseases we were eager to take up the challenge. The results of our formal presentations and discussions are recorded in this book.

The success of the Symposium was largely due to the way in which the participants came from so many countries, mainly in Europe, willing to discuss their mutual problems. In particular it was unique in bringing together so many experts from Government Health Departments with those responsible for the production and testing of vaccines. Although it was not possible to arrive at a common immunization schedule, since each community must take into consideration local difficulties, we nevertheless left with a greater understanding of the part played by different conditions. It was possible to bring together so many scientists because of the tremendous efforts of Mr H. C. C. Wagner, who obtained such generous financial support from Merck Sharp & Dohme International and we are most grateful to them for this. His tireless vigilance in making all the arrangements for our travel and comfort during the meeting are greatly appreciated. I feel sure that Mr Wagner would wish me to acknowledge the great help he received from his secretary Miss Muller in these arrangements. The scientific programme was helped very much by Miss Bond and Mrs Johnson, whose assistance I am pleased to acknowledge.

This symposium was indeed a new venture for our International Association and the participants felt that it had been a great success. I hope that the record of our meeting will be accepted with the same enthusiasm.

F. T. PERKINS

OPENING ADDRESS

Your Serene Highness Princess Grace, Ladies and Gentlemen,

The International Association of Biological Standardization has held some 45 Symposia and 12 Congresses but never before have we had the privilege of opening one of our Symposia in the presence of a Princess. Not only are we delighted to be able to do so on this occasion, but to have a most beautiful Princess with us is indeed a real pleasure.

As our title suggests, our International Association is concerned with the standardization of biological substances and it is understandable, therefore, that the majority of our meetings are concerned with the scientific disciplines leading towards the standardization of prophylactics against infectious diseases. On this occasion, however, we felt the need to bring together the scientists who produce and control vaccines with those responsible for their use. Accordingly, we have a number of scientists with us today who may not be familiar with the work of our Association and we are very happy that they have found the time to come and join in our discussions during the next three days. In Europe 23 Ministers of Health or their representatives were invited to attend and no fewer than 19 are present, 18 of whom are to talk to us about the immunization schedules that they apply in their own particular country.

In all there are 29 countries represented at our meeting and in these countries there is a gross population of some 738 millions with an annual birth rate of just over 11 millions, the average rate being 17·5 births per thousand. Our discussions, therefore, will concern no less than one fifth of the total population of the world. It is interesting to note that we are meeting in one of the smallest countries in Europe with a population of no more than 23 thousand, who bring into the world 214 babies a year. With a birth rate as low as 9·2 per thousand, it is clearly a privilege to live and to be born in Monaco – quality is often contained in small packages. We have a serious duty to perform, therefore, in discussing our common problems concerned with the immunization of our total population against infectious diseases and I feel sure that we shall return to our various countries much the wiser having benefited from our exchange of ideas.

It is, of course, a great honour to have Princess Grace with us today, not only because of her interest in the health of children but also because of a link with the past. The hosts at our social occasions are Merck Sharp & Dohme International and many of us remember with great affection the late Dr Joseph Stokes, Jnr. who worked so closely with this pharmaceutical company in Philadelphia. As each new vaccine was developed there was a need for clinical trials and frequently one found Joe Stokes in the forefront of such investigations. It so happens that, when Princess Grace lived in America as a small child, Dr Joseph Stokes was her personal paediatrician and I hope that she too has happy memories of him.

Already we have experienced a warm welcome in most comfortable surroundings in Monte Carlo and undoubtedly we shall take back the most pleasant memories of our meeting in your picturesque Principality. In order that you will carry away a permanent record of our meeting, Princess Grace, our International Association would be delighted if you would accept this pair of silver candlesticks. They come to you with our respect and affection and we hope that you will find a place for them in your home.

It now gives me great pleasure in officially declaring our 45th Symposium on Vaccination against Communicable Diseases to be open.

F. T. PERKINS
President, IABS

ADRESSE À SAS LA PRINCESSE GRACE DE MONACO

Altesse Sérénissime,

En tant que past president de l'Association Internationale de Standardisation Biologique, l'honneur m'échoit à l'initiative de mon ami Frank Perkins, de vous adresser notre respectueux hommage en langue romane en cette vielle cité latine de Grimaldi.

Nous ne pouvions mieux choisir que la Principauté Monégasque pour cette conférence sur les vaccinations contre les maladies transmissibles, sachant combien vous êtes, Madame, toujours activement préoccupée de la protection de l'Enfance, de la Croix Rouge, des Oeuvres de Secours et admirant l'immense soutien que vous accordez à l'AMADE sans oublier la part personnelle que vous apportez aux services de transfusion sanguine.

L'Association groupe fraternellement unis ceux qui à titre de chercheurs (et vous avez dans l'assemblée quelques unes des grandes figures de la microbiologie et de l'immunologie) de producteurs (assumant la préparation des vaccins et sérums) ou de responsables des autorités de santé publique (chargés du contrôle des produits et de la surveillance de leur application) se préoccupent de protéger l'homme et en particulier l'enfant contre les maladies transmissibles qui n'ont reculé que grâce à l'effort opinâtre de ceux qui poursuivent l'oeuvre pastorienne.

Protéger l'homme sans oubli nos frères inférieurs, Madame, car médecins et vétérinaires oeuvrent conjointement au sein de notre Association et, connaissant votre mansuétude à l'egard des animaux, elle ne vous en sera que plus sympathique.

Au cours de ces journées ou, sous l'oeil attentif de l'OMS, nous allons essayer de perfectionner notre stratégie contre une partie fort agressive de l'environment, nous ne manquerons pas non plus de penser à l'ensemble douloureusement préoccupant de la protection du milieu et vous nous ferez l'honneur, Madame, transmettant à votre Sérénissime Epoux nos félicitations pour l'oeuvre qu'il accomplit dans la lutte contre la pollution des mers.

Nous vous remercions de tout coeur d'avoir voulu soutenir notre effort par votre présence et pour votre charme et nous ne pouvons pas mieux dire notre reconnaissance qu'en songeant parmi tous les enfants du monde à ceux qui vous sont les plus chers et pour qui nous formons les meilleurs voeux.

A. LAFONTAINE

SESSION I

INTRODUCTION

Chairman: Dr F. T. PERKINS (UK)

International Symposium on Vaccination against Communicable Diseases, Monaco 1973; Symp. Series immunobiol. Standard, vol. 22, pp. 3–10. Printed in Great Britain

OBJECTIVES OF THE SYMPOSIUM

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INTRODUCTION

Europe is one of the few regions of the world in which immunization has been effectively used and the achievements have been so great it is difficult to realize that in most of the region immunization programmes covering a high proportion of susceptible populations have been established only since the last World War.

The extent of the change is shown in Fig. 1 and Table I. The figure – an old one – is a reminder of the dramatic fall in the incidence of diphtheria in England and Wales as soon as a nationwide campaign was initiated. Table I shows the equally dramatic reduction in poliomyelitis in countries with good vaccination programmes between 1951–5 and 1966–70.

INTERVAL BETWEEN DEVELOPMENT AND APPLICATION OF VACCINES

Looking back over the immunization era and comparing the early years with the later, an outstanding feature has been the reduction of the interval between the development and the application of a new vaccine. A satisfactory diphtheria toxoid was available in 1923 – but in England and Wales 19 years passed before mass immunization was introduced. The required stimulus came from war conditions and the fear of epidemics among the children brought together in large numbers from different cities as a result of evacuation. Contrast this with the brief intervals which elapsed between the development of the inactivated and live vaccines against poliomyelitis.

USE OF PROPERLY DESIGNED FIELD TRIALS

The acceleration owes a great deal to the realization that new or improved vaccines must be tested in properly designed field trials at an early stage. The investigation of pertussis vaccines carried out between 1946 and 1958 under the auspices of the British Medical Research Council – in which 50 000 children were enrolled and kept under observation, on average, for two years – was one of the earliest examples of what could be achieved on a relatively large scale by happy collaboration between laboratory workers, health officers and field observers **(6, 7, 8)**.

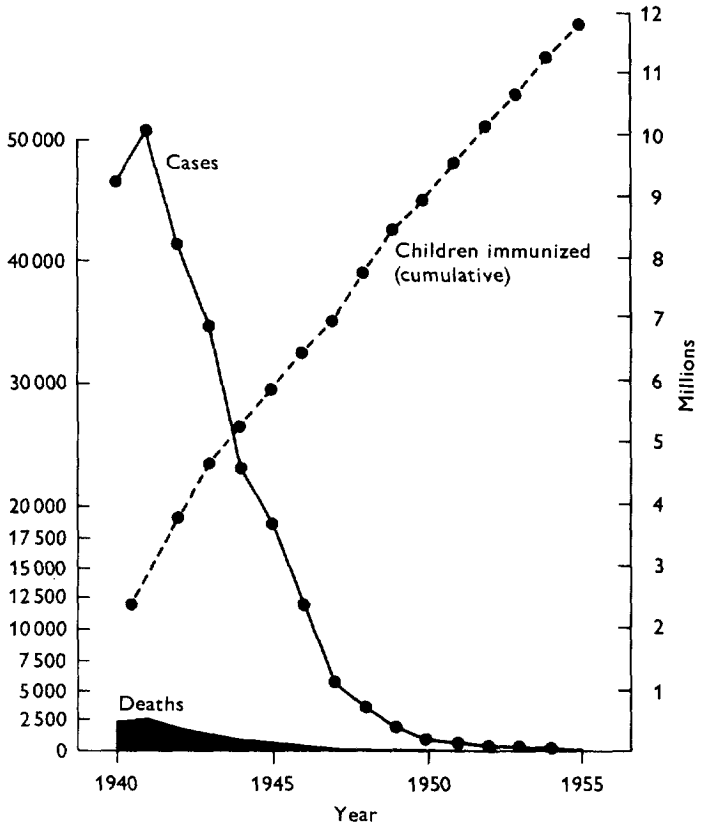

Fig. 1. Diphtheria in England and Wales (immunization, incidence, deaths).

Table I. *Average annual number of cases of poliomyelitis reported to WHO*

Countries	No. of countries	1951–5	1961–5	1966–70
N. America, Australia and New Zealand	4	44 378	852	57
Europe	23	28 359	6 665	732
Africa	35	3 660	3 932	4 005*
Central and South America	20	4 639	3 903	3 055
Asia	17	4 718	4 647	3 912

* 1966–9.

The much larger numbers in the field trials of the Salk poliomyelitis virus vaccines, set up in the United States in the early 1950s, were a further demonstration of successful collaboration between laboratory and field workers and health authorities, not only in many different areas of one country but also in different countries. These trials clearly showed that valid information on the efficacy and safety of a new vaccine against a disease of relatively low incidence could be obtained rapidly only if enormous numbers of subjects were observed according to standardized methods, and they are a memorial to the organizing ability of those who planned them and supervised their execution.

HAZARDS

A second feature of the era is that each of the immunizing agents carried actual or potential risks, as has recently been extensively documented by Sir Graham Wilson(9). However, the hazards – actual or potential – do not in any way detract from the overwhelming success. Immunization is one of the most effective methods of disease control ever devised and also the one which gives the speediest results.

Against this background of a success undreamt of 50 years ago, what ought to be the objectives of this meeting?

ESTABLISHED VACCINES

Look first at the established vaccines – smallpox, diphtheria, pertussis, tetanus, BCG and poliomyelitis. Have they become unalterable pillars of public health structure or ought we to be thinking of modifications and changes in the use of them?

So far as smallpox vaccine is concerned one country in Europe no longer recommends its universal use. Should other countries be thinking along the same lines or is it too soon to do so? In my view this depends very largely on the continuing success of the WHO smallpox eradication programme, which has given such unexpectedly good results in the past five years.

What is likely to be the next to come up for a reassessment of the need? BCG perhaps. It is many years since Frost showed that the prevalence of active tuberculosis in a given age group followed throughout their lives appeared to be determined by the incidence of infection in their youth. The generations with the highest rates are rapidly falling over the cliff and their deaths must lead to a rapid fall in the weight of infection in communities. Particularly when the success of current methods of treatment is also taken into account. At some point of time, therefore, the need for BCG vaccination will have to be reconsidered.

In contrast, the need for poliomyelitis vaccination will continue in the foreseeable future and this is true of diphtheria, pertussis and tetanus.

One factor to be borne in mind when contemplating the possibility of discontinuing a vaccine is the risk of introduction of infections from countries where the diseases are still uncontrolled, and, sadly, such countries are still in the

majority and very few of them have so far succeeded in establishing effective immunization programmes.

Among the established vaccines I believe that pertussis vaccine is the one which requires most urgent review, but not because the need for it is disappearing. Recently there have been several influential reports that the vaccine is often not very effective and that it carries too high a rate of reactions and untoward sequelae. The problem of effectiveness does not appear particularly difficult to overcome. Given a sufficient quantity of antigen and an antigenic spectrum covering the prevalent subtypes the vaccine protects as well as ever.

The problem of reactions and untoward sequelae is more difficult to solve. The minor local or general reactions which occur in 20–40 per cent of children usually disappear in 24–48 hours and the use of vaccines containing alum probably reduces these reactions considerably. However, other reactions are more serious. Shock and persistent screaming, which may occur in 1 in every 2000 children vaccinated, are alarming to parents and physicians alike(**2**). Fortunately no lasting ill effects have been reported in the children exhibiting these symptoms. Convulsions, which have been estimated to occur in about 4 per 10000 vaccinated(**1**), are nearly always of the simple febrile type without long-term ill effects. Encephalopathy, the pathogenesis of which is unknown, is exceedingly rare and much less common in the vaccinated than in those suffering from the natural disease. When it does occur it may result in complete mental degeneration of the victim and psychological tragedy in the family. In considering these possible untoward results of the use of the vaccine let us also remember that pertussis is a serious long, drawn-out disease. Vaccination materially reduces its incidence, severity and duration. What is now required is a concentrated effort to remove the remote dangers which use of the vaccine entails.

NEWER VACCINES

Measles vaccine bids fair to join poliovaccine as one of the most effective and safest viral agents. Very few authenticated untoward sequelae have been reported. Measles is universal in Europe and is almost exclusively a disease of the youngest age groups – mainly the first four years of life. Mortality rates vary widely between countries, even in Europe. In the 1–4 year age group in 1963–4 the rates per 100000 varied from 0.4 in Norway to 72 in Yugoslavia. The rates were usually higher in Eastern Europe than in the West where they were generally between 0.5 and 2 per 100000(**4**). Recent studies confirm that, though EEG changes are found in up to 30 per cent of cases, encephalitis occurs in about 1 per 1000 cases but that late sequelae are very uncommon. The other complications – otitis media and bronchopneumonia – are relatively easily handled. Therefore the high incidence of measles, rather than the severity of the disease, is the justification for vaccination.

Pečenka(**5**) reported that a questionnaire on the use of measles vaccine sent to 30 countries in Europe was answered by 27. Thirteen (Table II) had a national measles vaccination programme. Eight – Austria, Denmark, West Germany,

Table II. *Countries with systematic programmes for measles vaccination* (after Pečenka(5))

Country	Year begun	Age group (yr)	Number annually vaccinated	Vaccine strain
Albania	(1965) 1970	1–15	893 000 (1970)	Peking 55
Bulgaria	1969	1–8	125 000	Leningrad 16
Czechoslovakia	1969	1–4	220 000 (1971)	Schwartz-type
East Germany	1970	9/12–8 yr	626 000 (1971)	Leningrad 16 (dog kidney)
France	1968	1–4 (mainly)	100 000 (1971)	Schwartz-type
Hungary	1969	9/12–4 yr	150 000	Leningrad 16
Norway	1969	1–3	50 000	Schwartz-type
Spain	1966*	1–8	125 000	Schwartz-type
Sweden	1966	8/12–5 yr	5 000	Schwartz-type. ? other vaccine also
Turkey	1968	8/12–1 yr	?200 000	Leningrad 16. ? other vaccine also
UK (England and Wales)	1968	9/12–15 yr	623 000 (1970)	Schwartz-type
USSR	1968	10/12–8 yr	'up to 6 million'	Leningrad 16
Yugoslavia	1968	8/12–10 yr	500 000 (1971)	Beograd 2, Leningrad 16

* No vaccination 1969–71.

Greece, Monaco, Netherlands, Poland and Romania – had no systematic programme though there was some vaccination either in field trials or by private practitioners. Six – Belgium, Finland, Ireland, Italy, Malta and Portugal – had no measles vaccination. In Table II is also given some information about the programmes in the 13 countries – the most important being the age groups covered and the vaccine strains employed.

It is notable that 7 of the 13 countries are in Eastern Europe. Obviously there are great differences in the use of measles vaccine in Europe, particularly in Western Europe.

Information on the use of rubella vaccine in Europe is not readily available but it appears that very few countries have a systematic programme, though trials are in progress, and small-scale use of vaccine is being encouraged in some countries. No doubt the different approaches in the USA, where vaccination is offered for children 1–5 years of age, and the UK, where vaccination is concentrated on females 10–14 years of age, will be discussed here – as will the use of live mumps vaccine alone or in combination. The application of these newer vaccines may well be considered one of the main objectives of the meeting.

FUTURE POSSIBILITIES

Looking to needs and possibilities in the future, I believe that we are on the threshold of another period of great expansion in vaccine development and that in another decade the list of effective vaccines, particularly viral vaccines, will be greatly extended. The enormous toll of illness and death from the acute respiratory diseases must now receive far greater attention than it has in the past. In all parts of the world and in most age groups pneumonia, bronchitis and influenza are (taken together) among the first ten most common causes of death; this is true of the tropics as well as of temperate climates. The respiratory diseases are of course only partly amenable to vaccination, but the next decade ought to see improvements in the influenza vaccines, whether killed or live, and the development of effective vaccines against respiratory syncytial and parainfluenza infections. Possibly pneumococcal vaccines will have a place – especially in certain defined population groups.

The ubiquitous and high-incidence hepatitis has not yet yielded sufficiently to the investigator to permit a too hopeful forecast of the possibility of prevention by vaccination but the prospects for hepatitis B (serum hepatitis) are brighter than before and current work gives promise of having a vaccine under test in a relatively short time. In Europe, however, and in most temperate climates, hepatitis A (infectious hepatitis) causes the higher morbidity (though perhaps not mortality) and here prospects are less good.

Vaccination against cancer, though much spoken about, is still a good long way off – but I imagine that a majority of workers on the aetiology of cancer now believe that some forms of human cancer will eventually be preventible by some sort of vaccination and perhaps we may not be so far away from the use of, for example, herpes virus vaccines for this purpose.

GENERAL CONSIDERATIONS

Moving from specific vaccines and diseases to more general points, there is a great need to increase the stability of many of the vaccines – particularly measles and rubella. The more stable the product the greater the certainty that it will be potent when it reaches the end of the distribution chain and is injected. The use of combinations and/or simultaneous administrations is another means of ensuring the protection of greater proportions of the susceptible populations – and both stability and the use of combinations are of even greater importance in warm-climate countries than in most of Europe.

One problem which looms larger every year is the vaccination of human beings, generally children, in experimental studies of new or improved products.

The public are now very much aware that serious sequelae may follow the use of immunizing agents – and are becoming increasingly concerned with possible hazards when large-scale field trials are proposed. They are right to be cautious and we ought to be searching for means to reduce our dependence on the large-scale studies with which we have become familiar in the past thirty years.

Of course, immunization of human beings is the ultimate test of efficacy – and indeed safety. But the question is how to reduce the numbers in experimental studies to the minimum, because the logical conclusion of present trends on human experiments and on the requirement of 'informed consent' is that in due course it will only be permissible to approach the most intelligent groups of the population for participation in such studies. It is essential therefore that all possibilities of the use of animals other than man should be explored. In addition, we ought to be thinking whether recent new knowledge provided by immunologists can be used to assess accurately and in small numbers of persons the potential efficacy of new or improved products. Also, in addition to protecting the rights of the vaccinated, we have to think of protecting investigators and other users of vaccines from the consequences of unexpected and unforeseeable ill effects. The establishment of committees competent to judge the quality of proposed research projects has done a great deal to protect the public and the investigator, but I believe governments and not individual persons or firms must now face up to paying compensation for untoward sequelae from the use of both established and new products – as indeed is already the case in at least one country in Europe.

Once a product has passed the experimental stage we come to two aspects of control; one is the control of quality and the other is surveillance. All agree, at least in theory, that the quality control laboratory should be independent of the producers but even in Europe not all countries have yet appreciated how important is this matter of independence and I hope the discussions in the Symposium will bring it out clearly.

Surveillance of disease, of immunity status and of safety are as necessary as quality control, and this subject is on the agenda. Here I shall only point out that when a disease has been reduced to the level of, for example, poliomyelitis in Europe, there is much to be said for an intercountry surveillance system with specific objectives. In WHO such a scheme has been in progress for two to three years in eleven countries, mostly in Europe. It is primarily concerned with cases of persistent spinal paralysis temporally related to live poliomyelitis vaccination, but information on rates of vaccination acceptance, and on serological surveys, is also collected.

This scheme will have to be continued for several years, but already it has brought out that the number of vaccine-associated cases varies between countries and a thorough effort to determine the reasons for the variations is now being made. Another possibility for intercountry comparisons was mentioned by my colleague Dr Guld (3) who pointed out that Norway, Sweden and Denmark all used BCG but in different age groups – Norway vaccinates adults only, Sweden the new-born only and Denmark schoolchildren. Obviously there is scope for comparative studies in these three countries.

Other objectives of the Symposium are how to persuade the economic and health planners to provide the funds – cost benefit analysis; how to communicate to the public the need for continuing immunization after a disease has been brought under control; how to reduce costs and risks. Some countries believe both costs and risks could be reduced by concentrating production and quality

control in fewer hands. This could mean better equipment, more highly qualified staff, better internal control of quality and easier external control. This means intercountry collaboration on a large scale. Commercial pressures are already influencing producers. Has the time come to rationalize quality control in a similar fashion?

Obviously there are many possible objectives of this Symposium, and a great deal of room for mutual exchanges of opinions and experiences. This is the first occasion in Western Europe when makers of public health policy, laboratory workers, epidemiologists and vaccine producers have had an opportunity to meet together and we may be sure that by Saturday morning all of us will have greatly benefited from the discussions between workers interested in all aspects of immunization.

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SESSION II

ESTABLISHED VACCINES FOR REGULAR PROGRAMMES

Chairman: Dr F. T. PERKINS (UK)

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ACHIEVEMENTS IN EUROPE

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European experience of routine vaccination against smallpox, tuberculosis, diphtheria, tetanus, whooping-cough and poliomyelitis ranges over periods of between 15 and 170 years (Table I) and has varied considerably according to the epidemiology of the disease and the nature, quality and usage of vaccine.

Table I. *First vaccinations in Europe*

Infection	Vaccine first used	Routine vaccination started
Smallpox	1796	1801
Tuberculosis	1921	1928
Diphtheria	1913	1938
Tetanus	1927	1938
Whooping-cough	1929	1946
Poliomyelitis	1955	1956

SMALLPOX VACCINATION

Vaccination dates back to 1796 when Edward Jenner inoculated material from a cowpox lesion on the hand of a milkmaid on to the arm of a young boy whom he reinoculated six weeks later with matter from a smallpox pustule, without producing any ill effects. Cowpox was known at the time to produce immunity to smallpox and variolation had been practised sporadically in several European countries for two or three hundred years, but Jenner's report in 1798 had considerable impact, leading to the vaccination of 100000 persons in London, Hanover, Vienna and Greece before the end of 1799. The procedure was rapidly adopted almost throughout Europe and was made compulsory in some Italian states in 1806, Bavaria in 1807, France 1809, Norway and Denmark 1810, and Sweden 1816. During the Paris epidemic of 1825, it became obvious that primary vaccination did not confer lifelong immunity and that revaccination was necessary after a few years.

By the early 1870s, child vaccination was compulsory throughout Europe, but most countries had high vaccination rates long before then. Nevertheless, extensive childhood vaccination did not prevent the European epidemic of the early 1870s causing a heavy loss of life, even in some of the countries where infant

vaccination and childhood revaccination rates had been maintained at a high level for decades.

Routine vaccination and revaccination has been mainly confined to infants and young children, whereas persons of all ages are susceptible to smallpox. The infant vaccination programmes rendered smallpox into a disease primarily of adults and allowed it to remain endemic, sometimes epidemic, in the adult population throughout the nineteenth and well into the twentieth century. Control and, indeed, eradication of smallpox was achieved largely by routine vaccination of infants but this took well over a hundred years, during most of which about 80 per cent of all infants were vaccinated. It is conceivable that a single mass vaccination campaign involving the entire population, followed by a revaccination campaign a few years later, would have been considerably more effective with considerably fewer deaths than were due to smallpox during subsequent years.

Although smallpox ceased to be endemic in Europe more than thirty years ago, infant vaccination has remained compulsory in most European countries (Table II).

Table II. *Smallpox vaccination policies: European countries* 1964*

	Infant vaccination compulsory	Age revaccination recommended or compulsory (years)
Belgium	Yes	School entry
Bulgaria	Yes	—
Czechoslovakia	Yes	7 and 14
Denmark	Yes	No
Finland	No	10
France	Yes	10–11 and 20–21
East Germany	Yes	11–12
West Germany	Yes	12
Greece	Yes	6
Hungary	Yes	12–13
Ireland	No	5 and 14
Italy	Yes	8
Netherlands	Yes	—
Norway	Yes	No
Poland	Yes	7
Portugal	Yes	Every 5 years
Romania	Yes	7
Spain	Yes	Every 5–7 years
Sweden	Yes	—
Switzerland†	Yes/no	4–6
United Kingdom‡	No	8–12
Yugoslavia	Yes	7 and 14

* Based on *Wld Hlth Statistics Annual* (1968) ii, 145.
† Cantonal differences.
‡ Not recommended since 1971.

Table III. *Smallpox vaccinations in 20 European countries 1961–8*

Year	Number of vaccinations and revaccinations* (millions)
1961	16.75†
1962	23.50‡
1963	17.50§
1964	11.00
1965	10.75
1966	11.00
1967	11.25
1968	11.75

* Based on *Wld Hlth Statistics Annual* (1961–8).
† Includes 5 million extra in Spain.
‡ Includes 6 million extra in United Kingdom; 2 million extra in Greece.
§ Includes 7.8 million extra in Poland.

In some countries, revaccination of children has remained compulsory, partly in an attempt to secure or maintain an immune population. This target is however remote, as shown by the need to resort to mass vaccination in a number of countries during the last decade after importation of smallpox. Some of these countries had previously maintained high vaccination rates. Between 10 and 11 million persons are vaccinated or revaccinated each year in 20 European countries (Table III) which have a total population of over 400 million and about 7.5 million births a year.

The overall infant vaccination rate in these countries was probably around 75 per cent so most children are rendered immune to smallpox, but waning immunity in adults and a substantial proportion of unvaccinated persons means that the immune status of the population as a whole is subject to speculation. It appears that over a hundred years of compulsory vaccination of infants has failed to render the population as a whole immune to smallpox but the immune status of the well vaccinated population of some countries, such as Czechoslovakia, may be fairly high.

Routine vaccination of infants is recommended in order to protect them individually, in an attempt to secure herd immunity and lastly so as to considerably reduce the risk of serious complications later in life, were mass vaccination of adults deemed necessary. Revaccination is considerably safer than primary vaccination in adults, but primary vaccination of infants is not without attendant risks (Table IV).

As the smallpox endemic areas in the world diminish and the risk of smallpox importation recedes, so does the value of routine vaccination of infants for this purpose decline. For this reason, routine vaccination of infants is no longer recommended in the United Kingdom(5).

Table IV. *Complications of primary vaccination of infants in England and Wales* 1951 *to* 1960*

Number of primary vaccinations of infants under 12 months of age	2 661 488
Number of deaths attributed to vaccination	31
Number of non-fatal complications	154
Number of revaccinations (all ages)	1 240 644
Number of deaths attributed to revaccination	3
Number of non-fatal complications	20
Number of deaths from smallpox (19 in 1951–3)	22

* Based on Conybeare, E. T. (1964). *Monthly Bulletin of the Ministry of Health*, **23**, 126, 150, 182.

BCG

The development of BCG as a live attenuated bovine strain of the tubercle bacillus by Calmette and Guerin during the years 1906–20 is now of historical interest only. The live vaccine was initially administered orally to newborn infants in Paris in 1921 by Weill-Halle(**25**) who, in 1925, proceeded to give it subcutaneously to older children. This method of administration was developed further by Heimbeck(**8**) in Norway, who also showed the value of tuberculin testing before and after vaccination and produced data indicating that BCG provided tuberculin-negative nurses with a substantial degree of protection against tuberculosis. The intradermal technique of vaccination was developed by Wallgren (**24**) in 1927. Greenwood's attack in 1928 (**7**) on Calmette's statistical presentation of data on the efficacy of BCG, and the Lubeck disaster of 1931, greatly hindered the acceptance of BCG, except in France and the Scandinavian countries where studies by Hyge (**9**) (schoolchildren) and Dahlström & Difs (**4**) (army recruits), in particular, lent support to the view that BCG provided a substantial degree of immunity to tuberculosis. By 1948, only 7 million persons, mostly infants, had been vaccinated throughout the world.

An evaluation of BCG vaccination was undertaken by the Medical Research Council in 1950, coinciding with the commencement of a new era in the treatment of tuberculosis by antibiotics. This study showed that, under conditions prevailing in Britain at the time, BCG vaccination of tuberculin-negative adolescents produced a substantial degree of protection against tuberculosis over a period of 15 years after vaccination (**12**, **15**, **16**, **17**) (Table V). The level of protection decreased from 80 per cent during the first 5 years to 59 per cent during the third 5-year period. BCG was particularly effective in preventing miliary and meningeal tuberculosis.

The use of BCG increased rapidly after 1950. Most European countries initiated routine vaccination programmes for infants (Czechoslovakia, Finland, France, West Germany, Hungary, Poland, Romania) or adolescents (Britain, Norway) and household contacts of tuberculosis. BCG vaccination has proved

Table V. *Results of the Medical Research Council's BCG vaccine trial*

Initial tuberculin sensitivity state	Number of participants	Annual incidence of tuberculosis per 1000 participants (years after vaccination)				
		0–2½	2½–5	5–7½	7½–10	10–15
Pos. 3 TU (15+ mm)	6 866	3.75	1.83	1.01	0.42	0.48
Pos. 3 TU (5–14 mm)	8 838	0.77	0.86	0.55	0.32	0.37
Pos. 100 TU only	6 253	0.77	1.22	0.58	0.39	0.23
Neg. BCG vacc.	13 598	0.41	0.38	0.38	0.27	0.10
Neg. Not vacc.	12 867	2.12	2.89	1.30	0.83	0.26

to be remarkably safe but has not been a major contributor to the remarkable reduction in the incidence of tuberculosis in Europe during the last 20 years. Chemotherapy, by considerably reducing the period of infectivity of open cases of tuberculosis and thereby minimizing the risk of infection, was the main factor. Improved social conditions and smaller families were additional factors. It is now estimated that in Britain 1000 tuberculin-negative adolescents have to be vaccinated in order to prevent one treatable case of tuberculosis during the next 10 years. In 10–15 years from now, 10000 vaccinations will be necessary to prevent the one treatable case. Since routine vaccination is necessarily restricted to tuberculin-negative children and tuberculosis is a treatable disease of the older section of the population, its contribution to the prevention of tuberculosis has been minimal in Europe except in high risk groups, such as family contacts and medical services personnel, even though more than 6 million scarring vaccinations have been carried out each year.

DIPHTHERIA

Children were first immunized against diphtheria by Behring (**1**) in 1913 but his toxin–antitoxin mixtures were neither safe nor particularly antigenic. Ramon (**22**) obtained better results in 1923 with a formalized toxin and, with the recognition of primary and secondary immune responses by Glenny & Südmersen in 1921 (**6**), an effective method of immunization developed. Trials of the formalized toxoid and later an alum-precipitated toxoid were conducted from 1920 to 1935 in Britain by the Medical Research Council. Meanwhile, immunization of infants with toxoid had become common practice in the Netherlands. In France, combined typhoid–paratyphoid–diphtheria toxoid had been used after 1929 and diphtheria immunization was made compulsory for the armed forces in 1936. Immunization of children with diphtheria–tetanus toxoid was made compulsory in 1938, but the campaign was bedevilled with antagonists and uncooperative persons so that it did not become effective until 1946.

Several enthusiasts had been immunizing children in Britain during the 1930s

but in 1941–3 a mass campaign was carried out with the intention of immunizing children between the ages of 1 and 15 years. Nearly 5 million children were immunized during the campaign. The incidence of diphtheria rapidly declined, particularly as subsequent routine immunization ensured that about 90 per cent of children were protected. Before immunization programmes were introduced on a national scale, there were between 50000 and 60000 cases of diphtheria with 2000 to 3000 deaths a year in England and Wales and also in France. In the whole of Europe there were about a million cases in 1943 with 50000 deaths. The peak age incidence was 4–6 years, with 50 per cent of cases under 5 years of age and 80 per cent under 10 years. Mass immunization campaigns aimed at all children between the ages of 1 and 14 years therefore rendered most diphtheria-susceptible and potential transmitters immune to diphtheria, since adults were already immune as a result of infection during childhood. The mass campaigns initially shifted the peak incidence to adults and then reduced the total number of cases in the population as a whole to insignificant levels. In 1970, diphtheria had ceased to be a public health problem, except in a few countries bordering on the Mediterranean (Table VI).

There can be no doubt that a mass campaign aimed at the immunization of the entire diphtheria-susceptible population, consisting almost entirely of children, brought about the control of the infection more effectively and more rapidly than would have been achieved by routine immunization of infants only.

Table VI. *Diphtheria in Europe in* 1960 *and* 1970

Country	No. of cases*	
	1960	1970
Austria	831	24
Belgium	567	38
Czechoslovakia	626	2
Finland	2	—
France	913	46
West Germany	1 946	62
Greece	4 204	189
Hungary	291	3
Italy	6 390	837
Netherlands	112	3
Norway	1	—
Poland	6 380	23
Portugal	1 538	277
Spain	1 941	74
Sweden	2	—
Switzerland	48	7
England and Wales	49	22
Yugoslavia	1 856	156
Total	27 698	1 763

* *Annual Epidemiological and Vital Statistics* (1960), **1**, 594; *Wld Hlth Statistics Report* (1971), **24**, 419.

TETANUS

Tetanus toxoid was first used in man by Ramon & Zoeller in 1927(**23**) but since tetanus caused relatively few deaths in peacetime, in comparison with some communicable diseases, active immunization was not widely practised until just before the 1939–45 war. Since the risk of tetanus was a problem in wounded combatants, the armed forces of some countries were actively immunized after 1938. The extremely low incidence of tetanus in these, as compared with that in non-immunized armies, was accepted as convincing evidence of the value of active immunization with tetanus toxoid. Immunization of infants with diphtheria–tetanus toxoid had been made compulsory for French children in 1938, but routine vaccination of children was not carried out in any country until after 1945. Combined vaccine consisting of diphtheria and tetanus toxoid was initially used, but during the 1950s a third component, pertussis vaccine was added.

Since tetanus is not transmitted from one person to another and natural immunity does not occur, susceptibility to tetanus is universal except in the passively or actively immunized. Vaccination provides protection for the individual, it does not reduce the risk of infection for the non-immunized. Therefore, reduction in the incidence of tetanus in a population is related, in general, to the proportion of the population that is actively immunized. Since routine immunization has been offered in Europe only to infants, children and armed services personnel, a high proportion of persons over the age of 45 years has been left unprotected. Partly because of this, more than half of the deaths due to tetanus in Europe in 1968 were in persons over the age of 45 years (Table VII). Children under the age of 5 years accounted for another 25 per cent (450 cases); 95 per cent of these (427 cases) were infants under the age of 12 months, mostly from Greece, Portugal, Spain and Yugoslavia. This suggests that tetanus neonatorum, a preventable condition, still occurs occasionally in some European countries.

Safe and effective vaccine, suitable for administration with jet injectors in mass campaigns, is cheap and freely available but nevertheless the tetanus mortality rate in Europe has not been greatly reduced during the last 10 years. It is still about 4 per 100 000 persons per annum.

WHOOPING-COUGH

Clinical trials by Madsen in the Faroe Islands in 1923–4 and 1929(**10**) indicated that pertussis vaccine provided some degree of protection against whooping-cough. Subsequent studies in North America stimulated the Medical Research Council to carry out a series of trials which lasted from 1942 until 1959(**11**, **13**, **14**). They confirmed that some pertussis vaccine preparations gave a high level of protection whereas others gave indifferent results. Meanwhile, the use of pertussis vaccine in young infants had gradually increased during the 1940s in several countries. Since 10 to 12 per cent of all cases of whooping-cough are under 12 months of age and the condition runs a particularly severe course in the very young, immunization was started early in life during the 1940s and the

Table VII. *Tetanus deaths* 1968*

Country	Total deaths	0–4	5–14	15–44	45+	Population (millions)
Austria	28	1	1	4	22	7.3
Belgium	16	1	1	2	12	9.6
Bulgaria	33	5	3	16	19	8.4
Czechoslovakia	64	0	2	6	56	14.4
Denmark	3	0	0	1	2	4.9
Finland	2	0	0	1	1	4.7
France	228	5	0	7	216	49.9
West Germany†	84	4	8	17	48	58.0
Greece	53	14	3	5	21	8.8
Hungary	68	2	0	12	54	10.3
Ireland	6	0	1	1	4	2.9
Italy	261	23	18	45	175	52.8
Netherlands	2	0	0	0	2	12.7
Norway	2	0	0	0	2	3.8
Poland	92	6	2	13	71	32.3
Portugal	165	110	2	18	35	9.5
Spain	163	65	12	22	63	32.6
Sweden	3	0	0	0	3	7.9
Switzerland	12	0	0	2	10	6.1
England/Wales	13	0	1	3	9	48.6
Yugoslavia	299	204	3	23	69	20.2
Total	1597	450	57	198	884	405.7

* Based on mortality figures in *Wld Hlth Statistics Report* (1971), **24**.
† 1967 figures.

course completed before the child was due to receive its first dose of diphtheria–tetanus combined vaccine. The production of a diphtheria–tetanus–pertussis vaccine in the early 1950s eased administration problems by reducing the number of immunizing injections that had to be administered to children.

In England and Wales the case fatality rate for whooping-cough sharply decreased between 1946 and 1950 but the incidence of new cases remained unaltered. Presumably, this was brought about by improved forms of therapy, including antibiotics, for complications, which would have no effect on the infective phase of the disease. Vaccine was not widely used until 1949–52 and then only in young infants, so the total number of cases of whooping-cough was unlikely to fall until after 3 to 5 years later. Routine vaccination of young infants can hardly be expected to immediately reduce the incidence of whooping-cough in schoolchildren who account for more than 50 per cent of all cases. Since 80 to 90 per cent of all cases of whooping-cough are, however, under 10 years of age, routine vaccination of infants should have an accumulative effect over a period of up to 10 years, provided the vaccine produced durable immunity. This is precisely what happened in England and Wales and, indeed, in several other European

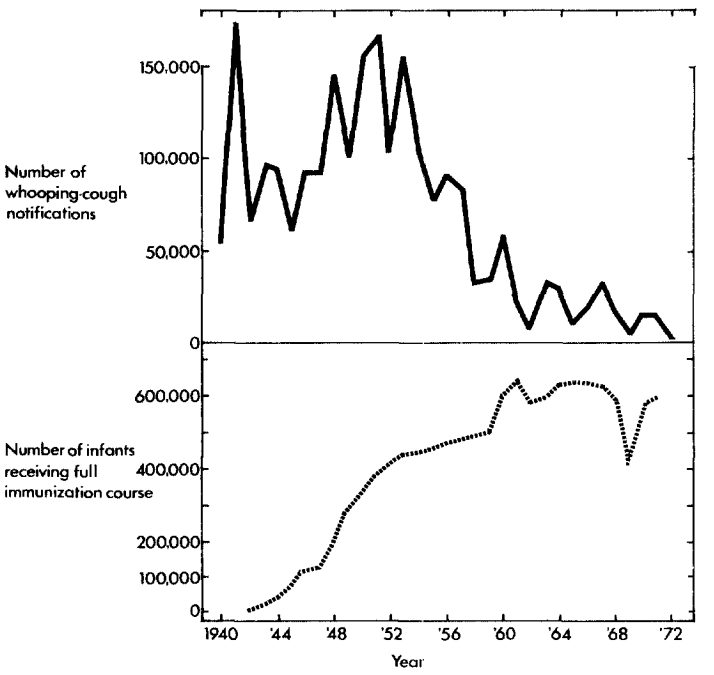

Fig. 1. Whooping-cough notifications and immunizations, England and Wales 1940–72.

Table VIII. *Whooping-cough in European countries in* 1960 *and* 1970

Country	Number of cases*	
	1960	1970
Austria	2 761	1 436
Czechoslovakia	7 918	408
Denmark	79 503	792
Finland	1 135	261
France	4 309	920
Greece	7 547	6 518
Hungary	1 860	355
Italy	21 980	9 013
Norway	24 304	3 766
Poland	95 968	10 002
Portugal	1 205	175
Sweden	8 817	2 335
England and Wales	58 030	16 753
Yugoslavia	28 764	6 657
Total	344 101	59 391

* *Annual Epidemiological and Vital Statistics* (1960), p. 609; *Wld Hlth Statistics Report* (1971), **8**, 496.

countries. Vaccination has proved effective; it has reduced the incidence of whooping-cough by 98 per cent in Britain between 1952 and 1972 (Fig. 1) and is proving similarly effective in other European countries (Table VIII).

The slow rate of decline in the incidence of whooping-cough since the introduction of routine vaccination about 20 years ago has generated speculation that vaccines are not as effective as they were years ago. A course of three doses in infancy is expected to provide immunity for 10–15 years or longer without revaccination at school age in some countries. This killed vaccine is therefore expected to be more effective than smallpox vaccine and to be as effective as BCG and possibly measles vaccine. In fact, it has stood up to the challenge. Nevertheless, it has been held that vaccines were prepared in the 1950s from the predominant serotypes at the time and were effective against those serotypes only, leaving the heterologous serotypes to be the new predominant organisms(**18**, **19**, **20**). Protection studies(**2**) in mice, however, do not support this hypothesis and, indeed, the agglutinogenic composition of isolates from a child with whooping-cough seems to vary during the course of the illness(**21**).

Routine infant vaccination against an infection which is prevalent throughout childhood is a slow method of bringing that infection under control. A mass campaign along the lines of the diphtheria immunization campaign could have been considerably more effective in reducing the incidence of whooping-cough. Reservations concerning administration of this vaccine to schoolchildren has prevented that approach. In some countries, however, where nearly all infants and schoolchildren have been vaccinated, there has been a sharp fall in the incidence of whooping-cough. Elsewhere, routine vaccination of a high proportion of infants with 4+ potency unit vaccine will ensure that the downward trend in the incidence of whooping-cough will be maintained.

POLIOMYELITIS

Following a large-scale trial of formalized poliovirus vaccine in the United States in 1954, which had shown that it gave substantial protection to young children, small-scale trials were started in Europe in 1955. Mass vaccination was carried out in Eastern Europe during 1956 and was extended in 1957. Initially, two doses of intradermally administered vaccine were given during these campaigns, but the level of protection achieved was disappointing and the virus continued to spread in the population, uninfluenced by vaccination. With the development of more antigenic vaccine and the adoption of three subcutaneous doses for a vaccination course, the protection rates improved considerably but nevertheless varied from one country to another.

Following field trials of live poliovirus vaccine in Russia during 1958, Czechoslovakia, Poland, Hungary, East Germany and Albania carried out mass vaccination campaigns in 1959, using monovalent vaccines. During the next two years, the campaigns were extended in those and other European countries, using trivalent vaccine, but some countries which had already achieved remarkable results with killed vaccine continued to use that vaccine exclusively. Killed vaccine used

Table IX. *Poliomyelitis in European countries in* 1960 *and* 1969

Country	No. of poliomyelitis cases*	
	1960	1969
Austria	404	—
Belgium	300	2
Denmark	22	1
Finland	273	—
France	1 663	69
West Germany	4 139	25
Hungary	38	2
Ireland	183	7
Italy	3 555	56
Netherlands	29	15
Norway	59	1
Poland	301	6
Portugal	244	1
Spain	1 632	387
Sweden	18	—
Switzerland	139	1
United Kingdom	378	15
Yugoslavia	1 680	24
Total	15 057	612

Annual Epidemiological and Vital Statistics* (1960), p. 626; *Wld Hlth Statistics Report* (1971), **24, 71.

in Scandinavia gave results as good as those obtained in other countries with live vaccine(3). A dramatic decrease in the incidence of poliomyelitis occurred in all countries (Table IX). This was achieved mainly as a result of intensive campaigns aimed at the vaccination of the poliomyelitis-susceptible population, including adults. About 100 million doses of vaccine were used annually in Europe during that period. Poliomyelitis has now been reduced to insignificant levels in all countries except those bordering the Mediterranean, but isolation of the virus is still not uncommon.

CONCLUSION

In conclusion, vaccines have proved most effective when used initially in mass campaigns aimed at immunizing the entire infection-susceptible section of the population and then routinely in infants. Where only a section of the susceptible population has been a target for vaccination, the incidence of disease has declined only slowly and the vaccines have appeared less effective in protecting individuals than when used for immunizing the entire susceptible section of the population.

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ADAPTATION DU CALENDRIER DE LA VACCINATION BCG EN HONGRIE, PAYS AVEC ECONOMIE INTERMEDIAIRE ET EPIDEMIOLOGIE DE TUBERCULOSE DISSOCIEE

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ECONOMIE ET SANTE PUBLIQUE

On présente la situation économo-sanitaire des pays en fonction du développement économique et du pourcentage du revenu national dans les dépenses de santé publique. Les données internationales disponibles donnent sur ces chiffres des valeurs extrêmes. Le revenu national par personne oscille entre 50$ et 3000$ dans les différents pays du monde. Ces valeurs numériques n'expriment pas réellement: (1) la nature des sources, variables d'un pays à l'autre, (2) le dynamisme du développement du revenu national, soit le pourcentage de l'augmentation de moyenne annuelle, (3) la répartition du revenu national parmi la population.

Dans les analyses économo-épidémiologiques on utilise deux notions restrictives, les termes de: (1) *pays en voie de développement* et (2) *pays développés*. Ces termes sont en réalité non dynamiques et très difficilement utilisables sur le plan international pour l'évaluation comparative de la situation de santé publique. Il faudrait introduire une terminologie économique plus différenciée dans le domaine économo-sanitaire afin de pouvoir déterminer avec une plus grande précision les caractéristiques économiques des *pays ayant une situation intermédiaire ou élevée.*

EPIDEMIOLOGIE DE LA TUBERCULOSE

La conception statique existe dans la description analytique internationale des relations comparatives de l'*épidémiologie de la tuberculose*. D'une façon traditionnelle, les pays sont classifiés avec (1) *faible* ou (2) *forte incidence, prévalence et mortalité*. Il faut considérer que ces catégories ne sont acceptables que dans les pays ou elles sont valables pour toute la population. Par exemple, on peut appliquer les termes de faibles incidence et prévalence seulement aux pays ou la morbidité a diminué parallèment dans les différents groupes d'âge de la population pendant plusieurs dizaines d'années comme résultats de méthodes classiques

de la lutte contre la tuberculose. De même les termes de fortes incidence et prévalence ne sont valables que dans les pays où la morbidité est vraiment forte dans tous les groupes d'âge de la population.

VACCINATION BCG

Un *programme* de vaccination par le BCG dont le but est de viser et de renforcer le contrôle de la tuberculose des enfants peut modifier dans un délai très court la situation épidémiologique des différents groupes d'âge de la population. La vaccination efficace par le BCG peut diminuer en quelques année d'une facon significative l'incidence chez les enfants jusqu'à un taux très bas alors que dans ce même intervalle l'incidence dans la population adulte déjà allergique et non vaccinée ne diminue que graduellement. Ainsi se forme une *morbidité dissociée*, soit: *faible incidence des enfants* et *fortes incidence* et *prévalence des adultes*. L'analyse comparative internationale de l'épidémiologie de la tuberculose peut démontrer que la dissociation de l'incidence des différents groupes d'âge ne se forme pas dans tous les pays et dans toutes les situations malgré des mesures de contrôle extrèmement poussées. Dans ces cas, il est nécessaire de rechercher les raisons de l'inefficacité des mesures appliquées: vaccination inefficace, facteurs démographiques ou économiques.

BCG EN HONGRIE

La situation épidémiologique a amené la Hongrie à introduire en 1959 la revaccination obligatoire jusqu'à 20 ans. On a effectué 4753708 vaccinations chez les enfants de 1959 à 1971. Parallèlement d'autres mesures antituberculeuses (dépistage, isolation, traitement) ont été prises de facon identique pour toute la population dans un contexte socio-hygiénique conditionné par la situation économique intermédiaire du pays. L'analyse de regression avec les log des taux de morbidité de 1958 à 1968 démontre que la forte morbidité des adultes et des enfants en 1958 devient dissociée en 1968. Les figures montrent que l'incidence et la prévalence sont fortes encore chez les adultes: 152% per 1000 et 1166% per 1000, mais faibles chez les enfants: 10% per 1000 et 39% per 1000. La question se pose en Hongrie de reduire de programme de revaccination systématique mais dans cette situation épidémiologique de tuberculose dissociée dans des conditions d'économie intermédiaire (Rev. nat. par pers. en $US: 1958 = 390, 1968 = 748) la modification du calendrier de vaccination est un risque.

Hongrie, tuberculose toutes formes	Popul. M+F âges	Tuberculosis per 100 000		1958–68	
		1958	1968	Anal. regr. lin. $\log y =$	Dimin. moy. ann. (%)
Incidence	>14	335	152	$-0{,}0391x+2{,}5842$	8,6
	<14	236	10	$-0{,}1503x+2{,}3685$	29,3
Prévalence	>14	1352	1166	$-0{,}0106x+3{,}2173$	2,4
	<14	454	39	$-0{,}1318x+2{,}7489$	26,2

SUGGESTION

Les notions socio-économiques et les paramètres épidémiologiques de tuberculose actuellement utilisés sont statiques. A cause du changement permanent des situation économiques et épidémiologiques ils ne peuvent plus exprimer les différences et les nuances existant parmi les pays. Afin de pouvoir démontrer d'une facon dynamique et comparative la situation réelle des différents pays et planifier leur programme antituberculeux, il est suggéré d'introduire l'application de notions et de principes plus différenciés. Le Tableau I montre une compilation économo-sanitaire et la suggestion de la politique de BCG en fonction de la situation économique et épidémiologie de tuberculose des pays. La terminologie et les définitions proposées pour les pays sont les suivantes:

(1) *Economie:* (*a*) faible, (*b*) intermédiaire, (*c*) élevée, (*d*) forte.

(2) *Technique:* (*a*) sous-developpée, (*b*) en voie de développement, (*c*) développée, (*d*) avancé. (3) *Morbidité de tuberculose:* (*a*) forte, (*b*) intermédiaire, (*c*) dissociée selon le groupe d'âge, (*d*) faible.

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Tableau I. *Compilation de données pour comparaison de la situation économique, démographique, sociale, de la santé publique et de l'épidémiologie de tuberculose des pays en vue de proposition d'un plan et d'un modèle de décision des modalités, de la stratégie et du calendrier de la vaccination par le BCG*

Rang économique et technique des pays									
Définitions		Accroiss. annuel du revenu national par pers. (%) (3)	Alimentation: calories besoins (%) (4)	Dépenses pour la santé du revenu nation (%) (5)	Accroiss. naturel de la popul. (%) (6)	Taux mortal. infant. pour 1000 enfants nés vivants (7)	Nbre de médecins pour 10^4 hab. (8)	Nbre de lits hopit. pour 10^4 hab. (9)	Tuberc. des bovid. reaction + tuberculinique (%) (10)
Economie: revenu national par pers. ($/an) (1)	Développement technique (2)								
Faible, < 300	Sous-développé	< 2,5	< 90	2–3	> 2	> 50	< 5	< 25	> 25
				Seuil de développement économique					
Intermediaire, 300–700	En voie de développement	2,5–3,0	100–10	3–4	1–2	< 50	> 5	> 25	< 25
Elevé, 700–1500	Développé	3,0–3,5	110–120	4–5	1–2	< 25	> 10	> 75	< 10
Fort, > 1500	Avancé	> 3,5	> 120	5–6	1–2	< 15	> 15	> 100	< 1

Economie: revenu national par pers. ($/an) (1)	Développement technique (2)	Gpe d'âge de popul. (ans) (11)	Epidémiologie de la tuberculose. Indices de toutes formes. 2 sexes. Taux pour 100 000 habitants					Test Tub. Stand. OMS >6 mm (%) (17)	Vaccination par le BCG; application intradermique; modalités, stratégie, calendrier (18)
			Mortalité (12)	Morbidité					
				Incidence		Prévalence			
				Cas actifs (13)	BK+ (14)	Cas actifs (15)	BK+ (16)		
Faible, <300	Sous développé	>14	>50	>200	>100	>1000	>300	>50	Campagne de masse avec équipes mobiles, integrée, méthode indiscriminée, simultanée avec antivariolique, sujets de 0 à 20 ans
		<14	>5	>20	>10	>100	>50	>20	
			Seuil de développement économique						
Intermediaire, 300–700	En voie de développement	>14	<50	<200	<100	<1000	<300	<50	Obligatoire pour nouveau-nés. Revacc. systématique des 3, 6, 10, 14, 17, 20 ans tuberculino négatifs: <5 mm ind. Test Tuberc. Stand. OMS
		<14	<5	<20	<10	<100	<50	<20	
Elevé, 700–1500	Développé	>14	<20	<100	<50	<500	<100	<20	Obligatoire pour nouveau-nés et/ou omission par randomisation. Revaccination: début et/ou fin d'études scolaires
		<14	<1	<10	<5	<50	<25	<10	
Fort, >1500	Avancé	>14	<5	<50	<20	<200	<50	<10	Méthode sélective pour contacts familiaux et groupes exposés: infirmières, étudiants, militaires, employés des communications, travailleurs immigrants
		<14	<1	<10	<5	<20	<10	<5	

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EFFICACITE DE LA VACCINATION SYSTEMATIQUE PAR LE BCG HONGRIE DEPUIS 1959. ANALYSE COUTS/AVANTAGES

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L'interaction de la souche BCG, de la méthode de fabrication et du contrôle du vaccin, de la situation épidémiologique et économique de la population vaccinée détermine l'efficacité de la vaccination par le BCG.

En Hongrie (pays de 100000 km^2, 10000000 d'habitants dont 25% d'enfants de moins de 14 ans), avant 1959, la morbidité par tuberculose de la population adulte et infantile était surélevée par rapport aux pays ayant alors déjà une tendance de diminution au 'seuil de contrôle' ou au-dessous de celui-ci. Après la campagne de l'UNICEF (1947–9) l'application méthodique du BCG n'a pas été poursuivie. Ainsi un système de vaccination efficace avait en fait 10 ans de retard et la situation épidémiologique adulte–enfant avait en 1959 un décalage défavorable par rapport aux pays plus avancés.

Entre 1953–8 la Hongrie avait une morbidité par tuberculose critique. La régression de l'incidence (toutes formes, 2 sexes) étaient; population > 14 ans: $\log y = -0{,}0190x + 2{,}5840$, soit 4,3% de la diminution moyenne annuelle; population < 14 ans: $\log y = +0{,}0010x + 2{,}3488$, soit 0,2% de l'augmentation moyenne annuelle.

A partir de 1954 la vaccination BCG, obligatoire chez les nouveau-nés mais sans application systématique et facultative chez les écoliers – par manque de continuité – n'a pas diminué l'incidence des enfants de 0 à 14 ans jusqu'en 1959. Avant 1959, l'utilisation de la sous-souche BCG Budapest descendante de la souche 458 de l'Institut Pasteur et entretenue depuis 1933, démontrait la diminution de sa virulence résiduelle et de sa capacité immunogénétique.

Afin d'assurer la protection des enfants, la Hongrie a introduit en 1959 la revaccination obligatoire par le BCG jusqu'à 20 ans. Pour redresser la situation et recupérer les 10 ans de retard, la primo et revaccination systématiques de 0 à 20 ans ont été effectuées dans 200 dispensaires antituberculeux. Le Laboratoire du BCG de Budapest utilise depuis 1959 la souche 'Pasteur 1173P2' en système de seed-lot selon les normes de l'OMS relatives à la fabrication. Entre 1959–72 4,8 millions de vaccinations ont été effectuées.

Le Tableau I montre les données démographiques de la situation économo-sanitaire, les mesures de lutte antituberculeuse en Hongrie de 1959 à 1971. Selon

Tableau I. *Données démographiques. Situation économo-sanitaire. Mesures de lutte antituberculeuse en Hongrie de* 1953 *à* 1971

Ans	Population dont × 10^3, tous ages (1)	dont × 10^3, 14 ans (2)	dont × 10^3, 14 ans (3)	dont nouveau-nés vivants (4)	Revenu National par pers. ($ US) (5)	Dépenses pour la Santé (% du Rev. Nat.) (6)	Nbre tot. de lits pour tbc hopit. et sana (7)	Nbre tot. de dispens. anti-tub. (8)	Nbre tot. exam. radiol. syst. dépis-tages (9)	Vaccin intracutané préparé dans le Laboratoire de BCG de Budapest (Doses produites) Liquide (10*)	Lyophilisé (11*)	Nombre total des vaccinations par le BCG Primo-vacc. des nouveau-nés (12)	Revacc. des enfants et adultes 3–20 ans (13)	Total (14†)
1953	9 545	7 121	2 383	206 926	327	—	9 805	176	—	—	—	—	—	—
1954	9 645	7 203	2 429	223 347	310	—	10 557	180	—	—	—	—	—	—
1955	9 767	7 259	2 490	210 430	337	2,37	11 118	181	—	—	—	—	—	—
1956	9 883	7 327	2 534	192 810	296	2,91	11 929	184	—	—	—	—	—	—
1957	9 829	7 264	2 540	167 202	368	2,64	12 626	185	2 980 217	—	—	—	—	—
1958	9 850	7 293	2 532	158 428	390	2,93	12 872	185	3 346 519	—	—	—	—	—
1959	9 913	7 356	2 533	151 194	415	3,13	13 140	186	3 587 956	3 100 000	—	134 876	234 833	369 709
1960	9 961	7 432	2 529	146 461	453	3,25	13 262	187	3 989 366	2 940 000	—	134 076	253 717	387 793
1961	10 007	7 481	2 525	140 365	479	3,26	13 445	190	4 509 759	3 065 000	—	133 575	248 498	382 073
1962	10 050	7 535	2 515	130 053	498	3,32	14 225	193	4 511 182	3 155 000	148 000	125 979	191 604	317 583
1963	10 073	7 597	2 474	132 335	543	3,32	15 505	194	5 387 074	3 183 150	214 000	127 904	146 183	274 087
1964	10 104	7 673	2 431	132 141	549	3,56	16 138	195	5 940 313	2 181 315	1 196 000	130 549	171 198	301 747
1965	10 135	7 749	2 387	133 009	551	3,52	16 978	194	6 107 040	—	1 280 000	132 813	307 332	440 145
1966	10 161	7 823	2 337	138 489	603	3,44	16 442	193	6 866 839	—	1 430 000	137 097	291 575	428 672
1967	10 195	7 900	2 297	148 886	661	3,30	16 073	191	6 976 483	—	1 323 000	146 497	294 998	441 495
1968	10 236	7 966	2 270	154 419	748	3,28	15 617	190	7 193 861	—	1 222 000	153 265	250 683	403 948
1969	10 275	8 047	2 228	154 318	841	3,07	15 371	188	7 284 804	—	1 471 800	151 412	225 426	376 838
1970	10 313	8 142	2 171	151 819	896	3,22	14 508	186	7 365 949	—	1 310 500	151 827	190 626	342 453
1971	10 345	8 223	2 122	150 640	978	3,31	13 421	186	7 289 798	—	1 325 800	148 829	138 336	287 165
1972	—	—	—	—	—	—	—	—	—	—	1 104 340	—	—	—
Total										17 624 465	12 025 440	1 808 699	2 945 009	4 753 708

* Cout du vaccin liquide et lyophilisé préparé du 1959 à 1972 = $300 000.
† Investissement dans la vaccination BCG du 1959 à 1972 = $4 800 000.

le revenu national la Hongrie est un pays d'économie intermédiaire. L'investissement dans la vaccination BCG du 1959 à 1971 a été $4800000.

Le Tableau II montre les données épidémiologiques sur la tuberculose en Hongrie de 1953 à 1971. L'analyse de régression linéaire démontre la dissociation de la tendance évolutive de l'incidence adulte–enfant entre 1958–68. La regression de l'incidence des adultes est: $\log y = -0{,}0391x + 2{,}5842$ (dimin. moy. ann. = 8,6%) et celle des enfants: $\log y = -0{,}1503x + 2{,}3685$ (dimin. moy. ann. = 29,3%). L'incidence (toutes formes, 2 sexes) des enfants qui était de 234% per 1000 en 1958 a diminué en 1972 à 5% per 1000 mais celle des adultes a été encore de 152% per 1000, signe de 20 ans de retard par rapport aux pays plus avancés.

La réalisation conséquente de la vaccination BCG en Hongrie à partir de 1959 peut être présentée comme un modèle de l'efficacité de la vaccination systématique. Les résultats montrent que dans un pays d'économie intermédiaire un programme de BCG intensif, en tant qu'influence spécifique, accèlere la régression de la morbidité de tuberculose des enfants.

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Tableau II. *Données épidémiologiques sur la tuberculose en Hongrie de* 1953 *à* 1970

Ans	INCIDENCE Taux pour 100 000 habitants Toutes formes. 2 sexes. Fréquence des nouveaux cas actifs enregistrés 1. i. – 31. xii					PREVALENCE Taux pour 100 000 hab. Toutes formes. 2 sexes. Fréquence globale au 31. xii				MORTALITE T.p. 100 000 hab. Toutes formes. 2 sexes. Décès 1. i. à 31. xii.			MENINGITE TUBERCULEUSE Taux pour 100 000 habitants. 2 sexes					
	Tous âges	dont		>14 ans	<14 ans	Tous âges	dont	>14 ans	<14 ans	Tous âges	>14 ans	<14 ans	INCIDENCE Tous âges	>14 ans	<14 ans	MORTALITE Tous âges	>14 ans	14 ans
	(1)	BK+ (2)	recid. (3)	(4)	(5*)	(6)	BK+ (7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)
1953	368	83	—	417	227	910	—	1 086	390	44	53	17,0	2,0	—	—	3,4	1,9	7,9
1954	320	69	—	352	229	1 062	—	1 258	490	36	45	10,9	2,1	—	—	2,2	1,4	5,4
1955	306	66	—	337	218	1 183	—	1 397	567	34	42	9,4	2,1	—	—	1,4	0,7	3,7
1956	298	60	—	327	217	1 335	—	1 569	664	35	45	7,5	2,2	—	—	1,0	0,8	2,2
1957	284	56	—	306	221	1 425	—	1 666	732	34	44	5,5	1,8	—	—	0,9	0,7	1,9
1958	309	60	—	335	236	1 122	—	1 352	454	31	40	4,1	1,4	—	—	0,6	0,4	1,3
1959	296	59	—	334	184	1 296	—	1 554	534	32	42	2,1	1,3	—	—	0,5	0,4	0,9
1960	280	62	19	329	136	1 367	—	1 657	502	31	41	1,6	1,9	—	—	0,3	0,3	0,3
1961	258	57	17	314	93	1 372	—	1 702	386	29	38	1,6	1,2	—	—	0,4	0,4	0,4
1962	230	57	15	286	57	1 326	—	1 671	267	30	40	1,3	0,8	—	—	0,2	0,2	0,3
1963	224	60	16	285	32	1 243	—	1 588	153	26	34	1,0	0,6	—	—	0,3	0,3	0,4
1964	188	75	13	239	23	1 127	338	1 451	76	26	34	0,3	0,5	0,5	0,5	0,2	0,2	0,1
1965	156	63	14	197	17	1 098	245	1 407	66	25	32	0,3	0,3	0,4	0,1	0,1	0,1	0,1
1966	139	57	12	175	13	1 053	203	1 344	54	22	29	0,1	0,2	0,3	0,1	0,1	0,2	0,0
1967	128	56	12	160	12	1 001	182	1 272	48	23	30	0,2	0,3	0,3	0,2	0,1	0,1	0,1
1968	121	47	13	152	10	922	158	1 166	39	22	28	0,4	0,3	0,3	0,2	0,1	0,1	0,2
1969	107	38	12	134	10	860	137	1 084	34	21	26	0,2	0,1	0,1	0,04	0,1	0,1	0,1
1970	96	34	11	120	8	797	117	1 008	29	19	25	0,1	0,2	0,2	0,1	0,05	0,1	0,0
1971	91	33	11	113	5	740	98	938	23	18	22	0,1	0,2	0,3	0,0	—	—	—
d % 53–8	3,4	6,5	—	4,3	+0,2	+5,7	—	+5,7	+5,9	5,2	3,9	23,3	6,1	—	—	28,4	24,2	30,4
d % 58–68	9,8	1,1	5,1	8,6	29,3	3,1	16,6	2,4	26,2	3,4	3,8	27,0	19,3	12,3	10,8	17,7	13,9	19,9

* Regression de l'incidence des enfants <14 ans du 1959 à 1972 = de 236 °/$_{0000}$ à 5 °/$_{0000}$.

d %: Après l'analyse de régression linéaire: 'd' % = 1 – num log ($-b$) = exprime le pourcentage de la diminution (ou augmentation) de moyenne annuelle de la variable dépendante: 'y' log taux pour 100 000 des indices den fonction du temps; x = ans.

GENERAL DISCUSSION

CHAIRMAN Are there any comments concerning diphtheria, tetanus, pertussis, poliomyelitis and BCG vaccines?

UNGAR (Switzerland) I should like to make some comments regarding BCG. In spite of the improvements in hygiene and chemotherapy in many countries I think that BCG vaccination still has an important role to play, particularly in certain population groups. Although in America, Britain and other countries the mortality due to tuberculosis has dropped considerably, nevertheless every year there are new cases of tuberculosis. The evidence from the United States for example shows that every year there are between 70 000 and 90 000 new cases of tuberculosis. The majority of these new cases are due to infection with antibiotic-resistant mycobacteria, but people must be treated as known cases with a virulent mycobacterium tuberculosis.

The age group most exposed to tuberculosis is between 12 and 20 years, and I think, therefore, that we should be very careful not to minimize the importance of BCG in a population where it can have an influence if immunization is done properly and on a large scale.

CHAIRMAN Thank you, Dr Ungar. Would you like to say anything in reply to that, Dr Griffith?

GRIFFITH I was dealing with vaccination in Europe and the two ages at which BCG is given routinely. Given at birth, its prophylactic effect is mainly against generalized tuberculosis and meningeal tuberculosis. Tuberculosis is, however, mainly a disease of adults but even when given routinely to adolescents, as in Britain, the number of persons that have to be vaccinated in order to prevent one case of tuberculosis is rapidly increasing. I purposely avoided the problem of BCG vaccination outside Europe and the question of BCG effectiveness against atypical mycobacteria.

VASSILOPOULOS (Cyprus) I should like to hear Dr Griffith's comments on the prophylactic effect of BCG vaccination, not only as regards tuberculosis but also leprosy prophylaxis.

GRIFFITH (UK) I should like to avoid this again, because I would rather keep to my subject of Europe and European experience.

CHAIRMAN I think it is true to say that one trial showed some effect, but another one failed. I am sure that many of these points will be discussed again.

Now, we will ask Dr Sencer, Chief of the CDC, to talk to us about cost–benefit analysis.

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COST BENEFIT ANALYSIS

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Benefit–cost analyses in the delivery of immunization services are tools that the administrator of a health service can use to justify what may seem to be inordinate costs. Examples can be seen in:

(1) An analysis of the costs associated with the protection of the United States against smallpox in relationship to the benefits and costs of global smallpox eradication and the savings to date as a result of discontinuing routine vaccinations for children.

(2) An analysis of the first ten years' experience of the immunization effort against measles in the United States and some analysis of measles immunization campaigns in developing countries where the United States provided technical assistance.

The smallpox endemic area is shrinking rapidly throughout the world. The number of countries reporting smallpox has decreased from 91 in 1945, to 42 in 1967, 30 in 1969, 23 in 1970, and 17 in 1971 – the 175th year since the first vaccination against smallpox by Jenner. The eight nations where smallpox is now endemic are directing efforts toward the eradication of the disease with the leadership of the World Health Organization. The threat of smallpox importation from areas where a reservoir remains has led smallpox-free countries to continue smallpox protection programs. The rapidly declining number of countries with smallpox has directed attention to the continuing policy of routine vaccination of the population, with its recognized risks of complications.

First, I will briefly review the epidemiologic data with respect to routine vaccinations, the estimated cost of the effort to protect the civilian population in the United States in 1968. Major cost estimates included those for medical services associated with routine vaccinations, medical care for complications of vaccinations, governmental protection services, and governmental support for international disease eradication. The latter is included in this analysis since public health officials must face the question 'What is the most rational distribution of our Nation's resources between domestic protection and international disease eradication?' The problem is complicated because the benefits associated with the domestic protection policy are influenced by support for, and success of, international disease eradication. In deciding upon a strategy of protection from

smallpox, total benefits and costs of both the domestic protection effort and the international smallpox eradication program must be considered, recognizing that the benefits are interdependent.

A national probability sample survey in the United States estimated that 14.2 million persons in the civilian population were vaccinated in 1968; 5.6 million received a primary vaccination, and 8.6 million were revaccinated. Table I presents the smallpox vaccinations by age group and population coverage. Overall, 21.4 per cent of the children 1–4 years of age and 15.3 per cent of the persons in the age category 5–9 years were vaccinated in 1968.

Table I. *Smallpox vaccinations by age and vaccination status, United States, 1968*

Age	Primary	Revaccinations	Total	Population covered (%)
<1	614 000	—	614 000	17.6
1–4	2 733 000	478 000	3 211 000	21.4
5–9	1 553 000	1 643 000	3 196 000	15.3
10–19	406 000	2 657 000	3 063 000	8.1
20+	288 000	3 796 000	4 084 000	3.4
Total	5 594 000	8 574 000	14 168 000	7.2

Table II presents the estimates of the complications based on surveillance and surveys in the same year. Overall, 8024 complications were estimated, or a rate of 566.3 per one million vaccinations. The 152 major complications represent a rate of 10.8 per one million vaccinations. Of the 153 cases, 16 cases were diagnosed post-vaccinial encephalitis, 11 cases vaccinia necrosum, and 126 cases eczema vaccinatum. Overall, 3.0 per cent of the 8024 cases were hospitalized for an average of 9 days and a total of 2142 patient-days of hospitalization. Of the 16

Table II. *Complications associated with smallpox vaccinations of civilian population, by degree of severity, United States, 1968*

Complications	Complications medically attended		Hospitalized complications		Permanent disability	Deaths
	No.	Rate*	No.	Avg. stay		
Post-vaccinial encephalitis	16	1.1	16	11.3	4	4
Vaccinia necrosum	11	0.8	8	37.5	—	4
Eczema vaccinatum	126	8.9	87	11.2	—	1
All other	7 871	555.5	127	5.9	—	—
Total	8 024	566.3	238	9.0	4	9

* Complications per 1 000 000 vaccinations.

Table III. *Costs associated with smallpox vaccinations, United States, 1968*

	Amount ($ million)
Direct, medical services	
Vaccinations	92.8
Complications	0.7
Indirect, loss of productivity	
Work losses, vaccination and complications	41.7
Permanent disability, complications*	0.4
Premature death, complications*	0.1
Total	135.7

* Future years discounted at 6%.

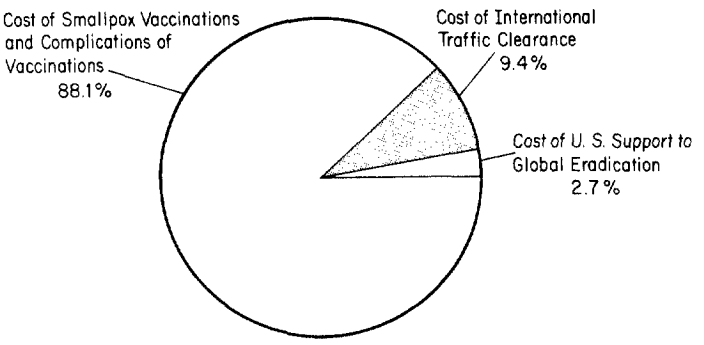

Fig. 1. Economic cost associated with protection of the United States against smallpox, 1968.

patients with post-vaccinial encephalitis, three have permanent mental damage, including one requiring institutionalization for life. Nine vaccine-associated deaths occurred in 1968.

Table III indicates that the economic cost of smallpox vaccinations among civilians in the United States totaled an estimated $135.6 million in 1968. Physician services for vaccine administration accounted for 68 per cent of the total cost. Earnings lost due to time off from work for vaccinations and complications involved 30 per cent of the total.

Fig. 1 presents the cost of the effort to protect United States citizens against smallpox which is estimated at $153.9 million in 1968. Eighty-eight per cent of the cost was associated with vaccination of the civilian population.

The cost of quarantine traffic clearance and surveillance totaled 4.2 per cent and cost of time lost by the maritime industry in waiting for traffic clearance accounted for 5.2 per cent of the total cost. The United States' support to the World Health Organization's global smallpox eradication program and the US

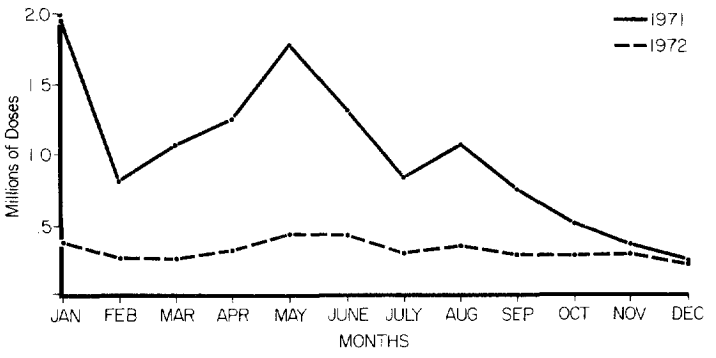

Fig. 2. Smallpox vaccine. Net distribution by month, United States.

developmental assistance to 20 countries in West Africa for smallpox eradication totaled only 2.5 per cent.

Fig. 2 illustrates the change in the distribution of smallpox vaccine between 1971 and 1972. The savings in delivery of routine vaccinations and the medical services associated with complications between 1971 and 1972 are valued at $63.5 million. The results clearly indicate that the public policy decision to discontinue routine vaccination of the general population released substantial resources for other uses.

The analysis does not consider the costs associated with a possible introduction or importation of smallpox into the United States. In the United States, a patient with chickenpox was misdiagnosed as smallpox in 1965, and the resultant public health control efforts, without secondary spread, cost approximately $65000. Of the total cost, 64 per cent involved expenditures for surveillance of the primary ring of contacts, 30 per cent for hospital isolation care, 4 per cent for laboratory services, and 2 per cent for communications. About 85 per cent of the total cost involved diverted personnel time.

Several importations into Europe in recent years have also been analyzed regarding cost. The costs for the England and Wales importations with secondary spread of 62 cases in 1961 and 1962 were estimated at $3.6 million. Again, over 80 per cent of the cost involved diverted local health personnel time. The Swedish importation experience in 1963 cost about three-quarters of a million dollars. Some 27 persons were diagnosed as having smallpox. About 2500 persons exposed to smallpox had to be isolated, and some 200 persons had vaccination reactions severe enough to require hospital care.

These costs would be incurred in the event of an importation of smallpox regardless of how much is spent on routine vaccinations or other smallpox protection efforts. Only world-wide smallpox eradication will eliminate the risk of possible importations and subsequent potentially expensive secondary-spread control efforts.

In summary, this analysis indicates the costliness of an internationally important and emotionally fearful infectious disease in a country where the disease has

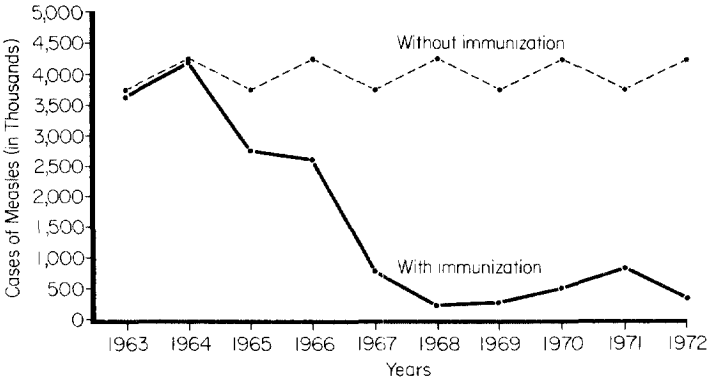

Fig. 3. Measles incidence in the United States, 1963–72.

not occurred since 1949. It also suggests that the magnitude of global benefits of the forthcoming world-wide eradication of smallpox is substantial, and the importance of the World Health Organization smallpox eradication program as a part of our national protection strategy in order to realize the full benefits of the policy change.

Unfortunately, not all disease problems are in this desirable situation. Next I would like to discuss the comparison of the benefits and costs of the immunization effort against measles in the United States. Prior to the licensing of the measles virus vaccine in 1963, the incidence of measles was approximately 4 million cases per year. From the time of licensing of the vaccine in early 1963 through the middle of 1966, some 15 million children were immunized, and reported cases have been reduced some 50 per cent. By October 1966, it looked as if measles could be eliminated in the United States. The Public Health Service, through CDC, and with the support of professional and voluntary health organizations, spearheaded a national campaign to eliminate measles in 1966. The campaign emphasized community immunization programs. Fig. 3 depicts the successful reduction of the disease to a low of a quarter million cases in 1968. Unfortunately, with the termination of measles vaccine as a part of community immunization programs in 1969, measles incidence again increased sharply from 290000 in 1969 to 533000 in 1970 to 847000 in 1971. Looking at the problem another way, Tables IV and V contrast the lack of uniform measles immunization rates for poverty and non-poverty populations in the metropolitan areas and the relatively uniform rates achieved with the community rubella immunization programs during the first two years. The concern about the lack of uniform immunization levels and the build-up of pockets of susceptibles, coupled with the sharp increase in measles incidence, resulted in the decision by many States to return measles vaccine to the community immunization programs in 1971. Table VI indicates the marked change in the number of doses of measles vaccine distributed between 1970 and 1971. A sizable number of doses involved the newly licensed combination measles/rubella vaccine. Fig. 4 indicates the 10-year

Table IV. *Percentage of population with history of measles and rubella vaccine by standard metropolitan statistical areas and poverty status, United States, 1970*

	Measles 1–13 years	Rubella 1–12 years
Central cities		
Poverty	40.7	42.9
Non-poverty	54.5	40.8
Remaining SMSA		
Poverty	45.6	33.9
Non-poverty	57.6	40.8

Table V. *Percentage of population with history of measles and rubella vaccine by standard metropolitan statistical areas and poverty status, United States, 1971*

	Measles 1–13 years	Rubella 1–12 years
Central cities		
Poverty	51.1	57.0
Non-poverty	59.6	56.6
Remaining SMSA		
Poverty	53.7	56.3
Non-poverty	62.4	56.1

Table VI. *Measles virus vaccine. Total doses distributed, United States, 1966–72*

Year	1966	1967	1968	1969	1970	1971	1972
Doses (millions)	7.9	6.4	5.3	4.9	4.5	8.3	8.2

trend of the annual benefits and the costs of immunization against measles. The sharp increase in estimated benefits between 1970 and 1971 shows most directly the salutary effect of community immunization programs. The benefits can be expected to increase with time, given continuation of a reasonable uniform level of immunizations for each new birth cohort. Table VII summarizes some of the health and resource savings for the first decade of the immunization effort against measles. Substantial resources were released for other uses. Medical resource savings included 1.4 million hospital days and more than 12 million physician visits. Among the savings in educational resources were 75 million school days in the regular school program, and because the program prevented 7900 cases of

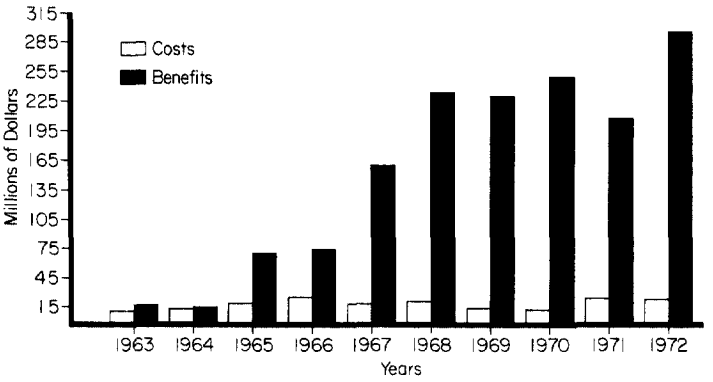

Fig. 4. Annual benefits and costs of immunization against measles, United States, 1963–72.

Table VII. *Summary of health and resource savings due to immunization against measles, United States, 1963–72*

Cases averted	23 707 000
Lives saved	2 400
Cases of retardation averted	7 900
Additional years normal and productive life by preventing premature death and retardation	709 000
School days saved	78 000 000
Physician visits saved	12 182 000
Hospital days saved	1 352 000

mental retardation, it saved substantial resources associated with special schooling of these children. By preventing premature death and retardation, it assured that more than 10300 persons would have an opportunity to lead productive and normal lives measurable at about 709000 years. The net benefits totaled $1.3 billion for the 10-year period.

Possibly the most salient feature of these statistics is that they make explicit the resources consumed by a mild children's disease and damage associated with a preventable disease.

Like my developing country, many other developing nations are facing the need to justify public health programs on economic as well as humanitarian grounds. I would like to share with you some of the thinking of economists in this area.

Table VIII provides some hypothetical examples of the present value of economic worth in a developing country. Column 2 provides some typical dollar values of average consumption for each age group; column 3 shows the dollar values of the marginal product for each age group; column 4 gives the difference; column 5 provides some estimates of the life expectancy at the end of each age group; columns 6 and 7 provide the undiscounted and discounted expected

Table VIII. *Example of economic worth of individuals by age in developing countries*

Age (years)	Average consumption ($)	Marginal product* ($)	Net contribution ($)	Life expectancy† (years)	Undiscounted present value ($)	Discounted present value‡ ($)
0	0	0	0	43	1 887	−310
5	113	0	−113	53	2 636	−587
10	150	32	−118	49	3 280	−325
15	150	103	−47	45	3 947	261
20	150	281	131	42	4 299	913
25	188	302	114	38	3 795	867
30	188	302	114	34	3 370	905
35	150	309	159	31	2 946	994
40	150	280	130	28	2 299	843
45	150	271	121	24	1 782	764
50	150	270	120	20	1 293	678
55	150	244	94	17	798	522
60	113	242	129	14	404	406
65	113	167	54	11	−24	182
70	113	153	40	9	−352	−23
75	113	0	−113	6	−789	−478

Source: Enke and Brown (1972). *J. Biosoc. Sci.* 4, 301.

* Marginal product equals the average product: national annual output is equal to $150 per capita.

† Years of life expectancy beyond given age.

‡ At 15% a year compounded.

future contribution, or the economic worth of the individual at each age interval. A discount rate of 15 per cent was assumed to approximate the interest rate for capital in a developing country.

It is significant to note that in these examples the present value of the economic worth (the last column) is negative for the age groups less than 15 years of age and the age groups over 65 years of age. While the estimates of the worth may vary slightly depending on the economic and actuarial assumptions, it is important for public health officials to note the significance of these examples for health expenditures.

Child-targeted immunization programs in developing countries as in developed countries will have to be justified from an economic standpoint in terms of savings in scarce medical resources rather than their contribution to economic development. Recently, the United States has assisted a number of developing countries in measles control in West Africa. Table IX depicts the cost of immunization and the benefits in terms of medical care savings in Senegal during the period 1968–70. Senegal's experience suggests that the benefit–cost ratio during the community mass campaign was 1.2, and during the first maintenance year 3.8. In the case of measles, prevention is economically beneficial because

Table IX. *Cost of measles immunization and benefits in terms of medical care saved in the Green Cape region, Senegal, 1968–70 (in US dollars)*

Type of program	Cost of immunization		Benefits – medical care saved			Benefit–cost ratio
	Cost per individual	Total cost	Dispensary care	Hospital care	Total	
Initial mass campaign	0.80	142 800	77 500	97 900	175 400	1.23
Annual maintenance	0.40	20 400	35 500	42 800	78 300	3.84

Source: M. Rey, M. Beck, R. Helmholz, P. Gzebo and A. Sow (1971), *6th Conference, OCEAC Technical Conference*, Yaounda, 10–14 March.

many developing countries have very few physicians, nurses, and hospitals. In the long run, the permanent complications of measles – blindness, mental and motor retardation – constitute some cost to the developing economy. The individuals with permanent complications may not be able to enter the labor force, thus resulting in increased consumption and no contribution to the marginal product.

Concerning the mortality effect, past consumption costs are not appropriate to consider in the assessment of the future worth of individuals. However, the cost of bringing up a child before death due to measles and other childhood diseases may involve up to 5 per cent of a country's income.

Despite the minimal cost of delivery of measles immunizations, developing countries, as well as developed countries, may need to look further into alternative ways of minimizing costs through technology such as multiple antigen

Table X. *Comparison of two alternative immunization intervention proposals in a developing country in the Americas*

	Type of intervention	
	Option A Single disease immunization mass campaign	Option B Multiple antigen vaccination mass campaign
Disease	... Measles	Measles, polio, TB, smallpox, diphtheria, tetanus, pertussis
Target population	1- to 4-year age group, 825 000 children	1- to 2-year age group, 275 000 children
Length of campaign	1 year	3 years
Vaccine cost		
Undiscounted	$454 000	$526 000
Discounted 14%	$454 000	$459 000
Multiple country vaccine purchasing	No	Yes

vaccines and through group purchasing of vaccines. Table X provides an example of some of the economies of group purchasing of vaccine coupled with the use of multiple antigen vaccines. This slide compares two alternative immunization interventions in a developing country in the Americas. Under option A, 825 000 children in the 1–4 year age group are vaccinated against measles in a one-year mass-type campaign. The measles vaccine would be purchased by the government at an estimated cost of $454 000. Under option B, 275 000 children in the 1–2 year age group are vaccinated against measles, polio, diphtheria, tetanus, pertussis, smallpox and tuberculosis each year for a period of three years. The multiple antigen vaccines would be purchased each year at a cost of $175 000 through a multiple country group purchasing agreement. Given an equal number of children vaccinated and approximately equal levels of measles protection at the end of the three-year period under both options, the multiple disease program – option B, on a present value basis – costs $5000 more than the measles immunization alone when the vaccine is purchased on a multiple country basis. Epidemiologically, option B provides more uniform measles immunization levels and less opportunity for any build-up of susceptibles.

In summary, the analysis recognizes the importance of the World Health Organization's smallpox eradication program as a part of the US protection strategy in order to realize the full benefits of the policy change to discontinue routine vaccinations of the population.

The net benefits of the immunization effort against measles totaled $1.3 billion for the first decade of use in the United States. The Senegal analysis suggests that the benefits of measles immunization exceed the cost in developing countries. Despite these favorable benefit–cost analyses, child-targeted immunization programs may need to take advantage of further opportunities of minimizing costs through multiple antigen vaccine technology and through group purchasing of vaccines.

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DISCUSSION OF COST BENEFIT ANALYSIS

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No country, irrespective of its stage of development, can dispose of unlimited resources for its health service. The more it is of importance to investigate carefully where these resources can be used with maximum benefit.

Many a spectacular medical achievement which, in recent years, has stirred the press of the world, has been realized with such a high expenditure in terms of personnel and resources that one could question whether these resources, if used for other purposes, would have promoted the health of many more people.

In most cases, the efficiency of individual projects is described by an aggregate of data and opinions, for the assessment of which there exist objective criteria only in a few instances.

During the last 20 years, a method has been developed which permits, at least from the economic aspect of these problems, an objective assessment. It is based upon the theoretical principles of welfare economy and of operational investment calculation. All the advantages and disadvantages (benefits and costs) of a public project are recorded independently from the fact of who will benefit by it and who will bear the costs, then assessed as far as possible in monetary value and compared. Even if not all factors are quantifiable and if, for the implementation of public projects, economic criteria alone should not be the determining factors, the total calculation will be easier for the decision-maker if the economic implications are known.

Such an investigation was made concerning the oral polio vaccination from 1962 to 1970. There were taken into consideration only the quantifiable economic advantages and disadvantages linked to the vaccination; qualitative aspects were not covered by this investigation.

As costs, there are included: the amounts spent annually for vaccines, personnel, propaganda, forms, etc., as well as rents and other factual costs in prices of 1970. An amount of 0.66 Deutschemark per vaccination was established as an average value and applied to the 76.5 mio vaccinations performed during the period from 1962 to 1970. The total costs amounting to 50.5 mio Deutschemarks was increased by an additional sum of 20 mio Deutschemarks for possible vaccination damages. The calculation of this cost factor is based on the assumption that one case of serious vaccination damage is to be expected per 1 mio vaccinations.

For the determination of benefits, the number of new diseases avoided during the period under review due to the oral polio vaccination (altogether 52 180

cases), was taken as starting point. For these cases, the various treatment, care and rehabilitation costs avoided were computed in 1970 prices – altogether 3259.5 mio Deutschemarks. Taking into consideration the years of gainful activities to be expected on the average in the various age groups of men and women, there were, furthermore, computed the contributions to the social product gained by the avoidance of new diseases and assessed according to the average national income in 1970 (net social product at factor costs), referring to the gainfully employed – altogether 3188.1 mio Deutschemarks.

The disease costs saved by the non-occurrence of new cases of illness and the contributions not lost to the social product as benefit factors were opposed to the total costs. The established cost–benefit ratio amounts then to 1:90, i.e. every Deutschemark spent for vaccination purposes saved 90 Deutschemarks costs.

The expenditures incurred for polio vaccination thus prevent not only illness, grief and death, but are also of considerable economic benefit.

GENERAL DISCUSSION

CHAIRMAN Has anyone any discussion concerning cost benefit analysis? This concerns the established vaccines as well as the two particular vaccines that Dr Sencer used for his illustrations, namely smallpox and measles.

LAFONTAINE (Belgium) Has the cost benefit or rather the balance between advantages and disadvantages of smallpox vaccination been evaluated on a world-wide scale, because I do not think that we can stop smallpox vaccination until eradication has been achieved? I think that the cost benefit must be evaluated on a world level and not only for one country.

SENCER (USA) I would hesitate to get into further discussion of the decision of some countries to discontinue smallpox vaccination as a routine matter. I do not think that is the subject of this conversation. I am wondering whether Dr Henderson would care to give us anything on the cost of the world-wide effort.

HENDERSON (WHO) It is difficult to come up with an accurate figure as to the total cost of the programme as this includes not only funds channelled through WHO but also bilateral contributions and substantial national contributions. Our best estimate is that the total global cost is around $30 to $50 million per year which includes $3 million provided by the regular budget of WHO. The overall amount is, in fact, rather a small sum of money compared to the savings realized by the USA as a result of modifying its vaccination policy. We would, of course, be most happy to receive the $60 million which has been saved in the USA.

SENCER (USA) As you know, the United States is limiting its contribution to the WHO to 25 % of the budget.

UNGAR (Switzerland) If I remember correctly, Dr Sencer said that before the last war, in the 1930s, there was a report by Dr Winslow on the costs of infectious diseases in children in the New York area where they knew their hospitalization costs. A year after they had started vaccination against diphtheria and whooping-cough they found that the cost of vaccination was about one-tenth of the cost of hospitalization. I think this was the first time it had been demonstrated from a financial point of view that vaccination could be tremendously beneficial in terms of costs in certain countries.

HOFMAN (The Netherlands) I should like to make a general remark on this question of cost benefit analysis. I think that two elements have to be discerned in these calculations. One is the saving in medical care and the prevention of a greater or lesser degree of invalidity, and on this I think no-one would disagree. The other element, however, is that of considering the future earning capacity of a human being, and that is a consideration of man as *Homo economicus*, but I doubt whether everybody would be concerned about this aspect of cost benefit analysis.

HALONEN (Finland) Many European countries are aware of a low ratio of cost benefits in smallpox vaccination and would like to follow the example of the United States. However, there is one element which is not entirely under our control and that is vaccination of men in military service. In countries where all men enter military service, as in Finland, we shall face very great problems in 15 or 20 years' time if we stop smallpox vaccinations now without at the same time making plans for the future. I should like to ask Dr Sencer what plans there are in the United States to deal with this problem.

SENCER (USA) I am completely optimistic that there will be no smallpox 15 or 20 years from now in the World and that there will no longer be a rationale to immunize the military. I believe that most of the great nations of this world have signed agreements that they will not use biological warfare and I believe that will be the fact. So I think that there will be no need for immunizing military troops 15 or 20 years from now. The concurrent use of vaccinia immunoglobulin would be a way out, but I am an optimist in terms of eradication of smallpox, abolition of biological weapons, and peace.

CAMERON (Canada) Reference has been made already to the desirability of considering cost benefit on an international scale. I think that a point in Dr Sencer's presentation which possibly escaped notice and ought to be emphasized is that if we talk about cost benefit in the developing countries we must realize that, in fact, the more prevention of illness there is in these countries the greater are the problems with which they are faced. When talking about developed countries, on the other hand, cost benefit analysis reveals the economic advantage from the application of mass programmes. So I think we must be very careful to distinguish between the two. I do not think anyone would suggest that, on the basis of the negative figures which Dr Sencer produced, one would dream of stopping vaccination programmes; that is ridiculous. However, I think we must realize that cost benefit here refers to the most economic use of the programmes which are being developed. Nevertheless, they are leading to greater social problems.

SENCER (USA) The point I was trying to make was that such programmes cannot be justified in the less developed countries, on the standard economic evaluation of cost benefit analysis, but they can be justified by the fact that it will no longer be necessary to use hospital beds for measles, or physicians to take care of ill children. These are perhaps more important resources than money.

HENDERSON (WHO) The question has been raised of possible problems of primary vaccination in adults. Data available in the past have not been very satisfactory and it has been assumed that primary vaccination in young adults would necessarily be fraught with many problems. However, a recent CDC study of primary vaccination in very large numbers of military recruits showed a very low incidence indeed of complications, quite contrary to what had been thought.

So far as cost benefit ratios in relation to the developing countries, there is an intangible feature which has not been mentioned and this relates to the problem of implementation of family planning programmes. Recently, in certain of the endemic areas of India, resistance has been encountered because of smallpox epidemics. The villagers wanted nothing to do with family planning programmes having just lost large numbers of children in their villages. It would seem sensible, therefore, to introduce immunization programmes with family planning programmes, the latter of which is increasingly recognized to be important to economic development and the future of all countries.

Lastly, I should like to reiterate that in global terms the costs of the smallpox eradication programme are not very great. As Dr Sencer has noted, the savings to the United States have been substantial. At the same time, the United States has, first of all, undertaken to eradicate smallpox in the twenty countries of western and central Africa, and they have been successful. More recently they have made personnel and vaccine available to the Organization recognizing that this is a very worthwhile investment for the protection of the United States itself. Other countries have contributed likewise. Nevertheless, the amount of money available is still marginal and does not begin to approach the potential savings which would be realized were global eradication a reality. With a more substantial world-wide commitment, the programmes could proceed considerably faster and with greater certainty of ultimate success.

SENCER (USA) If I could just have the last word, Sir, the United States did not undertake to eradicate smallpox; it undertook to help the countries of West Africa to do this.

There is another intangible benefit in this. I was asked during the coffee break how I

could be sure that smallpox had been eradicated from the Congo, and one of the intangibles is that, in all parts of the world where the smallpox eradication effort has been going on, a surveillance mechanism has been set up that is perhaps more important in the long run than the eradication effort. The surveillance apparatus in the Congo is sensitive enough to pick up a single case of monkeypox and bring it to differential diagnosis. I think that this type of thing is an intangible benefit that will go on.

CHAIRMAN Thank you very much. We have had a fairly full discussion of that subject and I am sure that the next session on newer vaccines, measles, mumps and rubella, will also be a very full session.

SESSION III

NEWER VACCINES

Chairman: Dr F. T. PERKINS (UK)

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NEWER VACCINES (MEASLES, MUMPS, RUBELLA): POTENTIAL AND PROBLEMS

S. KRUGMAN

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During the past decade live attenuated vaccines for the prevention of measles, mumps and rubella were licensed for use in the United States and in other countries of the world. Measles vaccine became available for general distribution in 1963, mumps vaccine in 1967, and rubella vaccine in 1969. Studies to evaluate the safety, potency and efficacy of these vaccines preceded their licensure by periods ranging between three and five years. Extensive use of these vaccines since licensure has highlighted their potential value as well as the occurrence of various problems. Certain problems were solved promptly; others are more appropriately designated as 'issues of concern'. This discussion will include a review of the present status of three live attenuated vaccines: measles, mumps, and rubella.

MEASLES

The use of more than 50 million doses of measles vaccine in the United States since 1963 has provided an opportunity to further assess the safety, immunogenic capacity, and efficacy of the vaccine.

SAFETY

The safety of live further attenuated measles vaccines has been well established. These vaccines have been well tolerated in spite of the occasional febrile reaction. The possible occurrence of measles encephalitis was an issue of concern 10 years ago when measles vaccine was licensed for use. The experience in the United States since 1963 has allayed this anxiety. As indicated in Fig 1, the increasing use of live measles vaccine has been associated with a progressive and significant decline in the incidence of encephalitis.

The question of possible association of the use of live attenuated measles vaccine and subacute sclerosing panencephalitis (SSPE) has been another issue of concern. However, the epidemiological evidence which has been accumulated to date is reassuring. The survey by Jabbour *et al.*(3) identified 219 cases of SSPE which were associated with measles infection during the period 1960 to 1970. In 14 cases there was a possible association with live attenuated measles vaccine. Additional data accumulated by Jabbour during the past two years (1971, 1972) have doubled these figures to approximately 400 cases of SSPE of

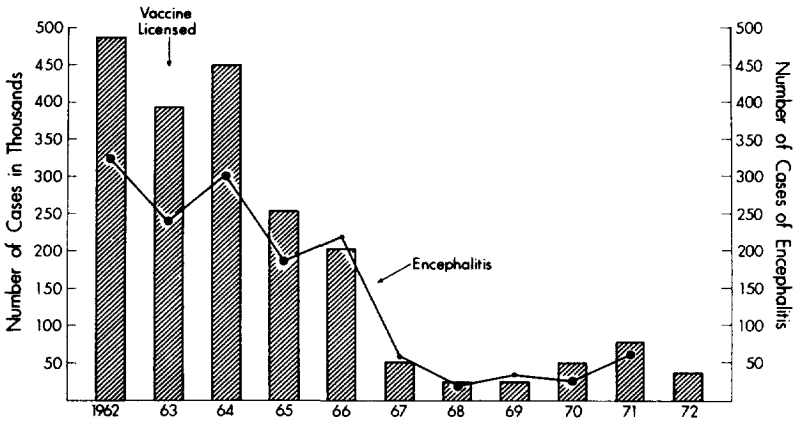

Fig. 1. Measles and measles encephalitis: number of reported cases in the USA, 1962–72.

which 40 were vaccine-associated. If there were a significant association between the use of measles vaccine and SSPE, it should have become more apparent by this time, because 10 years have elapsed and more than 50 million doses of vaccine have been used. In addition, the measles-like viruses which have been recovered from patients with SSPE have not been characterized by the biologic markers which are typical of attenuated measles-virus vaccine. In summary, the data to date are encouraging and reassuring, but not definitive as yet. At the present time the risk of a central nervous system complication of measles is greater following natural measles infection than following attenuated measles vaccine-virus infection.

IMMUNOGENIC CAPACITY

The results of an 11- to 12-year longitudinal study on persistence of measles hemagglutination inhibition (HI) antibody following natural infection and immunization with or without gamma globulin are shown in Fig. 2. These studies were conducted at an institution in which measles has not occurred since 1963. Consequently, the opportunity for reinfection, followed by a booster response, has been lacking. The pattern and persistence of the antibody response have been similar in children who had natural measles infection or live measles vaccine. The geometric mean HI antibody titers have been lower in children who received vaccine than in those who had natural infection.

A previous study involving children in a community where measles was endemic revealed a four-fold higher antibody titer in immunized children who were exposed to measles as compared with the unexposed institutionalized children (**6**). In other studies it was observed that measles reinfection was characterized by a boost in antibody and an absence of symptoms.

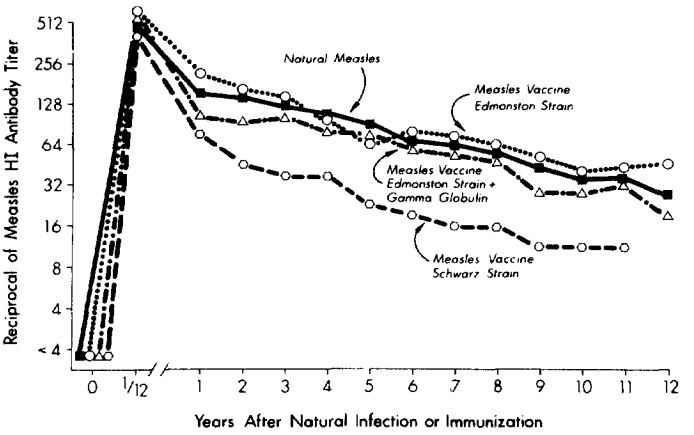

Fig. 2. Measles antibody response and persistence. Geometric mean hemagglutination-inhibition antibody titers following natural infection and immunization with live measles vaccine.

EFFICACY

The effect of the immunization program on the incidence of measles in the United States is shown in Fig. 1. Prior to the licensure of measles vaccine in 1963, approximately 500000 cases of measles were reported annually to the Center for Disease Control of the United States Public Health Service. Since licensure of the vaccine and the subsequent use of more than 50 million doses, the number of reported cases has declined significantly. The number of reported cases of measles in 1972 was 31425, a decreased incidence of more than 90 per cent. As indicated previously, a comparable decrease was observed in the incidence of post-measles encephalitis.

The increased incidence of measles in 1971 was chiefly due to the occurrence of the disease in unimmunized children. However, some cases of measles occurred in children who had received measles vaccine in the past. The causes of measles vaccine failure have been well documented in previous reports(11). In brief, the failure has been due to one or more of the following factors: (1) the seroconversion rate following vaccination has ranged between 95 and 98 per cent, even with the best technique; (2) the immunosuppressive effect of (*a*) persistence of maternal antibody in a small number of infants, or (*b*) the use of gamma globulin with measles vaccine *prior to* one year of age; (3) inactivation of measles vaccine virus by faulty refrigeration or overexposure to light; and (4) the prior use of killed measles vaccine which sensitized the individual and failed to protect against measles.

CONCLUSION

Live attenuated measles vaccines have been safe, potent, and highly effective. The evidence to date indicates that immunity will be long lasting.

MUMPS

Approximately 11 million doses of live attenuated mumps vaccine, Jeryl Lynn strain, have been distributed since licensure in 1957. An additional 3 million doses of mumps vaccine have been distributed in combination with measles and rubella vaccines. Experience during the past six years has revealed that this vaccine is well tolerated, immunogenic and protective(**9**). Clinical reactions associated with vaccination have been very rare. The antibody response following vaccination has exceeded 90 per cent but the antibody levels have been much lower than those observed following natural infection.

The issues of concern about mumps vaccine have been as follows: (1) the possibility that immunity may not persist because of low antibody levels; and (2) the unknown effect of reinfection which could be favorable or unfavorable. If reinfection is characterized by absence of clinical manifestations and by a boost in mumps neutralizing antibody, it will be a favorable event which may lead to lasting immunity. More time and more experience will provide answers to the questions about duration of immunity and pathogenesis of reinfection.

RUBELLA

Since licensure of rubella vaccine in 1969 more than 45 million doses have been distributed in the United States. Additional large quantities of vaccine have been distributed in various countries of Europe. It is now possible to further assess the safety, immunogenic capacity and efficacy of the vaccine. The issues of concern about the vaccine have been as follows: (1) joint manifestations and neuropathy; (2) risk of communicability; (3) risk of fetal infection; (4) duration of immunity; and (5) significance of reinfection.

JOINT MANIFESTATIONS AND NEUROPATHY

The occurrence of joint manifestations and neuropathy has been associated with the use of the following live rubella vaccines: the HPV-77 strain in duck embryo cell culture (DE-5), the HPV-77 strain in dog kidney cell culture (DK-12), the Cendehill strain in rabbit kidney cell culture and the RA 27/3 strain in human diploid cell culture. The HPV-77 DE-5, Cendehill and RA 27/3 strains of rubella vaccine have been well tolerated. In contrast, the HPV-77 DK-12 strain has not been as well tolerated because it has caused a higher incidence and an increased severity of arthritis, arthralgia and neuropathy.

A recent survey by Cooper *et al.*(**1**) revealed a similar incidence of joint manifestations in susceptible women of comparable age who received either the Cendehill or the HPV-77 DE-5 strain of rubella vaccine. The results of a survey of two groups are shown in Table I. Group 1 included 285 women who were new hospital employees or student nurses. Group 2 included 259 women who received rubella vaccine during the immediate post-partum period. The data in Table I indicate that (1) the reaction rates in women were essentially the same following vaccination with Cendehill or HPV-77 DE-5 strain rubella vaccines, and (2) the

Table I. *Comparative incidence of joint manifestations in susceptible* women immunized with Cendehill or HPV-77 DE-5 strains of rubella vaccine (from Cooper* et al.(**1**))

Group	Type of vaccine	Number vaccinated	Number and % with joint symptoms
1†	Cendehill	126	13 (10.3 %)
	HPV-77 DE-5	159	17 (10.7 %)
2‡	Cendehill	117	4 (3.5 %)
	HPV-77 DE-5	142	6 (4.2 %)

* Rubella HI antibody titer of $< 1:8$.
† Hospital employees and student nurses.
‡ Women in the post-partum period.

joint manifestations were less common in women who were immunized during the immediate post-partum period.

In a recent publication Grand *et al.* reported two studies describing the results of a comparative evaluation of three rubella vaccines(**2**). In one study 21 571 children received the HPV-77 DE-5 strain and 18470 received the Cendehill strain. Under the conditions of this study the incidence of joint manifestations and neuropathy was similar in both groups. In contrast, another study involving 1299 children who received the HPV-77 DE-5 strain and 1803 who received the HPV-77 DK-12 strain revealed (1) a higher rate of arthralgia, (2) a longer duration of symptoms, and (3) a higher rate of arthritis and neuropathy associated with the use of the HPV-77 DK-12 strain of rubella vaccine.

The available data indicate that the problem of joint manifestations and neuropathy has been alleviated in great part by discontinuing the use of the highly reactive HPV-77 DK-12 strain of rubella vaccine. In addition recent surveys have revealed a correlation between the incidence of joint manifestations and age; the highest ratio of reaction occurred in women over 25 years of age(**10**).

Reports by Judelsohn & Wyll(**4**) and by Landrigan *et al.*(**7**) have presented data which indicate that joint manifestations occur more frequently following natural rubella infection than following rubella immunization. In the Bermuda epidemic(**4**) 40 per cent of 125 patients with rubella had transient joint pain or discomfort; the frequency in children under 13 years was 25 per cent. In the outbreak described by Landrigan *et al.* the frequency of transient joint manifestations was higher in male adolescents who had natural rubella than in those who received the Cendehill strain of rubella vaccine.

RISK OF COMMUNICABILITY

The lack of communicability of individuals who have been immunized with rubella vaccines has been well documented(**8**). More extensive use of the vaccines has indicated that this issue of concern has not proved to be a problem.

RISK OF FETAL INFECTION

The Center for Disease Control has received reports of the inadvertent vaccination of more than 200 pregnant women. Since licensure of rubella vaccine 79 women were referred to the New York University Rubella Project because they received rubella vaccine shortly before or during pregnancy. The following details about one of these women studied by Kanra & Cooper(5) highlights the risk of fetal infection following rubella immunization.

Patient – 21-year-old nurse who had no rubella HI antibody before vaccination.

Vaccination – Rubella vaccine (HPV-77 DE-5) was given 22 days after onset of last menstrual period (LMP). Precautions had been reviewed and a consent form was signed. Seroconversion following vaccination was confirmed by a rise in rubella HI antibody from less than 1:8 to 1:256; CF antibody rose from less than 1:8 to 1:16. Later, it became obvious that pregnancy had occurred shortly after the vaccine was given. Therapeutic abortion was performed by saline induction 96 days after vaccination and 118 days after the LMP.

Fetus – weight was 120 g; the length was 20 cm (crown rump). Gross and microscopic examination of organs and placenta was unremarkable. Because of the use of hypertonic saline, only lung, liver, testicle and placenta were examined histologically.

Virus isolation – rubella virus was isolated from the umbilical cord, the amniotic fluid, the placenta and the following organs – kidney, heart, liver, urinary bladder, intestine, lung, bone, ureter, and ear. The isolates were confirmed as rubella by neutralization tests. This experience indicates that congenital rubella infection may be caused by attenuated as well as wild rubella virus. It provides additional evidence to support the recommendation that vaccination be avoided during pregnancy.

DURATION OF IMMUNITY AND REINFECTION

The pattern and persistence of the antibody response following rubella infection, mumps infection and measles infection are similar. In general, natural infection provokes a higher antibody response than attenuated vaccine virus induced infection. As indicated in Fig. 1, the antibody levels which decline with the passage of time are consistently lower following an attenuated virus infection. Since reinfection is more likely to occur in the presence of low levels of antibody, it is more apt to occur after vaccination than natural infection.

The differences between primary rubella infection and reinfection are listed in Table II. It is reassuring that unlike primary infection, reinfection has not been characterized by viremia. Consequently, it is unlikely that reinfection will be associated with congenital rubella. In addition, during reinfection either minimal or no detectable amounts of rubella virus are present in the pharynx. Therefore, a reinfected individual is unlikely to be a source of infection. However, more time and more experience will provide a definitive answer to the questions of duration of immunity and significance of reinfection.

PRESENT STATUS OF THE RUBELLA IMMUNIZATION PROGRAM IN THE UNITED STATES

The impact of the rubella immunization program on the epidemiology of rubella in the United States is shown in Fig. 3. During the period 1928 to 1964 epidemics

Table II. *Comparison of primary rubella infection and reinfection*

Features	Primary infection	Reinfection
Rash	Present or Absent	Absent
Interval between exposure and antibody *rise*	14–21 days	8–10 days
Antibody response	IgM, then IgG	IgG only
Virus detected in pharynx	Yes. Duration: 1–3 weeks. Titer: high	Yes or no. Duration: 1–4 days. Titer: low
Virus detected in blood	Yes. Duration: 1 week. Titer: high	No

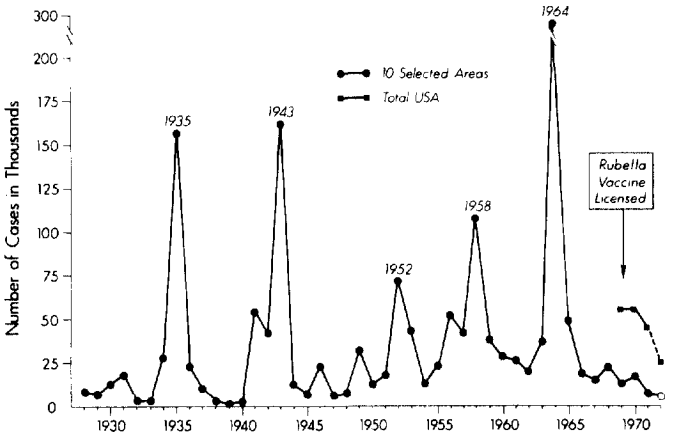

Fig. 3. Reported cases of rubella in the USA, 1928–72.

of rubella occurred at 6- to 9-year intervals. Since 1964, however, the number of reported cases of rubella has decreased progressively, reaching an all-time low in 1972. If the trend observed during the first eight weeks of this year continues, another all-time low will be reached in 1973.

The preliminary data which have been accumulated by the New York University Rubella Project have revealed a corresponding decline in the incidence of congenital rubella. Approximately 30 per cent of all cases of congenital rubella in the New York Metropolitan area have been referred to this project. The declining incidence of rubella and congenital rubella can be attributed to the use of more than 900000 doses of rubella vaccine in children in New York City since 1969 (Fig. 4 and Table III).

During the past two years extensive epidemics of rubella have occurred in Bermuda (1971), Czechoslovakia (1972) and Israel (1972). It is possible that similar outbreaks would have occurred in the United States if the present rubella immunization program had not been recommended and implemented. The final answer to the solution of the rubella problem will require many more years of

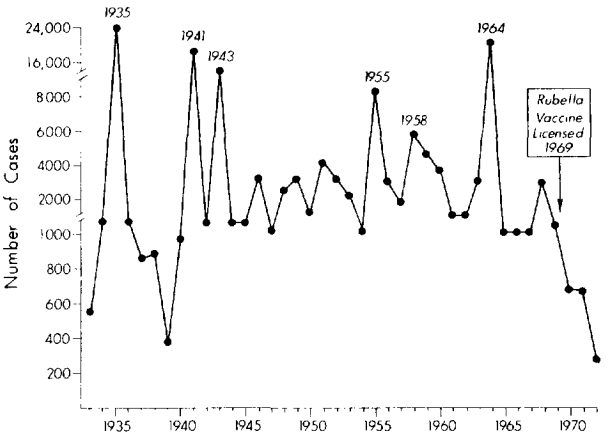

Fig. 4. Reported cases of rubella in New York City, 1933–72.

Table III. *Number of reported cases of rubella in New York City and number of cases of congenital rubella referred to New York University Rubella Project (from Cooper* et al.(1))

Year	Rubella in NYC	Congenital rubella
1964	21 922	407
1965	1 031	
1966	1 036	11
1967	1 030	10
1968	3 074	43
1969	1 189	20
1970	685	3
1971	626	12
1972	271	1

study and surveillance. In the meantime, it is likely that many thousands of cases of congenital rubella will be prevented during the study period.

CONCLUSION

Live attenuated measles, mumps and rubella vaccines have great potential value. Experience during the past decade has revealed that their use has been associated with a decreased incidence of morbidity and mortality. The problems associated with the use of these vaccines have been relatively unimportant when compared with the consequences of the natural infection. It will be necessary to continue surveillance and long-term observations on the persistence of immunity following immunization with these vaccines, in order to assess the need for possible revision of current recommendations for the use of these vaccines.

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DISCUSSION OF NEWER VACCINES (MEASLES, MUMPS, RUBELLA): POTENTIAL AND PROBLEMS

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The past decade has been a period of unprecedented activity in the development and use of live virus vaccines. Three of these new vaccines, those for measles, mumps and rubella have been used rather extensively in the United States as compared to many other countries. In fact, talking in terms of all three, well over 100 million doses have been administered to American children. My remarks will deal with the concerns and expectation of yesterday and today based upon an assessment of this broad experience.

Several versions of measles vaccines were licensed in the United States over a period of years beginning in 1963. Initially there was considerable concern over the acceptability of the reactivity associated with live measles vaccine administration. For this reason there had been parallel developmental effort with both killed and live experimental preparations and both versions were licensed. Reactivity of the live Edmonston B-type vaccine did not prove to be a major problem as the vaccine came into general use, and by 1964 it was clear that most physicians were choosing to use the live rather than the killed vaccine. This choice proved to be fortunate when shortly thereafter the totally unexpected hazard of disease enhancement as a result of killed measles vaccination was recognized. Also in the mid-1960s the first of the more attenuated versions of live measles vaccine was licensed. Today in the USA after the use of over 50 million doses of live measles vaccines one hears little discussion of acceptability and reactivity.

Acute encephalitis was another early concern. Clinical evidence of central nervous system (CNS) involvement occurs with a frequency of about 1 in each 1000 cases of measles in the USA. By the time of licensure it was known that encephalitis had not been observed during the experimental vaccine experience involving several tens of thousands of children. Now, after the extensive experience of the past several years, it is possible to state that CNS involvement in vaccinated children has been reported with about the same frequency as in unvaccinated children. The US Public Health Service Center for Disease Control has noted some tendency toward clustering of reported CNS disease during the period one to three weeks after measles immunization. However, if this is indicative of a vaccine relationship it would appear to occur with a frequency of less than one per million vaccinations.

A theoretical risk not recognized at licensure relates to subacute sclerosing pan encephalitis (SSPE). This intensively studied but poorly understood tragic disease is thought to be associated with a recrudescence of measles virus some years after the primary infection. However, epidemiologic data indicating a largely rural distribution of cases suggest that agents other than measles may play a role. There may need to be a primary measles infection followed by some 'triggering factor'. If this supposition is true, then vaccine safety as regards SSPE needs to be considered in both connections. In other words, could early vaccination prime a child for later SSPE or could a child primed by natural measles be triggered into SSPE by vaccination?

One is always dealing with an assessment of theoretical risks in relation to practical needs in vaccine programs. Trying to put SSPE in reasonable perspective, I would say that the experience gained during ten years of vaccination suggests that attenuated measles virus use is unlikely to cause an 'epidemic' of SSPE. However, one needs a great deal more epidemiologic data to make a valid comparison of the relative risks of natural and attenuated measles viruses in this regard. I stress epidemiology because I suspect that epidemiologic studies will prove more profitable than virologic studies in evaluating the question of SSPE and vaccine safety.

Live mumps vaccine was licensed in the USA in 1967. I recall two concerns that were extensively discussed. They were reactivity and immunogenicity. Mumps is a 'tricky' virus that, when serially propagated in the laboratory, rapidly shifts from being fully reactive to being over attenuated. Consequently a mumps vaccine strain is only a few passages above wild-type virus and a few passages below non-immunogenic virus. The early questions about reactivity focused chiefly on the safety of attenuated mumps for adults. Since it is difficult to find large groups of mumps-susceptible adults most of the experimental vaccine experience involved children. While no vaccine-associated mumps-like symptoms had been seen at the time of license it was recognized that the total experience in adults numbered only several hundred. Now with a total experience with mumps vaccination numbering about 14 million it is reassuring to find that the attenuated strain has continued to prove virtually non-reactive for both children and adults. Immunogenicity was an early concern since the attenuated virus induced considerably lower levels of neutralizing antibodies than the wild virus. Also there was some question about seroconversion rates. Our group and others have confirmed Hilleman's initial reports of seroconversion in excess of 90 per cent and satisfactory antibody persistence through the period of observation to date.

Rubella vaccines were licensed in the United States in 1969 and 1970. The recentness of this event coupled with another more obvious source of bias makes it difficult for me to consider rubella with the same detachment as measles and mumps. Dr Krugman has given an excellent summary of the status of rubella vaccination and of the issues most frequently discussed. Perhaps the most acute concern at the time of license was that of possible vaccine virus communicability. Now after more than 45 million rubella vaccinations in the USA it is accepted that communicability has not been a problem and one no longer hears the spirited

contagiousness debates of 1968 and 1969. Dealing very briefly with reactivity, with the advantage of 20–20 hindsight, it seems that the dog kidney-produced vaccine was somewhat more reactive and that the duck embryo vaccine was somewhat less reactive than some anticipated. With well over 40 million doses of Cendehill and HPV duck embryo vaccine distributed in the United States it is apparent that both have acceptably low levels of reactivity. The quality of vaccine-induced immunity has been extensively scrutinized. This is a complex subject and my views are well known, having been expressed in several publications dating back to 1969 and 1970.

Based on the experimental data available it has been predicted that vaccinated persons, exposed to rubella at a later date, are unlikely to contribute to the continued transmission of rubella in communities. The expectation that wide use of vaccine in children will interrupt the 6- to 9-year cycle of epidemic rubella is based on this assumption. While one needs several more years of observation for conclusive proof, the continued decline in rubella in the United States in association with increasing vaccine use is reassuring. Another aspect of immunity relates to fetal protection. Will the fetus be protected when a woman vaccinated some years earlier is exposed to rubella during her pregnancy? Dr Krugman has cited the data bearing on this question. The evidence indicates that persons with vaccine-induced immunity do not develop demonstrable viremia after an exposure to rubella. It is on this basis that one assumes that vaccine-induced immunity will provide significant fetal protection. However, full definition of the degree of fetal protection to be expected will require years of observation of vaccinated populations.

Turning to the broader issues regarding the use of measles, mumps and rubella vaccines, it is well to focus on the reasonable expectations for the future. In the United States measles and rubella are regarded as consequential health problems justifying routine vaccination. Opinions differ on the importance of mumps, and mumps prevention is generally considered to be lower on the order of priorities. The thrust of measles and rubella vaccine use is both on individual protection and upon community protection through the reduction in the prevalence of these viruses in the population. This is much the same as the expectations associated with the use of live polio vaccine and pertussis vaccine. In this approach the degree of reduction in mortality and morbidity depends upon the effectiveness of continuing efforts to deliver vaccines to the target groups in the population. A failure to continue vaccination tomorrow, next year or in the next decade would lead to a renewed acquaintance with epidemic disease. There are no prospects for global elimination of such diseases as measles, rubella, mumps, polio and pertussis. Nevertheless, vaccination with all of its problems, theoretical and real, does provide a method for maintaining acceptable control.

GENERAL DISCUSSION

CHAIRMAN Is there any discussion of these two papers concerning measles, mumps and rubella?

COCKBURN (WHO) I do not disagree at all with Dr Meyer in his approach to continuing field studies. The point I was making was a different one, namely that in the early stage of development one had to be extremely careful about the experimental work.

The question I should like to ask Dr Krugman is whether he has any idea of the proportion of children, either in the United States or in New York, let us say, who are being vaccinated against measles at the present time.

KRUGMAN (USA) Dr Witte may wish to respond to this question.

WITTE (USA) Each year the CDC conducts a national survey in co-operation with the US Bureau of Census. The most recent data show that the immunity levels for pre-school children, children in the 1–4 age group, are 66 per cent. For children in the 5–9 age group it is between 80 and 85 per cent.

GRIFFITH (UK) There are two questions I should like to ask. Dr Krugman showed a graph of the mean antibody levels 10 and 11 years after the administration of measles (Schwarz) vaccine. What percentage of the children who had Schwarz vaccine were sero-negative 11 years after vaccination? I believe that the mean titre then was 1 in 12.

KRUGMAN (USA) The slide which I presented summarizes a prospective study which has been in progress since 1960 at the Willowbrook State School. It is important to note that the use of live measles vaccine eradicated measles from this institution by 1963. Since that time there hasn't been a single case of measles amongst the residents of Willowbrook. Consequently, in this setting the children who received the Schwarz strain of measles vaccine have not been reinfected. During the 11-year follow-up period we have prospective observations on 114 children who received the further attenuated Schwarz strain vaccine. One child has no detectable antibody ($<1:2$) at 10 years, but it was detectable at a level of 1:2 at 11 years. The geometric mean antibody titre was at least four-fold higher (1:50) in a group of home-dwelling children who received Schwarz strain measles vaccine. This group had repeated exposures to measles and undoubtedly they had asymptomatic reinfection.

GRIFFITH (UK) May I ask a second question? We have to be clear in our minds whether a national rubella vaccination programme is primarily aimed at personal protection or reduction in infection in the community. The programme in Britain relies on children becoming infected naturally, with the result that only about 10 per cent of females are susceptible to rubella when they reach child-bearing age. The aim of vaccination in Britain is to reduce this 10 per cent of females not immune to rubella without reducing the incidence of rubella infection in childhood which ensures that 90 per cent of adolescent females are rubella-immune. If 65–80 per cent of all children are vaccinated the incidence of childhood infection will be greatly reduced and consequently 20–35 per cent of children will reach adolescence sero-negative. A programme of vaccinating all children as opposed to adolescent girls may, therefore, in the long term increase the risk of natural rubella infection during pregnancy.

KRUGMAN (USA) The British rubella immunization programme has theoretical advantages and practical disadvantages. Our experience with girls and women of child-

bearing age since 1969 has revealed (1) that it is difficult to convince them that they should avoid pregnancy in the post-vaccination period, and (2) if the immunization programme concentrates chiefly on pre-pubertal girls in school, the immunization programme will not have a significant effect for at least 10 to 15 years. In the meantime many infants will have been born with congenital rubella.

A 1972 survey in the United States revealed that 80 per cent of children 5 to 9 years old had a history of rubella and/or immunization. Prior to the availability of rubella vaccine in 1969 only 50 per cent of this age group had rubella. If the immunity continues to be long-lasting, there should be no increased susceptibility of adults. When the rubella immunization programme (like polio, measles and DTP) is incorporated with the school health programme, it should be possible to reach more than 85 per cent of the childhood population. If immunity is not long-lasting, it should be possible to give a second inoculation to 11- or 12-year-old schoolchildren.

MEYER (USA) I want to add just a positive comment. One thing that has not been stressed and I feel is extremely important is that the United States programme is usually thought of as a child-based programme, but that is only one aspect of it. CDC and other groups in the country are stressing very much vaccinating the adolescent girl and the adult women in so far as they can be vaccinated with reasonable safety, thinking of the question of pregnancy. Although we do not have exact figures, the total number of doses of vaccine given to adult women in the United States may, I suspect, be greater than the number of vaccine doses given to adolescent girls or adult women in any other country. The problem is to try to get even more. As our programme goes on the idea is that any woman who has not been vaccinated against rubella during childhood, one would like to find a way of vaccinating her as well, recognizing the limitations.

KRUGMAN (USA) In our institution we have given rubella vaccine to approximately 600 susceptible women of child-bearing age. They include 292 women who received rubella vaccine in the immediate postpartum period, and 294 health personnel, such as nurses, nurses-aides and attendants. The procedure is as follows: a sample of blood obtained during the prenatal period or immediately after admission to the hospital is tested for presence of rubella H.I. antibody. If antibody is not detectable rubella vaccine is given after the recipient agrees not to become pregnant for at least two months after immunization.

It is interesting that joint manifestations have not posed a problem. Of 292 women who received vaccine in the postpartum period, the results were as follows: (1) joint complaints in 4 of 11 (3.5 per cent) women who received Cendehill vaccine and in 6 of 142 (4.2 per cent) who received the HPV-77 strain in duck embryo cell culture (HPV-77 DE5). Of 294 health personnel who received vaccine, the results were as follows: (1) joint complaints in 13 of 126 (10.3 per cent) of women who received Cendehill vaccine and in 17 of 159 (10.7 per cent) of women who received HPV-77 DE5 vaccine. Thus, the reactions were less frequent in the postpartum group of women and the vaccine was well tolerated by both groups.

LUNDBECK (Sweden) I have a question pertaining to the SSPE. I have heard some rumours about the relationship between the administration of vaccine and gamma globulin at the same time. These may be simple rumours, but I should like to hear if there is any experience or any evaluation of whether the incidence of SSPE is higher in the groups who have received vaccine and gamma globulin at the same time.

KRUGMAN (USA) I have not heard that rumour, but I do know that there is an ongoing surveillance programme in the United States to try to determine the incidence of SSPE. I believe the latest count indicated that there have been 400 reported cases of SSPE which occurred in association with measles infection. Of the 400 cases, 40 were associated with the use of vaccine. Whether they were related to it or not I do not know. I do not know how many of the 40 received the combined vaccine and gamma globulin. Perhaps

Dr Meyer knows about this rumour, I have not heard it. However, it is important to note that since 1963 when the vaccine was first licensed for use in the United States the number of cases of post-measles encephalitis declined dramatically and is now at an all-time low. At the present time we are not aware of a problem, but it is extremely important to continue surveillance.

MEYER (USA) I do not think there are any hard data in that connexion. We have recently been looking at data from the National Institute of Neurologic Diseases and Stroke, who are the people who are accumulating the data. We are dealing with so few cases, and so few of them have had vaccine at any time. I know of no association specifically with gamma globulin. You would presume that there might be a 6- or 7-year lag period after the original measles infection before SSPE occurs. So I do think that this is an ongoing experiment, but at least the data thus far do not look alarming.

GEAR (South Africa) I should like to ask Dr Krugman three questions, all interrelated. In South Africa DPT and polio virus vaccine are available, they are freely available and they are available free; rubella, measles and mumps vaccine are freely available, and they are available free in certain large centres but they are not yet generally available free to the whole population.

The questions are, first, has Dr Krugman seen any case of congenital defect due to vaccination, or following vaccination, against rubella? We have a number of cases of women who become pregnant after rubella vaccination – I am not suggesting there is a relationship between the two – and it is sufficient to cause concern.

Arising out of that, if the foetus is infected is there any difference in the titre which the pregnant woman shows of antibody against virus as compared with that following simple vaccination?

Thirdly – which perhaps Dr Sencer might deal with as well – would it be worthwhile in costs to make rubella immunity tests freely available to all who need them in the population?

KRUGMAN (USA) Approximately 200 women received rubella vaccine in the United States and subsequently became pregnant. Unfortunately, antibody studies were performed in only a small number of this group. Since only 15 to 20 per cent of women are susceptible, approximately 20 to 30 women were at risk. Many therapeutic abortions were performed. It was impossible to determine if congenital rubella occurred in association with vaccination.

The one disturbing experience that we have had I referred to in my presentation. This involved a nurse whom we immunized; subsequently it was obvious that she was pregnant. We do not know what would have happened at the time of birth in terms of congenital defects, but we do know that the virus was present in most of the organs in the foetus at the time of therapeutic abortion.

CHAIRMAN Does that answer your question, Dr Gear, or would you like further information?

GEAR (South Africa) We have had several such cases, exactly as described in regard to this nurse, and therapeutic abortions have been done.

The other question which I think is important is whether it is worthwhile making rubella antibody tests freely available in the same way as Rh tests are freely available and done routinely.

SENCER (USA) If rubella antibody determination should be made available to those in need, we first have to determine who is in need. I would say that it is extremely cost beneficial to provide a rubella antibody test for any woman who is about to be immunized in the post-pubertal period. Beyond that I think it would be wasting resources to examine large numbers of women who were not at risk of becoming pregnant.

I think that one other factor should be taken into account. Determination of rubella antibody will be of benefit only if the laboratory performing the determination is capable of performing it in a manner that is adequate to give an accurate answer.

NETTER (France) I have a question to Dr Krugman about measles vaccine failure. As one of the causes is over-exposure of the vaccine to light, would it not be possible for producers to make the vaccine in yellow-coloured ampoules?

KRUGMAN (USA) The problem may occur after the vaccine and diluent are drawn into a syringe which is placed on a table for prolonged periods of time. Either Dr Meyer or Dr Hilleman may have a comment on this question of the coloured ampoule. I should like to emphasize that most children who receive measles vaccine do have an antibody response.

HILLEMAN (USA) We do not know about this. The simple precaution is to leave the vaccine in the box until it is needed and to use it within hours after rehydration. It should be kept at 4 °C.

CHAIRMAN We have a session on the use of vaccines, so please could we leave the practicalities of this until later?

SCHILD (UK) I was very impressed by the relatively long duration of antibody to measles virus. I think you could still detect it after 12 years. This is strikingly different from the situation with influenza where the half-life of antibody might be measured in months rather than years. I wonder whether you have any comment on the difference in the systems. Is there any evidence, for example, of measles antigen persisting after vaccination?

KRUGMAN (USA) I do not think one can really compare antibody persistence following measles, where you have an infection characterized by not only local multiplication of virus, but rather extensive viremia and then antibody formation, with influenza. It is an entirely different disease. You are talking not about influenza vaccination but influenza as a disease, is that right?

SCHILD (UK) I think that the half-life of antibody would be similar whether induced by vaccine or infection.

KRUGMAN (USA) Persistence of antibody following measles cannot be compared with persistence of antibody following influenza. The pathogenesis of these infections is not the same. Measles infection is characterized by local multiplication of the virus in the respiratory tract, a prolonged viremia, and antibody formation which persists for many years. In influenza infection the viremia is insignificant and the antibody levels do not persist. I believe you were referring to influenza infection rather than influenza vaccination.

CHAIRMAN Thank you very much, Dr Krugman, for answering all those questions. I would like to remind Dr Krugman that in the United Kingdom we market RA-27/3 strain rubella vaccine made in human diploid cells (WI-38), and have done so for several years.

SESSION IV

VACCINES FOR LIMITED USE

Chairman: Dr F. T. PERKINS (UK)

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INFLUENZA VACCINES AND THE ROLE OF THE WHO IN INFLUENZA SURVEILLANCE

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Influenza is a world-wide problem of considerable impact in terms of morbidity and mortality. Epidemics of influenza also have important economic consequences, causing considerable amounts of absenteeism in industry and the disruption of social life. The pattern of recurrence of influenza epidemics is due to the fact that the naturally acquired immunity of human populations to the disease is overcome from time to time by the emergence of new antigenic variants of influenza virus. Vaccination against influenza is based on the use of inactivated influenza antigens or, in some countries, live attenuated virus vaccines. Although in the past the efficacy of inactivated vaccines was variable, recent developments in technology now enable the preparation of vaccines with improved standards of purity and efficacy. However, recommendations for vaccination against influenza in most countries are confined to special-risk groups and so far it has not been possible to use vaccines on a wide scale to control the course of influenza epidemics. Influenza vaccination is beset by problems not encountered with other viral vaccines. Because of the antigenic variability of the influenza virus, vaccines become redundant from time to time and must be replaced by up-to-date strains, but inevitably with some delay. The aims of the global surveillance of influenza carried out by the World Health Organization are to obtain current information on influenza epidemics and the emergence of new antigenic variants of influenza and eventually to control the disease through immunization.

INTERNATIONAL SURVEILLANCE OF INFLUENZA

Influenza viruses are classified into three types, designated A, B and C. Of these, type A is the most important, being the one responsible for large influenza epidemics and the pandemics that have spread rapidly throughout the world from time to time. Influenza type B viruses are more frequently associated with localized epidemics and these are often limited to institutionalized populations. However, occasionally influenza B epidemics occur which are associated with an increase in morbidity and mortality in the general population. Influenza C viruses, although apparently producing frequent infection, are not associated with epidemics of illness. The epidemiological features of the three types of influenza may be correlated with the varying degrees of antigenic variation in the various influenza

virus types. Influenza A virus exhibits a high degree of antigenic variability which is manifest in two ways. First, complete changes in the haemagglutinin and neuraminidase antigens of the virus surface may take place, resulting in the appearance of a completely new virus subtype. The mechanism of this complete replacement of one antigenic subtype by a new one is now known but there is circumstantial evidence that non-human sources of influenza A viruses may act as sources of new pandemic strains. It is the appearance of new subtypes which is related to the occurrence of influenza pandemics. Secondly, more gradual changes (antigenic 'drift') in the haemagglutinin or neuraminidase antigens may take place during the period of prevalence of a given influenza A virus subtype. Antigenic 'drift' results from the progressive modification of the envelope antigens under the pressure of natural immunity on the population. In influenza B virus, the antigenic changes are gradual and represent antigenic 'drift' within a single subtype. A further difference between influenza A and B viruses potentially of great importance in relationship to the appearance of new pandemic subtypes, is that influenza A viruses are common pathogens of a number of non-human hosts, including swine, horses and many avian species. However, in general the influenza A viruses infecting animals fall into different antigenic subtypes from those infecting man (reviewed by Tumova & Schild(**17**)). In contrast there are no confirmed reports of influenza B virus infections in non-human hosts.

The WHO influenza programme was established in 1947 when it became apparent that significant advances in the understanding of the epidemiology of influenza, and in the eventual control of the disease, could be made only as a result of world-wide surveillance. The World Influenza Centre at the National Institute for Medical Research commenced its activities 25 years ago, in 1947, under the direction of Sir Christopher Andrewes and with the support of the Medical Research Council. Later the International Influenza Centre for the Americas was established at the Center for Disease Control, Atlanta, Georgia, USA. There are now some 80 national influenza centres in 55 countries which contribute to the WHO influenza programme through the surveillance of epidemics and by isolating virus strains. The main activities of the programme are the rapid identification of new influenza virus strains, the maintenance of reference collections of influenza strains and reagents and the distribution of such reference materials. Information of immediate epidemiological importance is promptly passed on to the World Health Organization in Geneva for dissemination to the appropriate national authorities. Of immediate practical importance when a new antigenic variant of influenza virus appears is the preparation of influenza vaccines containing the variant.

Besides its activities in the field of human influenza the WHO influenza programme includes the study of animal influenza viruses. Animal influenza systems provide useful models for the laboratory slides of influenza. However, the main reason for the considerable emphasis now placed on the study of the ecology and antigenic spectrum of influenza A viruses in birds and non-human mammals is because of the possibility that new pandemic subtypes of human influenza A virus may evolve, directly or indirectly, from such sources (see **18**).

RECENT EPIDEMIOLOGICAL EVENTS

In 1968 a new antigenic variant of influenza A virus designated as A/Hong Kong/1/68 (H_3 N_2)* appeared in the Far East. This strain contained a haemagglutinin antigen (H_3) which was of a distinct subtype from that (H_2) of the previous 'Asian' influenza viruses which had circulated from 1957 to 1967, whilst its neuraminidase was of the same subtype (N_2) as that of the 'Asian' influenza viruses. The Hong Kong virus produced epidemics of moderate severity in most areas of the world in the years 1968 to 1970. During 1970 there was very little evidence of influenza activity in any country, whilst 1971 was again marked by moderate influenza outbreaks. The influenza A isolates examined up to autumn 1971 showed little or no evidence of antigenic differences from the prototype A/Hong Kong/1/68 in their haemagglutinin antigens. Although evidence of antigenic drift in the neuraminidase antigen of the Hong Kong virus was observed as early as 1969–70(**1**) it is not clear whether this was of epidemiological significance.

From 1971 onwards an increasing proportion of isolates showed antigenic variation from the prototype A/Hong Kong/1/68 (H_3 N_2). The variants could be separated into the two groups on the basis of their haemagglutinin antigens:

(i) strains resembling A/Hong Kong/107/71 (H_3 N_2) [This is identical to reference strain A/Hong Kong /5/72 (H_3 N_2).]

(ii) strains resembling A/England/42/72 (H_3 N_2).

The two types of variants were readily distinguished from A/Hong Kong/1/68 on the basis of their reactions in haemagglutination-inhibition tests (Table I).

Table I. *Haemagglutination-inhibition reactions of rabbit antisera prepared against purified influenza haemagglutinins*

	Antiserum				
Virus strain	Rabbit anti-Ho (BEL)	Rabbit anti-H2 (Sing)	Rabbit anti-H3 (HK/68)	Rabbit anti-H3 (HK/5/72)	Rabbit anti-H3 (Eng/42/72)
A/BEL/42 (Ho N1)	12 800	<100	<100	<100	<100
A/Singapore/1/57 (H_2 N_2)	<100	6400	<100	<100	<100
A/Hong Kong/1/68 (H_3 N_2)	<100	<100	12 800	200	800
A/Hong Kong/107/71 (H_3 N_2)	<100	<100	400	3200	1 600
A/Hong Kong/5/72 (H_3 N_2)	<100	<100	800	3200	1 600
A/England/42/72 (H_3 N_2)	<100	<100	3 200	800	12 800

* For new system of influenza nomenclature see (**19**).

Table II. *Comparison of neuraminidase antigens in influenza A viruses isolated between* 1957 *and* 1972. *Results of neuraminidase-inhibition tests*

Source of neuraminidase	Anti-neuraminidase rabbit sera: anti-N2 A/Jap/57	anti-N2* A/HK/68	anti-N2 A/HK/5/72
A/Sing/1/57 (H2 N2)	5 000†	100	< 10
A/Eng/12/64 (H2 N2)	1 000	300	30
A/Tokyo/3/67 (H2 N2)	75	1 000	150
A/HK/1/68 (H3 N2)	50	5 000	750
A/HK/5/72 (H3 N2)	20	50	10 000
A/Eng/42/72 (H3 N2)	20	100	10 000
A/Eng/42/72 (H3)–A/PR8/34 (N1)‡	—	< 10	20
A/PR8/34 (Ho)–A/Eng/42/72 (N1)	—	< 10	5 000

—, Not tested.

* WHO reference serum from CDC Atlanta.

† Serum dilution giving 50 % reduction in neuraminidase activity.

‡ Recombinants (reciprocal antigenic hybrids) of A/England/42/72 (H3 N2) and A/PR8/34 (Ho N1).

Tests on the other envelope antigen, the neuraminidase, indicated that this antigen had also undergone variation (Table II).

Immuno-double-diffusion tests with antisera specific for the haemagglutinin and neuraminidase antigens have been found to be of value in studies on antigenic variation in influenza viruses. Application of such tests to the recent influenza virus isolates(**13**) confirmed and extended the observations made by haemagglutinin and neuraminidase-inhibition tests and provided clear evidence of antigenic 'drift' in the haemagglutinin and neuraminidase antigens away from those of prototype A/Hong Kong/1/68 virus. Confirmatory evidence was produced that the haemagglutinin and neuraminidase antigens of the variants were of the same subtypes (i.e. H3 and N2) as in prototype strain A/Hong Kong/1/68 (H3 N2).

Viruses resembling the variant A/Hong Kong/5/72 were initially identified in autumn 1971 amongst strains isolated in Hong Kong. Further isolations of this type of variant were made in other countries in the winter and spring of 1971–2; from an outbreak in Korea all isolates were like A/Hong Kong/5/72. In the moderate outbreaks of influenza A which occurred in European countries in the winter 1971–2 the majority of isolates were of prototype A/Hong Kong/1/68. Sporadic isolations of variant A/Hong Kong/5/72 were obtained in both Europe and the USA during this period. Amongst European countries from which reasonably large numbers of isolates were examined, Hungary yielded the highest proportion (approximately 30 per cent) of isolates resembling A/Hong Kong/5/72. From September 1972 new isolates resembling A/Hong Kong/5/72 were not encountered and thus the preparation of vaccines against this variant is not indicated.

The variant A/England/42/72 was initially identified in the UK in January 1972 as one of over 750 isolates from the UK which were examined. Retrospective studies indicated that variants of this type predominated amongst influenza isolates from an outbreak of influenza in southern India in autumn 1971. The viruses isolated during influenza outbreaks which occurred in Singapore and Malaysia in May and June 1972 and in August and September in Australia and New Zealand, were exclusively this type of variant. Subsequently, A/England/42/72 appeared as the predominant strain isolated during influenza epidemics in December 1972 and January 1973 in several European countries and in North America. In some areas these epidemics were severe but other areas suffered only moderate outbreaks with little increase in mortality. In September 1972 it was recommended that A/England/42/72 should be incorporated in current inactivated influenza vaccines as soon as possible to replace the older A/Hong Kong/1/68 component. The A/England/42/72 virus appears to have replaced completely the former variants and has become widely disseminated. It has been recommended that vaccines being prepared for use in 1973–4 should contain this strain. It is of interest that in the winter of 1972–3 when A/England/42/72 was the epidemic strain, the possibility arose of comparing the efficacy of inactivated vaccines containing A/Hong Kong/1/68 and the new variant, A/England/42/72. In a number of studies (Dr M. S. Pereira, Professor Michaeljohn, Dr F. B. Brandon – personal communications) both vaccines reduced the incidence of respiratory disease by 50–70 per cent but the protective efficacy of the A/England/42/72 vaccines was only marginally greater than for vaccines containing A/Hong Kong/1/68. It seems that in some circumstances antigenic 'drift' may not have a great effect on vaccine efficacy. However, until more detailed knowledge on this subject is available it is important to incorporate new variants into vaccines as soon as is practically possible. Difficulties will arise in making a decision on changes in vaccine composition when, as in 1972, two variants are circulating concurrently.

From 1967 to 1972 there was little evidence of significant antigenic variation in the prevalent influenza B viruses. Inactivated vaccines during that period and those in current use include influenza B viruses such as B/Roma/1/67, B/Victoria/98927/70 or B/Massachusetts/1/71. In December 1972 and January 1973 strains of influenza virus were isolated from sporadic cases of influenza in Hong Kong and Victoria, Australia, which showed a considerable amount of antigenic 'drift' away from the 1967–72 strains. The reactions of these strains in haemagglutination-inhibition tests are shown in Table III. Whether these new variants will produce an epidemiological impact is not yet known. Nevertheless it will be of importance for health authorities and manufacturing agencies to be alerted to the potential need for changes in the influenza B component of influenza vaccines in the near future.

Table III. *Antigenic comparisons of influenza B virus strains. Results of haemagglutination-inhibition tests*

Virus strains	Post-infection ferret sera								
	B/Lee/40	B/JHB/58	B/Sing/64	B/Roma/67	B/Vict/70	B/Mass/71	B/HK/1/72	B/HK/5/72	B/HK/5/73
B/Lee/40	960	40	20	20	20	20	<	<	<
B/JHB/33/58	80	160	320	80	20	40	20	<	<
B/Sing/3/64	40	40	1920	320	640	640	320	<	<
B/Roma/1/67	<	<	160	640	640	1280	480	<	<
B/Vic/98926/70	<	<	320	320	640	1280	480	<	<
B/Mass/1/71	<	<	160	240	320	1280	480	<	<
B/HK/1/72	<	<	80	240	320	1280	480	<	10
B/HK/5/72	<	<	<	<	<	10	<	80	80
B/HK/5/73	<	<	<	<	10	20	<	320	480
B/HK/8/73	<	<	<	<	10	20	<	160	480
B/Vic/102/72	<	<	<	<	10	20	<	320	240
B/Eng/847/73	<	—	—	160	320	320	240	80	160
B/Hann/1/73	<	—	—	160	160	320	240	80	80
B/Hann/2/73	<	—	—	160	320	320	240	80	160

Strains B/England/847/73 and B/Hannover/1/73 and 2/73 appear to represent variants of influenza B which are antigenically intermediate between the 1967–72 variants and strains resembling B/Hong Kong/5/72. However, this conclusion should be confirmed in tests with antisera to these viruses.

TYPES OF VACCINE

Inactivated influenza vaccines are used most commonly in most countries with the exception of USSR and certain East European countries where live attenuated vaccines are commonly used. In this article it is not intended to discuss live attenuated vaccines in detail. Inactivated vaccines are prepared by growing the virus in embryonated eggs and the allantoic fluids are used as a source of antigen after some degree of purification. Inactivation is accomplished by treatment with formalin or β-propriolactone. The final product consists conventionally of a saline suspension of intact virus particles of varying degrees of purity. Standardization has been mainly based on haemagglutinating activity (CCA or international units). However, there is some dissatisfaction with this as an assay system, since the results may be dependent on many variables such as the source of erythrocytes and on the physical state of the antigen (disrupted or intact virus, spherical, filamentous, aggregated or single particles). Other techniques, for example those based on single radial diffusion(**10**, **12**) are currently under investigation as methods for assessment of the antigenic content of influenza vaccines. Animal protection studies and the assessment of the antibody response in human volunteers are also used to assess vaccine potency, but the ultimate evidence of efficacy must come from clinical trials in the human population in epidemic conditions. It is generally accepted that local inflammatory reactions and the occa-

sional febrile reactions which are encountered with inactivated vaccines are associated with total protein content and these phenomena have in the past imposed a limit on the antigenic content which could be used in vaccines. Two recent advances have led to a considerable improvement in the quality and availability of the vaccines now available. Kilbourne(**8**) suggested that the use as seed in inactivated vaccine production of genetic recombinants with high growth potential derived from one parent virus (usually A/PR8/34 (Ho N1)) and antigenic character derived from another (the currently prevalent strain). This method enables high-yielding strains to be manufactured quickly after the appearance of a new variant in nature so that manufacture of vaccine can commence promptly and rapidly. It has replaced the older technique of 'adaptation' which was time-consuming and unpredictable. Furthermore, techniques for virus purification have been developed which have been applied to influenza vaccine production. In particular, the use of continuous flow zonal centrifugation(**11**) which enables a high degree of virus concentration and purification to be made in a single process, has been widely adopted for vaccine manufacture and has resulted in products of improved quality and efficacy. The use of zonally purified vaccines has enabled increases in the virus dose to be made. In some studies, doses of 3000 CCA of zonally purified virus were used, the conventional dose being 300 CCA. It was shown(**5, 9**) that doses containing 3000 CCA did not induce unacceptable reactions but did induce a much higher level of protection than the conventionally used 300 CCA. It would seem that the development of these improved techniques of manufacture will enable vaccines of increased antigenic content (and efficacy) to be manufactured in many countries and will inevitably lead to the introduction of more demanding standards of quality control.

Most inactivated influenza vaccines for routine use are bivalent and contain both influenza A and influenza B antigens. However, in such preparations the influenza B component is conventionally present at a lower concentration than the influenza A, the recommended antigenic content being controlled by national authorities and variable from country to country. Recently, the wisdom of using bivalent vaccines has been questioned on the grounds that the influenza B component is present in too low amounts to provide immunity and also that the B component contributes most to the toxicity of vaccines, thereby limiting the amount of A component which can be incorporated and also compromising their general acceptability. Indeed it would seem reasonable to use suitably potent monovalent vaccines for influenza A and B which could be used either singly or in conjunction, according to epidemiological considerations in the vaccinee population. Attempts have been made to reduce toxicity by the disruption of virus particles with various reagents, including ether(**3, 4**) or sodium dodecyl-sulphate (**18**). These procedures do not necessarily lead to purification of the essential envelope subunits associated with immunity, i.e. haemagglutinin and neuraminidase, and the term 'subunit vaccines' used to describe such preparations is a misnomer.

It is generally accepted that anti-haemagglutinin antibody confers immunity to influenza. However, there is now evidence that anti-neuraminidase antibody is

also protective (**14, 15**). Studies with a neuraminidase-specific inactivated vaccine (i.e. one which contains the neuraminidase antigen of the currently prevalent strain but with an 'irrelevant' haemagglutinin antigen) have recently been reported by E. D. Kilbourne and his colleagues in the USA (personal communication). It is of interest that this vaccine, which induced only anti-neuraminidase antibody, protected human volunteers against illness but not against infection. Thus vaccinated persons had the advantage of developing natural immunity because their susceptibility to infection was not modified, but did not suffer the disadvantage of clinical illness. It will be of interest to investigate the potential value of such vaccines under conditions of natural infection on a wider scale.

There would be considerable attraction in the possibility of using as vaccines highly purified envelope proteins of influenza virus, thus avoiding the injection of materials (internal components of virus and RNA) which are irrelevant to immunity. An interesting development in this respect has been the development of techniques to obtain highly purified (crystalline) haemagglutinin (**2**). This type of preparation was found to induce immunity in ferrets when injected with adjuvant. Such preparations are not potent antigens without adjuvants and their widespread use in man will depend on the availability of a generally acceptable adjuvant. Because of the possible role of the neuraminidase antigen in immunity it may be necessary to use preparations which included both surface antigens in purified form. Whether the use of such preparations will be economically feasible depends on the development of relatively simple methods for their preparation on a large scale.

Two of the outstanding problems with inactivated influenza vaccines are the necessity for annual revaccination and the effects of antigenic drift in the influenza viruses. Adjuvants are known to prolong the immune response and to broaden its specificity. Stuart-Harris (**16**) showed that when used in combination with oil adjuvants, inactivated vaccines gave higher and more prolonged antibody responses than aqueous vaccines. However, severe local reactions to adjuvants, although very infrequent, have prevented the use of conventional oil adjuvants on a wide scale (**7**). However, the metabolizable vegetable oil adjuvants (**6**) seem to be free of many of the disadvantages of conventional oil adjuvants and may be of value in influenza vaccination.

Impressive progress in the field of influenza vaccination has been made over the past few years. There is abundant evidence that inactivated vaccines with appropriate antigenic composition and potency are effective in preventing disease. Evidence is also emerging that such vaccines may considerably influence related mortality in high-risk populations. The questions to be answered now are concerned less with whether vaccines protect and more with the choice of population which should receive route immunization.

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SMALLPOX AND SMALLPOX VACCINE

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Since 1967 when the smallpox eradication programme was begun, the extent of the smallpox endemic areas as well as smallpox incidence have progressively diminished and such changes are continuing. At the same time, the demand for potent and stable freeze-dried vaccines has risen steadily in countries throughout the endemic world. In contrast, in a few of the developed countries vaccine consumption has fallen sharply as programmes of routine vaccination have been discontinued due to the decreased risk of smallpox importations. It is apparent that the future requirements for smallpox vaccine as well as the motivation to undertake research to improve presently available vaccines are closely correlated with the progress of the global programme. Thus, it would seem appropriate to review first the evolution and expectations in the global programme before discussing certain questions pertaining to smallpox vaccine itself.

In 1967, WHO, on the decision of the World Health Assembly initiated the global programme for smallpox eradication. At that time many, if not most authorities, were openly sceptical of the concept of eradication as a realistic objective. Such doubts seemed not unreasonable as the history of eradication efforts to date *have* been disappointing. Pertinent, of course, is the fact that the global eradication of any disease has no precedent.

However, during the past six years, sufficient progress has been made in the smallpox eradication programme to permit, in the autumn of 1972, the inauguration of what has been termed the 'final phase' – the objective being to reduce smallpox incidence to nil throughout the world by the summer of 1974. How realistic is this objective and where now are the problems which conceivably could thwart this realization? Present problems and uncertainties must be gauged in the perspective of the past.

Although the concept of smallpox eradication was proposed by Jenner himself in 1801 (**6**), more than a century later few countries were free of smallpox. As recently as 1930, for example, England and Wales recorded almost 12000 cases and the United States that year reported over 48000 cases (**15**). Beginning in the late 1930s smallpox began to recede perceptibly. Better preservation of vaccine, more potent vaccines and improved health services all played a role. In 1959, when the World Health Assembly first proposed to begin a global eradication programme, both Europe and North America had become free of endemic smallpox. Also smallpox-free were the countries of Central America and several in Asia. This was especially significant as a practical demonstration that smallpox

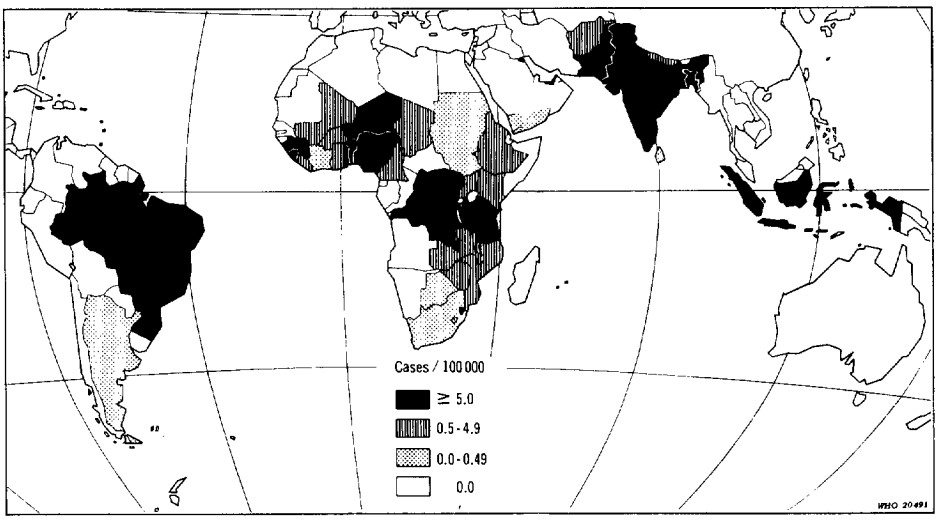

Fig. 1. Smallpox cases per 100000 inhabitants, 1967.

transmission could be interrupted even where health facilities were limited and transport and communication problems were difficult.

Between 1959 and 1966, a number of countries mounted what were termed eradication programmes – in fact, most were little more than mass vaccination campaigns. Comparatively few countries became free of the disease. Deciding that greater technical and logistical support as well as better co-ordination of efforts were required, the World Health Assembly in 1966 decided to provide a special budget for the programme with the expressed hope that eradication might be achieved within a 10-year period.

The intensified programme thus began in January 1967. That year, 42 countries reported a total of over 131000 cases(**17**) (Fig. 1). Surveys since then suggest that, at most, one case in 20 was actually reported. Thus, it is estimated that at least 2500000 cases occurred that year.

Progress during the past six years has been gratifying. During 1972, 19 countries reported 65000 cases (Fig. 2). Reporting, however, has been greatly improved to the extent that it is estimated that at least one-third of all cases are now being recorded. The actual number of cases which occurred in 1972 is thus estimated to be not more than 200000 as contrasted to 2.5 million cases in 1967. Of the 19 countries reporting smallpox, 11 experienced cases as a result of importations. As of March 1973, in fact, only four countries are considered to be endemic – Ethiopia, India, Bangladesh and Pakistan.

Two factors have contributed significantly to this rapid change – (1) universal use of fully potent freeze-dried vaccine in endemic areas and an improved technique for its administration; and (2) perhaps most important, a change in strategy of the programme from one consisting solely of mass vaccination to one which emphasizes surveillance.

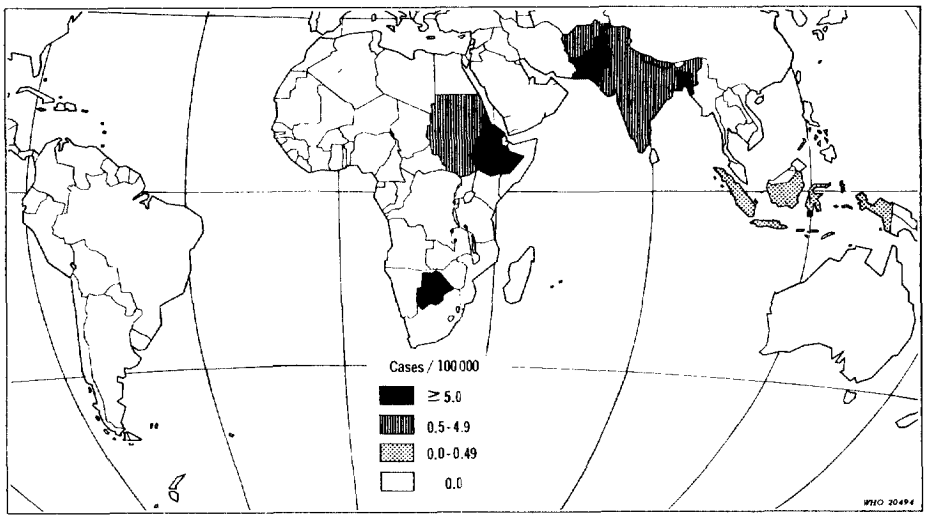

Fig. 2. Smallpox cases per 100 000 inhabitants, 1972.

Of obvious importance in any programme based on vaccination is the need to be assured that vaccine is fully potent when it reaches the arm of the recipient. In this respect, freeze-dried vaccines which maintain acceptable levels of potency for one month at 37 °C have proved indispensable, especially in tropical areas where refrigeration facilities are limited. Distribution systems which permit vaccines to be kept at ambient temperatures for one month have proved comparatively easy to establish, even in the least developed areas. However, despite the development almost 20 years ago of practical methods for producing such vaccines(**5**), not more than 10 to 15 per cent of the vaccine in use in 1967 in the endemic countries was freeze-dried and met requisite standards. Assistance was given to vaccine producers in the endemic areas, reference centres were established for routine quality control of vaccine, and donations were received from many countries. By 1969, more than 95 per cent of the vaccine in use met accepted standards. Today, two-thirds of the more than 200 000 000 doses required annually in endemic areas are produced in the developing countries. Vaccination programmes were further facilitated by the introduction in 1968 of the bifurcated needle. With this needle and the multiple puncture technique, the efficacy of vaccination improved and a saving of approximately 50 per cent in vaccine consumption was realized.

Whilst these improvements in the vaccination programme were of importance, it was apparent from the inception of the programme that mass vaccination, while serving to *retard* transmission, rarely was successful in *interrupting* transmission. Particularly emphatic among many examples was the experience in Central Java, Indonesia, where in 1968 a survey revealed that more than 95 per cent of the province's 23 million persons bore scars of vaccination(**2**). Nevertheless, during the year that surveys were conducted, almost 1700 cases occurred; 85 per cent of

all cases were in persons who had never been successfully vaccinated. In brief, smallpox continued to be transmitted principally among the unimmunized who constituted less than 5 per cent of the population. While a superficially simple solution would have been to vaccinate the remaining 5 per cent, the logistical problems and costs of so doing would have been prohibitive.

It had been apparent from experience with outbreaks of smallpox resulting from importations into Europe, that even in much less well vaccinated populations than those in Indonesia, smallpox spreads comparatively slowly, infecting those in close contact with the patient. Even limited vaccination of those at immediate risk was shown to be effective in stopping outbreaks. Smallpox in endemic areas consists of nothing more nor less than a series of such outbreaks. Thus, a change in the strategy of the programme from one of mass vaccination to one emphasizing containment of outbreaks seemed sensible. Accordingly the strategy of the programme and measurements of progress have focused not on the vaccination of x millions of persons but on the reduction of smallpox incidence to nil levels.

Necessarily this implied the need for reporting systems to permit the early detection of outbreaks and trained epidemiological teams to investigate and contain them. At the beginning of the programme, basic reporting networks in most endemic countries were found to be limited or non-existent. The key to their development has been the establishment of national and/or regional surveillance teams who regularly visit all health units within their jurisdiction to assure that weekly reports regarding smallpox are sent and to encourage reporting to the health units by other groups. Such teams, in addition, investigate all suspect cases, take containment measures and trace the source of infection to other possibly infected villages. The regular visits of the teams and their immediate response if cases are reported, considerably facilitate co-operation in reporting. While reporting systems are still not functioning optimally in most countries, they have so far functioned well enough to permit the interruption of smallpox transmission in 26 of the 30 originally endemic countries.

We have now entered the 'final phase' of the programme with the objective of reaching a nil incidence by the end of the 1974 smallpox season. Superficially, this might appear unduly ambitious. In 1972, 65000 cases were recorded – approximately 20 per cent more than in 1971; a significant setback was experienced when major epidemics occurred in Bangladesh, previously a smallpox-free country.

As the present smallpox season began, however, there were for the first time, surveillance activities in every endemic area. More cases are being discovered but more chains of transmission are being interrupted. The surveillance efforts are not yet of the quality desired in some of the endemic areas but the gap is rapidly narrowing. This is important as experience has shown that when surveillance activities, even of a moderate quality, are extended throughout an endemic area, transmission is almost invariably interrupted within two years.

In sharper focus, what is the status of the programme today? In 1967, endemic smallpox was present in Brazil, in most African countries south of the Sahara and in six countries of Asia. In South America, the last case was detected two

years ago near Rio de Janiero. Brazil, the only endemic country in the Americas during the past 6 years, has now 26 surveillance units and over 5000 reporting posts. None have reported cases since April 1971. A special active search for cases was conducted between March and October last year, during the usual peak of the smallpox season. In all, 448 municipios (counties), almost 10 per cent of the country's total, were searched for cases. A total of 875 000 persons were contacted. No cases were found. In brief, we now believe that after 450 years smallpox has been eliminated from the Western Hemisphere.

In Africa, smallpox now appears to be confined to one country – Ethiopia. Outside of Ethiopia, Sudan and Botswana, no endemic foci have been detected on the African continent for 19 months. Botswana experienced major outbreaks in 1972 following an earlier importation from South Africa. This has been aggressively dealt with – the last cases were detected over four months ago. An intensive programme in Sudan during the past 12 months has rapidly reduced smallpox incidence to the extent that no cases have been discovered this year. The programme in Ethiopia, now two years old, has made excellent headway as is graphically illustrated in Fig. 3. By June, smallpox is expected to be confined to but three of the country's 14 provinces. By the end of 1973, a nil incidence in Ethiopia and on the continent of Africa itself is not an unreasonable expectation.

In Asia, the picture is mixed. Three of the six countries which were endemic in 1967 now appear to have stopped transmission – Indonesia, where cases last occurred in January a year ago; Afghanistan, where all cases for more than a year have been among nomads infected in Pakistan; and Nepal, where all cases since June have been traced to importations from India. Problem areas in Pakistan are now virtually confined to 10 districts containing only 15 per cent of the country's population.

In terms of achieving eradication within the time targets noted, the most difficult problem appears to be that of interrupting transmission in certain areas of India and Bangladesh. Bangladesh after 18 months of freedom from smallpox was reinfected in February 1972 by returning refugees from India. Emergency measures were implemented and additional staff provided but over 10000 cases occurred during 1972. The epidemics are now widespread; intensive emergency measures are now in force but, as yet, no significant reduction in incidence has been achieved. In India, the southern states have virtually interrupted transmission and about half of the country's population lives in states which are smallpox-free. However, major epidemics are occurring in almost a solid band across the whole of northern India. Paradoxically, perhaps, health services in these areas are far better developed than in most previously endemic countries; transport and communications are likewise less of a problem; and five to ten times as many smallpox staff per capita are employed. The failures to date in these areas can be attributed to an almost complete reliance by health officials on a poorly supervised vaccination programme with virtually no attention having been paid to the development of surveillance activities. Government officials have finally taken steps to remedy the situation and additional assistance is being given by the Organization. Much remains to be done.

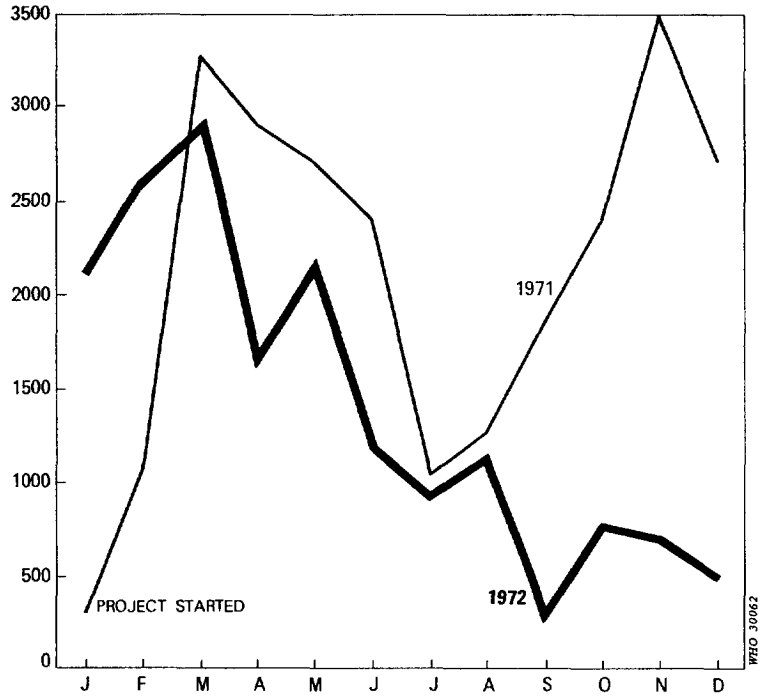

Fig. 3. Ethiopia: smallpox incidence, 1971–2.

Thus the problems of northern India and Bangladesh at this moment are of greatest concern and appear to pose the principal threat to the realization of global eradication. Many new measures have recently been implemented and a strategy agreed upon, which could succeed in interrupting transmission by the summer of next year. As we all know, however, there is often a significant gap between plan and implementation and unexpected problems such as civil disturbances and natural catastrophes may intervene. Thus, prudence is indicated and with it continued work to further develop and improve existing smallpox vaccines.

Seventy-six laboratories are currently producing freeze-dried smallpox vaccine(**3**). Fifty-six (73 per cent) now employ one of the three strains of vaccinia virus adjudged to be the least reactogenic but, at the same time, satisfactorily immunogenic(**10**). These strains are the Lister (Elstree) strain, New York Board of Health strain and Ecuador strain. Virtually all vaccine donated to WHO is produced from these strains, as is the vaccine produced in all but one of the developing countries.

Quality control is monitored by the WHO Reference Centres for Smallpox Vaccine (Rijks Institute, The Netherlands and Connaught Laboratories, Canada) who independently test vaccines submitted for donation, as well as batches of vaccine produced in other laboratories supplying vaccine to the programme. Over

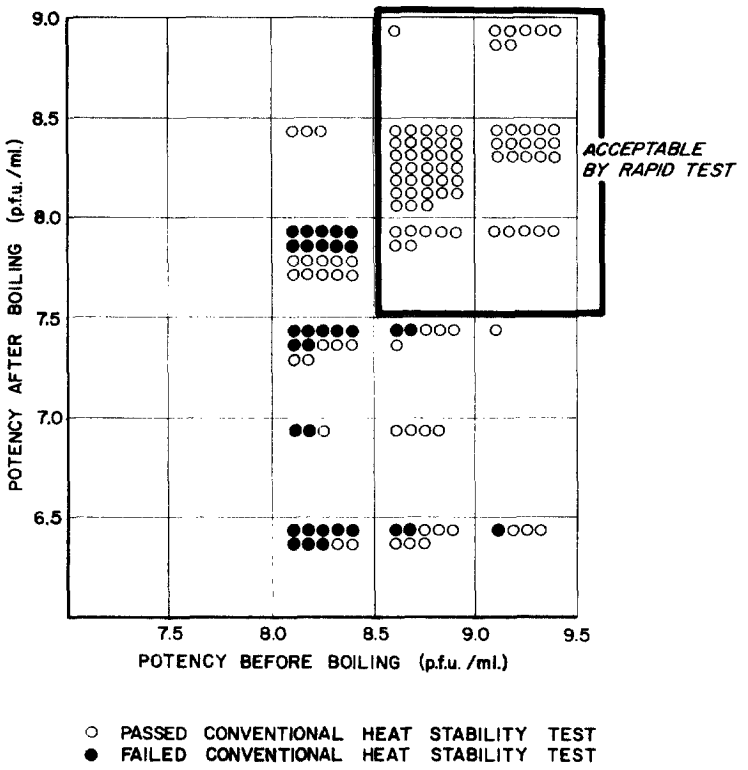

Fig. 4. Rapid screening versus conventional heat-stability test. Results from 139 batches of smallpox vaccine.

400 batches were tested during 1972. All vaccine employed in the programme is now freeze-dried and meets WHO accepted standards of potency and purity. Over 95 per cent of the vaccine used also meets prescribed standards of stability – specifically, maintenance of a titre of 10^8 p.f.u./ml after incubation at 37 °C for four weeks.

Recently, testing procedures in regard to stability have been altered to permit more rapid testing of the vaccine. Studies were conducted at the Rijks Institute to correlate the results obtained when vaccine was subjected to 100 °C for one hour with the results obtained following the standard four-week period of incubation(3) (Fig. 4). These studies showed that vaccines from various manufacturers which contained more than $10^{8.5}$ p.f.u./ml in initial potency and maintained a titre of more than $10^{7.5}$ after boiling, consistently met requisite standards. Almost two-thirds of all batches now tested in this manner are accepted for stability on the basis of this test.

Virtually all vaccine today is produced on animal skin – calves, buffalo or sheep being employed. Efforts to produce a stable vaccine on egg membranes or in tissue cultures have, until recently, proved disappointing. During the past year, however, the Vaccine Institute in Porto Alegre, Brazil, has succeeded in pro-

ducing routinely a potent and stable vaccine grown on chorio-allantoic membrane(14). In addition, a stable vaccine produced in monolayers of primary rabbit kidney tissue cell culture has been developed and extensively tested at the Rijks Institute in the Netherlands(7). This will be subjected to final, large-scale field trials within the next few months. For laboratories in the developing countries, calves and buffalo must remain the principal source of vaccinia virus, but for those laboratories equipped for work with tissue cultures, alternate methods for production now seem feasible.

A potentially important break through in the packaging of vaccine has recently been reported by Majer and his colleagues working at the Swiss Serum Institute (8). They have reported that freeze-dried vaccine dispersed in a high-viscosity silicone oil maintains a high degree of stability and can be administered directly without reconstitution. Early clinical trials appear promising, although further work is yet required to obtain consistent and reproducible results in titration.

Finally, among recent developments in smallpox vaccination, note must be made of alternate approaches to vaccination directed toward a reduction in the frequency of complications. Studies to date have been based on the premise that if inactivated vaccine or strains of reduced pathogenicity were first administered followed by vaccination with proved traditional strains, the frequency of complications might be significantly reduced. The approach of pre-immunization through use of inactivated vaccine now seems doubtful. Boulter(4) showed that antibody to inactivated cell-associated virus does not neutralize cell-free virus nor does it prevent the spread of pox virus in tissue culture or in experimental animals(1). Conventional vaccinia virus suspensions consist almost wholly of cell-associated virus and thus inactivated vaccines prepared from such suspensions would be expected to have a limited effect in preventing viraemia and presumably many, if not most, of the more serious vaccinal complications. Since cell-free virus constitutes little more than 1 per cent of the total infective virus in a culture(16), the preparation of a presumably more suitable inactivated cell-free vaccine would seem to be prohibitively expensive and perhaps ineffective for undefined reasons(13).

Initial results obtained through pre-immunization with the CVI(12) and MVA (11) attenuated strains appeared more promising. Cutaneous responses were less marked and there were few constitutional symptoms. Subsequent vaccination with traditional strains was also usually associated with less pronounced reactions, suggesting that rare but serious vaccinal complications might also be reduced in frequency. However, the degree of protection against variola which is afforded by this approach is open to doubt. Approximately one-third of those first vaccinated with the attenuated vaccine and subsequently with traditional strains, develop no neutralizing antibody(11, 9). In contrast, essentially all children vaccinated with traditional strains developed neutralizing antibody. Admittedly the correlation between the presence of neutralizing antibody and protection against human variola infection has never been evaluated satisfactorily. However, based on a considerable experience with other virus diseases, it is difficult to dismiss this

observation as irrelevant. It is clear that much yet remains to be clarified before use of an attenuated strain can be considered.

In summary, the smallpox situation has radically changed in recent years – the prospects for eradication are encouraging but the certainty of its accomplishment can perhaps be better assessed after another year. Two countries, the United States and the United Kingdom, have terminated routine vaccination; other developed countries on the smallpox-free continents have so far decided to defer reconsideration of policy pending further progress in the global programme; developing countries throughout the world have continued and have been encouraged to continue routine vaccination programmes. Further efforts to improve existing vaccines and to develop suitable attenuated strains would thus seem prudent. At the same time, we shall endeavour to do our best to make such work redundant as soon as we possibly can.

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GENERAL DISCUSSION

CHAIRMAN Thank you very much indeed, Dr Henderson. Both of these papers are now open for discussion, but General Sachs has particularly asked to have a word.

SACHS (UK) Mr Chairman, we must not treat smallpox too cavalierly and let our guard go down. I have been at the receiving end of several quite extensive outbreaks, and my experience is that it does not spread slowly; it spreads pretty rapidly. In places like India where I spent 17 years, one does not know the true incidence, whether one is dealing with smallpox or other communicable diseases because in the fatal cases, the bodies are disposed of very rapidly and, be it smallpox or be it cholera, you have not a clue of numbers. I do not know how many people here, when they talk about this Utopia of the future, realize the conditions of overcrowding in the villages, and I have found smallpox to be a disease of communications. I remember in the war that one case of smallpox, not diagnosed at the time in the field, was responsible in a very short time for 87 cases of smallpox among medical staff and other soldiers in a so-called protected community, of whom nine were subsequently found to be unprotected, and of these six died.

I think we have to be very careful, particularly in countries like the United Kingdom, as in another few years the vast majority of the population will be non-immune. Subclinical types are not always typical, even though they have a rash. Can you imagine one case in a crowded tube, with perhaps 50–100 people being at risk and some of them going into other tubes? I think that we should always have available really potent vaccine.

With regard to the complications of vaccination, nobody has related them to the techniques used. My own experience is that since the introduction of the multiple pressure technique there seems to have been a definite diminution in the number of complications. It is important to be careful of the number of pressures one gives to definitely non-immune people and those adults in whom there is a long interval since vaccination in infancy. Failure to take this precaution may be one of the reasons for the incidence of complications referred to, small as it is.

Some years ago, we were surprised to get many negatives in soldiers who should have had a positive take. It was then found that if they were vaccinated on the other arm, a positive result was obtained in a number of cases. It is of interest that in some cases there was a sort of allergic reaction at the site of the first vaccination. I do not quite know the explanation but there was obviously some form of local tissue immunity after the original vaccination.

Just to finish, I think we must be careful that this Utopia is not one like 'Hope springs infernal in the human beast'. I feel that if we can cure VD in Europe, we may have a chance of eradicating smallpox.

DIANZANI (Italy) I have a question for Dr Schild. As it was pointed out, we do not know for sure whether circulating antibodies are really important for the protection of people against a disease in which viraemia perhaps is not critical. Has Dr Schild any further information about the possible role of other immune systems like IgA, or sensitized lymphocytes, or delayed hypersensitivity?

SCHILD (UK) It is a very difficult question to answer because, in most of the studies that have been done looking for immunity to influenza in both man and experimental animals, the techniques we used were such that one could look only for the antibodies that one knew of. One was inclined to think that, because one could measure an antibody, this was

important. I think it was on this sort of basis that the idea that anti-haemagglutinin was probably the most important aspect of immunity developed. However, it is quite possible that anti-haemagglutinin might be an index of exposure to infection rather than the basic mechanism of immunity. This is why I said that it is very important that we should now go ahead and look at other aspects of immunity such as cell-mediated immunity about which we know very little indeed.

VASSILOPOULOS (Cyprus) I read in the Press some time ago, Mr President, that at the Pasteur Institute in Paris they have recently introduced an anti-influenza vaccine which can afford prophylaxis against all types and strains of influenza. I wonder whether this is true or not.

SCHILD (UK) These data have not been published, so it is very difficult to comment on them in detail. I can go only on the basis of personal communication between me and Dr Hannoun. I think that this is an extremely interesting experiment. Starting from the Hong Kong virus isolated in 1968 they produced a series of antigenic variants using immunologic pressure. On the basis of this sort of study Dr Hannoun produced variants which were closely related to the England 42/72 strain, so that at least he seems to have been able to anticipate the changes between 1968 and 1972. However, he has gone further than that and has produced strains which he says are senior to the 1972 variant. Whether this, in fact, will turn out to be correct only time will tell.

This is not a new approach to the problem; many people had done this sort of thing previously, but the novel approach lies in the characteristics of the junior/senior relationship which is the result of several studies by Dr St. Groth. This hypothesis of a junior/senior relationship suggests that, if you have a senior strain, antibody to this will protect against all junior strains along the line. Dr Hannoun claims to have produced a senior strain which may be related to the strains which will circulate in future years and if so, it is hoped that antibody to this senior strain will protect all the various stages of antigenic drift between now and 1968.

GEAR (South Africa) I heard Dr Henderson talk on smallpox vaccination in 1970 and expressed some doubts similar to those of General Sachs at that meeting. He said he would suspect I came from Missouri if he had not known that I did not. I did not tell him my middle name was Henderson.

Arising out of his most impressive account, I must say that he has succeeded beyond most people's expectations, particularly perhaps his own. We hope that he will be fully successful. However, I believe that one should bear in mind the fact that, as I pointed out at the time, South Africa for instance had been carrying out mass immunization for 170 years and blanketing epidemics, but had always failed to remove the danger permanently because the infection was reintroduced from the outside. Until the disease was eliminated completely from the world, this danger would remain. In South Africa the last time infection was introduced from beyond her borders there were 165 cases which occurred before the outbreak was brought again under control. Many of these were in a religious group who objected to vaccination and were not vaccinated. A situation is developing in the world similar to this religious group where more and more people in Western Europe are not being vaccinated and, should the disease be introduced into such a population, the infection would spread much more widely than it would have if the population had been vaccinated. I was wondering whether Dr Henderson would like to comment on this evolution of the situation.

HENDERSON (WHO) I appreciate the concerns expressed. Certainly, so long as there is smallpox anywhere in the world, there is indeed a risk that it may be imported. The probability of further transmission is, of course, inversely related to the level of population immunity. In the developing countries, we recommend that immunization be maintained at a high level to deter transmission. In the developed countries, the probability of early detection and effective containment is much better. Thus, even though an importa-

tion may occur, rarely does the outbreak spread extensively – the outbreak of 175 cases in Yugoslavia representing the exception rather than the rule.

In determining vaccination policy one must balance the risk of complications following vaccination, the risk of importation and the risk of spread. Each country has to weigh these risks for itself as circumstances are different from continent to continent and country to country.

SMITH (UK) Perhaps I might suggest a note of caution in considering influenza vaccination among factory workers. One often hears the claim that this could have great economic benefits, and we are trying to test this in the United Kingdom from our own laboratory. The best estimate I can make at the present time is that about 4 per cent of the working population are affected on average by influenza each year. The acceptance rate for influenza vaccine among factory workers is, we find, on average 40 per cent. In other words, 60 per cent do not take the vaccine that is offered to them. If the vaccine is about 75 per cent protective, all one is going to save in every 100 employees in a factory is about one case a year. In our own studies in the Post Office, we found in the winter 1971/1972 that 14 days per 100 employees were saved over the whole influenza outbreak. The economic saving is not nearly as great as is sometimes suggested by the advocates of widespread vaccination.

SESSION V

PRODUCTION AND PRESENTATION

Chairman: Dr F. T. PERKINS (UK)

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MANUFACTURE, DISTRIBUTION AND HANDLING OF VACCINES

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Many of us have been fascinated during the recent past how man entered the universe and by the conquest of the moon. Only few of us, however, realize that our daily work – the manufacture of vaccines – is being considered to be among the first technological tasks to be performed in space or sky laboratories. This paper is an attempt to examine whether our present technology in vaccine manufacture is sufficiently advanced to warrant such an effort as to do the most sophisticated steps in production of vaccines under conditions operational in a space laboratory. The same will be attempted as check of the maturity in our present distribution and handling of vaccines.

It is well understood that a number of vaccines still represent rather crude preparations containing more unwanted foreign material than active antigen. There is ample room for improvement in the future. But the more advanced vaccines are the pacemakers for the future and they look different. Let me give some examples for progress made hitherto.

SUBSTRATES

First there are the substrates from which antigens are obtained. Data collected by Regamey(5) show that improvement of the media for tetanus toxin production led to an increase in the yield during the last 30 years (Fig. 1). This increase began very modestly about 1930, it doubled during the next 10 years. From 1949 on it grew in a logarithmic scale. At the same time sensitizing agents such as blood group substances and high molecular substances were removed from the medium. The raw toxin now obtained is not only more concentrated but also devoid of many unwanted impurities. If there is a limit of growth we have no indication that we have reached it.

Another even more striking progress on substrates is the development of human diploid cell strains (HDCS). With the development of these cell substrates it is now possible to exclude extraneous agents from viral vaccines, especially live vaccines, before the cells are used for production. The advantages are clear: these and other tissue culture systems will permit, for example, the production of a rabies vaccine in the foreseeable future that is reduced in extraneous nitrogen content about one thousand fold. Lipids will not be present at all(3).

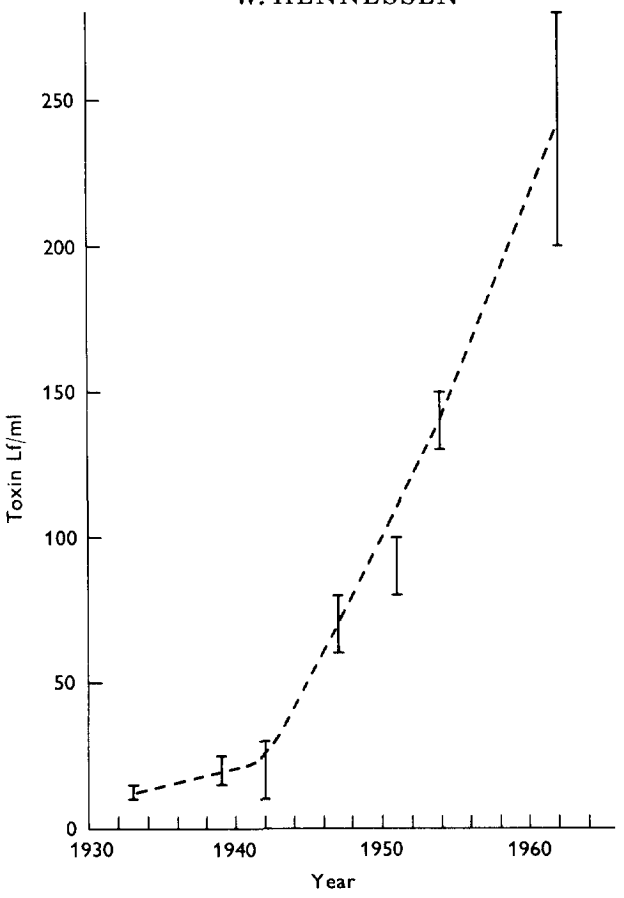

Fig. 1. Tetanus toxin yield, 1933–62 (from Regamey(5)).

PURIFICATION

Purification of antigens is another aspect to be considered in this context. Technological advances originating from space research are being used now in the production of influenza vaccines. The antigens arrived at with zonal ultracentrifugation are short from being crystallized. Mechanical purification as well as chemical precipitation leave the antigen molecules more or less as they are in nature; they remain native antigens just as sera remain native as long as they are not degraded or digested(4). With sera, for example tetanus antitoxin, it took about 30 years to depart from the native serum and to arrive at the horse globulin and from there another 30 years to reach tetanus immunoglobulin from man. For some antigens development was not much faster. From the first influenza vaccines of the early 1940s it took a further 30 years until virus particles were split into their subunits to be used as vaccine antigens. The biochemistry of the process had been known since Hoyle(2). A much longer time elapsed until similar approaches were tried for bacterial or toxoid antigens. Many experiments are

being done all over the world to extract bacteria, to reduce toxoids down to their immunogenic fractions. An example of faster progress may be seen in measles subunit vaccines now in use in some European countries.

GENETIC MANIPULATION

Reviewing developments of recent years leads one to the impression that present vaccine makers are aware of whatever possibility is applicable towards improvement. This can best be elucidated by examples of what can be called genetic manipulation. In the production of antigens two levels for such manipulation are feasible: one is the substrate, the other is the microbe or virus. Both levels have been stepped upon with various success. The substrate, the proliferating tissue culture, has been genetically manipulated in the case of a veterinary vaccine against foot and mouth disease. Baby hamster kidney cells were transformed by latent infection with polyoma virus (DNA) which resulted in a higher yield of foot and mouth disease virus (RNA). Other examples are known, more are conceivable. Both microbes and viruses have been manipulated. Typhoid bacteria have been hybridized in order to attenuate their pathogenicity; cholera vibrios have been cross-bred to change their toxin production. Polio virus may be attenuated by selection or by genuine mutation provoked by the conditions of cultivation. The same holds for yellow fever virus and others. With influenza, however, we have examples both for hybridization and for environmental influences. The influenza A42/72 England virus strain of poor reproductive capacity was cross-bred with other strains of better growth qualities(**6**). In attempts to be faster than nature Fazekas de St. Groth(**1**), in the laboratory, derived from old virus strains mutants that were identical with new strains in nature. Genetic manipulation on both levels mentioned above require the highest degree of purity in working conditions. It may be that such conditions will best be present in a space or sky laboratory. At an IABS meeting it is not without satisfaction to state that all advances described so far would not have led to any improvement without increased knowledge of, and willingness for, standardization.

DISTRIBUTION

Research in the galenicals of vaccines proceeds so much slower than in manufacture. Let me give some examples: Proteins in vaccines are mainly impurities. They are at the same time excellent stabilizers. Their stabilizing effect can be understood in many instances only with the knowledge of enzymatic activity within the vaccine. When inactivated viral vaccines were mixed with bacterial antigens, it was first observed that the efficacy of the bacterial antigens deteriorated in the presence of the virus antigen. It was then found that formaldehyde had inactivated the virus but not the enzymes originating from tissue culture. Their proteolytic activity started lysis of the bacterial proteins. Both purification of the virus tissue culture fluids and blocking the enzyme activity by chelating agents such as EDTA solved the problem.

The pH in fluids and the electric charge of particles, as well as the surface of the containers, may become important factors for the stability. Live polio vaccines can lose their activity because the virus particles can stick to the glass surface due to their opposite charges. This can be avoided by the use of a buffer which, by its pH and ionic quality, keeps the particles in suspension. Stabilizers may be excellent for one antigen, but bad for another. This is the case for antigens seemingly so similar as tetanus and diphtheria toxoids. Preservation may have an equally unpredictable behaviour depending on the nature of the antigens. Research in this multi-variant system is necessary, though sometimes laborious. On the other hand practical check-ups may clarify complicated situations quite easily. When samples of live measles vaccine were brought back from pharmacies we found that less than one-quarter retained more than 25 per cent activity. This loss was not due to the stabilizer but to the poor cooling system used during distribution.

HANDLING

Those of the medical profession handling vaccines are not the doctors doing clinical research. They are therefore not familiar with biologic material, its delicacy and vulnerability. This can be overcome by information, but there are examples that resist and defeat any information or recommendation. Some years ago children were tested for neutralizing antibodies before and after live polio vaccination. The results in a certain district were so far inferior to all others that it was felt something unknown had interfered with the takes. It turned out that the medical officer in charge had all containers taken out of the ice box every day of the one-week campaign. They were placed next to the heating radiator. The unopened containers were used for the second campaign 8 weeks later.

Another observation was made during a controlled BCG vaccination campaign in a number of schools in a metropolitan area. Conversion rates were in the range of 90 per cent and higher in all but one district. A check-up in that district revealed that both vaccination and tuberculin testing was done principally on the skin wet with propyl alcohol, that dosage of the vaccine was controlled by size of intracutaneous depot not by volume, and that the vaccine was reconstituted with the doctor's own diluent which was double the volume recommended.

These examples could be continued almost indefinitely. They are more of a nuisance than of serious consequence. The serious cases, however, stem also from ignorance.

The intramuscular or even intravenous injection of live polio virus is still sometimes carried out, so far, luckily, without any damage to the child. The injection of 10 or 50 doses of BCG germs into a child invariably requires tuberculostatic treatment for many months. The indiscriminate use of corticosteroids during treatment of persisting lymph nodes after BCG vaccination may lead to serious damage and even death. The ease of administering some vaccines with jet injectors may be paralleled by insufficient questioning regarding the state of health of the vaccinee. Contraindications may be overlooked due to the haste of mass vaccination, and they have caused fatalities. Failing aseptic precautions

have provoked fatal cases in several countries of the world. Modern abuses of potent drugs will be a future source of vaccine failure; immunosuppressive drugs including corticosteroids, cytostatic treatment, even certain antibiotics already play their role as interfering agents. The ever-increasing number of allergic reactions among our populations will lead to increasing numbers of such reactions, even to the most purified vaccines hitherto well tolerated.

Returning to the point at which we started, we should realize that manufacture, distribution and handling of vaccines are in different stages of advancement. While manufacture of certain antigens meets the highest requirements for specificity and purity, others are in earlier phase of development. Distribution and handling do not show comparable progress. Basic knowledge of the interdependances within the multi-variant biologic system contained in the ampoule is lacking. Intelligible information, foolproof devices and training seem to be indispensible to make more satisfactory use of today's and tomorrow's vaccines.

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THE SAFETY AND EFFICACY OF EMULSIFIED PEANUT OIL ADJUVANT 65 WHEN APPLIED TO INFLUENZA VIRUS VACCINE

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The increasing demand to prevent infectious diseases necessitates the development of methods whereby the immunizing capacity of killed whole virus or subunit vaccines may be improved. Immunologic improvement may consist of increase in height and duration of protection, in greater breadth of protection against antigenically different strains, or in decrease in the amount of antigen needed in each dose of vaccine. The most effective means to date for achieving such improvement has been by use of oil adjuvants(**1**) in which the aqueous vaccine is emulsified.

Freund's incomplete mineral oil adjuvant(**2**) has been the most commonly used emulsified oil adjuvant and has been licensed for use with influenza virus vaccine(**3**) in some countries. Though highly effective, Freund's adjuvant has never gained wide popularity because of too-frequent occurrence of abscesses and nodules(**3–5**, see also **1**) at the injection site sometimes requiring surgical removal, and because of the nagging apprehensions that have been expressed concerning the essentially non-metabolizable nature of mineral oil and its long-lasting retention in the tissues (for review, see **1**).

Another emulsified oil adjuvant, called adjuvant 65, has been developed(**1**, **6–21**) that is almost as effective immunologically as Freund's adjuvant but does not have the latter's disadvantages. It consists of peanut oil with isomannide monooleate emulsifier and aluminum monostearate stabilizer. All the components are readily metabolizable, all have been used in human injectables for many years, and the emulsified vaccine does not cause abscesses.

Extensive studies with adjuvant 65 have been carried out in our laboratories during the past 10 years(**1**, **6–21**) in several species of animals and in man with good results. The composition of the adjuvant, as shown in Table I, has been improved by substituting chemically pure reagents for the more crude materials

Table I. *Sequential improvement in the composition of adjuvant* 65

Adjuvant formulation	Component			
	Aqueous vaccine	Oil	Emulsifier	Stabilizer
Adjuvant 65 (1961)	Influenza vaccine	Peanut oil USP	Arlacel A® (Mannide monooleate)	Aluminum monostearate USP
Adjuvant 65–1 (1971)	Influenza vaccine	Peanut oil USP	Isomannide monooleate CP	Aluminum monostearate USP
Adjuvant 65–4 (1971)	Influenza vaccine	Peanut oil USP	Isomannide monooleate CP	Aluminum monostearate CP

that were previously available. Though essentially the same, the terms adjuvant 65–1 and 65–4 have been applied to designate the use of the chemically pure components in the adjuvant 65 formulation.

INFLUENZA

Virus influenza is a disease of worldwide importance and is a major cause of death in the human community, especially among the debilitated and the elderly. Though optimally constituted aqueous vaccines may be 70–90 per cent effective, they become outdated rapidly because of the continuing changes that take place in the antigenic make-up of the prevalent virus strains. The major changes or shifts in the virus antigens that occur at approximately 10- or 11-year intervals result in worldwide pandemics of the disease and render the current vaccine useless. The less drastic alterations or antigenic drifts in the virus that occur in the interpandemic periods result in widespread epidemics of the disease at 2- to 3-year intervals and greatly reduce the effectiveness of the contemporary vaccine. Unfortunately, the time lapse between detection of the altered virus and the widespread occurrence of the disease is less than the required time for practical updating of the vaccine to include the new strain and to render it fully protective.

Clearly, then, influenza vaccine has been a most important candidate for improvement and has been an especially appropriate example for studies of adjuvant 65. This presentation, therefore, will summarize the highlights of the studies compared with adjuvant 65-type influenza virus vaccine to date.

INCREASED HEIGHT OF ANTIBODY RESPONSES

CIRCULATING ANTIBODY

Fig. 1 is presented to illustrate the degree of heightened antibody response that is obtained when ordinary bivalent aqueous influenza A and B vaccine is formulated in adjuvant 65. We are privileged to present the data from a clinical study

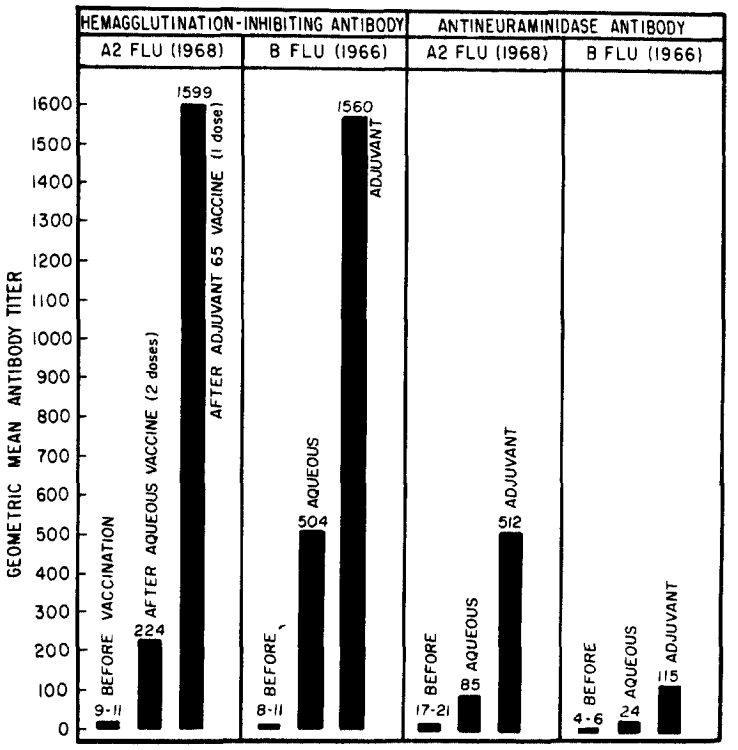

Fig. 1. Increase in serum hemagglutination-inhibiting and antineuraminidase antibody responses to influenza virus vaccine by use of adjuvant 65 (Marshall–Dudgeon study in the UK(**21**)).

carried out in 1971 by Drs Marshall and Dudgeon in the United Kingdom(**21**). Both hemagglutination-inhibiting (HI) and antineuraminidase antibodies were measured in serum samples taken before vaccination and two months after the first dose of vaccine. Two doses of aqueous type vaccine and only one dose of adjuvant 65–1-type vaccine were given. The virus antigen content of each dose of the two vaccines was the same. The findings are expressed as geometric mean antibody titers and are plotted on an arithmetic scale to emphasize the quantitative differences in response. It is seen that the mean pre-vaccination serum titers were near zero for both virus strains and for both kinds of antibody. The antibody responses to one dose of the adjuvant vaccine were 3- to 7-times greater than those obtained with two doses of the corresponding aqueous vaccine.

CIRCULATING AND NASAL ANTIBODY

Some investigators have taken the position that protection against virus influenza, to a large extent, depends upon the presence of antibody in the nasal secretions(**22**). Therefore, some of them(**23**, **24**) have advocated administration of influenza vaccine directly into the respiratory tract as a means for stimulating

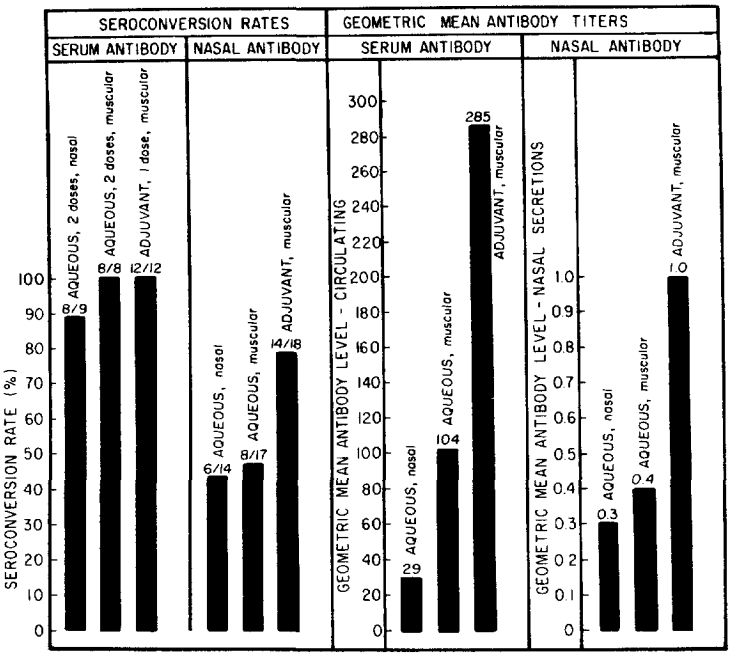

Fig. 2. Increase in serum and nasal antibody responses to A2 influenza virus vaccine by use of adjuvant 65 (19).

the production of secretory antibody. Though attractive in theory, the procedure does not hold up in practice, since more nasal antibody can be stimulated by parenteral immunization with vaccine in adjuvant 65 than by giving aqueous-type vaccine into the nose (19). Fig. 2 presents the findings in a study in which antibody in the serum and in the nasal secretions was measured following two doses of aqueous-type influenza A2 (19) vaccine given intramuscularly or intranasally compared with a single dose of adjuvant 65-type vaccine given intramuscularly. All subjects were without corresponding antibody before vaccination.

The circulating and nasal antibody responses to two doses of aqueous-type vaccine were highest when the vaccine was given intramuscularly. The marked increase in amount of circulating antibody following adjuvant 65-type vaccine was as demonstrated previously. Most importantly, the percentages of persons who had detectable antibody in their nasal secretions and the amount of antibody in the secretions were far greater in those who received the adjuvant 65-type vaccine than in those given the aqueous-type vaccine by the parenteral or nasal route.

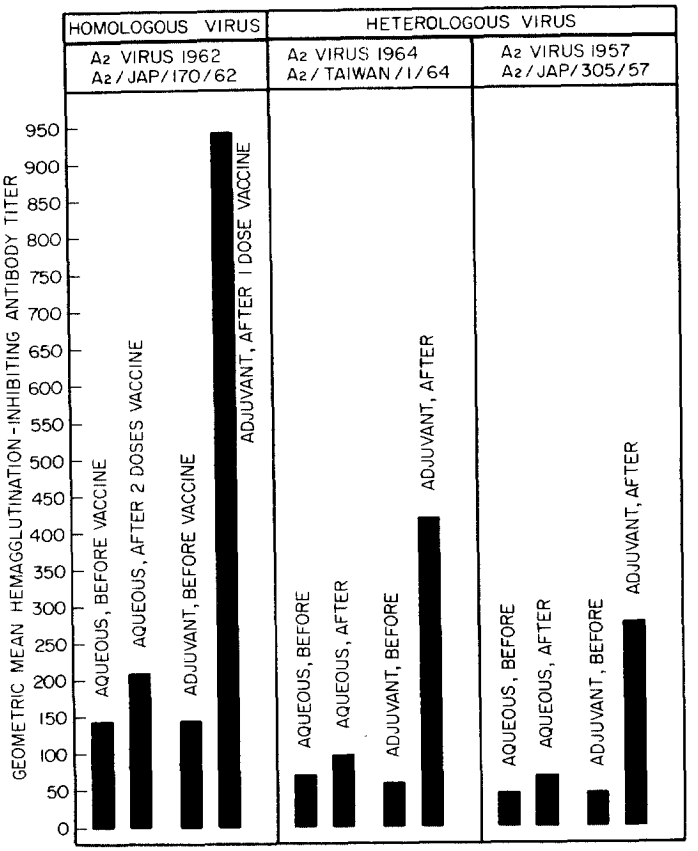

Fig. 3. Broadening of antibody response to cover minor antigenic changes in the interpandemic period (by the use of vaccine in adjuvant 65).

BROADENED ANTIBODY RESPONSE – DE-EMPHASIZING THE IMPORTANCE OF ANTIGENIC DIFFERENCES

MINOR INTERPANDEMIC ANTIGENIC VARIATIONS

A study (**10**) was carried out in which persons were given two doses of influenza A vaccine prepared using a 1962 A2 strain or a single dose of the same vaccine in adjuvant 65 with the results shown in Fig. 3. Hemagglutination-inhibiting antibody levels against the homologous 1962 A2 virus, the heterologous A2 virus that was prevalent in 1957, and the heterologous A2 virus that was prevalent in 1964 were measured. As shown previously, there was several-fold increase in height of antibody against the homologous virus resulting from use of the adjuvant. The antibody responses against the heterologous viruses were very poor following aqueous-type vaccine but very great following use of adjuvant 65-type vaccine. Such broadening of antibody response by use of the adjuvant reduces or even negates the importance of the minor antigenic shifts that occur at 2–3-year

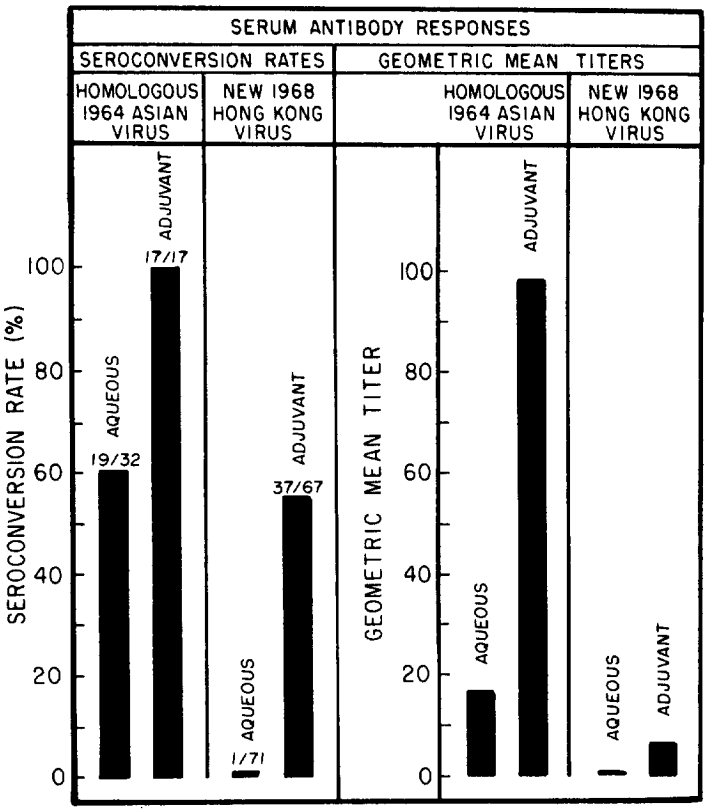

Fig. 4. Broadening of antibody response to cover major pandemic virus antigenic changes by use of vaccine in adjuvant 65.

intervals in influenza A virus during the interpandemic periods and that reduce the effectiveness of the vaccine.

MAJOR PANDEMIC ANTIGENIC VARIATION

In 1968, the new A2 Hong Kong influenza virus appeared. The antigenic change was very marked and resulted in a worldwide pandemic of influenza with loss of effectiveness of the aqueous vaccine. In 1967, one year before the Hong Kong variant appeared, human subjects (**16**, **17**) were given two doses of 1964 influenza A2 virus vaccine in aqueous or adjuvant 65 formulation. The hemagglutination-inhibiting antibody responses in the subjects were measured using the homologous 1964 virus and the new 1968 Hong Kong virus. As shown in Fig. 4, there was essentially no antibody response (seroconversion) against the new Hong Kong virus in the subjects who received the old aqueous-type vaccine. By contrast, more than half the subjects who were given the old formula vaccine in adjuvant 65 developed antibody against the new virus. The enhancement of antibody titer against homologous virus was as expected and the responses to the heterologous new virus were substantial. The antibody titers in individual

Table II. *Distribution of individual antibody titers against Hong Kong influenza virus in persons (Fig. 4) who were given 1964 aqueous or adjuvant influenza virus vaccine*

Antibody titer	No. of persons with titer	
	Aqueous vaccine	Adjuvant
<10	70	30
10	0	5
20	1	17
40	0	9
80	0	4
160	0	2
No. responding/Total	1/71	37/67
% responding	1	55

patients are given in Table II. Antibody at these levels might have provided substantial protection against the morbidity and mortality of Hong Kong virus before new vaccine incorporating the strain was available, and might also have contributed to limiting the spread of the virus in the population.

THE CONTEMPORARY A2 ENGLAND SITUATION

In 1972, a substantial antigenic alteration or drift in influenza A2 virus was noted(**25**) and the virus causing the epidemic was significantly different from that of the 1968 A2 virus used in the vaccine. A clinical study was recently carried out by Drs J. W. G. Smith, M. Peters and M. Westwood in the United Kingdom in which 83 human subjects were given one dose of 1968 A2 virus in aqueous formulation and 104 persons were given a single dose of the same vaccine in adjuvant 65–4 formulation. We are privileged to present the early results at this time. The findings presented in Fig. 5 are in agreement with previous experience. Thus, there was very marked increase in hemagglutination-inhibiting antibody response to the homologous virus by use of adjuvant 65–4. More important, there was a very excellent response to the new A2 England virus in the recipients of adjuvant vaccine whereas the response to the aqueous vaccine was very poor. Again, there was excellent broadening of the immunologic response to an antigenically different virus.

LONG-TERM PERSISTENCE OF HI ANTIBODY FOLLOWING INFLUENZA VACCINE IN ADJUVANT 65

Fig. 6 presents the representative findings in our studies to date(**14, 19**) to measure persistence of antibody induced by adjuvant 65-type vaccine compared with the corresponding aqueous-type vaccine. Groups of human subjects were given three doses of 1957 A2 influenza vaccine in aqueous or adjuvant 65 formu-

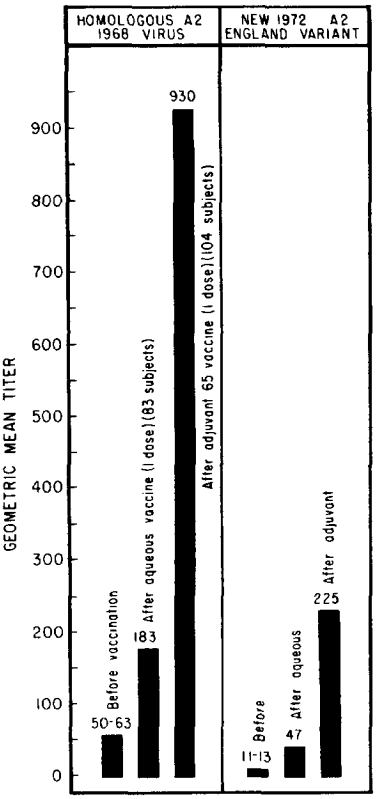

Fig. 5. Increase and broadening of hemagglutination-inhibiting antibody responses to A2 England 1972 virus following immunization with influenza virus vaccine in adjuvant 65–4 (Smith study in the UK).

lation at the time periods shown. Homologous antibodies were measured at various intervals up to 82 months after the initial vaccine dose. The figure shows the expected high-level potentiation of antibody response by use of the adjuvant. More importantly, this differential of elevated antibody level was maintained for at least four years and four months after the last dose of vaccine was given.

KINDS OF ANTIBODY RESPONSES

Interest has been focused in recent years on the type of immunoglobulin responses to immunizing agents. The findings in Table III, based on the results of immunofluorescence assays with sera from four persons in each group of the Marshall–Dudgeon(**21**) study who were initially devoid of detectable hemagglutination and neuraminidase-inhibiting antibodies, showed that the antibody globulin responses to influenza antigens were to all three major types, viz. IgG, IgM and IgA. Though the immunofluorescence assays for the globulins were not quantitative, the degree of fluorescence was greatest for IgG, suggesting that the

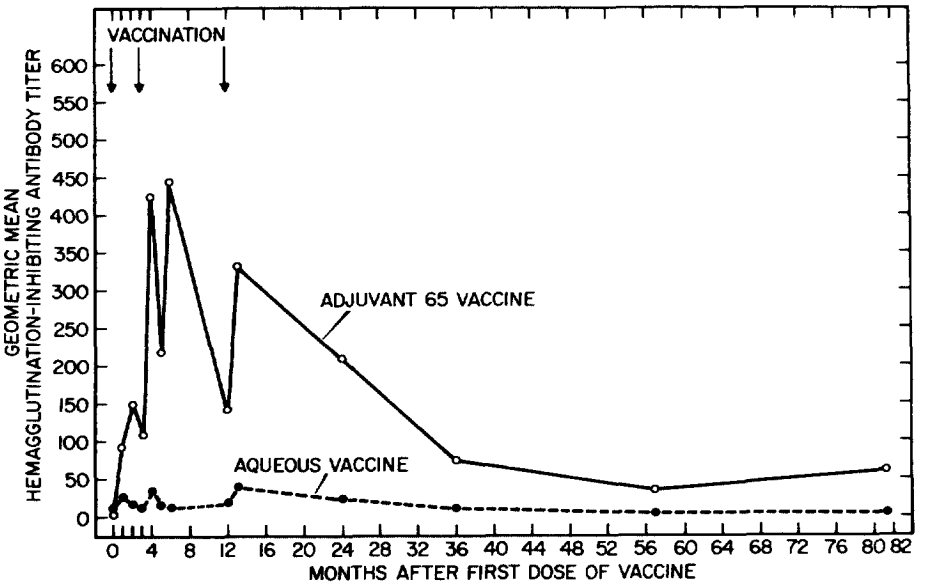

Fig. 6. Long-term persistence of hemagglutination-inhibiting antibody against 1957 influenza A2 virus vaccine.

Table III. *Serum immunoglobulin responses of persons who received either aqueous or adjuvant* 65–1*-type bivalent influenza virus vaccine (Marshall–Dudgeon study in the UK)*

		Serum immunoglobulin responses					
		IgA		IgM		IgG	
Vaccine	No.	Pre	Post	Pre	Post	Pre	Post
Aqueous	4	−	+	−	+	−	4+
Adj. 65–1	4	−	+	−	+	−	4+

responses were mainly to this particular immunoglobulin that is generally regarded as the long-term persisting antibody.

ASSAY FOR ANTIBODY RESPONSES

Important to the practical use of any vaccine is the need for a reliable test procedure whereby potency of a vaccine can be assayed. A highly reliable procedure (**21**) for assay for potency of adjuvant 65 vaccine has been developed. As shown in Table IV, guinea-pigs were given one dose of monovalent A2 or B influenza virus vaccines in aqueous or adjuvant 65–4 formulation. Whole untreated and ether/tween-treated virus vaccines were used. The HI antibody responses to homologous aqueous vaccines were modest. There was an 8- to 17-fold enhance-

Table IV. *Guinea-pig HI antibody titers to whole untreated or ether/tween-treated monovalent influenza virus vaccines used in aqueous or adjuvant* 65–4 *formulation*

Vaccine	Formulation	Geometric mean HI antibody at 2 months		
		A2/Aichi/2/68	B/Mass./3/66	B/Mass./1/71
Whole untreated virus	Aqueous	26	16	15
	Adj. 65–4	256	274	119
Ether/tween-treated virus	Aqueous	20	45	45
	Adj. 65–4	320	446	338

All pre-immunization antibody titers were < 10.

ment in the antibody responses by use of adjuvant. Interestingly, the ether/tween-treated vaccines usually elicited as high or greater antibody levels than did the corresponding whole virus preparations.

QUANTITY OF INFLUENZA ANTIGEN PER DOSE

It has been found in our studies (**8**) that the quantity of influenza antigen required per dose of vaccine in adjuvant 65 formulation is far less than needed for the corresponding aqueous-type vaccine. It is at least four times less. This finding may be of great importance in stretching the supply of vaccine in time of critical need before the appearance of a pandemic.

PROTECTION

Stuart *et al.* (**26**) carried out comparative controlled studies of adjuvant 65- and aqueous-type influenza vaccines in a retirement community in California from 1964–5. Persons who received adjuvant 65-type influenza vaccine more than a year before an outbreak of influenza A2 were protected as well as or better than persons who received aqueous-type vaccine just several months before the epidemic.

SAFETY OF ADJUVANT 65 VACCINE: LABORATORY TESTS

COMPONENTS

Present adjuvant 65-type influenza vaccine employs zonal purified killed influenza virus that is of high purity. All components of the adjuvant are appropriately tested (**1**, **20**) to insure quality, to guarantee freedom from possible contaminating carcinogenic substances (polycyclic aromatic hydrocarbons and aflatoxins), and to determine the presence or absence of irritants as measured in guinea-pig and mouse assays. The emulsified vaccine is tested to assure proper emulsification and potency and is assayed for sterility and irritancy for animals.

All components of the adjuvant are readily metabolizable and all have been used in man for many years. In studies of adjuvant 65 in rats(**11**), all the fatty components were absorbed from the site of intramuscular injection, metabolized, and metabolites were either excreted or taken into the normal body pools. Only a minor portion of the adjuvant remained at the injection site after 70 days. Mannitol did not accumulate in the tissues.

SHORT-TERM TOXICITY

Assessment for irritancy of the emulsified vaccine has been carried out(**7**, **20**) in rabbits and monkeys that were inoculated intramuscularly and observed for gross lesions and for micropathology at the injection site at appropriate times thereafter. The initial pathologic response to the adjuvant emulsion was acute inflammation, with progression to a subacute state in which there was decrease in heterophils and increase in lymphocytes, plasma cells, and macrophages. The macrophage was the predominant infiltrating cell after one month. Cell necrosis was only slight and the oily adjuvant was gradually removed with progressive resolution of the tissue damage. When oil cyst formation occurred, it was resolved within two to three months and no significant scar tissue formed. The vaccine failed to induce autoallergic hypersensitivity as evidenced by observations of the tissue responses to a second dose of the vaccine at the same or a distant site.

CHRONIC TOXICITY AND TERATOGENICITY TESTS

Long-term observations were made(**12**, **20**) of guinea-pigs and monkeys that were given the vaccine in multiple doses and sacrificed at various time periods up to 39 months after the first injection. Tests for teratogenic activity were performed in rabbits injected on the eighth day of gestation and terminated at one month.

Complete autopsies and representative microscopic examinations of sections of the major organs and injection sites were made from at least twenty organs and tissues from each animal. Aside from local reactions at the injection site, there was no evidence of immunopathologic lesions, disseminated granulomatous lesions, tumor formation, or other pathologic process. Nor was there evidence to suggest that adjuvant 65 would be likely to cause future abscesses or nodule formation. The tests for teratogenicity revealed no apparent effects on fetal development.

Male mice of the Webster strain have shown(**20**, **27**) a unique hypersusceptibility to tumor occurrence at the injection site when given any of a number of injectables or even when pinched as in grasping to catch hold of the animal for palpation purpose. Adjuvant 65 and its components injected subcutaneously also caused the appearance of tumor. Golberg has shown(**28**) in extensive investigations, that non-specific sarcomatous changes appear in rodents injected with a variety of substances including water, salt, glucose, and a host of common nutrients. In studies of adjuvant 65 and its components, Dr Golberg and his associates(**29**) found no manifestations suggestive of a chemical carcinogen in adjuvant 65 and attributed the lesions found to the well recognized physicochemical

Table V. *Long-term clinical observation for local lesions in the arm in persons who received aqueous or adjuvant 65-type influenza virus vaccine*

Vaccine injected	No. persons observed	No. reactions	
		Local nodules	Induration
Adjuvant 65	510	4 (0.8 %)	0
Aqueous	369	1 (0.3 %)	0
Uninoculated controls	190	1 (0.5 %)	0

Observation period: 2 years and 8 months to 10 years.

influences capable of eliciting non-specific sarcomatous change in the subcutaneous tissues of rodents.

LONG-TERM FOLLOW-UP IN MAN

A major factor in judging the acceptability of any injectable in man is in the observation for safety in man in long-term clinical observations for local and systemic effects. We recently observed (**21**) the site of injection in the arms of 1069 of 2008 persons given adjuvant 65- or aqueous-type influenza virus vaccines as well as the same general site in persons who served as unvaccinated controls. The time interval from initial vaccination to observation ranged from 2 years 8 months to 10 years. Table V shows that the only detectable effect was the infrequent finding of individual small nodules no larger than a pea that were present in roughly the same percentage of persons in the adjuvant, aqueous, and unvaccinated control groups. Thus, it was found that there were no significant local pathologic developments associated with use of adjuvant 65-type influenza virus vaccine during the 10-year study period.

The health records of the 2008 persons in the total group were examined. One hundred and fifty-six of the subjects died during the 10-year study period. The causes of death are shown in Table VI. The overall death rates were approximately the same in all three groups and there was no significant skewing in the distribution of deaths in the groups according to organ system or kind of malady.

These findings are in full accord with those of Beebe *et al.*(**30**) who followed 18000 soldiers given Freund's mineral oil adjuvant influenza vaccine 18 years previously. In the Freund adjuvant studies, however, increase in sensitivities were found that were apparently due to the presence of penicillin that was present in vaccine manufactured at that time but which has since been eliminated.

Adjuvant 65-type influenza vaccines have now been given to more than 22000 persons without apparent untoward effect. Most recently, 587 persons were given adjuvant 65–4 formulation influenza vaccine in the USA, 104 in the United Kingdom, and more than 5000 in Costa Rica – all without adverse effect to date.

Table VI. *Causes of death among persons who received aqueous or adjuvant 65-type influenza vaccine or who served as uninoculated controls (vaccines given 2 years 8 months to 10 years previously)*

Vaccinees	Group*		
	Adjuvant 65	Aqueous	Uninoculated controls
No. vaccinated	937	700	371
No. died	79 (8.4 %)	50 (7.1 %)	27 (7.3 %)
Cause of death			
Respiratory	32 (3.4 %)	25 (3.5 %)	16 (4.3 %)
Cardiovascular	28 (3.0 %)	13 (1.8 %)	5 (1.3 %)
Cancer	2 (0.2 %)	2 (0.3 %)	2 (0.5 %)
Other	17 (1.8 %)	10 (1.4 %)	4 (1.1 %)

* None of the above-compared differences was significant statistically.

SUMMARY AND CONCLUSIONS

The outstanding deficiencies of present influenza vaccine are its limited effectiveness, the relatively short duration of immunity, and the continuing need for change in the strain formula of the vaccine to make it contemporary with the viruses circulating in the population. Strains of greatest antigenic difference generally spread most rapidly in the population. As a consequence, the vaccine is least efficacious when it is needed most and when there is the least amount of time to prepare vaccine prior to the major occurrence of an epidemic or pandemic.

Incorporation of the vaccine into adjuvant 65 provides the means to reduce the problem of influenza vaccine by greatly heightening the levels circulating and nasal antibodies, by broadening the antibody response against heterologous viruses, even against new pandemic serotypes, by decreasing the required amount of antigen needed per dose thereby stretching the vaccine supply in time of critical need, and by lengthening the period of time that elevated antibody level is maintained.

The short- and long-term tests of adjuvant 65-type influenza vaccine in animals and in large numbers of human subjects have established its safety for routine use in human beings. All components of the adjuvant have been used in man for many years and oily preparations containing the same or similar components are included in injectables that are being used routinely in man at the present time(**31**).

It may be concluded, therefore, that the adjuvant 65 formulation provides a

safe and acceptable means for improving the protective efficacy of influenza virus vaccine and for reducing the toll of this important disease in its epidemic and pandemic excursions. The potential usefulness of the adjuvant for other killed antigen vaccines also appears to be promising but has not been extensively investigated to date.

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MINERAL CARRIERS AS ADJUVANTS

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The practical aspects of mass immunization demand that, as far as possible, a maximum immune response should be obtained with the minimal dose of the antigen, with the lowest possible number of inoculations and the smallest reactions. Immunologists have been working for many years to meet these requirements, and the possibilities may be summed up in three main groups:

1. to select an antigen of suitable quality;
2. the proper variation of the manner, number and spacing of inoculations; and
3. enhancement of the immune response by employing adjuvants.

The adjuvants, as immunological potentiators, have the following advantages:

(*a*) a smaller quantity of antigen can be used in single and combined vaccines;

(*b*) owing to the reduced antigen quantity, or its slower release, there are fewer local and systemic reactions;

(*c*) a better immune response is obtained, and this is especially important in diseases where a high antibody level is required for protection;

(*d*) many antigens can be included in a single combined vaccine;

(*e*) the number of inoculations required for efficient immunity can be reduced; and

(*f*) it is possible to reduce the total number of inoculations which are required for the administration of the many current types of vaccines.

The ideal adjuvant must not only possess the aforesaid advantages, but must at the same time produce a minimum of untoward reactions. At present we do not yet have such an ideal adjuvant. The purpose of this report is to present the results obtained with the most widely used adjuvants, the mineral carriers, with special regard to the most important ones, i.e. the aluminium compounds.

ALUMINIUM COMPOUNDS

Forty-seven years ago Glenny *et al.*(1) showed that in experimental animals the alum-precipitated diphtheria toxoid is a much stronger antigen than the fluid toxoid. With the exception of one or two countries, the application of aluminium compounds, such as alum, aluminium hydroxide and aluminium phosphate gels, for the adjuvation of vaccines has become general all over the world since then.

PRODUCTION OF THE ALUMINIUM ADJUVANTS

Two main methods are used for the production of toxoids or vaccines containing an aluminium adjuvant; in the first method, preformed aluminium hydroxide or phosphate, or mixed hydroxide plus phosphate, or γ-aluminium oxide gel is added to the antigen. In the second method the aluminium hydroxide or phosphate gels are formed as precipitates *in statu nascendi in situ*. The composition of such precipitates may vary greatly(**2**), and since the preformed gels can be produced under standardized conditions, the latter must be preferred to the former. The adsorbed vaccines obtained in this way are very stable. Both the preformed aluminium hydroxide and phosphate gels have proved equally suitable in practice(**3**). Their use is determined by technologies developed and well proved in various countries, and by good practical results; according to experience both types of gel have their adherents.

SOME THEORETICAL QUESTIONS OF THE EFFECT OF ALUMINIUM COMPOUNDS

Before discussing the practical application of the aluminium compounds, we must make mention of a few important theoretical questions. The fundamental investigations of Prigge(**4**, **5**) and Holt(**6**, **7**) have shown that in the case of the diphtheria and tetanus toxoid the adjuvant effect of aluminium hydroxide and phosphate depends on the quantitative ratio of antigen and adjuvant. For a given quantity of the antigen, maximum activation can be obtained with a specific concentration of both adjuvants. The addition of more adjuvant no longer increases activity; it drops below the maximum and the immune response may be even poorer than that produced by the non-adjuvated, fluid antigen. Prigge's and Holt's statements could also be confirmed with poliomyelitis(**8**) and influenza(**9**) vaccines. Thus the practical conclusion is that antigen and adjuvant must be present in the vaccine in such an optimally balanced ratio that a maximum adjuvant effect can be obtained with the fewest possible local and general reactions. Namely, it has been found that the chief causative factor of the so-called sterile abscesses – which occurred at a fairly high percentage according to data in the older literature – was a too high aluminium content of the precipitated and adsorbed vaccines ('alum cysts'). According to the WHO *Requirements for diphtheria and tetanus toxoids*(**10**), the concentration of aluminium per single human dose of the vaccine must not exceed 1.25 mg. Ever since the use of high aluminium concentration has been avoided in the production of vaccines, and the adsorbed vaccines have been administered strictly intramuscularly, sterile abscesses have practically vanished from immunization practice.

THE PRACTICAL APPLICATION OF ALUMINIUM ADJUVANTS

The various fields of application of the aluminium adjuvants are shown in Table I.

Toxoids The aluminium adjuvants have been used most often – and for the longest time – in diphtheria, tetanus, as well as DT and DTP vaccines. The results are good, and extensive field trials have shown that the adsorbed toxoids

Table I. *Mineral carriers as adjuvants*

Type of adjuvant	Application
Aluminium compounds	Diphtheria toxoid (D)
Alum	Tetanus toxoid (T)
Aluminium hydroxide	Pertussis vaccine (P)
Aluminium phosphate	Typhoid vaccine (Ty)
γ-aluminium oxide	Poliomyelitis vaccine (polio)
	DT
	DTP
	DT–polio
	DTP–polio
	DTP–polio–measles
	TTy
	DTTy
	DTPTy
	TABTD
	TABTD–polio
	Influenza vaccine
	Allergens
Calcium phosphate	D
	T
	Polio
	DT
	DTP
	DT–polio
	DTP–polio
	Allergens
Chrome alum	Ty

not only induce a more intense and longer lasting immune response than the plain toxoids, but also that their reactogenicity is milder, and untoward side effects are seen only sporadically after their administration(**11–19**). As a result of these excellent properties, the application of adsorbed toxoid preparations is now usually regarded as a method of choice. In Hungary we have been using since 1958 aluminium phosphate adsorbed DTP vaccines, because the results of comparative tests presented in Table II have shown that in children aluminium phosphate adsorbed DTP vaccines elicit a higher and longer lasting immune response than aluminium hydroxide adsorbed ones(**20**).

Bacterial vaccines In the case of bacterial vaccines, there is by no means such agreement of opinion. Although numerous laboratory experiments – such as active mouse-protection tests, determination of agglutinating antibodies in animals and humans – have shown that the adsorbed pertussis vaccine produces a more intense and longer lasting immune response than the plain vaccines, there are only few data to prove that the adsorbed pertussis vaccines have a higher potency in field application(**21**). Yet the necessity of using adsorbed pertussis

Table II. *The comparison of the immune response to aluminium hydroxide- and aluminium phosphate-adsorbed DTP vaccines*

	2 weeks after 2nd inoculation		1 year after 2nd inoculation	
Adsorbent...	Aluminium hydroxide	Aluminium phosphate	Aluminium hydroxide	Aluminium phosphate
	A. 6- to 11-month-old infants			
No. tested	16	18	20	19
Diphtheria (IU/ml)				
<0.1 %	6.2	5.5	70.0	36.8
Geom. mean	0.26	0.40	0.03	0.11
Tetanus (IU/ml)				
<0.1 %	6.2	0.0	45.0	15.8
Geom. mean	0.9	7.7	0.11	0.58
	B. 6-year-old children			
No. tested	21	20		
Diphtheria (IU/ml)				
<0.1 %	5.0	5.0		
Geom. mean	9.9	20.7		
Tetanus (IU/ml)				
<0.1 %	19.0	5.0		
Geom. mean	0.16	1.12		

vaccines is emphasized by the observation in Great Britain that there was a decrease in the potency of pertussis vaccines in children when the use of adjuvants was discontinued(**22**). In addition to the assumed increase of potency, it seems highly probable that the adsorbed pertussis vaccines cause fewer local and general reactions than the plain vaccines. This was confirmed by tests made with DTP vaccines(**16**, **17**, **18**). The good field results obtained with the adsorbed vaccines have led in most countries – also in Hungary – to a considerable reduction of the amount of the pertussis component of the DTP vaccine; while in the past the single human dose of the pertussis vaccine was 25000–30000 millions, by now this quantity has decreased to 10000–15000 millions. This reduction doubtless contributed to a further decrease of the reactogenicity of the DTP vaccines.

Opinions are contradictory about the adjuvant effect of aluminium compounds on typhoid vaccines. The alum-precipitated typhoid vaccine containing Boivin-type cell-free antigen was used in Hungary with good results for more than 20 years, though no strictly controlled field trials were made. It has been shown in mouse experiments(**23**) that with the Boivin antigen the maximum adjuvant effect of aluminium hydroxide can be obtained – similar to the toxoids – with a certain concentration of the gel; if more adjuvant is added, this does not increase activity further, and it drops abruptly after reaching the maximum. It has been concluded from these results that in the case of typhoid vaccines containing

Boivin-type antigen, the optimum gel concentration must be used. Yet these experimental results were not confirmed with whole-cell vaccines(24). Several very careful, strictly controlled field trials were carried out in the Soviet Union with various adsorbed cell-free typhoid vaccines, and these proved to be no more potent than the plain ones(25). In the light of these results, the application of aluminium adjuvants in the case of typhoid vaccines is not too promising. The use of adjuvants may play some part in reducing reactogenicity in the case of typhoid vaccines. Certain data indicate(26, 27) that the reactogenicity of the typhoid vaccines is determined by the presence of free dissolved antigens in the vaccines; this was observed in the case of adsorbed paratyphoid B vaccines – namely the adsorbed vaccines contain no free, dissolved antigens – where it appeared that the adsorbed vaccines were less reactogenic than the plain ones(28). When adsorbed and plain DT-Ty vaccines were administered it was found that the former produced fewer general and local reactions(29). But the quantity of the adsorbent must be chosen most carefully and cautiously, because the mouse-protective capacity of the whole-cell typhoid vaccines may be reduced considerably even by a very small amount of aluminium hydroxide.

In various animal models it has been found that the immune response to aluminium hydroxide-adsorbed whole-cell cholera vaccines was stronger and persisted substantially longer than was the case with plain vaccines(30–5). Yet it still has to be proved by controlled field trials whether the prophylactic effect of adsorbed cholera vaccines is better than that of the plain vaccines.

Inactivated virus vaccines Data are available on the effect exerted by aluminium adjuvants on inactivated virus vaccines. Animal experiments have proved that adsorbed inactivated poliomyelitis vaccines elicit a better immune response than the plain vaccines(9, 36–9); this effect was also seen in humans(40). The inactivated measles vaccine component of the adsorbed, combined DTP + poliomyelitis + measles quintuple vaccine seems also to be more potent than the plain vaccine(41). The immune response to inactivated influenza vaccines is also enhanced by aluminium hydroxide or phosphate (9, 42). There is some evidence to indicate that in experimental animals aluminium hydroxide or phosphate enhances the degree and promptness of the serological response to tissue culture rabies vaccine(43).

Allergens French workers have prepared so-called 'allergen retards' by adsorbing pollen and dust extracts to aluminium hydroxide(44, 45, 46); the advantage of this method is that the preparation can be administered less often and that the therapeutic results are good.

Aluminium adjuvants and provocation poliomyelitis During the serious poliomyelitis epidemics of the fifties, the investigations carried out by the BMRC(47) have detected that there exists a causal correlation between prophylactic vaccinations and the incidence of paralytic poliomyelitis. This correlation was manifest most markedly in the case of adsorbed combined vaccines, and was less marked with plain combined vaccines. Owing to this suspected risk of provoking

poliomyelitis, the use of adsorbents in British vaccines has been prohibited since 1955. But since the introduction and wide application of potent poliomyelitis vaccines, this problem has ceased to exist.

The mechanism of action of the aluminium adjuvants The mode of action of the aluminium adjuvants is a very interesting problem. The antigens are adsorbed to the very large network of the gels, whereby their active surface – their immunogenic effect – increases. Adsorption slows down the resorption of the antigen, the latter enters the organism slowly, continuously, and the antigen stimulus lasts longer. In addition, they stimulate more cells at the site of inoculation than the plain antigens. It seems highly probable that the cells stimulated by the adjuvated vaccine do not themselves produce antibodies; their function may rather be to forward the antigen to the antibody-producing centres.

CALCIUM PHOSPHATE

French workers have recently developed a calcium phosphate gel(**3**, **46**, **48**, **49**) and use it for producing adsorbed diphtheria, tetanus, poliomyelitis, DT, DTP, DT–poliomyelitis and DTP–poliomyelitis vaccines. According to extensive experience with humans, the calcium phosphate gel is equivalent to the aluminium gels, with regard to both adjuvant effect and tolerance.

CHROME ALUM

Japanese workers have developed a typhoid chrome vaccine(**50**, **51**), which they tested in experimental animals and in humans. This vaccine is very stable, less toxic and reactogenic than the generally used heat-killed vaccines, and proved to be more potent at the same time. But its value can only be established definitely by controlled field trials.

It appears from this brief survey that the aluminium compounds are used for the production and adjuvantion of very many types of inactivated vaccines. The aluminium hydroxide- or phosphate-adsorbed preparations are among the most widely used vaccines. This is explained by favourable experience in field application, with regard to both potency and reactogenicity. But, needless to say, research must be continued to produce better, more potent and safer adjuvants.

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GENERAL DISCUSSION

CHAIRMAN The section on production and presentation is now open for discussion.

RELYVELD (France) I think that this is a very good occasion on which to remind people present that it is now fifty years ago (1923) since Ramon discovered in France the preparation of stable and active diphtheria and tetanus toxoids. I want to remind you of this because I was astonished to see this morning on a slide that tetanus toxoid was introduced in 1927. One year later (1924) vaccination by tetanus and diphtheria toxoids was introduced in France, and not in 1938 as we were shown.

We have to give to Ramon credit for the work which he did; work which I think was very important.

Two years after his discovery of the toxoids, Ramon discovered the principle of adjuvants and introduced vaccination by adsorbed toxoids.

What happened after Ramon? In the first place, of course, vaccines by tetanus and diphtheria toxoids were quite active and gave the protection of which we know. Later on, what became important was the purification of the toxins or the toxoids. At the moment the most important thing is to have vaccines that give no post-vaccinal reactions – I think that is the point that was discussed here later on – and to have vaccines that are as pure as possible. That is what we try to have at the moment, and that is what some factories produce. The post-vaccinal reactions are mostly due to what we call accessory antigens, as has been proved with diphtheria. Seventy-five per cent of the adult population is allergic to antigens that are not diphtheria toxoid. By using a pure toxoid (made from crystalline toxin) we may vaccinate most of the population – and it is the same for tetanus – without having any post-vaccinal reactions.

NETTER (France) I should like to ask Dr Hilleman two questions.

First, are the emulsified oil adjuvant vaccines licensed in the United States?

Secondly, how do you titrate the potency of the final influenza emulsified vaccine?

HILLEMAN (USA) Adjuvant 65 influenza vaccine is not yet licensed in the USA. It is hoped, however, that it will be licensed in at least one country this year.

Potency of the adjuvant vaccine is controlled in two ways. First off, a specified amount of viral antigen is put in the vaccine. Second, groups of guinea-pigs are given the aqueous vaccine and the corresponding adjuvant vaccine. The antibody responses to the adjuvant vaccine are 8–16 times as high as to the aqueous.

SCHILD (UK) I was extremely interested to see Dr Hilleman's data that when he used an adjuvant with, I think it was an A64 strain, he developed antibody to Hong Kong 68. The tests I believe were haemagglutination-inhibition tests, and these two strains have haemagglutinin antigens of quite different subtypes, H_2 and H_3 respectively. Does he think that the heterotypic reactions may have been due to an enhanced anti-neuraminidase antibody response? Did he look for that at all?

HILLEMAN (USA) The basis for the 1967–8 cross with adjuvant vaccine was not determined. The cross might well have been due to N antigen since the two were the same; the H antigens were different.

SCHILD (UK) Have you any evidence about the protection?

HILLEMAN (USA) Stuart *et al.* have shown protection against influenza given by adjuvant vaccine during the second year after vaccination. But this was not during the 1967–8 period.

SCHILD (UK) It is just on the basis of antibody response?

HILLEMAN (USA) All we measured in the 1967 vaccine *vs* 1968 Hong Kong response was antibody. It was good. The old aqueous vaccine induced hardly any antibody to Hong Kong whereas the adjuvant vaccine induced antibody in 55 per cent of the recipients. That's pretty good.

SCHILD (UK) It has usually been the experience, I think, that with an aqueous vaccine the anti-neuraminidase antibody levels are very poor, and perhaps the adjuvant enhanced the level of anti-neuraminidase.

UNGAR (Switzerland) Cholera vaccines may give an antibody response that may last only for about 6–8 months. It is therefore essential to try to develop a vaccine in which the antibody response persists. This is possible, and some work is going on in this respect which shows that chemical bonding of some substances to antigens will improve the antigenicity and durability of antibodies. We know, for example, that gelatine is a very poor antigen, but if tyrosine is built into the molecule we obtain a much better response. Perhaps our future ambition should be to improve our antigens in this way in order to get a better response.

As a first dose giving a primary response, we should aim to give the highest concentration of antigen. The second dose, however, which gives a secondary response, may be quite a small dose.

We have today genetic codes that may be manipulated and I think it is high time for us to have a meeting at which these items could be discussed for a very important practical purpose.

Lastly, but not least, we should try to achieve a single-dose immunization, which may be vital for our developing countries.

CHAIRMAN Thank you very much, Dr Ungar.

GEAR (South Africa) Could anyone tell us the comparative value of adjuvant 65 and aluminium phosphate?

HILLEMAN (USA) You ask for a comparison of alum versus adjuvant 65. Alum is a good adjuvant but the heightened antibody responses after only one or two doses of vaccine are of very short duration. With adjuvant 65 the antibody responses are generally at least three or four times as high and the antibody persists for years. Alum commonly causes sterile abscesses; adjuvant 65 is readily metabolizable and does not.

REGAMEY (Switzerland) In the case of immunization against influenza, is it necessary to give three times the antigen with oil adjuvant? Or is it possible to give only one injection with adjuvant, as for instance in the case of diphtheria toxoid or tetanus toxoid, for the first simulation?

HILLEMAN (USA) The dose of antigen in the adjuvant vaccine can be as little as one-quarter the aqueous dose without impairing the response to the adjuvant vaccine. A single dose of adjuvant vaccine suffices to stimulate high antibody levels. You don't need more.

CHAIRMAN I would like to thank all those people who presented papers, and all the discussants in that session.

Now we come to the section dealing with either the combination of vaccines before administration, or the simultaneous administration of different vaccines.

I should like to call on Dr Hans Cohen to give his paper on 'Combined killed vaccines' and we shall discuss his paper after the comments from Dr Joó.

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COMBINED INACTIVATED VACCINES

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In many countries infectious diseases like pertussis, diphtheria and poliomyelitis which were a major problem 30 years ago, have been reduced to negligible proportions by vaccination. The population in the countries concerned is often no longer aware of the existence of these diseases. As a consequence many parents may no longer ask vaccination for their infants.

In the Netherlands we have set up a vaccination schedule based on the presumption that the acceptance rate of a vaccination programme by the parents would depend on three factors:

(1) Preparedness of the responsible health authorities to stick to a vaccination schedule during a relative large number of years once it has been fixed. This had the advantage of the schedule becoming a natural part of the routine medical attention, which infants receive in the health clinic during their first year of life.

(2) Simplicity of the programme which is determined by limitation of the number of separate vaccines and the number of injections used. This policy makes the programme easy to understand both for the doctor and the parents.

(3) A minimum of unfavourable side effects and virtually complete protection against the diseases corresponding to the components included in the vaccine.

At the time of introduction of polio vaccination, immunisation against diphtheria, pertussis and tetanus in the Netherlands was done with a combined inactivated vaccine with $AlPO_4$ as adsorbent. It was decided to try to incorporate inactivated polio vaccine in this triple vaccine. This decision was influenced by the, at that time, favourable results of a vaccination campaign with inactivated polio vaccine in children under the age of 15.

From 1962 on, a quadruple vaccine has been issued in the country, the polio component of which was concentrated 2- to 2.5-fold from 1965 on. This vaccine was administered in four doses at the age of 3, 4, 5 and 12 months and has been generally accepted in the population (Fig. 1). Reinforcing doses of DT–polio vaccine are given at the age of 3 or 4 and 8 or 9 years. The programme has been very effective. Since its introduction not a single case of poliomyelitis, diphtheria or tetanus has been reported in infants receiving at least three injections of the DPT–polio vaccine. (Morbidity figures of pertussis are not available.)

In our Institute Hofman(**3**, **4**) has assessed the results of the immunisation against the polio component by comparing the statistical data of the period before introduction of the vaccine with those of the period after introduction. In addition he found a clear inverse relation between the percentage of vaccinated

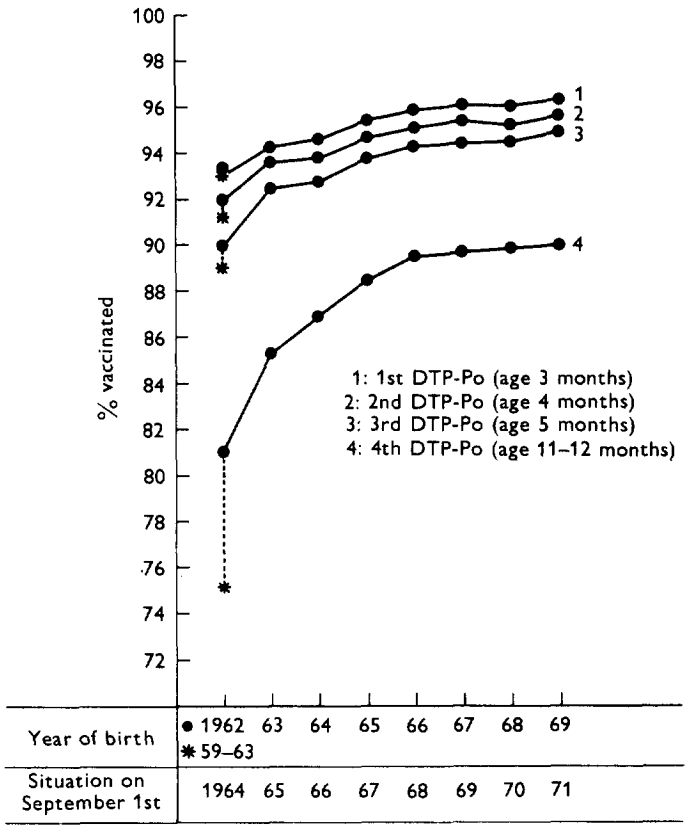

Fig. 1. Diphtheria, tetanus, pertussis, poliomyelitis (DTP–Po) vaccination status in the Netherlands of infants and children *vs* year of birth.

children per community and the number of cases (Fig. 2). His conclusion was that immunisation with inactivated polio vaccine confers a herd immunity. In this paper a different approach has been made. Using the mortality and morbidity data of the WHO our epidemiological service prepared the following four curves.

DIPHTHERIA (Fig. 3)

It is clear that as a consequence of the vaccination programme with DPT vaccine from 1953 onwards, diphtheria morbidity in the Netherlands fell off rather sharply as compared with the analogous figures in the surrounding countries. In 1964 the zero value was attained. Only a few cases have been observed since that time. It is tempting to attribute the complete disappearance of the disease in the last decade to a herd immunity, which is strongly enforced by the general acceptance in the population of the vaccination schedule with DPT–polio vaccine.

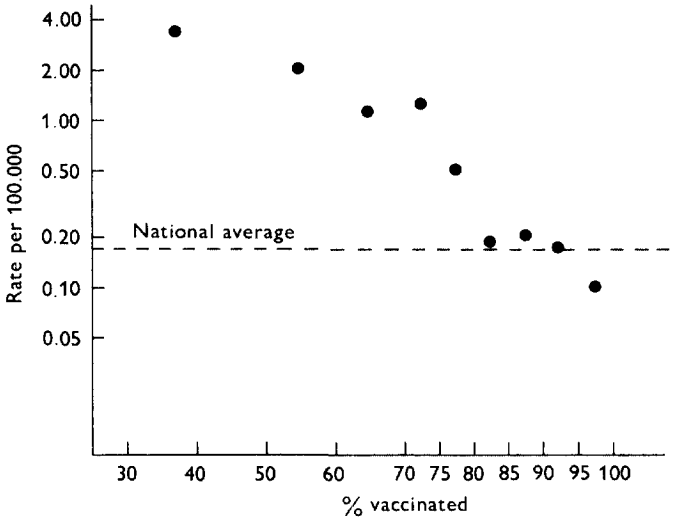

Fig. 2. Paralytic poliomyelitis 1958–69. Relation between average yearly morbidity and % vaccinated in different municipalities.

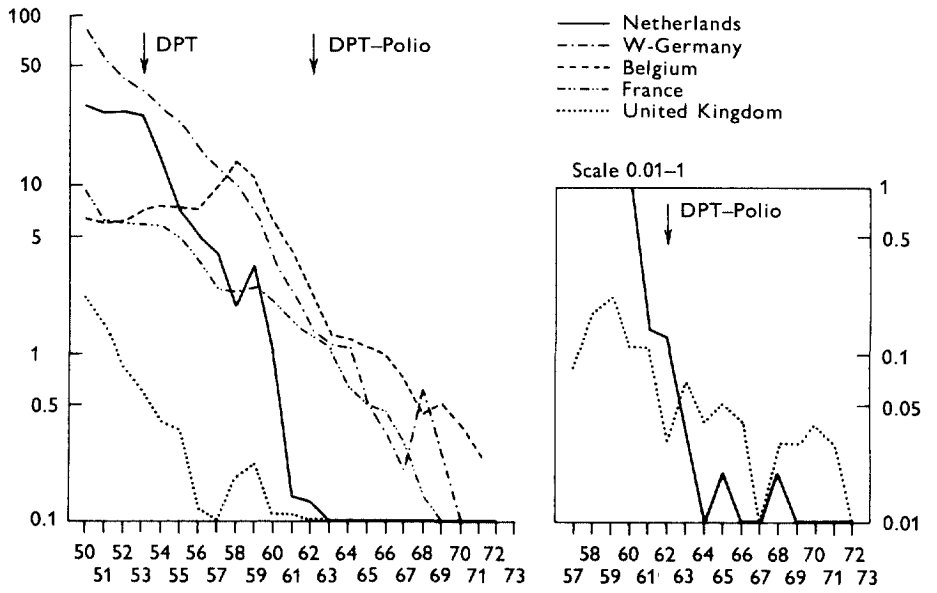

Fig. 3. Diphtheria morbidity per 100000 in the Netherlands and surrounding countries.

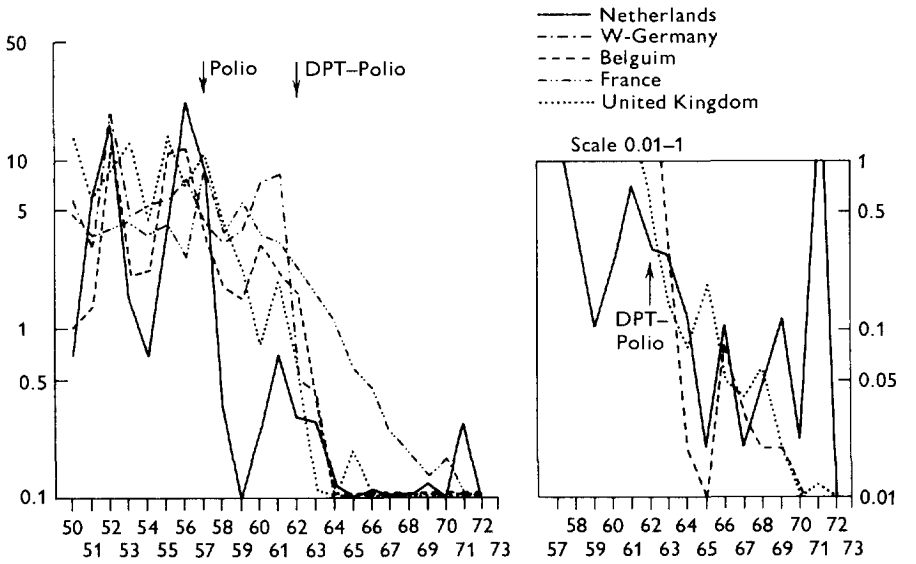

Fig. 4. Poliomyelitis morbidity per 100000 in the Netherlands and surrounding countries.

POLIOMYELITIS (Fig. 4)

After the mass vaccination campaign in 1957 with inactivated polio vaccine the morbidity curve initially declined more steeply than in the surrounding countries. The decline after the introduction of DPT–polio vaccine in 1962 is very similar to the curve of diphtheria morbidity with the exception that we have had a number of small outbreaks in villages with clusters of conscientious objectors. Still the decline in the morbidity curve runs very much parallel with the decline in the neighbouring countries, where live polio vaccine has been used. This may indicate the existence of a herd immunity created by inactivated vaccine, which is not much different from the situation elsewhere in Europe.

PERTUSSIS (Fig. 5)

Because reliable morbidity figures are not available for pertussis, we used mortality as an indicator of the effect of pertussis vaccination. Essentially the same effect as for the morbidity rates of diphtheria is shown to exist for the mortality rates of pertussis. After the introduction of triple DPT vaccine in 1953 about 70 per cent of each age-cohort was vaccinated. The result was a rapid decrease in mortality, although it was shown that protection by the vaccine used at that time was not more than 50 per cent. From 1959 onwards, the pertussis component in the vaccine in the Netherlands met the USA requirements for potency. This improvement resulted in a further decrease in the mortality rate. After introduction of the DPT–polio vaccine in 1963 the acceptance rate of the vaccine gradually

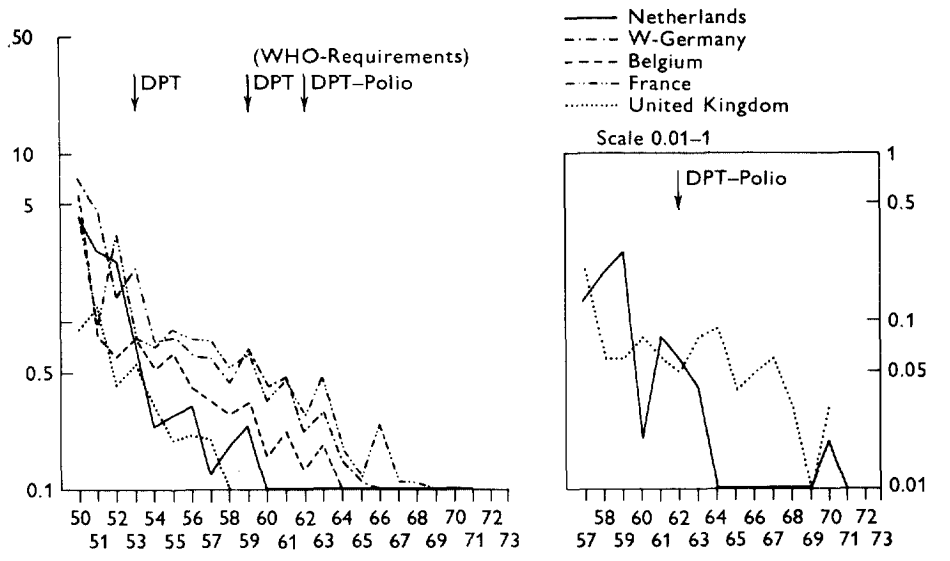

Fig. 5. Pertussis mortality per 100000 in the Netherlands and surrounding countries.

increased to more than 90 per cent. In addition, a fourth booster injection at the age of 12 months was included in the schedule. This resulted in a further drop in the mortality, which has been zero from 1964 onwards, apart from two isolated doubtful cases in older children. The steepness of the curve might again indicate the existence of a herd immunity against pertussis.

TETANUS (Fig. 6)

Vaccination against tetanus does not confer a herd immunity. In accordance with this fact the reduction in the mortality in all countries has been gradual, while the curves run more or less parallel in the various countries.

The conclusion is warranted that the introduction of an inactivated DPT–polio vaccine in the Netherlands has contributed to a large extent to the acceptance by the population of a vaccination programme based on the use of this vaccine. As a consequence of this programme, the corresponding diseases (of course with the exception of tetanus) have virtually disappeared. Nevertheless there remain three problems, which have to be discussed.

LARGE-SCALE PRODUCTION OF POLIO VIRUS AT A LOW COST

This is primarily a technical problem. The production of concentrated inactivated polio vaccine, according to the traditional 'Salk method', is expensive, as it requires a relatively large, highly skilled technical staff and a relatively large number of monkeys. In principle these problems have now been solved. The

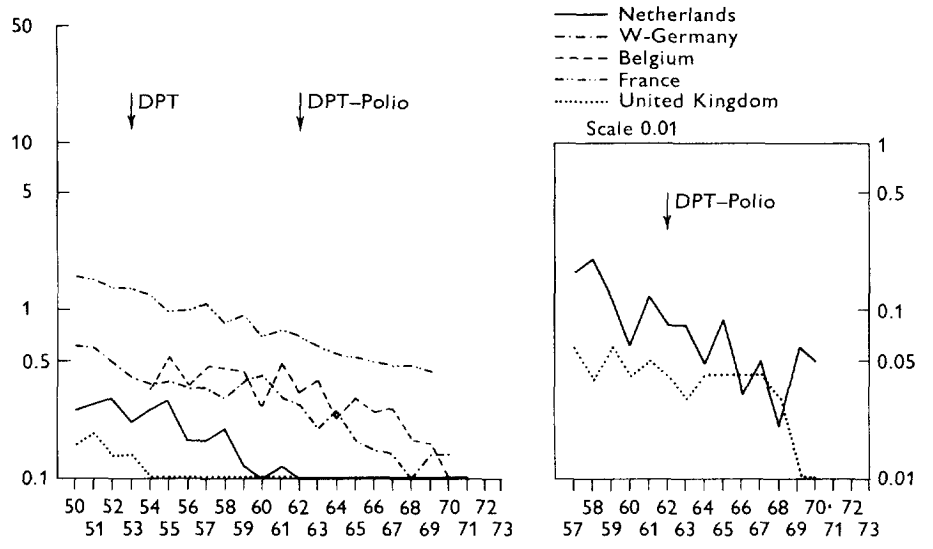

Fig. 6. Tetanus mortality per 100000 in the Netherlands and surrounding countries.

yield of monkey kidney cells can be increased at least seven-fold by perfusion of the kidney *in situ* with trypsin(**6**). This has reduced the number of monkeys required annually for production from several thousands to several hundreds. In addition monkey kidney cells can now be grown in 40-litre glass vessels in homogeneous cultures under well controlled cultural conditions instead of in 500 ml quantities in monolayer cultures in Povitsky bottles.

The use of homogeneous cultures has been made possible by the efforts in our Institute by Van Wezel(**5**). It was shown by him that monkey kidney cells could be grown on DEAE–sephadex beads, suspended in the culture medium. The virus yields in such cultures are as high as 10^9 virus particles/ml and we expect the yield of antigen to be so high that in the future concentration of the vaccine will no longer be necessary.

SIDE EFFECTS DUE TO THE PERTUSSIS COMPONENT

The second problem is connected with side effects due to the pertussis component, which consists of killed whole bacterial cells. These side effects are reported regularly in many countries. Minor local and general reactions which disappear within 24 hours do occur in 30 per cent of the children. Such reactions are accepted by the population. They can be kept within reasonable limits by heating the bacterial cells at 56 °C and by using vaccines which meet the WHO requirements for the mouse toxicity test. Also very serious complications such as convulsions and encephalopathy which have been described by many authors do occur very seldom when such vaccines are used.

On the other hand Hannik observed in one of our provinces the relatively frequent occurrence of two major reactions, shock and 'persistent screaming' (2). Both reactions occur within 6 hours after immunisation, particularly in young infants up to 6 months of age. Both sexes are affected. Although recovery is spontaneous and rapid, the symptoms may cause a considerable anxiety and may, together with the disappearance of clinical pertussis in children, finally affect the willingness for voluntary participation of the parents in the vaccination programme. We therefore give much attention to this problem. Recently Hannik observed (Table I) that the frequency of these complications is mysteriously decreasing, although no alterations in the preparation of the pertussis component of the vaccine have been made. Further studies on the purification of the pertussis component and more knowledge about the pharmacological effects of pertussis in infants are needed.

Table I. *Cases of shock and persistent screaming reported over a three-year period in the area under survey*

Area in the Netherlands	Number of infants vaccinated yearly	1970	1971	1972
The Hague	10000	13	5	0
South Holland (inclusive The Hague)	40000	22	7	2

INTRODUCTION OF VACCINATION AGAINST MEASLES

It is generally known that attempts to produce an inactivated measles vaccine have failed. This failure has been caused partially by serious side reactions of an allergic nature in some cases of an infection with wild measles virus occurring after vaccination with three injections of inactivated vaccine. It should be stressed that these reactions have only been reported after the use of one particular formalin-inactivated non-purified vaccine, prepared in monkey kidney cell cultures. Hitherto similar reactions have not been described after the use of measles 'split vaccine', prepared by treatment with Tween 80-ether, neither in Germany, where such a vaccine has been used on a relatively large scale, nor in Holland, where it was only used experimentally. I would like to emphasise that a successful incorporation of a measles component in DPT–polio vaccine, however far away it may seem to be at present, would be of an enormous advantage for public health. The importance of the continuation of trials using DPT–polio–measles vaccine can be inferred from some of the as yet unpublished results of a trial done by Brouwer in our Institute. In Tables II and III the results of the measles component in three groups of 100 children are given. One control group of 100 children received live measles vaccine at the age of one year together with the usual fourth DPT–polio injection of the routine schedule. The two other

Table II. *DPT–polio–measles trial (results from first 300 children)*

Groups of 100 children		Age (months) 3 Serum sample 1 HAI antibody	3, 4, 5 Inoculation 1–3	6 Serum sample 2 HAI antibody GMT	12 Serum sample 3 HAI antibody GMT	12 Inoculation 4	13 Serum sample 4 HAI antibody GMT	13 Sero-conversion (%)
A		18	3 × DPTP no measles	4	0	1 × DPTP 1 + live M	84	98
B	1	20	3 × DPTP–M	20	6	1 × DPTP	147	100
	2					1 × DPTP + live M	445	100
C	1	17	3 × DPTP–M	12	0	1 × DPTP–M	39	96
	2					1 × DPTP + live M	445	100

Table III. *Natural measles infection in infants of 6–12 months participating in the trial*

Group	Rise in HAI titre natural measles infection	Clinical symptoms
A (no measles vaccine)	13	11 (85 %)
B (3 × killed measles vaccine)	16	4 (25 %)
C (3 × killed measles vaccine)	17	11 (65 %)

groups received three injections of DPT–polio–measles vaccine prepared respectively by the Behringwerke in Marburg and in our own Institute. The latter two groups were divided into two; fifty children received a booster injection of live measles vaccine simultaneously with a DPT–polio booster and the other fifty were injected with DPT–polio–measles vaccine as a booster. It is obvious that the potency of the measles component in the lot of Marburg vaccine used is higher than in the vaccine lot prepared in our Institute. This is confirmed by the rate of protection of children in 6- to 12-month-old children in a measles epidemic which occurred during the trial. The most fascinating aspect is the extremely high titre in the haemagglutination-inhibition test after a booster either with wild virus or live measles vaccine in the groups pre-immunised with DPT–polio–measles vaccine.

A similar titre rise has also been reported in Germany(1). Its significance is not yet clear. It stimulates us, however, to proceed with this project and to investigate both the significance of the various antigens of measles virus for the

protection against infection with wild virus and the epidemiological consequences of vaccination as mentioned above with inactivated combined vaccines containing the measles component. We do not underestimate the difficulties which will be encountered in this work. We do hope however that it might enable us to propose in the next decade a simple schedule of preferably three injections to immunise against five diseases – poliomyelitis, diphtheria, tetanus, pertussis and measles. Such a schedule might make it possible for health authorities to carry on, on a voluntary basis, a successful immunisation programme against these diseases, in spite of the fact that they have practically ceased to exist in the memories of the parents concerned.

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DISCUSSION ON COMBINED INACTIVATED VACCINES

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I should like to make only a few comments on Dr Cohen's report.

DTP vaccine is the most important combined vaccine for early childhood. The potency of the diphtheria and tetanus toxoids is clearly proved by the excellent epidemiological results in those countries where a suitable vaccination schedule is consequently applied on a nationwide scale. In several countries the eradication of diphtheria has been achieved and the number of tetanus cases has dropped almost to zero in the well-immunized age groups. By the application of adjuvants and more potent whole-cell pertussis vaccines, the amount of the pertussis component could be reduced to a great extent and, as a consequence, the reactivity of DTP vaccines could be considerably decreased. In spite of these results an important task of the near future is the development of purified, potent non-toxic, non-pyrogenic, cell-free pertussis antigen which could be applied for large-scale production. In this way the acceptance and efficacy of DTP vaccine could be further increased.

In countries with a high incidence of typhoid fever, the combined typhoid–tetanus vaccine, especially in freeze-dried form, is the preparation of choice, since it is well known that the antigenicity of the tetanus toxoid is markedly enhanced by *S. typhi* bacteria. Here again the development of a potent and less toxic cell-free *S. typhi* antigen for parenteral use must be resolved; but we must be aware that perhaps a killed or attenuated oral typhoid vaccine will be the way of the future.

In countries where typhoid fever is prevalent in infancy a combined DTP–typhoid vaccine would be very useful. Some preliminary investigations have shown reliability of this preparation. Combined DT-typhoid vaccines have been applied with good results in several countries. In some countries combined cholera–tetanus, or cholera–typhoid–tetanus vaccines, especially in adsorbed form, may be also considered – if possible also containing cholera toxoid.

Nowadays, especially in developing countries, the jet method of vaccination is applied on a fairly large scale. Therefore, combined killed vaccines must also be made available for this purpose.

In concluding these few remarks I wanted to emphasize that even with combined killed vaccines a lot of important problems are yet to be resolved and their development must be a continuous task.

GENERAL DISCUSSION

CHAIRMAN Thank you very much, Dr Joó. We shall take one or two questions now, and then perhaps we shall have time to continue the discussion of this same subject after Dr Hilleman's paper.

LUNDBECK (Sweden) I have one question and one remark.

I should like to know whether any experiments have been done using diploid cells for the production of killed polio vaccines.

My remark is that allergic reactions of the type Dr Cohen mentioned have been described also with split vaccine by Norrby and his group. Recent observations by them indicate that the antigen is incomplete if it is inactivated with formaldehyde. I think that we have to find another method for the inactivation of the virus before we have a fully potent killed measles vaccine.

COHEN (the Netherlands) We have no experience with diploid cells for polio vaccine production. I believe that, for a strategic point of view it would be very difficult to do so because you would need enormous amounts of cells which would have to be controlled according to WHO requirements. It would probably be quite a job to do that; much more complicated than the monkey cells which have now been accepted and used for years without any unfavourable side effects.

I wholly concur with Dr Lundbeck's remarks moreover about the antigenicity of formalin-inactivated measles vaccines. Using such a vaccine, you would probably get allergic reactions. I think I mentioned that it was necessary to do a more thorough investigation of the antigenic composition of a measles vaccine before making a definitive decision to apply such a vaccine on a large scale. I would, however, like to draw your attention to the fact that the extremely high haemagglutination-inhibition titres which occur after three injections of DPT–polio–measles vaccine, followed by a booster with live vaccine, are at least of considerable serological interest. Perhaps Professor Hennessen could also comment on this.

HENNESSEN (Germany) I should like to mention a field trial which we have just done. It was a retrospective trial on 240000 children, roughly half of whom received the inactivated vaccine and 100000 of whom were re-vaccinated or given a booster with live measles vaccine. The other half, that is altogether another 100000, received live measles vaccine alone. In the four-year retrospective study we followed every breakthrough after exposure to natural measles infection, and of course reaction to the live measles vaccination. In these children we did not find any of these serious effects which were observed in the United States which were mentioned by Dr Cohen.

This work is being published next month. Although I agree with Dr Cohen that the antigen can be improved, it shows that the reactivity to the split antigen is different from that to the formaldehyde-inactivated measles antigen.

CHAIRMAN May I now call on Dr Hilleman to present his paper on this subject?

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IMMUNE RESPONSES AND DURATION OF IMMUNITY FOLLOWING COMBINED LIVE VIRUS VACCINES

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The systematic evolution of technology and systems for health care must necessarily place emphasis on prevention of illness as opposed to treatment or attempted cure. This is a social and economic necessity and is of special importance for certain of the viral diseases for which there are good means for prevention, no means for cure, and the possibility for long-term sequelae caused by the natural disease.

Presently, there are eight or more licensed virus vaccines (measles, mumps, rubella, smallpox, poliomyelitis, yellow fever, rabies, influenza) that are being used in various parts of the world. The newer among them are measles, mumps and rubella vaccines. Smallpox vaccine, up to recently, has been on the routine immunization list in most countries. Measles, mumps and rubella vaccines should eventually find application in most parts of the world and the basic problem is how to deliver them in the least costly way with minimum requirement for the time of health care personnel and with the least number of contacts between the doctor and patient.

A simple answer to the problem is provided in the application of multivalent combined live virus vaccines given in a single one-shot application. This topic is the subject of my presentation.

Irrespective of the implied advantages, combined vaccines must have three minimal attributes that are essentially non-violable. *First*, the individual components of the combined vaccines must be as efficacious in preventing disease as if the individual vaccines were given separately at different times. Thus, there

must be no substantial interference between the viruses in the vaccines and the antibody responses to all components must be adequate. *Second*, the duration of immunity must be as long for each virus represented following combined vaccination as when the single vaccines are given individually. *Third*, clinical reactions to the combined vaccines should not be significantly greater than occur when the most reactive of the individual components represented in the multivalent vaccine is given alone.

These minimum requirements have been met to date for the various combined vaccines that I shall discuss herein.

To date, six satisfactory combined live virus vaccines(**1–6**) have been developed in our laboratories, each tailored to a particular geographic or public health need. These are: measles–mumps–rubella vaccine (M-M-R), measles–rubella vaccine (M-R-VAX), measles–mumps vaccine (M-M-VAX), mumps–rubella vaccine (BIAVAX), measles-smallpox vaccine (RUBEOPOX), measles–rubella–smallpox vaccine (M-R-POX-VAX). Certain of these combinations have also been developed in the USSR(**7**) and are being used there.

The extensive clinical and laboratory investigations of the various combined vaccines demonstrated(**1–6**) conclusively that they can be administered in a single one-shot dose without impairing immune responses and without increasing clinical reactions beyond those seen when the individual vaccines are given singly. The available data indicate that immunity to measles, mumps and rubella vaccines are persistent, probably lifelong, and the findings in the follow-up investigations indicate that this will likely be true for the combined vaccines also (**8, 9**). The data in support of these conclusions are given below.

COMBINED LIVE VIRUS VACCINES

MEASLES, MUMPS AND RUBELLA COMBINATIONS

Antibody responses Table I summarizes the antibody responses obtained in clinical studies in children of four different combined live virus vaccines, viz. measles–mumps–rubella, measles–rubella, mumps–rubella, measles–mumps vaccines. In all the vaccines, the individual components were premixed and then filled and dried. For each of the combined vaccines, four different lots were tested. The serologic conversion rate for each component of each combined vaccine was satisfactory and ranged from 94 to 99 per cent. This was in the range of expectation for the individual vaccines given separately(**10, 18, 20**). The mean antibody titers after vaccination were within the expected level for the components given individually considering the vagaries and variations(**3**) in the laboratory procedures for assaying for antibody.

It was important to ascertain definitively whether there was any interference between the different viruses in the combined vaccines that would cause suppression in antibody response. To measure this, sera were selected at random from children who had received combined vaccine or the corresponding monovalent vaccines. The antibody titers were determined in tests in which the sera from children in each of the groups were tested side by side, thereby eliminating

Table I. *Antibody responses in initially seronegative children given combined measles (Moraten), mumps (Jeryl Lynn), and rubella (HPV-77 duck) virus vaccines*

	Antibody responses*								
	Measles			Mumps			Rubella		
	Seroconversion			Seroconversion			Seroconversion		
Combination	No./total	%	GM†	No./ total	%	GM	No./total	%	GM
Measles–mumps–rubella (M-M-R)	684/715	96	39	680/715	95	7	670/715	94	28
Measles–mumps (M-M-VAX)	279/281	99	80	272/281	97	10	—	—	—
Measles–rubella (M-R-VAX)	371/375	99	53	—	—	—	358/375	95	29
Mumps–rubella (BIAVAX)	—	—	—	397/415	96	7	390/415	94	36

* Measles and rubella are hemagglutination-inhibiting and mumps is neutralizing antibody.
† GM = Geometric mean.

Table II. *Antibody titers in direct-comparison studies in children who received combined or corresponding monovalent vaccines*

Vaccine (combined or single)	Geometric mean antibody titer*			No. children
	Measles	Mumps	Rubella	
Measles–mumps–rubella	95	15	52	24
Measles alone	80	—	—	25
Mumps alone	—	9	—	25
Rubella alone	—	—	70	25
Measles–mumps	64	6	—	53
Measles alone	54	—	—	27
Mumps alone	—	7	—	42
Measles–rubella	103	—	50	25
Measles alone	85	—	—	24
Rubella alone	—	—	68	25

* Mean titers between corresponding combined or monovalent vaccines were not statistically different.

variables that might arise from the test procedure itself. The findings in Table II show that the heights of the mean antibody responses to each component of the combined vaccines were not significantly different from those to the corresponding monovalent vaccines. This clearly indicates that interference is no problem in use of the combined products.

The matter of whether a particular combined vaccine will or will not perform satisfactorily depends in part at least upon the particular strains of virus that are used and upon the amount of virus given. In similar tests of Enders' original measles virus vaccine combined with Jeryl Lynn mumps vaccine, for example,

only 77 per cent of the children responded(1) to the mumps component indicating suppression of the mumps virus antibody response by the particular measles vaccine employed. The present combinations use the more attenuated Moraten line(10) of measles vaccine virus and no problem is encountered.

Clinical reactions Clinical reactions to the individual vaccine components were not increased by use of the combinations. Table III shows the fever patterns among children who received the combined measles–mumps–rubella vaccine or who were retained as unvaccinated controls and is presented as an example. Among children in the age group used, there is no discernible clinical reaction to rubella or mumps vaccine and hence the fevers were due to the measles vaccine component or to other non-vaccine cause. As shown in the table, there was a significant elevation in temperature in only a small percentage of children 5–12 days after vaccination, a net increase of 11 per cent at the 101–104.9 °F range and this was the same as expected for the monovalent measles vaccine(10). Similar acceptable clinical findings were found for the other combined vaccines(1–6).

Table III. *Occurrence of fever among 228 triple-seronegative children who received combined measles–mumps–rubella vaccine (Moraten measles, Jeryl Lynn mumps, HPV-77 duck rubella)*

Maximum oral temperature (°F)	Vaccinated children (228): days after vaccination		Unvaccinated controls (106): days observed	
	5–12	13–18	5–12	13–18
<99	105 (47%)	140 (64%)	57 (59%)	64 (66%)
99–100.9	86 (39%)	69 (32%)	36 (37%)	25 (26%)
101–102.9	26 (12%)	7 (3%)	3 (3%)	8 (8%)
103–104.9	6 (3%)	2 (1%)	1 (1%)	—
Not taken	5	10	9	9

Lack of alteration in clinical reactions is not always found for all combinations of vaccines, since we did note a substantially higher fever rate(1) in children who were given a vaccine that employed Enders' original measles vaccine and mumps compared with those who were given Enders' measles vaccine alone.

It is worthy of special emphasis that every combined vaccine must be clinically evaluated to prove its acceptability from the standpoints both of clinical reactions and antibody induction. Not all vaccine combinations work satisfactorily.

ADMINISTRATION OF COMBINED VACCINES WITH LIVE ORAL POLIO VACCINE

Recently, the Center for Disease Control, US Public Health Service reported (11) that when combined 'measles–mumps–rubella vaccine is given simultaneously with trivalent oral poliovaccine, antibody responses can be expected to be comparable to those which follow administration of the vaccines at different

times'. From this, it would be reasonable to expect that comparable responses might also be expected when only two of the measles, mumps or rubella vaccines are used in the combined vaccine and given simultaneously with polio vaccine.

MEASLES, RUBELLA, SMALLPOX VACCINE COMBINATIONS

Similar clinical studies have been carried out in large-scale trials with other combined live virus vaccines in which the smallpox vaccine component was added. This included Moraten measles–smallpox(**12**, **13**), measles–rubella–smallpox, and measles–mumps–rubella–smallpox.

Antibody responses The antibody responses shown in Table IV to all components of the measles–smallpox and measles–rubella–smallpox vaccines were quite satisfactory and the dermal reactions to vaccinia virus were not suppressed. Three or four lots of each vaccine were tested. When the four-component vaccine containing mumps as well as measles, rubella and smallpox vaccine was tested, there was a marked suppression of response to both the measles and mumps vaccine components. The data with the four-component vaccine relate to tests with only a single lot of vaccine and must be considered preliminary, but they do emphasize the importance of predetermination of adequate clinical and serologic proof of adequacy of all combinations.

Table IV. *Serologic and dermal reactions among initially seronegative children given combined vaccines containing smallpox vaccine*

	Seroconversions								Smallpox 'takes'	
	Measles		Mumps		Rubella		Vaccinia			
Vaccine*	No./total	%	No./ total	%	No./total	%	No./total	%	No./total	%
Measles–smallpox (RUBEOPOX)	469/480	98	—	—	—	—	474/480	99	476/480	99
Measles–rubella–smallpox (M-R-POX-VAX)	116/121	96	—	—	121/121	100	121/121	100	121/121	100
Measles–mumps–rubella–smallpox	73/89	82	53/89	60	88/89	99	86/89	97	89/89	100

* Moraten measles, Jeryl Lynn mumps, HPV-77 duck rubella.

Clinical reactions The febrile responses recorded in 162 children who received either of two lots of combined Moraten measles–smallpox vaccine are given in Table V. There was no significant elevation in temperature during the critical 5–15-day period after vaccination compared with the first four days. The temperature elevations were considerably in excess of those noted in previous studies of the Moraten line measles vaccine(**10**) given alone, but were in the range of those expected from smallpox vaccine. None of the febrile reactions was of clinical importance.

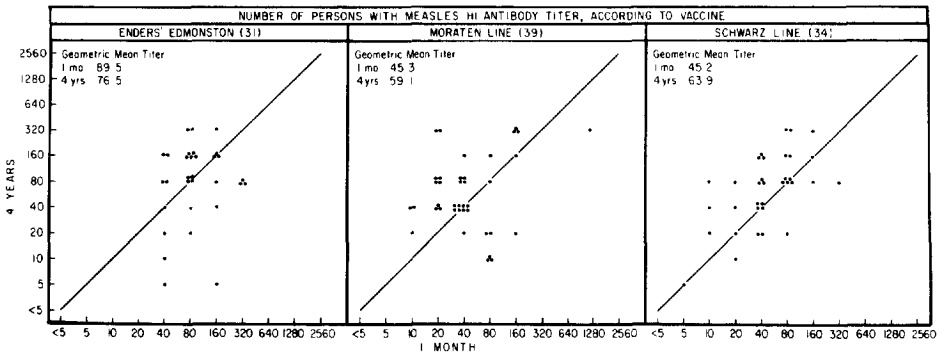

Fig. 1. Retention of measles HI antibody 4 years after vaccination with Enders' original, Moraten line, or Schwarz line measles virus vaccine.

DURATION OF IMMUNITY AFTER VACCINATION

Duration of protective effect of combined vaccines needs to be viewed in terms of protection following the individual components of the vaccine as well as following the combined vaccine itself. In measles, mumps and rubella, protection against illness equates well with persistence of antibody and the indication from all the accumulated data is that immunity following use of the live virus vaccines against these viruses will be lasting, probably lifelong.

MEASLES

Others(**14**, **15**) have followed the persistence of antibody following Enders' original live virus vaccine for at least twelve years and the levels have been retained very well. Protection has persisted also(**16**). Comparison was made in our laboratories of antibody retention in children following Enders' original measles virus vaccine compared with vaccines prepared using more attenuated Moraten and Schwarz lines of the virus(**9**). The results of tests presented in Fig. 1 show that antibody was retained very well for at least four years after all of the three vaccines. All of the children retained antibody and in measles, this means immunity. The elevations and declines in titer may reflect subclinical reinfection with the virus, minor declines in antibody, and variation in test results due to changes in the sensitivity of the test from time to time.

MUMPS

Antibody persistence Children in institutions(**9**, **17**, **18**) who received Jeryl Lynn live mumps virus vaccine in 1965 or were held as unvaccinated controls had blood samples withdrawn at frequent intervals during a 6-year period(**9**). The sera were tested for content of neutralizing antibodies against mumps with the results shown in Table VI. Not all individuals in the total group were present during the entire time period. The geometric mean neutralizing antibody levels did not change appreciably during the six years. The early (1-month) and the late

Table V. *Febrile reactions observed among the children who received combined Moraten measles–smallpox vaccine and who were initially seronegative to measles and vaccinia viruses*

Vaccine lot no.	Maximum temperature (°F, oral)	Total no. of children	Children with temperature (%) shown: Days 1–4 No.	Days 1–4 %	Days 5–15 No.	Days 5–15 %
971	<99	67	25	37.3	1	1.5
	99–100.9		30	44.8	38	56.7
	101–102.9		10	14.9	22	32.8
	103–104.9		2	3.0	6	9.0
952	<99	95	55	57.9	9	9.5
	99–100.9		38	40.0	59	62.1
	101–102.9		2	2.1	27	28.4
	103–104.9		0	0	0	0

Table VI. *Duration of mumps antibody in children in institutions**

Time after vaccination	Mumps neutralizing antibody titer: Study 1 No. children	Study 1 Range in titer	Study 1 GMT†	Study 2 No. children	Study 2 Range in titer	Study 2 GMT†
1 month	28	2–32	7	14	4–32	11
3 months	—	—	—	14	2–32	8
5 months	26	2–32	6	13	2–32	6
6 months	—	—	—	12	4–16	7
1 year	23	2–32	7	11	2–64	7
1½ years	21	1–32	5	12	1–64	6
2 years	21	1–64	6	11	1–64	5
2½ years	—	—	—	9	2–32	5
3 years	18	1–128	9	9	2–64	5
4 years	18	1–128	13	9	2–64	5
5 years	15	2–128	15	8	1–32	6
6 years	11	2–64	12	7	4–32	8

* During the 6-year period, mumps antibody did not develop in any of the 7 initially mumps-seronegative, unvaccinated contact controls from Study 1, nor in any of the 12 from Study 2.

† GMT = geometric mean antibody titer.

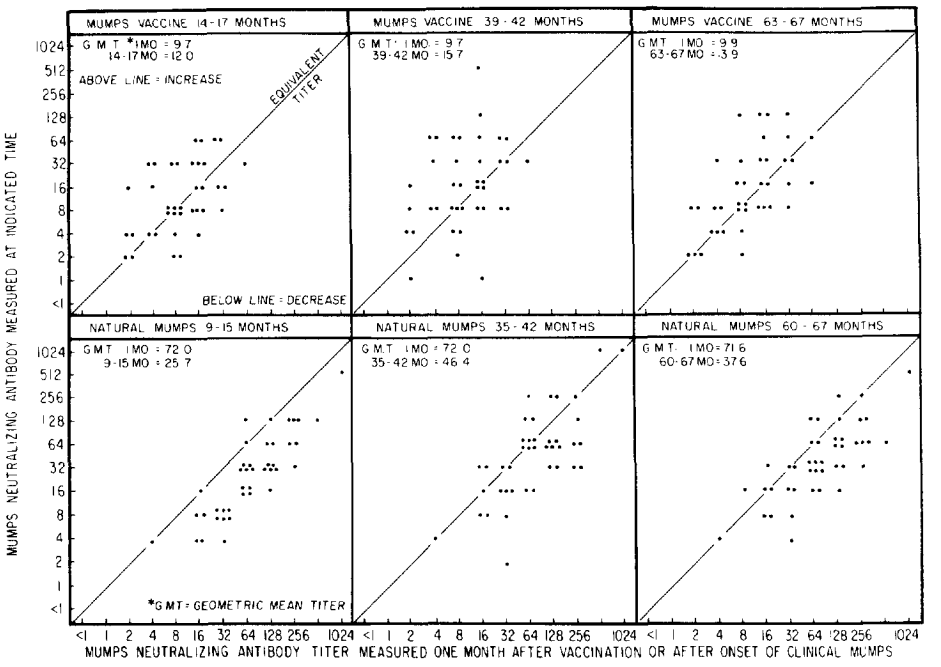

Fig. 2. Duration of neutralizing antibody following Jeryl Lynn strain live attenuated mumps virus vaccine compared with that following natural mumps.

(6-year) mean titers were 1:7 and 1:12 respectively, for study 1, and were 1:11 and 1:8 for study 2. None of the vaccinated children became seronegative. None of the 19 initially seronegative contact controls, who were still present in the institution, developed mumps antibody during the intervening period. This indicates lack of natural infection in the populations observed during the 6-year period of the study. Thus, mumps antibody persisted in the vaccinated persons without the need or opportunity for reinfection with mumps in nature.

Controlled field evaluations(**18**, **19**) of Jeryl Lynn mumps virus vaccine were initiated in the fall of 1965 in children in schools and families in the Havertown–Springfield suburb of Philadelphia. Children who were given the vaccine and their unvaccinated contact controls who developed mumps naturally were bled at periodic intervals up to 67 months after vaccination or onset of natural mumps and the sera were tested for mumps neutralizing antibody with the results shown in Fig. 2. The persistence of antibody was as good after vaccination as after natural infection. The initial level of neutralizing antibody that was reached after natural mumps infection was usually considerably greater than that following vaccination. However, it must be noted that a mumps neutralizing antibody titer of 1:1 or greater provides solid protection against natural mumps in all but rare instances.

Table VII. *Duration of protective efficacy of Jeryl Lynn live mumps virus vaccine against natural mumps*

Population	Time period after vaccination	Mumps cases: Vaccinated Cases/no. at risk	Mumps cases: Vaccinated Rate (%)	Mumps cases: Controls Cases/no. at risk	Mumps cases: Controls Rate (%)	Protective efficacy (%)
Schools	1st school yr	2/86	2	45/76 or >	59	96
	2nd school yr	1/34	3	25/46 or >	54	95
	3rd school yr	0/32	0	42/52 or >	81	100
	4th school yr	0/25	0	28/37 or >	76	100
	5th school yr	0/27	0	44/59 or >	75	100
	6th school yr	0/18	0	27/35 or >	77	100
Families	0–9 months	2/30	7	50/62	81	92
	10–19 months	1/14	7	23/25	92	92
	20–31 months	0/15	0	22/28	79	100
	32–44 months	0/20	0	36/38	95	100
	45–54 months	0/1	0	2/2	100	100
	61–69 months	0/13	0	28/28	100	100

Protective efficacy(**9**) Mumps continued to occur among unvaccinated children in the Havertown–Springfield community and the children who had been vaccinated continued to be exposed to natural mumps in their classrooms and in their families. Table VII shows that the protective efficacy of the vaccine among the children in the schools was 95–96 per cent for the first two years and was maintained solidly thereafter at 100 per cent through the sixth year. The similar situation in the families showed 92 per cent protection during the initial year and a half and 100 per cent protection thereafter. The contact controls included those children who were originally in the study plus new members of the family who were not present when the original study was initiated.

The persistence of mumps neutralizing antibody among children in institutions and in the community equates with protection and this has been confirmed in the studies of protection against the disease which has now been shown to persist for the six years since the study was started.

RUBELLA

First large-scale studies of HPV-77 duck cell-modified rubella vaccine were initiated during September of 1966 in the Havertown–Springfield suburb of Philadelphia(**20, 21**). Seventy-four children who received the vaccine in 1966 were selected at random and hemagglutination-inhibiting antibody titers were determined from their blood samples taken 2 months, $2\frac{1}{2}$ years and $3\frac{1}{2}$ years after the vaccine was given. The findings given in Fig. 3 show the expected small decline in antibody in a portion of the subjects during the first $2\frac{1}{2}$ years without

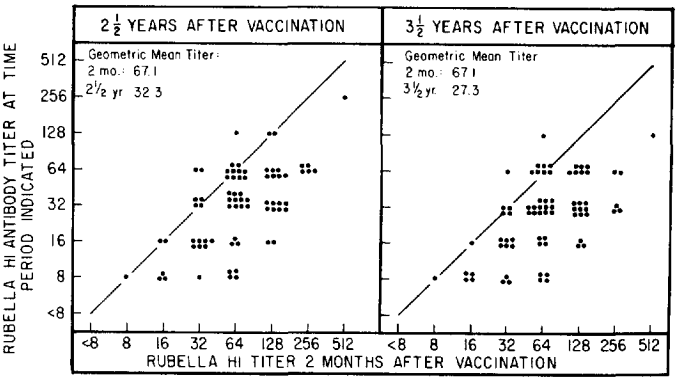

Fig. 3. Persistence of rubella HI antibody following HPV-77 duck rubella vaccine.

significant decline thereafter. None of the vaccinated children became seronegative. The geometric mean titers for the 2 months, $2\frac{1}{2}$ years and $3\frac{1}{2}$ years time period were 1:67.1, 32.3 and 27.3 respectively and this resembles the pattern for antibody persistence following natural rubella.

MEASLES–MUMPS–RUBELLA VACCINE

Children who received combined measles–mumps–rubella vaccine(**3, 9**) during 1968 were bled 3 years later and the antibody titers 6 weeks and 3 years after vaccination were compared. Fig. 4 shows that none of the children lost his antibody and the mean titers against measles and rubella were essentially unchanged. The increases in antibody against mumps virus probably resulted from subclinical reinfection in some instances.

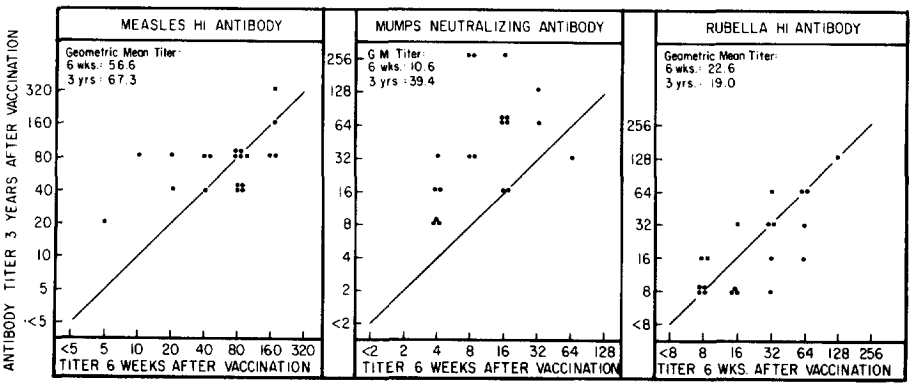

Fig. 4. Retention of measles, mumps and rubella antibodies 3 years after vaccination with combined live measles (Moraten)–mumps (Jeryl Lynn)–rubella (HPV-77 duck) virus vaccine.

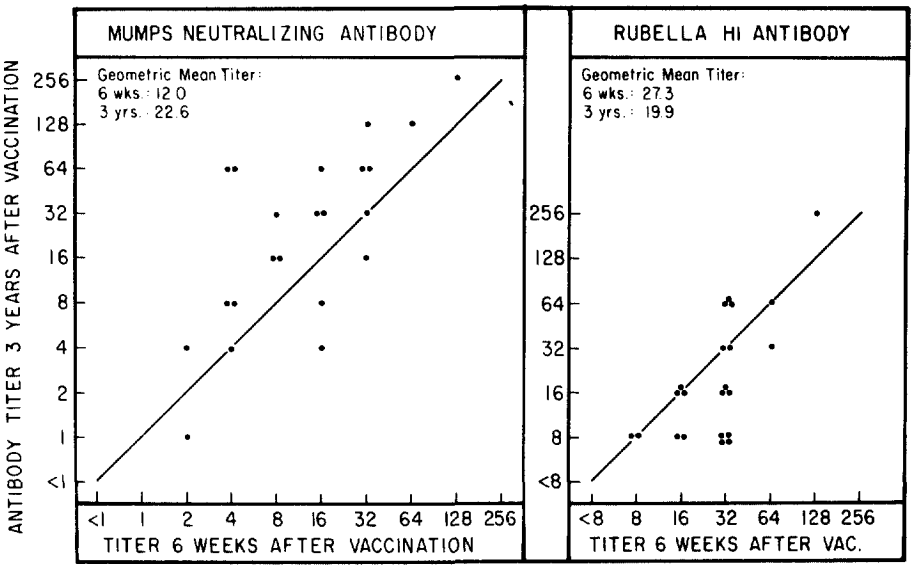

Fig. 5. Retention of mumps and rubella antibodies 3 years after vaccination with combined live mumps (Jeryl Lynn)–rubella (HPV-77 duck) virus vaccine.

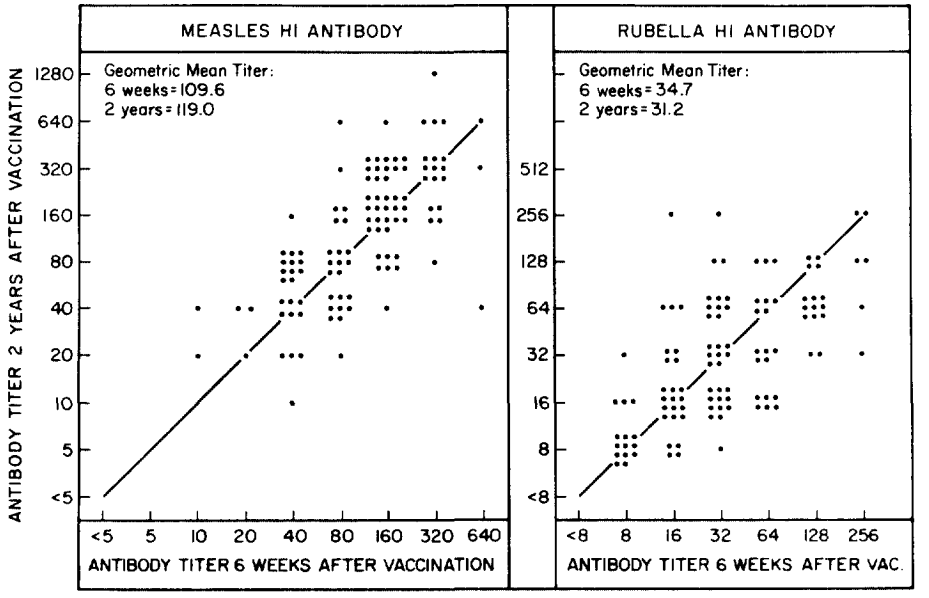

Fig. 6. Retention of measles and rubella antibodies 2 years after vaccination with combined live measles (Moraten)–rubella(HPV-77 duck) virus vaccine.

MUMPS–RUBELLA

Children who were given combined mumps–rubella vaccine were bled 6 weeks after vaccination and again 3 years later(**5**, **9**). Fig. 5 shows that none of the children lost his antibody and that the mean titers against rubella virus were retained without significant drop. There was indication of subclinical reinfection with mumps virus in a portion of the children.

MEASLES–RUBELLA

Samples of blood were collected from children 6 weeks and 2 years after vaccination with combined measles–rubella vaccine(**4**). Fig. 6 shows that none of the children lost his antibody and that the mean titers of antibody against measles and rubella were essentially unchanged.

SUMMARY AND COMMENT

It is evident from these studies that various combinations of measles, mumps, rubella and smallpox vaccines can be administered in a single dose without impairing immune responses and without increasing clinical reactions beyond those seen when the individual vaccines are given singly. The savings in medical manpower, the increased effectiveness of immunization campaigns, and the minimizing of discomfort to the recipient through use of combined vaccines scarcely require comment. The triple measles–mumps–rubella vaccine should be attractive for routine immunization of new susceptibles born into well vaccinated populations, and for vaccination of children up to 7 or 8 years of age in parts of the world where these vaccines have not yet been given. The mumps–rubella vaccine might find particular utility for populations in which sizable measles immunization programs have already been carried out. Combined measles–rubella vaccine appears less desirable than the triple measles–mumps–rubella vaccine but is designed for situations in which mumps vaccine might be deleted from the triple combination. The combined measles–mumps vaccine was developed for those countries that do not wish to carry out rubella immunization in young children. The combined measles–smallpox vaccine was designed for emerging nations where these two diseases are very important and where mass campaigns are carried out using the jet injector. The measles–rubella–smallpox combination might be used in underdeveloped countries that choose to include immunization against rubella along with measles and smallpox.

Combined vaccines point the way to effective control of several medically, economically and socially important diseases with the least possible cost, greatest savings in medical manpower, increased effectiveness of immunization campaigns, reduced numbers of patient–physician contacts, and reduction of discomfort to the recipient. The immune responses that follow measles, mumps, and rubella vaccines given individually are persistent and appear to be lasting and probably lifelong. These responses appear to be just as persistent following combined vaccine as following the individual vaccines administered separately.

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GENERAL DISCUSSION

CHAIRMAN Thank you very much, Dr Hilleman. Dr Krugman, did you wish to ask a question or make a comment?

KRUGMAN (USA) My comment is concerned with reactions which have been associated with the use of killed measles vaccine. The 'atypical measles syndrome' has occurred in children who received killed measles vaccine in the past and subsequently were exposed to individuals with naturally acquired measles infection. This syndrome is characterized by high fever, a generalized rash which may be maculo-papular, petechial or papulovesicular, oedema of the extremities and a pneumonitis with or without effusion. Most physicians do not recognize this syndrome as a complication of killed measles vaccine because (1) the time interval between immunization and subsequent exposure to wild measles virus may be as long as 6 years, and (2) the clinical syndrome is diagnosed as 'pneumonitis and toxic erythema', or Rocky Mountain spotted fever (which it resembles), or atypical varicella. It is important to recognize and identify a complication before one can assume that it does not occur. Moreover, since the factor or factors responsible for this hypersensitivity phenomenon are unknown, one should not assume that a purified inactivated measles vaccine is safe in this regard.

HILLEMAN (USA) About a year ago, Dr Eric Lykke reported his findings with a subunit measles virus vaccine. He showed that the vaccine induced excellent hemagglutination-inhibiting antibody responses in children but there was no protection against the disease. He thought this might be related to the fact that the vaccine did not induce antibody against the measles hemolysin. Now, here is an example of how a whole killed virus particle vaccine protects while a particular highly purified subunit vaccine does not. It raises the question of whether antibody responses alone suffice to establish efficacy of myxovirus vaccines or whether protective efficacy trials need be run. Perhaps someone is here from Sweden who could comment on this work.

CHAIRMAN I think that Professor Hennessen would be prepared to say something about that.

HENNESSEN (Germany) In the study I mentioned before we followed the protection as well as the antibody response in these children. We found that for the first year – as Dr Cohen showed for his study – the antibodies declined after 12 months down to zero. During that time, before they fell to zero, we got almost complete protection whenever antibodies were present.

DIANZANI (Italy) In order to avoid any interference due to interferon induced by a combined living vaccine, I agree that it is very important to select proper strains of virus. However, it may be also very important to consider the amount of virus injected. Did you have to reduce the dose of virus in order to avoid interference?

HILLEMAN (USA) Dosage is not all that critical. One has arbitrary maximum limits for each component of the combined vaccines. The minimal limits are the same as for the monovalent vaccines. The precise upper limits are not defined.

NETTER (France) I should like to ask Dr Hilleman some questions with regard to the association of smallpox and measles vaccine.

First, what is the dosage of each fraction of smallpox and measles?

Secondly, what is the route of injection of this combined vaccine, intradermally or subcutaneously?

Thirdly, is the febrile reaction the same for the combined vaccine as for each fraction?

Last, but not least, does the stability of the combined product fulfil WHO requirements regarding the stability of smallpox vaccine?

HILLEMAN (USA) Let me try to recall. The vaccinia dose is, I think, 10^5 plaque-forming units/0.1 ml. The 0.5 ml dose of vaccine is given by jet gun with 0.4 ml under the skin and 0.1 ml into the skin. Actually 0.2 ml under the skin with a total vaccine dose of 0.3 ml is adequate. The measles vaccine used induces little fever and the febrile responses are essentially the same as when the smallpox vaccine is given alone. The product is dried and is stable. I believe the product complies with WHO standards – perhaps Dr Meyer recalls more of the details.

MEYER (USA) We have additional standards for combined measles/smallpox in the United States, and these standards were based on field trial information which Dr Hilleman accumulated several years ago. There were a number of trials. Essentially a dilution of smallpox vaccine that will give the desired cutaneous and serologic response is used, and that dilution is defined in our standards as – that amount of virus contained in 0.5 ml of a 1 : 100 dilution of our reference virus – which is about the same as the WHO reference, with a titre of approximately 10^8 p.f.u./ml. So Dr Hilleman's estimation on dose is right. It is just under 10^6 p.f.u./ml. It is actually in the injected AFML quantity.

The minimum measles amount is that defined for monovalent measles, that is at least 1000 tissue culture ID_{50}. He has good seroconversion data using these dosages by the jet gun.

The jet route which he uses is the jet gun with a sleeve on it in which a portion of the vaccine is deposited intradermally, which is probably the most active part of the smallpox, and a portion goes subcutaneously. The measles virus appears to be somewhat more effective in seroconversion subcutaneous than in intracutaneous.

POLLOCK (UK) I wonder if Dr Cohen would be kind enough just to clear up two small points about screaming attacks following pertussis vaccine. We have also had reports of this phenomenon in England.

He pointed out the difference in the prevalence of these screaming attacks in the last two years, 1972 and 1971 as compared with 1970. This, of course, was not readily attributable to the vaccine. Was there any change in the age of the children vaccinated in 1971 and 1970 and was there any change in the system of reporting in these two years that could possibly have accounted for it?

COHEN (The Netherlands) No, there was no change in the age of the children. This was the routine vaccination starting at at least three months of age, and the system of reporting was exactly the same during these years. In these baby clinics the nurse or the doctor regularly asks about this type of reaction when the mother comes for a further visit, and immediately after a report is received our pediatrician visits the mother with the child in her home. I did not give the data, but the number of times we were called upon, was the same in the three years under investigation. The diagnosis of persistent screaming or shock was made less and less and we are at a loss to explain it.

GEAR (South Africa) I should like to ask Dr Cohen if BCG vaccine is given in the Netherlands.

Then I should like to ask Dr Hilleman if he has studied the effect of his combined vaccine, particularly the measles component, on the hypersensitivity state. Measles itself, natural measles, reduces the tuberculin reactivity, so that children previously positive become negative. I was wondering what the findings were following vaccination. Theoretically they might be a contra-indication to combining measles and BCG. Has this been studied?

COHEN (The Netherlands) The answer is no, and tuberculosis has virtually disappeared. BCG has never been given routinely.

HILLEMAN (USA) The measles vaccine given alone does interfere with dermal sensitivity to PPD for a limited period of time. This has not, to date, turned up any evidence for lighting up latent TB.

COCKBURN (WHO) This is a comment rather than a question about screaming attacks. In the Medical Research Council trials many years ago we found exactly the same thing as Dr Cohen. It was one batch of vaccine which was particularly associated with these attacks. This was used early in the study. It did not appear to differ in any way from the other vaccines, but it was definitely associated with a much higher incidence of these attacks than any subsequent batch of vaccine which was used.

CHAIRMAN Was that the batch that was the extract, or was it a whole bacterial vaccine?

COCKBURN (WHO) No, it was a whole bacterial vaccine. It was, in fact, the second batch which we used.

CHAIRMAN We will now ask Dr Witte to present his paper.

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SIMULTANEOUS ADMINISTRATION OF LIVE OR KILLED VACCINES

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The simultaneous administration of several vaccines is not a new concept in immunization practice. A combination of diphtheria toxoid, tetanus toxoid and pertussis vaccine, frequently referred to as D-T-P vaccine has been available for decades in many countries. An inactivated polio virus vaccine was introduced in the mid-1950s. This product includes a combination of the 3 types of polio viruses inactivated with formalin. During the early 1960s, a trivalent live attenuated oral polio virus vaccine became available.

These products have been widely used. Information about the total number of doses of vaccines distributed in the United States is available through a surveillance of biologics established by the Center for Disease Control in 1962. During this time, more than 200 million doses of the D-T-P combination vaccine were distributed. Since 1963, when trivalent oral polio virus vaccine (OPV) was initially licensed, 210 million doses have been distributed. The D-T-P, trivalent OPV and inactivated polio vaccines have been widely used in many countries of the world. There is no available data on the worldwide usage of these products, but it is likely that the amounts for the United States represent only a small proportion of the total use of these combined vaccines. The D-T-P and either the killed or oral polio vaccines are well accepted as part of routine immunization practice throughout the world. The killed and live attenuated polio virus vaccines have accounted for a dramatic decline in the incidence of paralytic poliomyelitis in the many countries where they have been utilized extensively.

The availability of the newer combined vaccines offers the opportunity to expand the practice of simultaneous administration of a number of killed and live vaccines. The clinical and immunologic responses to these newer products (described by Dr Hilleman) are impressive. The development of antibodies for each component antigen is comparable to that following the single administration of that antigen alone. In addition, there is no increase in either the frequency or the severity of clinical reactions to the component vaccines.

Additional studies of these newer combined vaccines and of their simultaneous administration with other vaccines were recently carried out by the Center for Disease Control. In most of these field studies, we have collaborated with Dr Harry Meyer and his staff at the Bureau of Biologics. This report will review the

results of some of these studies, particularly as they relate to changes in immunization practice. In addition, I will discuss the impact of the increasing practice of simultaneous vaccine administration on immunization programs and vaccine utilization in the United States.

During the past two years, we conducted several types of field trials of combined vaccines or simultaneous vaccine administration.

(1) The measles–rubella (M-R) and the measles–mumps–rubella (M-M-R) vaccines were given to susceptible children to confirm and extend the work reported by Dr Hilleman.

(2) The dosage of the component antigens of the measles–rubella and the measles–mumps–rubella vaccines was varied to determine the effect on the immunologic responses.

(3) The measles–mumps–rubella vaccine and trivalent polio virus vaccine – a total of six antigens – were given simultaneously.

(4) The measles–rubella vaccine was given simultaneously with D-T-P vaccine.

(5) Two other strains of measles and rubella vaccines, Schwarz (measles) and Cendehill (rubella) were administered to susceptible children simultaneously at separate sites and as a combined product.

All of these field trials were directed at pragmatic questions relating to either vaccine licensure or the recommendations for vaccine use.

Table I shows the seroconversion rates and geometric means titers (GMTs) of seronegative children to measles–rubella vaccine. A total of 408 children were studied in four different locations. The vaccines were given as a combined product in Tol (an island in the Trust Territory of the Pacific) and in Tampa, Florida, and simultaneously but at separate sites in Miami, Florida, and Norfolk, Virginia.

The seroconversion rates were 90 per cent or better for rubella and measles in all of the groups studied. Overall, the seroconversion rate was 95 per cent for measles and 94 per cent for rubella. The antibody levels, shown here as geometric mean titers (GMTs) were similar to titers obtained in our laboratories following the single administration of these antigens.

Table I. *Seroconversion rates and GMTs of seronegative children to measles–rubella vaccine*

	Method of administration	No. of children	Measles		Rubella	
			Rate (%)	GMT	Rate (%)	GMT
Tol	Combined	197	96	1:77	93	1:82
Tampa	Combined	114	94	1:58	96	1:25
Miami	Separate	61	97	1:54	90	1:24
Norfolk	Separate	36	92	1:33	94	1:26
Total		408	95		94	

Table II. *Seroconversion rates of seronegative children to measles–mumps–rubella vaccine*

Study	No. of children	Seroconversion rates (%)		
		Measles	Mumps	Rubella
Guam	106	100	89	99
Houston	80	91	95	89
Total	186	96	92	95

Table II shows the serologic response following administration of measles–mumps–rubella vaccine. The seroconversion rates to the three antigens were studied in 186 seronegative children in Houston, Texas, and the Island of Guam, a United States possession in the Mariana Islands. Of these, 96 per cent developed antibody to measles, 92 per cent to mumps and 95 per cent to rubella. The geometric mean titers are not shown on this table; however, they were comparable to the titers shown in the measles–rubella studies or when the antigens are administered singly.

These data, developed at the Center for Disease Control and the Bureau of Biologics, on the simultaneous administration of measles–rubella and measles–mumps–rubella vaccines confirms the work of the manufacturer and substantially enlarges our overall experiences with these products. These two vaccines (M-R and M-M-R) were licensed for general use in the United States in 1971. Following licensure, they were recommended as acceptable alternatives to single-antigen administration by the two advisory groups that traditionally make recommendations for vaccine use in the United States: the Public Health Service Advisory Committee on Immunization Practices and the American Academy of Pediatrics Committee on Infectious Diseases.

Shown in Table III are the seroconversion rates of seronegative children receiving various doses of the measles and rubella components of the measles rubella vaccine. A minimal potency is required for any lot of vaccine to be released in the United States, however; there is a range in the virus titers in the vaccines that are released for general use. The purpose of this study was to compare the serologic responses following various combinations of relative 'high' and 'low' dosage materials, and to see if a 'high' dose of one component vaccine would suppress the serologic responses to the other component. There were 197 children who were susceptible to both measles and rubella. The seroconversion rates were 90 per cent or greater in all groups for both the measles and rubella components. The rates of seroconversion and the GMTs were also studied in the children who were seronegative to only one of the antigens. These results were almost identical to those of the doubly susceptible group. It is clear that there was no interference between the vaccines in the dosages studied.

Table IV shows a similarly designed study with various dosage combinations

Table III. *Seroconversion rates of seronegative children following various doses of measles and rubella vaccines (Truk, 1971)*

Component titer		No. vaccinated	Seroconversion rates (%)	
Measles	Rubella		Measles	Rubella
High	Low	58	98.3	94.8
High	High	46	91.3	93.5
Low	Low	49	98.0	93.9
Low	High	44	97.7	90.9
Total		197	96.4	93.4

Table IV. *Guam combined vaccines study: seroconversion rates and GMTs of seronegative children to various combinations of measles–mumps–rubella vaccines*

Component titer (Me–Mu–R)	Measles			Mumps			Rubella		
	No. of children	Rate (%)	GMT	No. of children	Rate (%)	GMT	No. of children	Rate (%)	GMT
Avg–Avg–Avg	59	100	1:71	49	87	1:8	58	100	1:129
Low–Avg–Avg	22	100	1:66	16	94	1:10	24	100	1:53
Low–Avg–High	25	100	1:89	17	88	1:10	25	96	1:78
Total	106	100	1:82	82	89	1:9	107	99	1:100

of the measles–mumps–rubella vaccine conducted in Guam. The seroconversion rates and geometric mean titers are shown for children seronegative for the component antigens. The overall rates for measles and rubella are impressive, 100 per cent and 99 per cent, respectively. The rate for mumps was slightly lower but there was no evidence of suppression of immunologic responses to the components of the mumps vaccine in any of the dosage groups.

Based on these studies, we concluded that there was no measureable effect on either the seroconversion rates or the GMTs in any of these dosage combinations. Although the potency of the component antigens may vary somewhat from lot to lot, there is no evidence to suggest that a relatively higher 'dose' of one component will exert a suppressive effect on any of the other components. These data make us more confident that the lots of vaccine being released for general use will produce satisfactory immunologic responses despite variations in dosage.

The measles–rubella or the measles–mumps–rubella vaccines are most frequently administered during the second year of life, a time when a 'booster' or reinforcing dose of trivalent oral poliomyelitis vaccine is also recommended. It is also a time at which public health agencies in the United States have a very difficult time getting children to return for repeated clinic visits for immunizations. The ability to co-administer measles–mumps–rubella vaccine or measles–rubella

vaccine with trivalent oral polio virus vaccine would enable health agencies to reduce the number of clinic visits necessary to complete the requisite immunizations. In addition, fewer children would be lost to follow-up before immunizations were completed. Following licensure of the measles–rubella and measles–mumps–rubella vaccines, we were barraged with inquiries from health departments about the efficacy of the simultaneous administration of the measles–rubella or measles–mumps–rubella vaccines with a reinforcing or 'booster' dose of trivalent oral polio vaccine. At that time, there was no data available to enable us to give meaningful advice.

Two studies, using similar protocols, were designed to answer this question; they were conducted in Houston, Texas, and the Island of Guam. Shown in Table V are the seroconversion rates of seronegative children to measles–mumps and rubella vaccine with and without a reinforcing dose of trivalent oral polio virus vaccine given at the same time. The rates are almost identical for each antigen whether given alone or simultaneously with trivalent polio vaccine. In the simultaneous measles–mumps–rubella plus polio vaccine group, the seroconversion rates are excellent: 98 per cent for measles, 94 per cent for both mumps and rubella.

Table V. *Seroconversion rates of seronegative children to measles–mumps–rubella vaccine with and without polio vaccine in two studies*

		Measles		Mumps		Rubella	
Study	Vaccine	No. of children	Rate (%)	No. of children	Rate (%)	No. of children	Rate (%)
Guam	M-M-R	106	100	82	89	107	99
	M-M-R+P	44	100	42	95	45	98
Houston	M-M-R	80	91	80	95	80	89
	M-M-R+P	78	97	78	94	78	91
Total	M-M-R	186	96	162	92	187	95
	M-M-R+P	122	98	120	94	123	94

Table VI. *Guam combined vaccines study. Percentage of children with antibody to three types of polio virus before and after 'booster' inoculations*

	No. of children	Percentage with antibody		
		I	II	III
Polio vaccine alone	52			
Pre-boost		71.2	84.6	78.8
Post-boost		90.4	98.1	90.4
Polio vaccine with measles–mumps–rubella	43			
Pre-boost		76.6	88.4	69.8
Post-boost		93.1	97.7	88.4

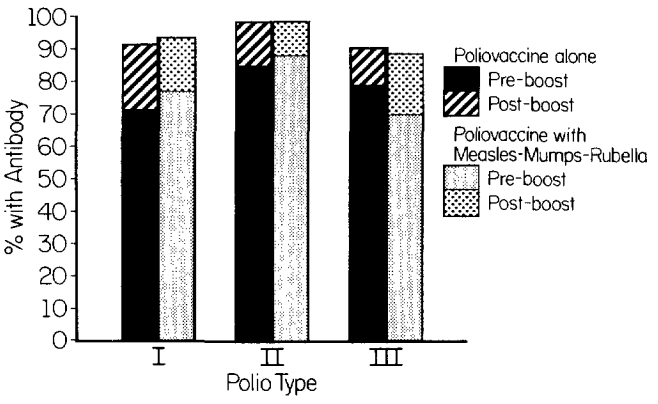

Fig. 1. Guam combined vaccines study. Percentage of children with antibody to three types of polio virus before and after 'booster' inoculations.

The serologic responses to polio are shown in Table VI. These children had all received at least two prior doses of polio vaccine, so none should have been susciptible to all three types of polio virus. A total of 52 children received only a reinforcing dose of polio vaccine and 43 received measles–mumps–rubella vaccine in addition to trivalent polio vaccine. The pre-booster immune status is similar in the two groups for each type of polio virus (71 and 77 per cent for Type I, 85 and 88 per cent for Type II and 79 and 70 per cent for Type III). Following the booster doses, the per cent of children with antibody to each of the three types of polio virus is remarkably similar in the two groups (90 and 93 per cent for Type I, 98 and 98 per cent for Type II and 90 and 88 per cent for Type III). The serologic responses to polio vaccine in the Houston study were almost identical.

The same information is shown graphically in Fig. 1. In addition, there was no increase in the frequency or severity of clinical reactions in the Guam or Houston studies.

It is obvious that there are no apparent adverse effects, either immunologically or clinically, following the simultaneous administration of these six live viral antigens. These data were reviewed by the Public Health Service Advisory Committee on Immunization Practices and the American Academy of Pediatrics Committee on Infectious Diseases. Both Committees issued statements permitting the simultaneous administration of measles, mumps and rubella vaccines with a reinforcing or booster dose of poliomyelitis vaccine particularly in circumstances where this is desirable in preventive medicine programs.

In addition to measles, rubella, mumps and trivalent polio vaccines, a booster dose of diphtheria–tetanus–pertussis (D-T-P) vaccine is also recommended during the second year of life. There is not sufficient information available at the present time to comment definitely on the co-administration of D-T-P with M-M-R. We are currently obtaining information on the immunologic responses and clinical reactions associated with the simultaneous administration of D-T-P

Table VII. *Seroconversion rates and GMTs of seronegative children to Schwarz measles and Cendehill rubella vaccines*

Study	Method of administration	No. of children	Measles		Rubella	
			Rate (%)	GMT	Rate (%)	GMT
Miami	Separate	61	97	1:54	90	1:24
Norfolk	Separate	36	92	1:33	94	1:26
Tampa	Combined	114	94	1:58	96	1:25
Total		211	94		94	

with M-M-R vaccine. The preliminary results are encouraging. There appears to be no suppression of serologic responses or increases in the clinical reaction rates associated with administration of this combination. We are hopeful that, in the future, we will be able to be more permissive in recommending the simultaneous administration of D-T-P vaccine with measles–rubella vaccine.

When the newer combined vaccines were first licensed in 1971, questions arose concerning the feasibility of simultaneous administration of the other available measles and rubella vaccines. The other licensed vaccines being distributed in the United States are a further attenuated measles vaccine developed by Schwarz and the Cendehill rubella vaccine. Because many health departments purchase these products, it was desirable economically as well as scientifically to study the simultaneous administration of these two vaccines.

Shown in Table VII are the results of field studies of the seroconversion rates and GMTs to Schwarz measles and Cendehill rubella vaccines. They were conducted in Miami, Norfolk and Tampa. The vaccines were given simultaneously but at separate sites in Miami and Norfolk and as a combined product in Tampa. In the three study areas, a total of 211 seronegative children were studied. The seroconversion rates, overall, were 94 per cent for both measles and rubella. The GMTs were comparable to the levels expected following administration of the antigens alone. The information from these studies allowed the Public Health Service and the Academy of Pediatrics Advisory Committees to issue statements permitting the simultaneous administration of the Schwarz measles and Cendehill rubella vaccines.

The availability of the newer combined vaccines and the more permissive recommendations regarding the simultaneous administration of a wider variety of vaccines have had a marked impact on immunization practice in the United States. The newer combined vaccines, particularly the measles–rubella vaccine, have proved to be very popular and represent an increasing proportion of preschool immunizations against both rubella and measles, particularly in public health programs. Because of the relatively low priority of the disease and the high cost of mumps vaccine, very little, if any, measles–mumps–rubella vaccine is being used by public agencies in the United States. Practicing physicians are using the triple M-M-R vaccine.

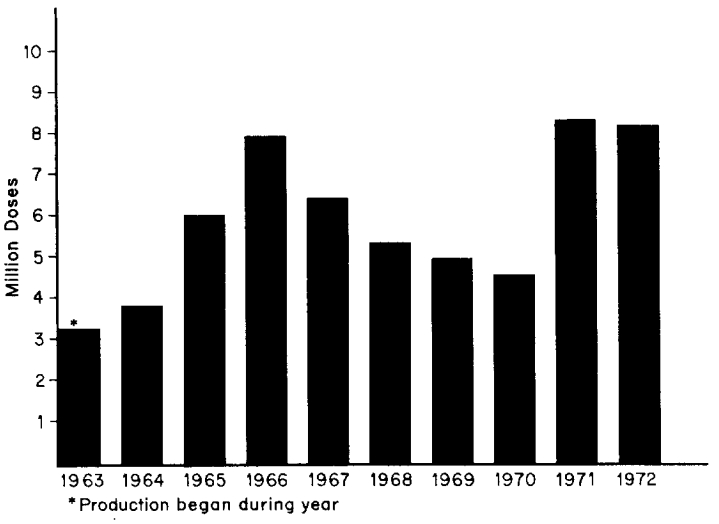

Fig. 2. Doses of live measles vaccine distributed in the United States, 1963–72.

In 1971, when the combined vaccines were licensed, federal dollars were not available for the purchase of measles vaccine, although there were funds to purchase rubella vaccine. At that time, the incidence of measles was increasing sharply in the United States. The number of reported cases of measles had previously declined from the time of vaccine licensure in 1963 to a low point of 22000 reported cases in 1968.

That same year, a federally assisted program to support immunizations, including measles, had expired. In 1969, there were 25000 reported cases. In 1970 the number increased to 47000 and by 1971 there were 75000 reported cases of measles. In three years, the incidence had more than tripled! This dramatic increase in the incidence of measles was part of the reason federal funds were again allocated specifically for control of communicable disease problems, including measles. This money became available late in 1971.

During the second half of 1971, the distribution of measles vaccine increased sharply. The distribution of measles vaccine in the United States for each year since licensure in 1963 is shown in Fig. 2. During 1971, 8.3 million doses of vaccine were distributed, higher than for any previous year. In 1972, 7.9 million doses were distributed. Although a number of factors obviously influenced the distribution of measles vaccine in 1971, the availability of combined vaccines, particularly the measles–rubella vaccine, helped to account for some of this increased distribution. The combined M-R and M-M-R vaccines are included in this distribution data for measles vaccine. The Center for Disease Control purchased 5 million doses of measles–rubella vaccine during the last year and a half for use in preschool immunization programs. This represents approximately 50 per cent of all the measles vaccine distributed during that time.

The current practice in most health departments is to administer the combined

measles–rubella vaccine at one year of age. In many areas, a reinforcing dose of trivalent oral polio vaccine is also given at the same time.

In an effort to raise immunization levels, an increasing number of states are enacting laws which require specific immunizations prior to entry into school. Thirty-eight states now have such laws. In six other states, similar laws are currently being considered by the legislatures. Polio, D-T-P and measles vaccines are included in almost all of these school entry laws. Rubella vaccine is now required in 23 states. The purpose of these laws is to provide immunizations to those children not adequately immunized at an earlier age. The simultaneous administration of a variety of vaccines is now a common practice in immunization programs for children entering school.

It is obvious that the simultaneous administration of an increasing number of antigens is changing the patterns of immunization practice in the United States. Immunization schedules have been simplified. This results in fewer clinic visits particularly during the second year of life. Fewer children are lost to follow-up and more are completing their immunization schedules. Therefore, simultaneous administration of vaccines has contributed substantially to increasing the immunization levels among preschool children particularly to measles and rubella.

The simultaneous administration of vaccines has also helped us to get away from single-disease approaches to vaccination. In the past, large programs for immunization against poliomyelitis, measles and rubella have been enormously successful in the United States. After these vaccines were introduced, large numbers of susceptible children were immunized very quickly and the disease rates declined. The same techniques, however, have been largely unsuccessful in sustaining the immunization levels achieved in these original mass programs. Simultaneous vaccine administration facilitates a necessary change in emphasis to broaden the approaches to immunization practice. This broader approach is resulting in more effective and more comprehensive ongoing immunization activities.

The technology of simultaneous vaccine administration has advanced rapidly in the last few years. Combined vaccines for measles–rubella and measles–mumps–rubella appear to be highly effective. Other antigens can be given with measles–rubella or measles–mumps–rubella with no loss of efficacy and no increase in the rates of clinical reactions. The increasing use of simultaneous vaccine administration should contribute substantially to the control and prevention of poliomyelitis, diphtheria, tetanus, pertussis, measles, and rubella.

GENERAL DISCUSSION

CHAIRMAN Thank you very much, Dr Witte. Are there any questions concerning this?

RELYVELD (France) I regret that we have no time to speak about our results and give details about vaccine combinations. We have studied about 18 combinations of vaccines and I should like to give you as quickly as possible some of our results and ask one or two questions.

We have three groups of vaccine combinations at the moment. First there are the recognized vaccine combinations. They are diphtheria/tetanus, diphtheria/tetanus/pertussis, diphtheria/tetanus/polio and so on, and also smallpox/yellow fever, and smallpox/BCG. These are recommended combinations.

Then there are combinations which we have found to be useful, but they have not been recommended officially until now. These are BCG/yellow fever – we had very good results with a combination of BCG and yellow fever. We had also very good results with smallpox/measles/yellow fever. I do not need to tell you that every time we tested the combinations and the vaccines alone, and we have made all the classical measurements for seroconversion. Another good combination is measles/BCG/smallpox.

Now I come to mixtures that have been tried of which the results were not very good. You were talking about DT/pertussis, measles and yellow fever. The results were not very good for measles. The results were also not very good for cholera/yellow fever. The results were bad for diphtheria/tetanus/typhoid/paratyphoid/polio, diphtheria/tetanus/pertussis/measles, diphtheria/tetanus/typhoid/paratyphoid/polio, cholera/yellow fever.

What is the conclusion to be drawn from this? Every time that we make a vaccine combination in which we have endotoxin-containing bacteria – that means cholera, pertussis, typhoid or paratyphoid – the results are sometimes not good for the viral vaccines.

SENCER (USA) I am quite comfortable when Dr Witte discusses the use of measles and rubella as a combination, measles, mumps and rubella as a combination, and I do not get too uncomfortable when we use trivalent polio vaccine at the same time as a reinforcing dose. However, when we begin to add DPT at the same time, I feel that we are beginning to adopt a vegetable soup approach. The children that we are concerned about are children who are difficult to follow, who come from families that have multiple problems that are amenable to preventive measures such as family planning and nutrition. I should hate to see us place our reliance on a one-shot approach – we get them in and give them everything at once – rather than placing some emphasis on good public health. What does the family need? If this is the only time we can do it, then fine, but I do not think that we should place complete reliance on the fact that it can be done with good antibody response. That does not mean that it should be done.

WITTE (USA) That you for reinforcing that, Dr Sencer.

J. W. G. SMITH (UK) May I ask Dr Witte one small point; I was not quite clear what he meant by a booster dose of polio. Is this a dose given after the child has previously had three doses?

WITTE (USA) Yes, I said 'booster or reinforcing'. The terminology sometimes becomes rather complex. We have a schedule of immunization in the United States, as recommended by the Public Health Service, of giving two doses of trivalent vaccine during the first year of life separated by at least six weeks. The American Academy of Pediatrics recommends three doses with a similar separation during the first year of life. Both groups

recommend a reinforcing dose during the second year of life. So the reinforcing, or booster if you will, follows either two or three previous doses during the first year of life depending whose schedule is being followed.

BIJKERK (The Netherlands) What has been said earlier has referred to simultaneous vaccination for national vaccination programmes, but we have also another category of people and that is the international travellers. We are confronted with people who want to be vaccinated as quickly as possible; they even want this completing tomorrow instead of in about a month. These people may go to tropical countries, or to areas where primitive conditions exist – for instance, camping – and poliomyelitis and typhoid fever may exist. We must try to protect these people against these diseases. I am thinking not only of smallpox, yellow fever or cholera, but typhoid fever, poliomyelitis, diphtheria, tetanus, and so on.

The problem is how can we do this? Is it theoretically possible to administer these vaccines simultaneously in order to have a certain percentage of these people protected against these diseases. We may not achieve 95 per cent, but perhaps 80 per cent or 85 per cent. I think that this is a fairly practical question for those who are engaged in public health and have to vaccinate these people.

HILLEMAN (USA) I should wish to comment on Dr Relyveld's questions about interference when killed bacterial and live viral vaccines are given. On the surface it would appear perfectly all right but it might not be. Combined live virus vaccines given together do not interfere, probably because it takes days before detectable interferon appears – likely related to quantity of viral substance. Bacterial antigens – endotoxin specifically – induce interferon within two hours. Thus, a bacterial vaccine might block live vaccine virus proliferation and this ought to be looked at before any decisions on simultaneous live virus–killed bacterial–live virus vaccine administrations are made.

HOFMAN (The Netherlands) I should like to ask Dr Witte about the vaccination required by law in some states of the United States. What has been the motivation behind requiring this by law against diseases like rubella, measles and so on, which are not so dangerous for a community as smallpox was in the past? What happens to parents who refuse to have this vaccination done? Are their children not allowed to go to school?

Thirdly, has this requirement by law had any success if you compare those states where it is required by law with those states where it is not?

WITTE (USA) The original motivation for the school laws was smallpox vaccination many years ago. In more recent years states have added polio, DTP and measles, and have found it an effective way of raising immunization levels against diseases which are often spread primarily among young school-age children – for example, measles. They can get very high levels of immunization in this way. In all of these laws there is always a way out for people who, for religious preference or other reasons, say that they do not want their child to be vaccinated. So the child is not in any way excluded from school if its parents refuse permission. He is just excluded from the program, but not from school.

LUGOSI (Hungary) I should like to know what is meant by a low and high titre for rubella and measles vaccines.

MEYER (USA) Let me just give a quick answer on the general experience. There are several groups who used a number of titre ranges: Dr Hilleman in his original studies; we and Dr Witte used rubella/measles and rubella/measles/mumps, and Dr Krugman has done some confirmatory studies. Generally the data indicate that one finds satisfactory seroconversion from a minimum level of 1000 tissue culture infectious doses – $10^{3.0}$ – up to $10^{4.5}$ to $10^{4.6}$. I think that there are few data beyond these extremes; thus the experimental experience to date covers approximately a 1.5 log range for both viruses, i.e. measles and rubella.

LUNDBECK (Sweden) I think we should remember that these studies with live vaccines given simultaneously have been done on quite a small scale, so far as I could judge from the tables.

The question of safety is rather different if you apply a vaccine on a very large scale. Therefore, I should like to ask whether you have any idea what happens with combined vaccine containing, say, three live vaccines in people having immunological deficiencies of some kind. You are likely to strike a few of such individuals in a large-scale test.

HILLEMAN (USA) In the United States, it is recommended not to give live virus vaccines to immunodepressed persons. One would not knowingly do it without good cause.

SESSION VI

QUALITY CONTROL

Chairman: Dr F. T. PERKINS (UK)

International Symposium on Vaccination against Communicable Diseases, Monaco 1973; *Symp. Series immunobiol. Standard, vol.* 22, *pp.* 177–182. *Printed in Great Britain*

SAFETY TESTING OF VACCINES

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Before we consider the modern methods used in the control of vaccines it is pertinent for us to look very briefly at the history of the development of vaccines.

It is now more than 170 years since Jenner first put forward his ideas on protection against smallpox by the use of cowpox virus and it is interesting to note that the next vaccine, the rabies vaccine of Pasteur, studied almost a hundred years later, was also a virus vaccine (see Table I). Even yellow fever vaccine, which was developed some fifty years later, was available before any virus particle had been seen.

The first prophylactics against bacterial diseases, for which there was a scientific understanding, were the antitoxins. These were developed following the discovery by von Behring and Kitasato that the toxin of diphtheria could be

Table I. *History of production of vaccines*

18th Century		19th Century		20th Century	
				1904	Tetanus antitoxin
1721	Variolation			1920	Diphtheria TAF
				1930	Diphtheria toxoid
					Pertussis
				1936	Yellow fever [live]
		1840	Variolation illegal	1940	Compulsory vaccination withdrawn
		1853	Vaccination compulsory	1955	Poliomyelitis [Salk]
				1960	Poliomyelitis [Sabin]
					Influenza [killed]
		1881	Rabies attenuated	1970	Measles [killed & live]
		1891	Diphtheria antitoxin		Rubella [live]
					Mumps [live]
1798	Jenner's publications			Routine vaccination stopped	

The Future:
RS vaccine
Cytomegalo vaccine
Hepatitis vaccine
Vaccines against some forms of cancer?

Table II

Test on bacterial vaccines

Live		Killed or toxoids	
BCG	Tests for:	Diphtheria	Tests for:
	Contaminants	Tetanus	Sterility
	Virulent organisms	Cholera	Toxicity
	Identity	Typhoid	Potency
	Skin reactivity	Pertussis	
	Viable count		
	Stability		

neutralized by an antitoxin. Some twenty years later, however, it was shown that the toxins could be toxoided so that active immunity could replace passive immunity and protection against diphtheria and tetanus was thereafter effected by the use of toxoids. The bacterial vaccines made from the whole organisms of pertussis, cholera and typhoid and indeed BCG, our only living bacterial vaccine, were to follow but they were not developed for forty years after the use of the antitoxins.

These bacterial vaccines, apart from BCG vaccine, have relatively simple controls (see Table II). Provided that the medium in which the organisms are grown does not add any substance to the vaccine that may cause sensitization in the inoculated subject, then the controls are directed entirely towards the safety, or lack of toxicity, and the efficacy or potency of the vaccine. By far the greatest effort in this respect goes into potency testing. These tests may be dependent upon the ability of the vaccine or toxoid to immunize animals against a lethal, paralytic or skin test challenge or, as with pertussis, they may appear to be wholly artificial by protecting against an intracerebral challenge with living organisms. Nevertheless, the potency assay for each vaccine has been investigated and is one shown to parallel the efficacy as measured in man. These two tests of toxicity and efficacy coupled with the demonstration in media that the vaccine is free from contaminating bacteria or fungi, complete the controls on killed bacterial vaccines. Even with the BCG vaccine the only additional controls are to ensure that the correct strain has been used during production and to make sure also that laboratory animals are sensitized, the degree of which is associated with its ability to induce immunity in man.

The technical developments in tissue culture techniques together with the determination of the critical concentration of formaldehyde that would kill poliomyelitis viruses and at the same time retain antigenicity, heralded the explosion of activity in the production of virus vaccines. As each new causative agent for a virus disease was isolated and grown in tissue culture so the vaccine was soon to follow. During the last ten years there has been a move towards the production of virus vaccines from living attentuated viruses which grow in the

vaccinated subject, thereby giving immunity rather than by attempting to grow large quantities of the virus and hoping to inoculate a sufficient antigen stimulus by means of the killed virus.

Just as the production of vaccines has awaited technical developments so the control of vaccines has taken advantage of these developments and has become more sophisticated throughout the last fifteen years. The more stringent controls that we apply to vaccines today started with the production of the potentially dangerous inactivated poliomyelitis vaccine, for although the virus was killed the possibility of living virus particles remaining undetected in the vaccine was a potential hazard. Such tests are in marked contrast to the rather perfunctory tests that were applied to the virus vaccines developed many years earlier (see Table III).

Table III. *Test on virus vaccines*

Live		Killed	
Vaccine	Tests	Vaccine	Tests
Poliomyelitis, Measles, Rubella, Mumps	Approval of strain	Influenza	Inactivation
	Tests on cell cultures for virus contamination		Virus antigen
			Identity
	Tests on virus harvests for:		Sterility
	(I) Bacteria, fungi, mycoplasma		
	(II) Neurotropic viruses (seed virus only for some vaccines)	Poliomyelitis	Inactivation
			Test for SV40
			Test for B virus
	(III) Virus contaminants in tissue culture and animals		Identity
			Sterility
			Safety (neurovirulence)
	Test on final bulk		Potency
	(I) Virus concentration		
	(II) Marker tests		
	(III) Tissue culture		
	(IV) Laboratory animals		
	(V) Bacterial, fungal and mycoplasma contamination		
	(VI) Toxicity		

The tests are both more numerous and more complex not only because the substrate needed for the growth of the virus is a living cell but also because of the more exacting tissue culture techniques. By far the greatest effort goes into the examination of the vaccines for the presence of extraneous agents, both at the monovalent virus harvest stage, done by the manufacturer as 'in process' controls, and when the harvests are blended to form a bulk, at which time both the manufacturer and the control laboratory examine the material. These tests were developed largely because in 1955 the most convenient and plentiful source of

tissue that would support the growth of poliomyelitis virus was monkey kidney tissue. The monkeys were caught in the jungle, transported long distances and, after a quarantine period of 6 to 8 weeks, the kidneys were used for the production of the cell substrates in which the virus was grown. It became apparent at an early stage that monkeys may harbour a large number of viruses (about 30 DNA viruses and 28 RNA viruses) and the most stringent tests were required to ensure that these viruses were not present in the living form in the final vaccine. Such tests involved the inoculation of many different cell cultures and demanded an observation period of at least twenty-one to twenty-eight days in order to ensure, to the best of our ability, that the vaccines were not contaminated.

The testing of the more modern live attenuated virus vaccines calls for even greater vigilence because there is no inactivation of the vaccine virus and, therefore, any contaminant arising from the cell substrate will be present in the living form in the final vaccine. Tests on these vaccines, therefore, involve an examination not only of the virus harvest but also of the cell cultures on which each virus harvest was made. There is in addition another complicating factor because antisera must be used in order to neutralize the vaccine virus and at the same time leave unneutralized any contaminating virus in order that it may be detected in the virus harvest.

Table IV. *Cell substrates for production of vaccines and sources of cell substrates*

Vaccines				
Polio, killed	Polio, live	Measles, live	Rubella, live	Mumps, live
Monkey	Monkey Human diploid cells	Dog Chicken Guinea-pig	Dog Rabbit Duck Guinea-pig Human diploid cells	Duck

It is because of the potential risk that the cell substrate, in which the vaccine is made, may be contaminated that the tendency today is to use a cell substrate derived from an animal grown in the laboratory under clean conditions such that the probability of a contaminating virus being present is much reduced. Thus when measles, rubella and mumps vaccines were produced, the manufacturers moved away from the use of monkey kidney with all its contaminating viruses and moved towards chickens, ducks, rabbits or dogs, all of which are grown under very clean conditions in the laboratory (see Table IV). It is interesting to note that of these cell substrates, very few viruses have been isolated and the use of them has removed a great deal of the hazard and wastage in the manufacture of virus vaccines.

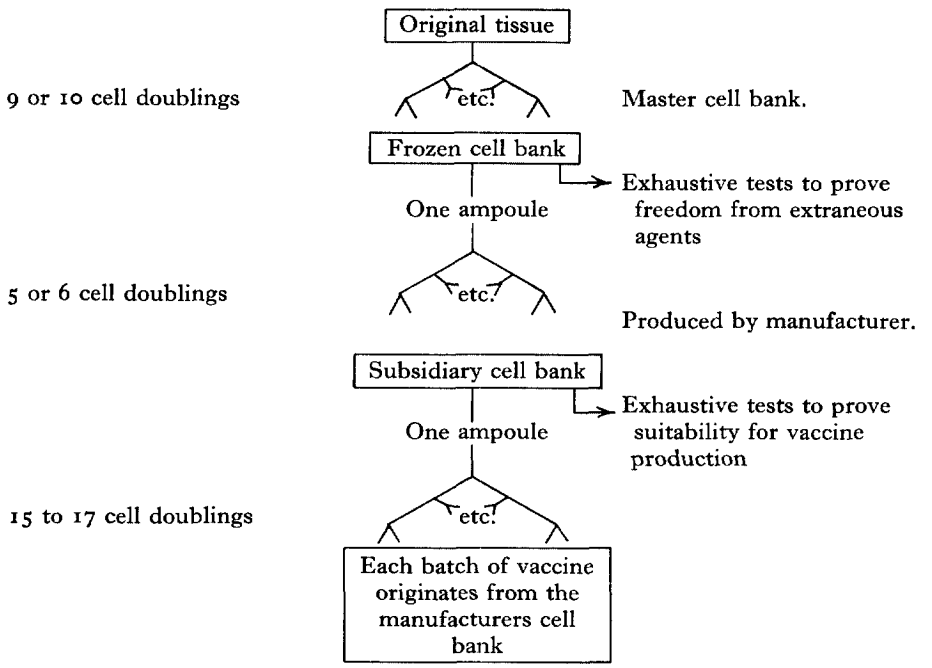

Fig. 1. The use of a cell bank in vaccine manufacture.

A more modern trend is to establish a cell bank (see Fig. 1) from a tissue that has been shown to be free from contaminants. In this way, a portion of such a virus-free cell bank, which may be stored indefinitely in liquid nitrogen, may be used for the production of each successive lot of vaccine and the probability of there being any extraneous agent in the final material is very remote. Such a cell bank can be established from a number of tissues, but the only one used on any scale today is that derived from a human embryonic lung.

All the vaccines produced from the viruses isolated within the last fifteen years, therefore, are subjected to stringent controls but in our whole test programme we have some anomalies. Smallpox vaccine is still grown in the skin of animals and the controls are far fewer than those of the more modern virus vaccines. Even though smallpox vaccine has been successful in the eradication of the disease without a high risk of complications, although of course some accidents have occurred, nevertheless, the trend today is to produce the vaccine in accordance with more modern techniques in cell cultures and to have a bacteriologically sterile vaccine.

The production of yellow fever vaccine started long before modern test methods were established. Although a great deal of testing is done with this vaccine there is no doubt that it is time we brought its control, especially with respect to the use of a seed virus free from extraneous agents, into line with those of the more modern vaccines.

Rabies vaccine currently produced in the brains of suckling animals is yet another example of a vaccine requiring much attention in order to improve the manufacture and control methods. It is reassuring to know that many scientists are currently paying great attention to these problems.

The virus vaccines must also be subjected to potency assay. For the killed influenza vaccines the haemagglutinin content is measured because it is believed that the ability of the vaccine to protect against the disease follows closely the concentration of haemagglutinin. Recent studies have suggested that another antigen neuraminidase may play a part in inducing immunity and when more is known about its mechanism of activity further controls may be necessary. For killed poliomyelitis vaccine, however, we must rely on the ability of the vaccine or its dilutions to give an antibody response in laboratory animals.

The live attenuated virus vaccines, measles, rubella and mumps must contain a minimum virus titre in the human dose in order to ensure that they will replicate in the host, establish an infection and give an effective antigenic stimulus. The potency assay of these vaccines, therefore, involve a determination of virus content by assays in cell cultures.

The control of vaccines today, therefore, is both stringent, time consuming and extremely expensive because of the expertise involved, Both the manufacturers and the control laboratories put a great deal of effort into ensuring that the vaccines are both safe and effective and will be freely available to the public health departments for the immunization of their children either individually or in community programmes. When a vaccine is released for use and has left the refrigerated storage of the manufacturer, however, there is no control, either by the manufacturer or the control laboratory, and the vaccines at that time are in the hands of health authorities or individual doctors. If they are incorrectly stored either in the clinic or in the doctor's surgery then much of the effort put into their production and control will have been wasted.

Not all countries have effective control of the immunological products used in their communities and the questions they must answer are 'how much should we be doing' and 'how much can we rely upon tests of the control laboratories in other countries'. Many countries appeal to WHO for help in this respect and their role is becoming more important. We know that accidents have happened in the past due to lack of adequate control and they will continue to happen unless an effective control mechanism is established in all countries in the future.

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QUALITY CONTROL

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As Dr Perkins emphasized in his report the two main factors involved in the quality control of vaccines are safety and potency. Accordingly, the requirements for vaccines – generally speaking for immunological products – must take in consideration both aims: highest degree of safety and suitable level of effectiveness. This purpose is greatly supported by the work of the World Health Organization in the elaboration and issue of requirements for manufacturing establishments, control laboratories, for virtually all important vaccines and by providing international standards, reference preparations and reference reagents. The WHO requirements are continually revised and adapted to the new results and achievements of immunology, immunochemistry, bacteriology, genetics and technology. The adoption and application of these requirements on a worldwide level have greatly contributed to the standardization of the production and control of immunological products and, consequently, to the approach of the two main aims: safety and potency.

The International Association of Biological Standardization considers as its duty the standardization of the production and control of biological preparations and the great number of congresses and symposia organized in the past 18 years by the Association on various fields has considerably contributed to this objective.

One of the purposes of international requirements for biological substances is also to facilitate exchange of these products between countries; therefore it would be very important if these requirements were adopted and applied by the national control authorities of all countries.

In Hungary, the requirements of the Hungarian Pharmacopoeia are in agreement with the WHO requirements for biological substances. A triple quality control system is adopted: each batch of all immunological products is controlled according to the requirements by the Production Department, the Biological Control Department of the manufacturing institute and finally by the national control authority – the Department for the Control of Sera and Vaccines of the National Institute for Public Health. The product can be released only if it meets the requirements in this triple control system.

In spite of the development and improvements of the laboratory control methods, comparative investigations have shown that in a considerable percentage of the cases there is a discrepancy between the results of the laboratory tests for potency and innocuity or toxicity and the results in the field. This is easy to

understand if we take in consideration the large differences between the human and animal organisms. To overcome this problem, a field control method of all large-scale applied vaccines was developed in Hungary by the National Control Institute; each batch of vaccine after having passed all laboratory tests for potency and innocuity is inoculated in groups of 50 persons of the same age as it is prescribed for the vaccine in question. After the inoculation the vaccinees are observed for reactivity and, two weeks after the inoculation, blood is taken and the antibody content of the sera is tested individually. The requirements are as follows:

DTP vaccine Two weeks after the last inoculation of the priming at 3, 4 and 5 months of age the diphtheria and tetanus antitoxin titre must be at least 0.1 IU/ml and the pertussis agglutinin titre at least 1:320 in 90 per cent of the infants. As reactivity is concerned, local infiltrations may be found in 4–8 per cent, temperature over 38 °C in 10–12 per cent of the cases.

Smallpox vaccine After the primary inoculation a positivity in at least 90 per cent of the vaccinees is required.

Measles vaccine Two weeks after the inoculation with live attenuated vaccine a seroconversion is required in at least 90 per cent of the vaccinated persons.

All changes in the composition of a vaccine – amount or quality of the antigen – are carefully controlled before acceptance and release on groups of persons. The same refers also to new types of vaccines.

In our opinion, by the consequent performance of the laboratory tests according to the WHO requirements and of our field control system, a safer and more reliable control of the innocuity and efficacy of the vaccines may be achieved.

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CONTROLE DES UNITES VIVANTES DU BCG

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La protection contre l'infection tuberculeuse est conférée par le BCG vivant, persistant dans l'hôte. L'efficacité du BCG est donc déterminée par les unités vivantes (UV) existant dans le vaccin.

Les résultats de la détermination des UV calculées à partir des comptes des colonies sur milieux solides sont influencés par les facteurs techniques, les différences de méthodes *in vitro* et les divergences des principes d'évaluation statistique.

Le but de cette présentation est: (1) faire l'évaluation comparative des milieux solides Acide-oléique-albumine-agar au sang (OAA-S) et Löwenstein–Jensen (L–J), (2) tester l'influence de la surface disponible de ces milieux déterminée par les containers: (*a*) boite de Pétri, (*b*) tubes de Legroux (Lx) et (*c*) tubes à essai de 22 (T22) et 16 (T16) mm de diamètre sur la détermination des UV du vaccin BCG par l'estimation des UV du compte des colonies développées sur la surface des milieux solides, (3) présenter la méthode de calcul avec le micro-ordinateur Olivetti Programma 101, (4) montrer une analyse statistique de l'évaluation comparative. Dans ce but on a réalisé une expérience comparative.

Le Tableau I montre l'effet du milieu et du container sur la détermination des unités vivantes du BCG, les données et résultats des comptes des colonies.

Le Tableau II montre les principes de l'analyse statistique pour comparer la différence entre plusieurs méthodes de détermination des unités vivantes du BCG.

Les Tableaux III et IV montrent le programme pour calculer les UV du vaccin BCG et comparer la différence entre deux méthodes de détermination des UV avec Olivetti Programma 101.

CONCLUSIONS

Il a été démontré que la possibilité de démonstration des unités vivantes existant réellement dans le vaccin BCG est influencée par le milieu et sa surface déterminée par le container. Comme expérience modèle on a ensemencé parallèlement le même échantillons de vaccin sur les milieux et containers sus mentionnés. On a trouvé que les nombres de colonies sont plus élevés sur le milieu au sang (incubation: 37 °C/17 jours) par rapport au milieu à l'œuf et les nombres des

colonies diminuent au fur et à mesure dans les containers de Legroux et des tubes de 22 et 16 mm de diamètre sur milieu Löwenstein–Jensen (incubation: 37 °C/ 28 jours). Plus la surface du milieu est réduite plus le nombre des colonies est bas ('Overlapping'). L'analyse statistique comparative des résultats (voir Tableaux I–IV) montre qu'une différence significative existe parmi les milieux et les containers utilisés pour la détermination des particules cultivables du BCG.

A côté de la virulence résiduelle de la souche, les UV existant dans le vaccin déterminent l'efficacité de la vaccination. Ainsi l'estimation la plus exacte des UV peut assurer l'étude de correlation entre les résultats des méthodes *in vitro* et ceux de la valeur protectrice de la vaccination et du test tuberculinique post-vaccinal. Autrement il est risqué de conclure qu'il n'y a pas de rapport et de correlation entre les résultats *in vitro* et l'efficacité de la vaccination par le BCG.

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Tableau I. *Effet du milieu et du container sur la détermination des unités vivantes du BCG*

(Données et résultats des comptes des colonies. BCG, Souche, Culture: P1102/824, Sp80S2, 8 jours âge. Vaccin, origine: Bpest. Lyophilisé. Lot no.: 083-150366. Diluent: Sauton 1+3+0,01 % Bovin V. Date inoc.: 120866.)

Milieux	Ensemenc. h	Ensemenc. Vol. (ml)	Incub. temp.	ω	λ	Lecture date
OAA	3 h intervalle	0,02	37 °C	20	50	290866
L–J		0,1	37 °C	40	100	090966

Milieu/lot, container, surface	Nombre de colonies par volume ensemencé	Degré dilut. ($\times 10^4$)	n	Sx	$\bar{x}$	t	Sx^2	X^2	UV/ml $\times 10^6$	
OAA-S/124, Petri	38 + + 31 + 23 26 30 33 40	2	13	434	33,4	−4,32	14 824	10,04	41,76	{44,27 LS 39,40 LI
	37 38 ct 38 + + 32 38 + 30									
	18 17 20 19 15 25 23 14 19 26	4	40	822	20,6	−1,05	17 674	38,05		
	15 20 24 21 16 17 20 25 22 28									
	21 13 26 32 20 20 16 18 19 25									
	11 18 19 22 26 25 25 16 24 22									
	8 11 10 9 9 9 10 19 11 12	8	20	222	11,1		2 618	13,86		
	9 12 12 10 9 18 12 11 9 12									
L-J/269, Legroux, 50 cm²	11 42 39 27 60	8	5	179	35,8	−1,23	7 735	37,06	32,00	{37,95 26,98
	26 25 18 22 18	16	5	109	21,8	−0,21	2 433	2,61		
	9 19 8 14 8 11 10 14 9 10	32	10	112	11,2		1 364	9,79		
L-J/269, Tubes de 22, 20 cm²	20 28 17 19 19 23 . 22 18 27	8	9	193	21,4	−2,71	4 261	5,70	20,07	{22,54 17,88
	8 20 13 19 15 15 11 15 10 20	16	10	146	14,6	−0,15	2 290	10,85		
	3 6 4 5 5 11 6 7 14 14	32	10	75	7,5		709	19,53		
L-J/269, Tubes de 16, 10 cm²	23 17 21 30 15 23 22 19 28 23	8	10	221	22,1	−2,80	5 071	8,46	20,39	{22,69 18,32
	17 9 18 10 19 17 17 18 13 22	16	10	160	16,0	1,22	2 710	9,38		
	12 9 1 6 4 10 7 2 6 8	32	10	65	6,5		531	16,69		

Tableau II. *Effet du milieu et du container sur la détermination des unités vivantes du BCG. Principes de l'analyse statistique pour comparer la différence entre deux méthodes de détermination des unités vivantes du BCG*

Milieux et containers comparés		Paramètres du I					Paramètres du II								
					UV/ml					UV/ml					
I	II	Sdf	SSx	SX^2	$\times 10^6$	log	Sdf	SSx	SX^2	$\times 10^6$	log	z	s_z	t	p 5 %
OAA, Petri	L-J, Legroux	70	1478	61,95	41,76	7,6208	17	400	49,46	32,00	7,5052	0,1156	0,0339	3,4134	S
OAA, Petri	L-J, Tube 22						26	414	36,08	20,07	7,3026	0,3182	0,0300	10,6168	S
OAA, Petri	L-J, Tube 16						27	446	34,53	20,39	7,3094	0,3113	0,0290	10,7265	S
L-J, Legroux	L-J, Tube 22	17	400	49,46	32,00	7,5052	26	414	36,08	20,07	7,3026	0,2026	0,0429	4,7181	S
L-J, Legroux	L-J, Tube 16						27	446	34,53	20,39	7,3094	0,1957	0,0413	4,7373	S
L-J, Tube 22	L-J, Tube 16	26	414	36,08	20,07	7,3026	27	446	34,53	20,39	7,3094	−0,0069	0,0342	−0,2008	NS

La différence des log des UV obtenues sur les deux milieux solides est exprimée par $z = \log UV_I - \log UV_{II}$ et son écart type est $s_z = \log e \sqrt{(SSX^2/SSdf)}\ \sqrt{(1/SSx_1 + 1/SSx_2)}$. Les tests $t = z/s_z$ faits deux par deux entre les milieux donnent les résultats de l'analyse statistique comparative montrant que sur les milieux OAA-S et L-J/Lx les valeurs des UV sont significativement plus élevées.

Tableau III. *Programme pour calculer les UV du vaccin BCG: Olivetti Programma* 101 *Microcomputer*

Cart 1			Cart 2		Calcul des UV du L-J/269 Tubes de 16					
AZ	d◊	B ↕	AV	B +		Z	17	S	23	S
b*	d ↓	Y	b ↓	c ↕	12	S	9	S	17	S
B*	e ÷	aV	B ÷	a ↑	9	S	18	S	21	S
c*	A◊	d ↓	A◊	d ↓	1	S	10	S	30	S
C*	D◊	BX	d ↕	b ↓	6	S	19	S	15	S
AY	a ↑	D ↕	d ↓	+	4	S	17	S	23	S
d*	d ↓	D ↓	B ÷	b ↕	10	S	17	S	22	S
D*	e ↓	BX	c ÷	B ↓	7	S	18	S	19	S
e*	—	e ↕	CX	DX	2	S	13	S	28	S
BV	c +	B ↕	A√	b ÷	6	S	22	S	23	S
S	c ↕	B +	A◊	/V	8	S		V		V
d ↓	D ↓	B ↕	C ↓	c ↓		V	10.00000	e◊	10.00000	e◊
+	eX	d ↕	c ÷	cX	10.00000	e◊	160.00000	d◊	221.00000	d◊
d ↕	d ÷	b +	b ÷	c ↕	65.00000	d◊	16.00000	A◊	22.10000	A◊
↓	d −	b ↕	A√	d ↓	6.50000	A◊	2710.00000	D◊	5071.00000	D◊
X	A◊	dX	D ↕	cX	531.00000	D◊	9.37500	A◊	8.45701	A◊
D +	C +	D ↕	a ↑	A◊	16.69230	A◊	1.6	S	0.8	S
D ↕	C ↕	D—	d ↓	d ↓	3.2	S	1.21642	A◊	−2.80350	A◊
a ↑	e ↓	D ↕	b ↑	c ÷						
d ↓	S	dX	c ↑	A◊						V
e ↓	÷	e +	D ↓	S					20.38857	A◊
+	e ↕	CX	B ↕	aV					1.09168	A◊
e ↕	b ↓	c ÷	AW	B ↕					22.68901	A◊
CV	/V	A√	c ↓	W					18.32136	A◊
AV	d ↓	D ↕								
e◊	b ↕	D ÷								
	e ↓	A◊								
		Y								

Tableau IV. *Programme pour comparer la différence entre deux méthodes de détermination des UV du vaccin BCG. Olivetti Programma* 101 *Microcomputer*

Cart 1				Différence des UV, Tubes de 22: Tubes de 16	
AV	AW	B +	B ↓		V
b*	B ↓	B ↕	A ↕	9	S
B*	C ↕	B ↓	A ↓	193	S
c*	B*	BX	d ÷	5.70	S
BV	CV	c ↕	/V		
S	AZ	a ↑	C ↓	10	S
↓	B ↓	d ↓	C +	146	S
a ↑	C +	d ↑	a ↑	10.85	S
d ↓	B ÷	C*	RX		
—	C ÷	BY	R ↑	10	S
b +	cX	B ↓	RS	75	S
b ↕	b ÷	d ÷	R ↕	19.53	S
S	A√	C +	d ↑		
B ↓	b ↕	C ↕	÷		W
+	S	B ↓	A◊	10	S
B ↕	↓	cX	b ↕	221	S
S	S	B ↕	÷	8.46	S
c ↓	÷	a ↑	A◊		
+	B ↕	d ↑	b ↕	10	S
c ↕	a ↑	d ↓	b ÷	160	S
/◊	d ↓	+	A◊	9.38	S
CV	B ↓	d ↕	V		
	+		aV	10	S
	B ↕		CY	65	S
	—			16.69	S
					Z
				20.07	S
				20.39	S
				−0.00687	A◊
				0.03416	A◊
				—0.20111	A◊

GENERAL DISCUSSION

CHAIRMAN I have been asked by Dr Schild if he may show three slides concerning the newer methods of control of influenza vaccine. I think it would be quite interesting if he would do so.

SCHILD (UK) As Dr Perkins mentioned in his report, the basis of current methods of quantitation of influenza vaccines is the haemagglutination test. This has certain disadvantages both in its variability, which is dependent on the source of chicken erythrocytes used and on a number of other factors, and, more important, in its dependence also on the physical state of the antigen, whether it is in the form of intact or disrupted virus particles. Ironically, the most pure potential influenza vaccines, which would be the crystalline haemagglutinin, would have an absolutely zero score in this test because it is a monovalent subunit and not capable of agglutinating red blood cells at all. So there is obviously a need for a different type of antigen assay if this type of vaccine comes into general use.

At the recent IAMS Conference on influenza in London there was a general discontent with the quality controls now available for influenza vaccines.

A recent advance in knowledge which can contribute quite a lot to the study of the purity of influenza vaccines is our ability now to say that the influenza virus contains seven polypeptides, and our ability to relate these seven polypeptides with known structural and antigenic components of the virus. This could obviously be adapted as a quality control for the purity of virus particle vaccines, or for subunit vaccines.

Analysis of the polyacrylamide gel electrophoresis pattern of a typical zonally purified influenza vaccine shows that there are seven polypeptides present and very little non-viral protein. This type of test could be adapted as a purity control for vaccines containing intact particles, or for subunit vaccine because, for example, a purified influenza virus haemagglutinin preparation should contain only two polypeptides corresponding to the haemagglutinin components HA1 and HA2.

We have been working also with a quantitative single radial diffusion test which can be used as an accurate method of assaying, the haemagglutinin antigen. This is an agarose gel in which is incorporated at a very low concentration anti-serum against purified haemagglutinin. Into wells in the gel are added the influenza vaccine preparations which have been diluted appropriately and treated with detergent to disrupt the particles enabling the haemagglutinin subunits to diffuse into the gel. The area of the zone of precipitation which forms is directly proportional to the amount of haemagglutinin antigen present and is not influenced at all by the original state of the preparation, whether it was intact particles or disrupted particles, because during the test the virus is broken down into its component subunits. Both with control antigen preparations and vaccines a straight-line relationship was found.

Another version of the single radial diffusion test is the accurate assay of antibody levels induced by vaccines. In this test purified influenza virus particles are incorporated in the gel at a standard concentration and antibody from animals which have been immunized with potential vaccines is introduced into the wells. The area of opalescence in this case represents the level of antibody. This is far more accurate than conventional methods of antibody assay. Conventional HI tests are subjected to approximately 200 to 400 per cent variation. The degree of variation in this test is not greater than 4 per cent, so it offers a far more accurate way of measuring antibody. Antibody to haemagglutinin or to neuraminidase may be assayed basically by the same procedure.

CHAIRMAN Thank you very much, Dr Schild. I might say that recently Dr Schild has made the purified haemagglutinin and the anti-haemagglutinin for use in these plates and we, in the United Kingdom are about to start a collaborative assay. It will be very interesting to see what close correlation we obtain with the measurement of the concentration of haemagglutinin in a number of vaccines that we shall select.

Would anyone like to discuss the control of vaccines?

HILLEMAN (USA) I might comment briefly on the use of cell bank *vs* primary cells for vaccine production that Dr Perkins talked about.

There is no question that primary cells of wild caught animals – such as the monkey – are a hazard and there is little justification in using them. The use, however, of primary cells from embryonic tissues or from tissues of animals that are specific pathogen-free and grown in quarantine is a different matter.

The cell bank–diploid cell concept has advantages and disadvantages just as do primary cells and I must preface my remarks by saying that I personally approve of both.

The so-called certification and 'guaranteed' freedom from extraneous agents of diploid cells is largely myth since certification is at the level of distribution (7–9th passage) and there must be many more passages – up to 15 or 18 before the cells can be used for production. During this time, exogenous agents from people, media, air, etc., can be introduced into the cultures and these can cover the spectrum of frankly recognizable bacteria and viruses to occult viruses and even the theoretical oncogene.

There is a real advantage of primary cells in that there is a limitation to a particular lot and a consequent limitation in number of persons who will receive that lot. With diploid cells and with an occult agent in the seed line, it becomes an omnipresent thing in all vaccine lots.

I say all this just to call attention to it. As I mentioned before, I think both the primary cell and diploid-bank approaches are acceptable, insofar as we now see it.

CHAIRMAN One of the technical developments that has taken place now that more people are using a cell bank technique is that no longer are people using 1 to 2 splits, as we call it. They have cut down markedly on the manual handling by using as high as 1 to 10 splits. So we no longer need 14 or 15 manipulations between the cell bank and the stage when we use the cells for the production of vaccine.

As to the possibility of there being an occult virus or virogene, Dr Hilleman has said that this is a theoretical possibility, and it is no more than that.

SACHS (UK) I should like to ask a question on the effect of the length of storage on potency and reaction. What prompts me to raise this is the comments of Drs Cohen and Cockburn about the screaming syndrome that sometimes occurs when vaccine is given soon after production, and then the falling off at a later date. In the early stages one would have a relatively fresh vaccine, and possibly in the later stages the vaccine would have been stored longer. I had to carry out some work on typhoid vaccine when we had an undue number of reactions. We found that these occurred in batches that were relatively fresh, issued by mistake, instead of being stored for a period. We followed this up and found that use of the same batch of vaccine after six months storage resulted in fewer reactions. We did various potency tests – mouse protection etc. – and we found there was no difference from the early batch.

Incidentally, these were phenol-killed vaccines. The question was raised about the possibility of a certain amount of denaturization continuing, possibly due to the phenol. Perhaps you could comment.

COHEN (The Netherlands) I can only comment so far as shock and persistent screaming are concerned. The ageing of the vaccine definitely does not play any role in causing these symptoms. We had at least two children who were injected three times with DTP-polio vaccine and got persistent screaming or shock: every single time they got a different lot of vaccine. I believe it is more the reaction pattern of the children to certain toxic com-

ponents in the vaccine, whatever they may be. I do not believe that ageing, at least in this vaccine, plays any role at all.

CHAIRMAN Would you not agree, Dr Cohen, that with pertussis vaccine the storage of vaccine does decrease the toxicity?

COHEN (The Netherlands) It depends how you handle the vaccine. We centrifuge the vaccine, which is very important in our opinion. We have carried out a clinical trial comparing acid-precipitated pertussis vaccine with the centrifuged vaccine: precipitated vaccine causes higher temperatures in infants.

The second thing is that we heat the vaccine at 56 °C for half an hour. The result is that we obtain complete detoxicification in the mouse toxicity test. When you test such a vaccine over and over again you will find exactly the same results in the mouse toxicity test.

So I believe that this storage problem has to do with actual exotoxin which may remain in the vaccine, because it is not properly detoxified by heating. During storage this exotoxin is gradually destroyed.

COCKBURN (WHO) In our early trials we did have batches of vaccine which had a rather high mouse toxicity. If we kept them for six months this was considerably reduced. However, I do not think there is any evidence that the screaming was associated with this type of mouse toxicity.

CHAIRMAN That is a very important point. There have been a number of studies that have not really correlated these two factors.

SENCER (USA) Mr Chairman, I do not hesitate to exhibit my naiveté. In all of our experience in the United States this is the first time I have heard the syndrome of persistent screaming mentioned. I wonder how many other countries experience this. Could this be a cultural situation rather than an immunological one?

CHAIRMAN I thought it was a very general phenomenon.

COHEN (The Netherlands) If you go out and look for them you will find them. Usually they are not reported. You could even see that from the slide I showed. We had this town under very good observation, and the province to a somewhat lesser extent, and even there you see the difference in the number of cases reported. The reason is that the symptoms occur within six hours. The mother suddenly finds her child in the cot. The child is very pallid and she thinks it will die. She takes the child out and the symptoms disappear. So she often does not mention it to the doctor. She believes it is something she can expect after vaccination. With the persistent screaming she is less worried about the child than about the neighbours, because the child may keep the neighbours awake for some hours.

I observed my own son – it is a general phenomenon – for six hours after vaccination, which is when the reactions take place. There may not be persistent screaming, but it is obvious that the child does not feel very well. After six hours he gradually resumes his play. We are now trying to find what happens pharmacologically in the child. It may well be caused by a failure of the adrenergic system.

NETTER (France) Though producers and controllers agree generally that control of vaccines is very strict, I should like to insist on a very important control which is not routinely made. It is a stability test for freeze-dried vaccine.

Yesterday Dr Henderson told us that for an eradication campaign against smallpox it was very important for WHO to have regular lots of potent vaccine, and that at the start of the eradication campaign this was not the case for all vaccine.

Mr Chairman, a moment ago you were insisting on the fact that the private practitioners were sometimes not keeping the vaccine at the right temperature. I therefore feel that it is important from the public health point of view to produce potent and stable vaccine, and maybe to include in the regulations routine potency tests for stability.

LUGOSI (Hungary) I have a question about BCG vaccine. The *in-vitro* determination of variable units gives one parameter for the quality and potency of BCG vaccine. According to the available control data there are large variations concerning the variable unit numbers amongst freeze-dried BCG products manufactured in the different BCG laboratories. The variable unit numbers can oscillate between 1 million and 50 million per ml. The protection against virulent infection depends on the persistence capacity of BCG in the host. So, for instance, giving 100000 BCG variable units intradermally from a vaccine prepared from a strain having normal residual virulence can afford correct post-vaccination allergy and protection. However, we see in practice the administration of 1 million or 5 million variable units intradermally from vaccines containing 10 million or 50 million variable units per ml.

My question is whether this large number of variable units is not superfluous in an immunological sense, in burdening or perhaps paralysing the cellular immune system of the host, which can be particularly dangerous in immunological deficiency states.

CHAIRMAN That is a very difficult question. Would anyone care to answer this?

You do raise an important point, Dr Lugosi, but all we can say in the United Kingdom is that the vaccine we use has been shown to be protective for 10 years and we know nothing more than that. What other people use, and why they use many more organisms, I really do not know because there are few data. Our international association has in progress a collaborative study with twelve countries measuring many laboratory parameters of the vaccine, and they will be subjected to field study in children when the first part of the study is completed.

Until we have these data I do not think that we shall be able to say much more about it.

LUGOSI (Hungary) Are you participating in this collaborative study?

CHAIRMAN Yes.

GEAR (South Africa) I should like to ask whether it is generally recommended that pertussis vaccine be not given to children over 3 years of age, and whether the problem of encephalopathy following its use has been satisfactorily eliminated by the careful selection of strains.

Thirdly, is there any further knowledge of its pathogenesis? I believe it is associated with fibrin deposition in the capillaries of the brain with associated capillary haemorrhages. One wondered whether this could not be accounted for by the occasional mistaken intravenous injection of a particulate suspension when some of the particles would end up in the end capillaries of the brain, setting off the encephalopathy within a short time after the inoculation.

CHAIRMAN I do not know whether Dr Cohen would wish to say something on this point. In the United Kingdom we do not include a pertussis component when a child has a booster dose at school entry, and I think that is in agreement with Dr Cohen.

Would you care to say something about this, or its pathology? I think there is very scant knowledge on the pathology, but perhaps you could say something.

COCKBURN (WHO) Dr Gear may be right, but I do not think that there is any real evidence about this at all. It is one of the great unknowns, unfortunately.

GRIFFITH (UK) It is interesting that there is no constant time relationship between the development of encephalopathy and administration of pertussis vaccine.

Hypsarrhythmia, a common condition in children, is usually recognized at about the age at which children are routinely vaccinated. It is a condition which develops in the second six months of life and is often attributed to vaccination, but there is no apparent time relationship between administration of the vaccine and development of the condition.

COHEN (The Netherlands) There is only one thing I can add to this. Encephalopathy after pertussis vaccination occurs very seldom, at least so far as we are informed. I would

say somewhere between 1 in 500000 and 1 in one million vaccinations. We had several cases in which we could not rule out an association with a virus infection, i.e. herpes encephalitis which was confirmed serologically.

UNGAR (Switzerland) There was a publication by a Medical Officer of Health (Dr Hopper), who pursued about 2000 families in his area. He has shown that there are certain familial predispositions to reactions. In certain families the children inoculated with a triple vaccine had reactions and I think that he showed that there is quite good evidence that these neurological symptoms are due to certain familial conditions.

SACHS (UK) There are two questions in connexion with yellow fever vaccine that I should like to raise. This concerns travellers, a point which was raised earlier, and this is also rather important in the Services; when it is necessary to give both yellow fever and smallpox. I am talking about primary vaccination against smallpox, and there seems to be some divergence of opinion. I believe that the French have given a vast number together. We recommend that yellow fever should be given first and smallpox afterwards. If smallpox is given first and there is a primary take, the interval should be 21 days. In the early 1950s there were some cases of encephalitis, although we were using the 17-D strain.

The second point is about yellow fever and BCG. We recommend a 10-day interval between the two if they are both required, irrespective of which is given first.

Could these two points be clarified, please, because of the divergence of opinion?

RELYVELD (France) I will give some results this afternoon about yellow fever and smallpox.

The only thing I wanted to say was in connexion with pertussis. Dr Cohen said that he centrifuged his vaccine and then found that there were fewer post-vaccinal reactions. I agree with him, because we found that we could still further reduce post-vaccinal reactions to pertussis if we adsorbed the vaccine and then took away the supernatant two or three times. If you leave the vaccine for, let us say, 14 days in an ice box, you will find that the vaccine becomes yellow. There is a material diffusing out of the pertussis bacillus. The vaccine settles down and you can take off the clear supernatant easily. If you do that twice, and replace the supernatant by sodium chloride solution, you will find that you have no more fever after vaccination, and we never had neurological reactions.

CHAIRMAN Does the vaccine protect?

RELYVELD (France) Of course it protects. We do not use vaccine that has not passed the mouse protection tests.

CHAIRMAN But how do you know?

RELYVELD (France) What we also did was to titrate the supernatant to find out whether there was some protecting antigen in it. We never found protecting antigen in the supernatant. So I think myself that there is some kind of endotoxin diffusing out of the bacteria. If you have a non-adsorbed pertussis vaccine it will not settle down so you cannot make a decantation, but if you have an adsorbed pertussis vaccine it decants very easily in about 5 or 6 hours and you can take away the supernatant.

I should also like to ask Dr Joó a question. We have spoken a great deal about vaccine here, but we have not spoken about oral vaccines. There was a question about typhoid vaccination, and I think that in Eastern Europe many countries at the moment use oral vaccination. Does he have any idea of the success of this method because I think it is important. If you can give an oral vaccine you have no post-vaccinal reactions. What is the situation?

JOÓ (Hungary) Of course, oral vaccines have their advantages in that they can be applied without any restrictions because of their non-reactivity. Some time ago a field trial was carried out with the oral typhoid vaccine prepared in Eastern Germany, and the epi-

demiological results seemed to be very promising. The test has to be repeated. It was a killed whole-cell vaccine, but in any case I must say that in my opinion at least the vaccine of the future must be an attenuated oral vaccine. But of course the problems to be resolved are much more difficult.

CHAIRMAN Can anyone answer General Sachs' question: what about yellow fever and smallpox, and yellow fever and BCG?

GORDON (UK) Probably you will remember, Dr Perkins, that this problem was considered on one occasion by the Joint Committee on Vaccination and Immunization which advises the health authorities in the United Kingdom. The recommendation that they gave then, which is quite recent, was that there should be an interval of three weeks between the two, but that if this was impossible the two should be given simultaneously.

HENDERSON (WHO) In the Francophone countries of Africa there is a fairly substantial and successful experience in the simultaneous administration of smallpox and yellow fever vaccines. Dr Meyer has confirmed these observations in studies which he and his colleagues conducted in Upper Volta. All evidence of which I am aware indicates that the two vaccines may be given simultaneously, albeit at separate sites, with safety and efficacy. In a study recently reported, smallpox vaccine and yellow fever vaccine were given sequentially at varying intervals of time to determine if there was interference either in seroconversion or in the proportion of take rates for smallpox vaccine. None was found.

NETTER (France) With regard to the stability test for measles freeze-dried vaccine, we find that after two to three days at 37 °C we have the same decrease in activity as in a refrigerator after one year.

CHAIRMAN It seems to me that General Sachs' question with regard to yellow fever and smallpox has been answered and that it can be given with safety. He asked also about yellow fever and BCG. I do not know of any data there, so I think we shall have to leave that with a question mark at the moment.

KRUGMAN (USA) I should like to return to the question of the optimum time to discontinue pertussis immunization. It has been suggested during this discussion that the vaccine should not be given to children over 3 years of age. It seems to me that this decision should be based on an evaluation of the relative risk of complications of vaccination against the relative risk of acquiring pertussis and its complications. In the United States many children from economically deprived areas have never been immunized before attending school between 3 to 6 years of age. In balancing the relative risks, we have recommended that diphtheria and tetanus toxoids combined with pertussis vaccine be given up through the pre-school age, but that pertussis vaccine should be discontinued after 6 years of age.

SESSION VII

IMMUNIZATION SCHEDULES

Chairman: Dr J. W. G. SMITH (UK)

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IMMUNIZATION SCHEDULES

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The choice of vaccines to be used in a community, the number of doses to be recommended, and their timing and spacing, are influenced by many factors which require to be taken into account when planning an immunization schedule, and they may for convenience be considered under the headings of epidemiological, immunological, and administrative factors.

The epidemiologist needs to consider the incidence, severity and mortality of the infectious diseases affecting the population, and the particular age or occupational groups who may be at special risk. He must also examine whether a communal immunity can be secured, with the possibility of perhaps eliminating the infection altogether. At the same time he must take into account adverse reactions caused by vaccines and ensure that they do not cause more illness than the diseases they prevent.

The immunologist aims to provide effective vaccines that will stimulate the optimum protective response – often measurable in terms of a long-lasting, high titre of circulating antibody. The optimum response depends on factors such as the timing and spacing of injections, the use of adjuvants, and avoidance of interference between different antigens, all of which must be considered.

The administrator who has to put into effect the programme also has important contributions to make in devising the schedule because he must balance what is expedient with what is immunologically and epidemiologically desirable. He must ensure that the programme is convenient and practicable, and must take into account social factors – such as that particular age groups may be difficult to reach. He must also evaluate costs and consider the need for recording both the vaccinations given to individuals and any adverse reactions or vaccine failures. It may also be necessary to consider the need for legislation to make vaccination programmes effective.

These different factors will be considered in this paper, particularly in relation to the schedule of immunization adopted in the United Kingdom.

EPIDEMIOLOGICAL FACTORS

A rational schedule of immunization for a particular community depends on an understanding of the incidence, distribution, and effects of those diseases for which vaccines are available. The importance of other control procedures, such as chemoprophylaxis or hygienic measures, must also be considered in order to

Table I. *Basic routine immunization schedule – United Kingdom*

Age	Vaccine
Under 1 year	Diphtheria–tetanus pertussis and oral poliomyelitis (three spaced doses)
1–2 years	Measles
5 years	Diphtheria–tetanus and oral poliomyelitis
10–13 years	BCG
Girls aged 11–13 years	Rubella
15–19 years	Tetanus and oral poliomyelitis

assess the role of vaccination. In the United Kingdom there are seven vaccines currently thought to be worth offering to all children – diphtheria, tetanus, whooping-cough, poliomyelitis, tuberculosis, measles and, for girls, rubella (Table I) – and the reasons for using each vaccine varies. In tetanus, for example, although the incidence is very low, the disease carries a high death rate, vaccination is very safe, and actively immunized persons do not usually require other, potentially hazardous prophylactic measures in the event of wounding. Rubella vaccine is used only with the aim of preventing congenital infections. The other vaccines were introduced because, at the time, the corresponding diseases caused an appreciable number of deaths or serious illnesses, but this is not always true today. Thus the epidemiology of an infectious disease is liable to change and the need for using, or not using, a vaccine requires to be kept under review. Changes in epidemiology may be caused by variation in the microbial pathogen, e.g. the selection of antigenic variants – as in influenza A virus; it cannot be certain that similar changes will not occur in other microbial pathogens for which vaccination is practised. The appearance of previously unimportant serotypes of whooping-cough bacilli has been suggested as the cause of a diminished effectiveness of pertussis vaccine in the United Kingdom (**54**). Although this suggestion has been criticized (**68**), manufacturers of vaccines have nevertheless taken steps to ensure that their preparations include all the known serotypes of *Bordetella pertussis*.

The epidemiology of an infectious disease may also change from alteration in environmental factors affecting the transmission of microbes, and the decline of enteric fever in developed countries, for example, is largely due to such factors. Alteration in the resistance of the individuals making up the population may also affect the epidemiology, e.g. from the effects of vaccination in smallpox, diphtheria and poliomyelitis. Whatever the cause of epidemiological changes they must be taken into account in an immunization schedule. In addition, the picture in other parts of the world must be kept in mind. Thus improved smallpox control in the world has allowed routine smallpox vaccination to be discontinued in the United Kingdom (**12**) and in the United States (**71**). On the other hand, although poliomyelitis and diphtheria are both rare in developed countries their

Table II. *Vaccines used selectively – United Kingdom*

Vaccine	Indication	Schedule
Anthrax	Workers exposed to special risks	3 doses spaced at 3-week intervals 4th dose 6 months later Reinforcing doses annually
Influenza	High-risk patients	Annual single injection
Smallpox	Health Service staff	Re-vaccinate every three years
Tetanus	Un-immunized adults	3 spaced doses

control is thought to depend on continuing widespread immunization(**40**, **64**, **65**) – stopping the use of these vaccines could not be considered until the diseases are controlled on a worldwide basis.

Other diseases exist in the United Kingdom for which the available vaccines are not recommended routinely, but epidemiological considerations may indicate the use of such vaccines for selected groups (Table II). Thus typhoid is too uncommon to justify use of the vaccines at present available, although in the Armed Forces it may be worthwhile(**47**), because troops may rapidly move to parts of the world in which typhoid is endemic and where they may operate under conditions where standards of hygiene and water purity can be difficult to maintain. Vaccination against smallpox is recommended in the United Kingdom at present only for nurses, doctors and certain other groups particularly liable to exposure. Anthrax vaccine is considered necessary only in the case of workers such as veterinary surgeons, who may have an occupational risk of exposure. BCG vaccine is given to newborn babies only when they are born into a household where a sufferer from the disease also lives(**11**); otherwise it is given after the age of 10 years.

The age incidence of a disease, or the age at which morbidity or mortality is high, may also require consideration. Influenza immunization in the USA is recommended annually for elderly people in whom the disease carries a significantly raised mortality rate(**21**). The main risk from pertussis is in the very young(**9**), and for this reason vaccination is started in many countries as early as possible in the infant's life, despite the immunological disadvantages. Diphtheria immunization is concentrated on infants, because, when the vaccine was first introduced, most deaths were seen in infants and most adults were immune (**75**). As the disease has come under control there has been some evidence of an increased susceptibility in older persons, and it is possible that it may become necessary to ensure that adults are boosted in order to maintain an adequate communal immunity(**19**, **64**, **65**). BCG vaccination in the United Kingdom is practised at 10–13 years of age because when it was introduced the duration of immunity was uncertain, and because the incidence was high in young adults, who have usually been regarded as particularly susceptible to tuberculosis(**52**).

The sex distribution of a disease is mainly important when the infection is liable particularly to affect the pregnant woman or the infant *in utero*, as with rubella, or when the vaccine may be harmful. Thus evidence exists that vaccination against smallpox in pregnancy may increase the risk of stillbirth or may sometimes affect the foetus (**40**, **70**), and schedules often include the proviso that pregnant women should not be vaccinated against smallpox. This exclusion is sometimes extended to other live vaccines such as mumps and yellow fever (**71**) or poliomyelitis (**47**).

Live rubella vaccines are particularly contraindicated in pregnancy owing to the risk of affecting the infant *in utero*; where rubella vaccination is now being introduced it may be confined to young girls at an age before they are liable to become pregnant, as is the practice in the United Kingdom (**11**). In the USA, on the other hand, widespread immunization of both sexes is recommended (**71**) in the hope that this may evoke a communal immunity whereby even the non-immunized are protected.

There are few known contraindications to the use of killed vaccines in pregnancy, but nevertheless some obstetricians are reluctant to immunize any pregnant patient. In the case of killed influenza vaccine it has been suggested that its use could promote ABO incompatibility (**20**). On the other hand immunization of pregnant women with adsorbed tetanus toxoid is advocated in countries where *tetanus neonatorum* is common in order to provide passive immunity to the newborn infant (**41**).

COMMUNAL IMMUNITY

The primary aim of immunization is usually the protection of the vaccinated individual, but in recent years efforts have been made to try, by vaccinating a high proportion of the population, to eliminate an infectious disease. Justification of this procedure is based on the success attributed to vaccination against smallpox, diphtheria and poliomyelitis. Following the introduction of smallpox vaccination by Jenner in the United Kingdom nearly 200 years ago the incidence of smallpox in the country steadily declined. Although the relative importance of social improvements and vaccination in causing this decline is uncertain, there seems little doubt that the irradication campaign successfully pursued by the World Health Organization in the last twenty years has been effected largely by means of vaccination (**30**). In the case of diphtheria, immunization is believed to have been responsible for the virtual elimination of diphtheria bacilli from communities in which vaccination has been extensive. The results of the poliomyelitis immunization programme, both with live vaccine (**46**) and with killed vaccine in Scandinavia (**24**), supports the view that immunization campaigns can have the effect of significantly reducing or even eliminating an infection from the community. Recently, therefore, both measles and rubella vaccination (**71**) have been introduced in the USA with elimination of the diseases as the conscious aim. An immunization schedule must take this aim into account since it usually demands a high immunization rate and to obtain this the schedule must be made as convenient as possible both to the health authorities and to the community at large.

VACCINATION AFTER EXPOSURE

Vaccination against most diseases is carried out, as far as possible, before exposure to infection occurs, but in certain instances it may be valuable to immunize, or to boost immunity, after exposure. Where a vaccine is particularly reactive and cannot freely be recommended to all who are liable to be exposed, immunization after exposure may be preferred. Thus, rabies vaccination using both Semple type and duck embryo vaccines has been used mainly after exposure to infection, the long incubation period of rabies allowing the development of an active immunity during the incubation period. It is unlikely that routine rabies vaccination would be introduced, even in countries where rabies is common, except for workers who might be exposed frequently.

Immunization with live, attenuated poliomyelitis vaccine in an exposed population has been shown to be of value, partly owing to interference with wild virus and also, presumably, due to the boosting of specific immunity (**29**). The use of live vaccines for contacts of a case of poliomyelitis is consequently advised (**71**).

Vaccination of exposed persons against typhoid is controversial. In the USA, for example, the procedure is recommended (**71**), but in the United Kingdom it is not (**11**) because the development of immunity following vaccination is believed to be slow, and because diagnosis by serological means might then be made difficult. There is, in addition, the possibility of 'provocation typhoid' (**55**) attributed partly to the effect of endotoxin and partly to a decrease in circulating antibody by absorption onto the injected antigen – the so-called 'negative phase' (**75**).

In tuberculosis the injection of BCG vaccine in persons who have already acquired infection with tubercule bacilli has been regarded as risky owing to the fear of reaction in hypersensitive subjects. However, with increasing experience of the use of BCG vaccine, the precaution of prior tuberculin testing is no longer everywhere regarded as essential (**56**).

Passive immunization with homologous or heterologous serum preparations is often practised after exposure, for example, in gas gangrene and infectious hepatitis. In diphtheria, tetanus, and rabies, passive immunization is commonly accompanied by simultaneous active immunization. In addition, immunization schedules often include recommendations concerning the use of booster inoculations in actively immunized persons who are exposed to tetanus by wounding or to diphtheria by contact with a case or carrier – in both instances the opportunity is taken to further boost the immunity that otherwise might be insufficient. The control of smallpox in the United Kingdom is now dependent on the vaccination or re-vaccination of persons exposed to an imported case. In countries where boosting at the time of exposure is impracticable, the schedule must take this into account to ensure a more permanent high immunity.

REACTIONS

The incidence, nature and severity of reactions to vaccine are important considerations. The observation that serious reactions to smallpox vaccines may be less

common in children primarily vaccinated after the first year of life(77), led to modifications of the schedule in the United Kingdom. Pertussis vaccine is recommended in the United Kingdom after six months of age, in part because reactions are believed then to be less frequent(28). For many years the occasional local or even generalized reaction to smallpox, pertussis and other vaccines has been accepted as a small price to pay for immunity in the individual and the community. However, as diseases are controlled, side effects become less acceptable; when they become more common or more serious than the effects of the disease for which the vaccine is being given, the question arises whether immunization should be continued. Thus, smallpox vaccination has been abandoned as a routine measure in both the USA and the United Kingdom, in part because reactions have been responsible for a greater number of serious illnesses than smallpox itself(14). Similar arguments are occasionally put forward to suggest that pertussis immunization might be discontinued(13). High reaction rates among particular categories of people must also be taken into account in planning an immunization schedule in order to specify contraindications; live vaccines in patients receiving corticosteroids, and the use of influenza vaccine in patients hypersensitive to eggs, are examples. The occurrence of reactions requires careful observation because, if infrequent, they may go unnoticed, and the possibility must be remembered that reaction rates to different batches or preparations of vaccines may differ. Although control procedures include laboratory tests of reactivity, the tests may not always measure clinical reactivity. Measles vaccine derived from the Wellcome strain of virus was withdrawn in the United Kingdom because a very few serious reactions had been noticed following its use(18).

For diseases that are not regarded as serious by the population at large, even minor reactions may be considered unacceptable. Only about 40 per cent of a factory population, for example, may accept vaccination against influenza, and the rate may drop to only about 20 per cent when vaccination is offered in a second year(67), presumably partly on account of the sore arms and malaise which not infrequently follow vaccination(69).

There is some evidence that the incidence of reactions to a vaccine may depend on the frequency of injections and on their spacing. Thus in a factory population the incidence of local reactions to tetanus toxoid was 0.9 per cent to the first injection, 2.7 per cent to the second injection, and 7.4 per cent to the third injection of the basic immunization course. To booster injections the rate was 1.6 per cent (74). The more widely spaced the injections of the vaccination schedule the less likely hypersensitivity reactions may be. This factor may become more important in planning schedules, owing to increasing public sensitivity to the side effects of any therapeutic procedure.

IMMUNOLOGICAL FACTORS

THE VACCINE

The immunologist works to provide vaccines which safely induce a solid durable immunity, and which are easy for the health worker to administer and for the vaccinee to accept. The degree of protection given by the different vaccines varies – in the case of tetanus and yellow fever for example, it is rare to encounter the disease in immunized persons (**1**, **63**), whereas in most other diseases protection is certainly incomplete. Clearly the effectiveness of each vaccine must be considered when assessing its place in an immunization schedule and the immunologist must work closely with the epidemiologist to conduct field trials and to develop laboratory tests that will reflect the field effectiveness of vaccines. It must also be remembered that the effectiveness of vaccines may differ in different communities – cholera vaccine may possibly be more protective in the population of Bangladesh in whom a basic immunity may exist, than in Europeans (**50**); in the USA population BCG vaccine appears to confer little benefit, whereas the trials in the United Kingdom population indicated valuable protection (**56**).

The duration of protection may be capable of improvement. Thus much attention has been given to developing live, attenuated virus vaccines which are often capable of producing a durable immunity after a single dose, whereas killed vaccines usually require more frequent administration. Certain dead antigens, tetanus toxoid for example, may produce a long-lasting immunity provided a properly spaced course of immunization is given, whereas others, influenza vaccine for example, may produce only short-term immunity – perhaps because the protective antigens have not yet been concentrated sufficiently or, possibly, because a solid durable immunity may not be capable of induction by killed antigens, as may be the case with cholera and other gram-negative bacterial infections.

Much immunological work aims at the improvement of vaccines, often by the purification and concentration of protective antigens – not only to enhance antigenic potency but also to remove impurities which may cause reactions. In some instances the injection of sufficient antigenic mass to stimulate protection may depend on purification, e.g. meningococcal vaccine (**76**) and subunit influenza vaccine (**58**). In other instances improvements may depend on the development of new types of vaccines, e.g. cholera toxoid (**7**), or live bacterial vaccine (**17**, **61**, **39**). All such developments could have marked effects on immunization schedules.

Purification of vaccines may sometimes result in a diminished antigenicity, presumably owing to the loss of impurities which may have an adjuvant effect (**15**) and there is evidence that this may have occurred with both diphtheria (**43**) and tetanus toxoids (**73**). New, or more purified or concentrated antigens should be incorporated into an immunization schedule only after they have been evaluated in the field.

Vaccine combinations are an important field of study to the immunologist, in order to allow the health worker to protect persons against a number of diseases with the fewest attendances as possible. The development of concentrated vaccines is often an advantage in producing combined vaccines in order to provide

sufficient antigenic mass with an acceptable injection volume. The development of combinations is not, however, straightforward and is affected by factors considered below.

ANTIGENIC COMPETITION

In formulating either new mixtures of vaccines or new schedules of immunization it is necessary to ensure that an adequate response is obtained to each of the antigens given, i.e. the possibility of antigenic competition must be taken into account(**2**). The possibility must also be kept in mind that the response to the components of the mixture may differ in persons immunized for the first time and in those who have previously encountered one of the components of the mixture – the response to the new antigen may be impaired or 'crowded out' by the secondary response to the other(**25**). As information on new vaccine combinations is accumulated, it appears that antigen competition may be of less practical importance than has been feared. Thus, for example, a recent report demonstrated the effectiveness of simultaneous immunization with BCG, diphtheria–tetanus, and oral poliomyelitis vaccines(**23**). Nevertheless it is advisable with each new mixture to ensure that the combination is effective in the population in which it is to be used.

INTERFERENCE

Interference between viruses in an animal host has long been taken into account in the use of live vaccines – most schedules of immunization recommend that injections of yellow fever and smallpox vaccine are separated by at least a three-week interval. More recent work suggests that this recommendation may be too cautious and that the simultaneous administration of two or more live vaccines may be both safe and effective(**45**, **72**). Thus, in the USA a combined live attenuated measles, mumps and rubella vaccine has recently been introduced(**36**). Nevertheless, it is usually recommended that two live vaccines should not be given between two days and two weeks of each other, owing to the risk of interference(**71**).

Interference may also occur as the result of natural infection; poliomyelitis vaccines given by mouth may not be very effective in developing countries where other enteroviruses are prevalent in infants(**60**). Poor responses are possibly due to a number of factors in developing countries (**49**), but in such communities the number of doses of vaccine to be given may need to be increased (**3**), and schedules often include the proviso that vaccination should be delayed in the presence of intercurrent infection (e.g. **11**).

ADJUVANTS

The incorporation of an immunological adjuvant into a vaccine to stimulate a greater and longer-lasting immune response may allow fewer injections to be given. In the case of combined diphtheria/tetanus/pertussis vaccine there is the added advantage that the addition of an aluminium adjuvant may reduce the frequency of adverse reactions(**5**). The most effective adjuvants appear to be oil

emulsions, but at present they are considered too reactive to be generally accepted. Should non-reactive oil preparations (**32**) become available considerable modifications of the current immunization schedules may be possible.

Adjuvants may sometimes be removed from vaccines, as was the case where alum was associated in the United Kingdom with provocation poliomyelitis in the 1950s (**48**). Alterations to the pertussis component of triple vaccine might well be made in order to diminish its toxicity, and such changes could impair its adjuvant effect on the diphtheria and tetanus components. Indeed, should the incidence of pertussis decline to levels lower than that of the incidence of complications due to the vaccine, the pertussis component could be omitted (**13**). Apart from any effect on the schedule due to the loss of the adjuvant effect of the pertussis vaccine, the age at which immunization was practised might also be affected.

SPACING OF VACCINE DOSES

To secure a good immunological response to killed vaccines, such as the toxoids, the principle is well established of inducing first a primary response and then a secondary response, and of later giving recall or reinforcing doses. Although much information exists on the number, timing and spacing of the injections necessary to obtain the highest and most durable response, the information is often incomplete – mainly owing to the difficulty in man of trying out the many possible different schedules in groups of volunteers. The lack of information is particularly marked in the case of vaccines such as typhoid and cholera, where immunity cannot clearly be related to the presence of circulating antibodies or to skin tests. Consequently, recommendations concerning the immunologically most suitable schedule for different vaccines is liable to change as more studies are reported.

Information on the *duration* of immunity provided by most vaccines may be particularly limited because many vaccines have been in use only for a short period of time. Even when vaccines have been used for many years, e.g. smallpox for nearly 200 years, cholera and typhoid since the 1890s (**27**), diphtheria toxin–antitoxin mixtures since 1915 (**4**), the duration of immunity produced by current preparations may be uncertain. This uncertainty arises in part from the lack of studies but, in addition, vaccines undergo changes in purification and preparation methods, and in their mixture with adjuvants, and these and other factors may well influence the duration of immunity produced (**19**, **43**, **73**). The dosage and number of injections recommended has also varied from time to time and between different countries – consequently evidence derived from one country may not necessarily apply to other countries (**37**).

The duration of immunity produced by live virus vaccines is also uncertain. Following smallpox vaccine a high level of protection is probably maintained for about three years (**8**), whereas yellow fever vaccine provides an immunity lasting for at least ten years (**26**). Immunity may well be long-lasting after poliomyelitis and measles live vaccines (**44**, **38**), but it is not yet possible to set a limit – if one exists. Should immunity be found to be less long-lived than expected, recom-

mendations would require careful consideration. Thus, if it becomes necessary to reinforce rubella immunity in women, careful precautions would be necessary to ensure that vaccinees were not pregnant.

AGE

Although newborn infants can respond to antigenic stimuli their ability to produce an antibody response improves during the first year of life. The response may also be impaired as a result of passive immunity derived from the mother, and this may be most important in the case of live virus vaccines such as measles (**22**). Antibodies in milk may impair the ability of the suckling infant to respond to live oral poliomyelitis vaccine (**34**). From an immunological point of view, therefore, a more certain response to vaccination may be obtained by delaying the start of an immunization schedule until the age of six months or more. The schedules at present recommended in the United Kingdom allows this point of view with the first dose of triple vaccine given at the age of six months (Table I). The improved response allows the omission of the fourth injection previously recommended at 18 months of age. In the United States, however, the view is taken that higher immunization rates will be secured by starting immunization earlier (**71**).

Evidence also exists that the antibody response may be impaired in old age (**59, 6, 35**); a vaccine proven in young people should not be assumed necessarily to be equally effective in the elderly. This factor may be particularly relevant to the use of influenza in elderly persons in whom the response may be poor (Howells, personal communication). On the other hand the possibility also exists that the response to influenza vaccine may, in certain circumstances, improve with age owing to previous natural exposure to the antigens (**42**).

PASSIVE IMMUNITY

As with naturally acquired passive immunity in the newborn, active immunization with the corresponding antigens may also be impaired by antibodies provided deliberately for prophylactic or therapeutic purposes. Inhibition has sometimes been avoided by delaying immunization until the passive antibodies have been eliminated from the body, as used to be the practice in wounded persons protected against tetanus with horse antitoxin (**51**). On the other hand, inhibition may be overcome by increasing the strength of the immunizing stimulus, as with the use of adsorbed tetanus toxoid in the United Kingdom to allow simultaneous immunization of passively protected persons (**66**), and in rabies by increasing the number of injections in the course of immunization (**71**). When human immunoglobulin is given to sickly children immunized with attenuated measles vaccine, the dose requires to be small to avoid completely neutralizing the vaccine (**57, 53**).

ADMINISTRATIVE FACTORS

VACCINATION RATE

Having decided the vaccines to be used, and with an understanding of the number of doses that should be given and of their timing and spacing, the vaccination programme should secure a high immunization rate in the groups to be immunized, whether infants or schoolchildren, particular occupational groups or, perhaps, elderly people exposed to the risk of influenza. It is possible that the highest coverage may not be secured by a schedule considered best from the immunological or epidemiological point of view. Thus, it may well be true that higher acceptance rates will result from starting immunization at perhaps two months of age rather than six months of age; the earlier time is recommended in the United States despite the immunological disadvantage and the possibility that reactions of pertussis vaccine may be commoner under six months of age (**71**).

A high vaccination rate may be ensured by introducing legislation to make acceptance compulsory, but the use of legal powers varies in different countries. No vaccination procedures are nowadays compulsory in the United Kingdom, although smallpox vaccination remained mandatory until 1947 (**16**). However, in the USA many states require certain immunizations prior to school entry (**33**). Where legislation is not possible or not justifiable, the administrator must consider the need for publicizing the need for, and availability of, immunization.

The cost of a vaccination programme must be related to the likely benefits. Thus, for example, *tetanus neonatorum* could be eliminated from developing countries by ensuring the active immunization of all pregnant women, but in many countries the cost would be too great. Again, it might be possible to cause a significant reduction in excess mortality due to influenza in the USA by securing a high immunization rate among old persons, but the cost of doing so is prohibitive. Considerations of cost may become increasingly important with the development of vaccines against diseases formerly considered to be relatively trivial. In the case of mumps vaccination, for example, most physicians would probably agree with the use of a safe, effective vaccine giving a long-lasting immunity, but the cost might be considered difficult to justify in view of the infrequency with which serious complications of mumps are believed to arise.

Recording of vaccinations must also be considered by the medical administrator, because health workers may wish to know who has been given vaccine and how many doses they have received (**62**). He may need also to ensure that the occurrence of reactions or vaccine failures can be noted and related, if necessary, to the vaccination procedure. Thus it may be preferred to give booster doses of vaccines during school years rather than in younger or older children, so that recording can be done by school health authorities rather than by general practitioners. The schedule must be planned to give time and facilities for whatever recording is considered necessary.

Administrative factors relating to immunization schedules may also change – directly from changes in legislation concerning vaccines, but also indirectly from, perhaps, alteration in the age of school entry or in the budget available for pre-

ventive medicine. Consequently, like the other considerations affecting schedules of immunization, administrative factors also require to be kept under review.

CONCLUSIONS

The design of an immunization schedule for a particular community must take into account epidemiological, immunological and administrative factors. Guidance may be obtained from published schedules (e.g. **11**, **71**) and from the considered views of experts – concerning both developed and developing countries (**10**, **31**). Although an established, effective schedule should be changed with reluctance, it is important to maintain a regular review. Thus, the epidemiology of infectious diseases is liable to change, new information will appear on the timing and spacing of doses of vaccine, and changes will occur in the choice of vaccines which are available, and also in administrative factors which may affect the immunization schedule.

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ETUDES SUR LES VACCINATIONS EN AFRIQUE

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Les vaccinations dans les pays en voie de développement se heurtent souvent à la difficulté de pratiquer plusieurs injections. Une solution du problème a été recherchée dans la réduction du nombre d'injections pour certains vaccins et en vaccinant en une seule fois contre le plus grand nombre possible de maladies. L'emploi d'un injecteur sous pression sans aiguille, permet de vacciner aussi dans un temps relativement court un grand nombre de sujets.

Il a été démontré qu'on obtient un taux élevé d'anticorps circulants après deux injections de vaccin antidiphtérique–antitétanique* à un an d'intervalle(**1**, **2**) et que les vaccins adsorbés sur phosphate de calcium peuvent être administrés à l'aide d'un injecteur sous pression de type Ped-O-Jet(**4**, **5**).

Les programmes de vaccinations présentés ici avaient d'une part comme but, d'étudier l'efficacité et l'inocuité de plusieurs associations vaccinales et d'autre part, d'étudier à nouveau la vaccination antidiphtérique-antitétanique en deux injections à un an d'intervalle.

ETUDE D'UNE ASSOCIATION VACCINALE QUINTUPLE

Cette étude, dont les résultats détaillés seront publiés ailleurs(**3**), a été entreprise par l'OCEAC (Drs C. Gateff, R. Labusquière, M. Mc Bean et D. Monchicourt), l'Institut Pasteur de Paris (Dr L. Chambon), l'Institut Pasteur de Garches (Dr E. H. Relyveld), et l'Institut Pasteur de Dakar (Drs G. Le Gonidec et J. Vincent). Les vaccins étudiés étaient: antivariolique (VAR); antiamarile (FJ); anti-

* Vaccin IPAD-DT de l'Institut Pasteur.

rougeoleux (ROUG), BCG et antitétanique (TET); les six protocoles de vaccinations réalisés après tirage au sort sont:

VAR; FJ; ROUG; BCG; TET
VAR; FJ
VAR; ROUG
VAR; BCG
VAR; TET; ROUG
VAR; Placebo (Soluté physiologique)

Chaque protocole comptait 100 sujets, des deux sexes, âgés de 1 à 5 ans, originaires d'une zone rurale située à 150 km au Nord-Ouest de Yaoundé, Cameroun.

On a pratiqué à l'aide d'un Ped-O-Jet:

La vaccination antivariolique à la région deltoïdienne droite en intradermique sous volume de 0,1 ml (minimum $1,10^5$ UFP/dose – vaccin lyophilisé 'Dryvax' – Wyeth).

Le BCG à la face antérieure de l'avant-bras droit en intradermique sous volume de 0,1 ml (vaccin lyophilisé de l'Institut Pasteur de Dakar contenant $9,10^6$ unités cultivables par mg et reconstitué à la concentration de 1 mg par ml).

La vaccination antiamarile à la face externe de la cuisse gauche par voie sous-cutanée sous volume de 0,5 ml (vaccin lyophilisé de l'Institut Pasteur de Dakar contenant 8300 DL 50 souris de la souche 17D par dose).

Le vaccin antitétanique adsorbé sur phosphate de calcium (IPAD-T) de l'Institut Pasteur de Paris à 120 UF/ml) a servi de solvant au vaccin antirougeoleux (Lyovac Attenuvac de Merck-Sharpe & Dohme). La dose vaccinante de 0,50 ml a été administrée à la seringue dans la région deltoïdienne gauche.

Les contrôles ont été pratiqués à des périodes différentes selon la vaccination dont il convenait d'évaluer les effets. Des prélèvements de sang pratiqués avant et après la vaccination ont permis de titrer les anticorps circulants et de connaître le pourcentage de sujets non-immuns protégés après la vaccination antiamarile, antirougeoleuse et antitétanique. Les taux de protection obtenus pour les 6 protocoles de vaccinations sont présentés dans le Tableau I. Les prises pour la vaccination antivariolique dépassaient 97 % dans tous les protocoles et n'ont pas été rapportés dans ce tableau.

L'association quintuple donne vis-à-vis de la fièvre jaune la même protection que le vaccin antiamaril administré seul, en moyenne de 85 %, ce qui correspond au taux habituellement obtenu.

Le nombre de sujets porteurs d'anticorps anti-rougeoleux avant la vaccination oscillait entre 50 et 58 %, ce qui a considérablement diminué les effectifs. Ceux des trois groupes vaccinés ne permettent pas d'affirmer que la différence des résultats soit significative, même si l'association quintuple fait apparaître une légère diminution de la protection. Les taux de protection sont néanmoins inférieurs à ceux qu'on aurait pu obtenir chez des sujets de cet âge.

Les résultats pour le BCG concernent des sujets non réagissant à la tuberculine avant la vaccination. Il n'y a pas de différence significative entre les résultats obtenus avec le vaccin administré seul ou associé. Les résultats sont toutefois

Tableau I. *Taux de protection pour six protocoles de vaccinations*

Associations vaccinales	Fièvre jaune		Rougeole		BCG		Tetanos	
	N°	%	N°	%	N°	%	N°	%
VAR-FJ-ROUG-BCG-TET	64	84,4	29	69,3	69	58	52	84,6
VAR-FJ	75	86,7	—	—	—	—	—	—
VAR-ROUG	—	—	38	81,5	—	—	—	—
VAR-BCG	—	—	—	—	71	53,5	—	—
VAR-TET-ROUG	—	—	32	81,2	—	—	45	93,3
VAR-Placebo	73	0	34	0	267	2,6	45	4,4

N° = nombre de sujets non protégés, contrôlés après vaccination.
% = pourcentage de ces sujets protégés après vaccination.

médiocres (environ 55 % de virage) pour un vaccin dont la qualité ne peut pas être mise en cause. Le même vaccin administré à la seringue a fait apparaître 95 % d'allergie dans une étude différente et il semble donc que c'est la technique de vaccination par injecteur sous pression qui est en cause, ce qui a même fait préconiser l'abandon de cette méthode de vaccination.

Il a aussi été vérifié que l'efficacité du vaccin BCG n'a pas influencé la production d'anticorps amarils ou rougeoleux, mais a fait apparaître un léger fléchissement du taux de protection antitétanique par rapport aux témoins.

Les résultats de la vaccination antitétanique montrent aussi une légère chute du taux de protection pour l'association quintuple. Cette association permet néanmoins de protéger 85 % de l'effectif en une seule injection.

Le titre moyen d'anticorps circulants de 0,5 UAI/ml contre 1 UAI/ml pour l'association triple, laisse augurer d'une protection moyenne durable jusqu'à l'injection de rappel un an après. Le fait d'avoir utilisé l'anatoxine tétanique adsorbée comme solvant du vaccin rougeoleux, n'a pas modifié la réponse immunitaire vis-à-vis de ces deux vaccins.

L'association des vaccins a, dans tous les cas, été bien supportée et n'a donné lieu à aucune réaction locale ou générale plus importante que celle observée avec les vaccins isolés. On peut donc conclure que l'association quintuple présente un intérêt certain pour les vaccinations dans les pays en voie de développement, même si l'efficacité n'est pas pour tous les composants aussi bonne que celle des vaccins administrés isolément.

ETUDE SUR LE CALENDRIER DES VACCINATIONS EN AFRIQUE SUD-SAHARIENNE (AU CAMEROUN)

Le Tableau II montre le calendrier de plusieurs associations vaccinales faisant actuellement l'objet d'une étude par le Centre International de l'Enfance (Drs C. Fillastre, M. Guerin, F. M. Lévy et N. Cabau), chez deux groupes d'enfants âgés de 2 à 6 mois et de 6 à 12 mois. Les résultats présentés ici comportent les

Tableau II. *Etude sur le calendrier des vaccinations au Cameroun*

	Enfants âgés de 2 à 6 mois		Enfants âgés de 6 à 12 mois Randomisation		
	Randomisation		Groupe 3	Groupe 4	Groupe 5
1er jour prise de sang ...	DT-BCG-VAR		DT-BCG-VAR-ROUG-FJ	DT-BCG-VAR-ROUG	DT-BCG-VAR
	Groupe 1	Groupe 2			
2 mois plus tard prise de sang + IDR	—	DT-ROUG	—	DT-FJ	DT-ROUG-FJ
12 mois plus tard prise de sang + IDR	DT-ROUG-FJ	DT-FJ	—	—	—
24 mois plus tard prise de sang	—	—	DT	DT	DT
26 mois plus tard prise de sang	—	—	—	—	—

contrôles effectués avant les vaccinations et après 2 et 12 mois et seront complétés par la suite.

Il s'agit de très jeunes enfants dont une partie est porteur avant vaccination d'anticorps d'origine maternelle; le taux de protection a été exprimé par rapport au nombre total de sujets.

La vaccination antidiphtérique–antitétanique a été effectuée avec un vaccin adsorbé sur phosphate de calcium (IPAD-DT de l'Institut Pasteur), titrant 30 UF de chacun des anatoxines par ml. Ce vaccin a déjà fait l'objet de plusieurs essais, en particulier pour l'étude de la vaccination par deux injections à un an d'intervalle(**1**, **2**). La dose vaccinante de 1 ml a servi comme solvant pour le vaccin antirougeoleux et a été administrée à la seringue.

Le Tableau III montre les résultats de titrages pour le tétanos; on note la présence d'anticorps circulants d'origine maternelle avec un taux de protection d'environ 23 % chez des enfants âgés de 2 à 6 mois et d'environ 11 % chez des enfants de 6 à 12 mois.

Les résultats de cette vaccination sont excellents, en particulier dans les groupes ayant reçu une seule injection (84,2 et 97,2 % de protection). L'étude faite antérieurement avait donné un taux de protection un peu moins élevé, mais tous les enfants, sans exception, avaient un titre élevé d'antitoxine à la suite de la 2ème injection effectuée un an après la 1ère.

Les résultats pour la diphtérie étaient par contre décevants: un taux d'anticorps circulants égal ou supérieur à 0,05 unités internationales anti-toxiques (UAI) par ml ne fut retrouvé après 2 mois, que chez 32 % des sujets du groupe 2 et après 12 mois chez 44 % du groupe 4. Des anticorps circulants d'origine maternelle à un taux $\geqslant$ 0,05 UAI/ml avaient été décelés avant vaccination, chez 39 % des sujets du groupe 1, 48 % du groupe 2 et 13 à 16 % des groupes 3 à 5.

Tableau III. *Etude sur les vaccinations en Afrique Sud-Saharienne (au Cameroun). Resultats des controles: Tetanos*

Age au 1er contrôle (mois)	Groupes	Vaccinations		Avant vacc.		Après 2 mois		Après 12 mois	
		1er jour	2 mois plus tard	N°	%	N°	%	N°	%
2 à 6	1	DT-BCG-VAR	—	63	23,8	49	81,6	38	84,2
	2	DT-BCG-VAR	DT-ROUG	60	21,7	52	76,9	44	93,2
6 à 12	3	DT-BCG-VAR-ROUG-FJ	—	62	9,7	36	83,3	36	97,2
	4	DT-BCG-VAR-ROUG	DT-FJ	55	10,9	40	70	42	97,6
	5	DT-BCG-VAR	DT-ROUG-FJ	50	12	30	76,7	34	100

N° = nombre total d'enfants contrôlés
% = nombre protégés

Il est donc fort possible que ces anticorps aient ralenti la réponse immunitaire. Seul l'effet de rappel permettra de juger de l'efficience de la primo-vaccination.

L'efficacité du vaccin BCG exprimée par le nombre de sujets réagissant à la tuberculine était de 65 à 76 % 2 mois après la vaccination, et de 77 à 90 % après 12 mois. Les résultats sont donc moins bons que ceux qu'on pouvait espérer.

Des anticorps antirougeoleux furent retrouvés au premier contrôle (avant vaccination) à un titre protecteur, chez 60 % des enfants des groupes 1 et 2 et chez 8 à 12 % d'entre eux dans les groupes 3 à 5. Les taux de protection après vaccination, étaient par contre cette fois-ci très décevants, et après 1 an au maximum de 53 % dans le groupe 5 vacciné en dernier lieu.

L'efficacité de la vaccination antiamarile n'était pas meilleure (seuls les groupes 3, 4 et 5 furent vaccinés). La présence d'anticorps maternels constatée comme auparavant avec un taux de protection élevé avant vaccination ne peut pas en être uniquement la cause, elle était pratiquement nulle dans les groupes 4 et 5 lors de la vaccination. La protection après 12 mois dans ces groupes, n'était pas supérieure à 25 et 42,5 %.

Les résultats préliminaires de cette étude ne permettent pas de formuler des conclusions définitives, mais montrent bien qu'à l'exception du tétanos, les enfants très jeunes se vaccinent moins bien qu'après l'âge de 1 an. La présence d'anticorps maternels joue certainement un rôle, pourtant pas toujours évident, un titre trop bas du vaccin antirougeoleux a aussi été évoqué.

A noter aussi que lorsque la réponse aux vaccins antirougeoleux et antiamaril n'est pas satisfaisante, le succès du BCG n'a pas provoqué de chute de protection vis-à-vis du tétanos, par contre, chez les sujets plus âgés, qui ont fait l'objet de la première étude et répondant mieux à ces vaccinations, cette concurrence peut s'ébaucher.

VACCINATION DE MASSE CONTRE LE TETANOS A COTONOU, DAHOMEY

Une étude au Cameroun avait déjà montré que la vaccination antidiphtérique–antitétanique par deux injections à un an d'intervalle de vaccin DT purifié et adsorbé sur phosphate de calcium confère un excellent taux d'anticorps circulants. Tous les sujets étaient immunisés après la deuxième injection(1, 2).

A la suite de ces résultats, des essais ont été réalisés pour vacciner contre le tétanos par un injecteur sous pression sans aiguille et comparer les résultats avec ceux obtenus par injection à la seringue. On a pu conclure que ce procédé de vaccination était éfficace et anodin. Tous les sujets vaccinés étaient protégés, les réactions à la vaccination se limitaient à une faible douleur passagère et une légère induration au point d'injection paraissant pendant 10 à 12 heures, et ayant totalement disparu après 42 à 36 heures. Il n'y a jamais eu de réactions générales et en particulier, pas de fièvre(4, 5).

Les résultats de ces essais ont justifié l'étude de l'immunisation antitétanique par deux injections à un an d'intervalle sur un nombre important de sujets et dans une région avec une endémie tétanique et une mortalité élevée.

Une campagne de vaccination de masse a été entreprise à Cotonou, (ville tropicale où le nombre de morts par tétanos était de l'ordre de 10 par mois pour une population de 120000 personnes) par les Drs M. Charpin et A. Massacrier du Centre Hospitalier sur place, et les Drs L. Chambon, E. H. Relyveld et R. Reynaud de l'Institut Pasteur de Paris. Toute la population, ainsi qu'un grand nombre de sujets des environs qui se sont présentés aux séances (venant même du Togo voisin), au total 200000 personnes, ont été vaccinés par 0,25 ml d'anatoxine tétanique adsorbée sur phosphate de calcium à 120 UF/ml (IPAD-T 120 d'Institut Pasteur). Les injections ont été faites à l'aide d'un Ped-O-Jet.

Le but de cette campagne était de comparer le nombre de tétaniques hospitalisés avant et après la vaccination, et de titrer les anticorps circulants chez des groupes déterminés de la population (écoliers, personnel administratif, dockers, etc.) avant et après l'injection de rappel au mois de Mars 1973 pour évaluer l'efficacité de l'immunisation.

Il avait aussi été prévu d'administrer sans attendre une injection de rappel antitétanique en cas de blessure avant la deuxième injection, et ainsi de protéger le sujet de façon certaine. Cette mesure ne s'applique malheureusement pas au grand nombre d'individus contractant le tétanos après une injection intramusculaire (en particulier de quinine) avec des seringues mal stërilisées.

Des sondages effectués 8 mois après la première injection ont montré qu'environ 50% des sujets possédaient des anticorps à un titre protecteur, ce qui correspond au taux déjà relevé précédemment(1). Les résultats avant et après l'injection de rappel seront rapportés par la suite.

RESUME

Les résultats de l'étude de 5 vaccinations associées (antivariolique, antiamarile, antirougeoleuse, BCG et antitétanique) chez des enfants de 1 à 5 ans ont permis de conclure que l'association présente un intérêt certain dans les pays en voie de développement, même si l'efficacité pour les composants n'est pas toujours aussi bonne que celle des vaccins administrés isolément.

Les premiers résultats composés de plusieurs calendriers de vaccinations associées chez divers groupes d'enfants de 2 à 6 et 6 à 12 mois, ont montré que les taux de protection ne sont pas aussi élevés que ce qu'on pouvait espérer en particulier pour la diphtérie, la rougeole et la fièvre jaune. Les anticorps circulants d'origine maternelle sont certainement une des causes de la faible réponse immunitaire. La production d'anticorps antitétaniques était par contre très bonne.

Une vaccination de masse contre le tétanos par 2 injections à un an d'intervalle à été entreprise à Cotonou (Dahomey).

SUMMARY

Wide-scale immunization in Africa encounters many difficulties and programs have been undertaken to study the simultaneous administration of several vaccines and to reduce the number of injections especially for tetanus.

Simultaneous vaccination against variola, yellow fever, measles, tuberculosis and tetanus was studied in Cameroun in groups of children aged 1–6 years. Even if the effectiveness of the association is not as good as when the vaccines are administered individually one can conclude that this method of immunization can be applied in developing tropical countries. The efficacity of the adsorbed tetanus toxoid was shown to be excellent, 93.3 % of the subjects of the control group and 84.6 % of those receiving the 5 vaccines were protected after one injection (mean antitoxin levels 1 and 0.5 units/ml).

Several vaccine combinations were studied in babies and it was found that with the exception of tetanus protection against yellow fever, measles and diphtheria was not as good in older children. Circulating antibodies of maternal origin can be the cause of the low antibody response.

Antitetanus vaccination of the population of Cotonou, Dahomey, and surroundings (about 200000 persons) by 2 injections with an interval of 1 year between each has been undertaken. Antibody titrations carried out 8 months after the first injection revealed a protection of 50 %, results before and after the second injection will be reported later on.

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VACCINATION PROGRAMMES IN BELGIUM

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Only two vaccinations are compulsory in Belgium, these are smallpox and polio.

Smallpox vaccine must be given during the first year of life and the reporting of both take rates and any side reactions is compulsory. These are mainly neurological disorders and generalized vaccinia seldom occurs. Unfortunately the criteria for evaluation are not standardized, which makes it difficult to have correct figures, so that the number of complications, between 1 in 50000 and 1 in 100000 must be considered as exaggerated.

The Council of Hygiene, taking into account that world wide eradication of smallpox has not yet been achieved and in order to avoid the spread of imported cases from abroad, has maintained vaccination at the present time in Belgium. Revaccination for smallpox is recommended at entry to elementary school and is usual for recruits and medical staff. Travellers going to an epidemic area are recommended to have a repeat inoculation against smallpox. Evidence is lacking for changing the present schedule of administration and for eventually giving the vaccine later than the first year of life.

After the first use of inactivated polio vaccine in 1959, with a consequent decrease in poliomyelitis incidence, a mass vaccination campaign was organized in Belgium in March 1963 giving three doses to about 50 per cent of the population between 3 months and 40 years of age. The campaign was followed by the disappearance of the disease in the country. Only exceptional cases, generally in unvaccinated people, have been reported between 1964 and 1972; in fact there were no cases in 1971 and 1972. In support of that programme, and because of the disappearance of motivation amongst the citizens, compulsory vaccination was begun in 1966 for children under sixteen months of age. The vaccine is well tolerated without noticeable side effects. The percentage of the population inoculated is very high but, as for other communicable diseases, problems which can influence the epidemiological patterns and the vaccination schedules are created by the introduction of immigrants in the country; random control revealed that polio virus is still in circulation (154 isolations of virus in 1971) but the general level of immunity seems to be sufficient to control the epidemiological situation.

No decision has been reached as to the need of polio revaccination. Continuous serological surveillance of selected groups, shows a progressive decrease of antibodies, mostly for Type III, and will indicate what action should be taken in the

future. However, certain groups of physicians do revaccinate on entry to the elementary school.

In the Belgian schedule, diphtheria, tetanus and pertussis vaccines are used in combination for the three primary inoculations which are given at 3, 4 and 5 months of age. This programme is not compulsory but generally is accepted. Normally, booster inoculations are given after one year for the trivalent vaccine and after a five-year interval for tetanus and diphtheria. Unfortunately the programme of revaccination is often neglected, which explained the occurrence of 31 cases of diphtheria in 1970 and 25 cases in 1971. The reported cases of tetanus, 16 in 1970 and 18 in 1971, usually occurred in old people and the problem of reaching a proper level of immunization in adults remains open. The one exception is that the high-risk groups who are exposed professionally to the infection are compulsorily vaccinated every three years.

BCG vaccination has not yet found adequate application although it is formally recommended and included in the vaccination schedule and the physicians usually use the vaccine only in highly exposed groups. This policy probably explains the disturbing fact that Belgium still has more than 2000 new cases of tuberculosis each year.

Rubella vaccine has been authorized in the country since 1969 and the Belgian rubella vaccine made from the Cendehill strain is the only one used. It has been shown to be well tolerated in all age groups. Official recommendations have been issued by the Ministry of Health to immunize systematically all prepubertal girls and to give protection to the susceptible adult women, except those who are pregnant, with priority to the high-risk groups, such as teachers, nurses, laboratory workers, etc. No decision has been taken as to the general vaccination of young children. At the present time these recommendations have not met with the general participation of all physicians. As rubella or congenital rubella are not reported in Belgium the evaluation of the efficacy of vaccination remains difficult. However, no significant outbreak has been observed.

Until now, no measles vaccine has been approved in Belgium. Here again the lack of systematic reports of the disease do not stimulate a great interest for the use of the vaccine by Belgian physicians. The problem is now being reconsidered by the Council of Hygiene and the approval of live attenuated vaccine may be expected. Undoubtedly the tendency will be to leave the vaccine to the paediatricians for private use in specific cases and not to perform mass vaccination campaigns. The influenza vaccines available today are only recommended in high-risk adult groups in closed communities. Preliminary trials have been supervised by the authorities using a new live attenuated flue vaccine administered intranasally.

As for the other vaccines such as yellow fever, typhoid and cholera, their use is restricted to travellers going to endemic countries. Vaccination against rabies is only performed when therapeutically indicated.

In concluding this review it appears appropriate to make an appeal to vaccine producers and control authorities to investigate further the possibilities of finding new tools for protecting against old microbial diseases which have been eclipsed

for the time being by viral vaccines. We are thinking particularly of meningococci, pneumococci, staphylococci and pseudomonas. The lack in recent years of effective chemotherapy against many of these should be and would be, I think, adequately corrected by preventive medicine measures including vaccination.

We should add also, that for the control of vaccines and sera a close collaboration exists between the three countries of Benelux.

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THE IMMUNIZATION PROGRAMME IN BULGARIA AND ITS EFFICIENCY

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A complex programme for the limitation and eradication of certain infectious diseases has been in progress in Bulgaria. A component part of this programme is the carrying out of systematic mass immunizations. The compulsory immunizations during the first and second year after birth are: BCG, combined diphtheria–pertussis–tetanus (DPT) vaccine, poliomyelitis and variola. Systematic re-immunizations are carried out in different intervals in accordance with the different infections.

The strict application of this programme gave some very significant results. Here we should mention the fact that in the course of a number of decades, no cases of variola have been registered in Bulgaria, in spite of the fact that during the same period of time, more especially last year, there was a variola epidemic in neighbouring Yugoslavia. Due to this in 1972 a mass reimmunization was carried out with variola vaccine and approximately 5 million persons were reimmunized. The post-vaccinal complications were of the order of 0.6 per 100000 of which 0.4 per 100000 were post-vaccinal encephalitis, but with no fatal cases.

I would like to present in the form of diagrams the morbidity rate of the infections against which the vaccination is compulsory.

As seen in Fig. 1 the tuberculosis morbidity has dropped sharply – from 400 per 100000 in 1952 to 73 per 100000 in 1971, which is nearly a five-fold reduction for a period of 20 years. In connection with this it should be borne in mind that the social conditions have changed for the better. An analysis of the morbidity rate shows that the non-vaccinated are afflicted three times more than the vaccinated.

Diphtheria (Fig. 2) has been reduced to single sporadic cases, while in 1972 there has not been a single registered case of diphtheria. The level of the collective immunity was traced according to the Schick test. It proved to be high, as of the 20350 persons in the age group from 0 to 17 years, 96.9 % proved to be Schick negative.

We have still not achieved entirely satisfactory results with pertussis (Fig. 3), which is due to the comparatively weaker efficacy of the vaccine. Bulgaria is among the countries with a low pertussis morbidity rate.

As a result of the immunizations carried out the tetanus morbidity rate has been reduced 4.5 times (Fig. 4). The level of collective immunity is high. Of the total of 4152 persons examined during the last 5 years only 8 % have proved without protective antitoxin titre.

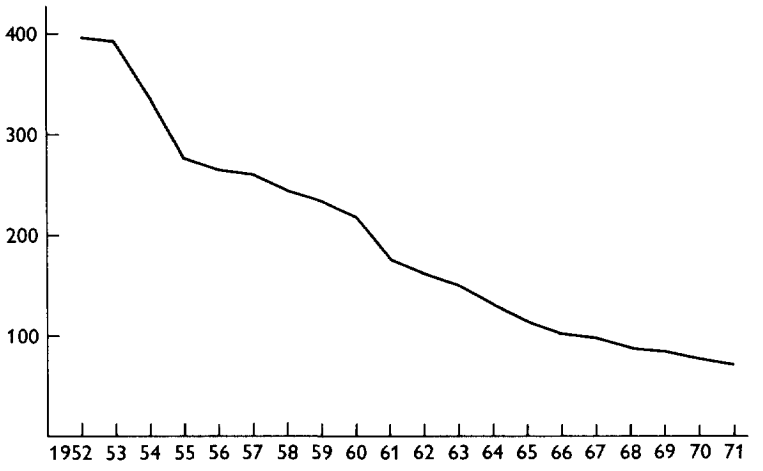

Fig. 1. Tuberculosis morbidity rate per 100000 population for the period 1952–71.

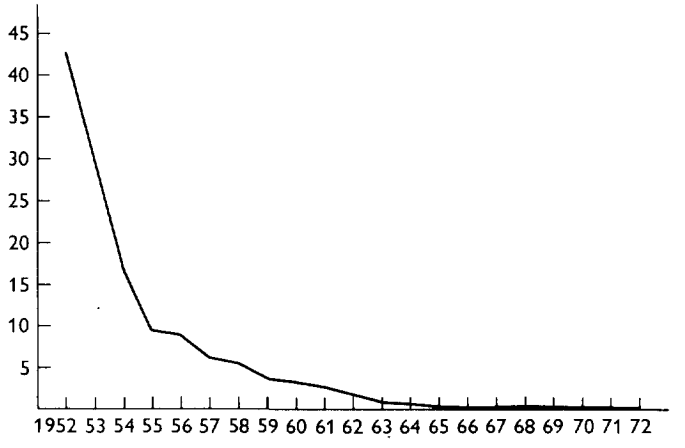

Fig. 2. Diphtheria morbidity rate per 100000 population for the period 1952–72.

After the mass immunization with live vaccine carried out in 1960 the poliomyelitis morbidity rate dropped sharply, no poliomyelitis case being registered in Bulgaria in the course of the last 2 years (Fig. 5). The level of the collective immunity is high, being tested during 1972 on 1540 persons from different age groups.

Definite contingents have been immunized with live anti-influenza vaccine, prepared from local strains and strains from the USSR. The epidemiological efficiency of the vaccines was shown to vary during the various years in the range from 2.0 to 7.9.

Four years ago we started a systematic immunization of the children up to

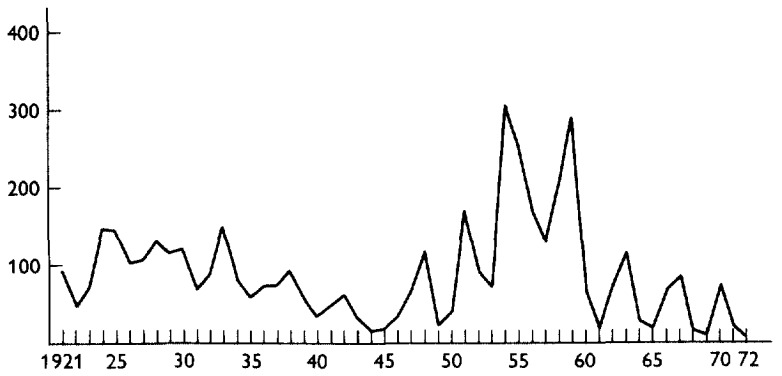

Fig. 3. Pertussis morbidity rate per 100000 population for the period 1921–72.

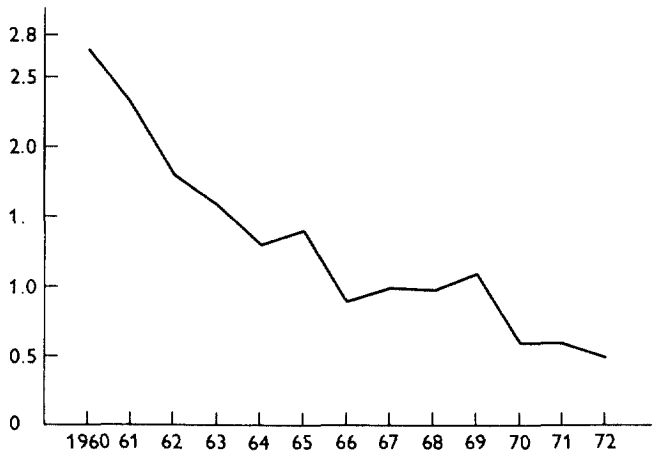

Fig. 4. Tetanus morbidity rate per 100000 population for the period 1960–72.

7 years of age with live measles vaccine – strain Leningrad-16. The percentage of children immunized in the different regions of the country of this age group varies from 19 to 80 (about 40.8 % for the entire country). The immune response is good (Fig. 6). The study of the epidemiological efficiency of the vaccine is in progress.

During the last 4 years approximately 200000 persons were immunized with live mumps vaccine, prepared from our Sofia-16 strain. The vaccine produces an immune response in 92 % of the immunized. The antibodies persist in the course of the last 4 years. Studies on the epidemiologic efficiency of the vaccine are presently in progress.

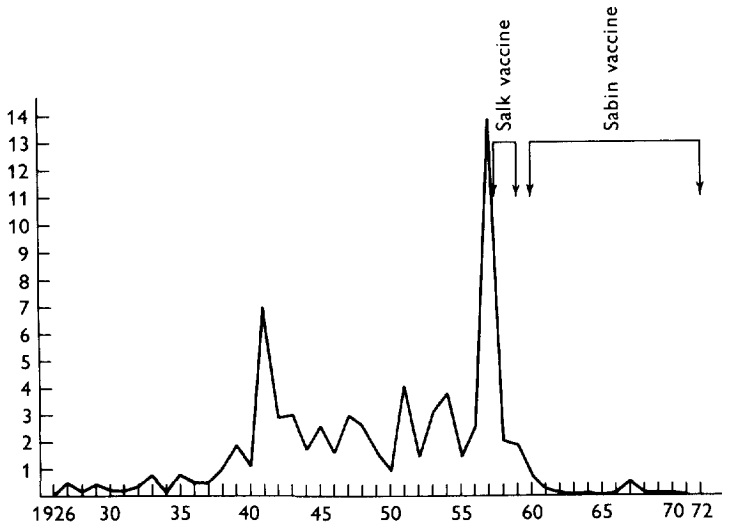

Fig. 5. Poliomyelitis morbidity rate per 100000 population for the period 1926–72.

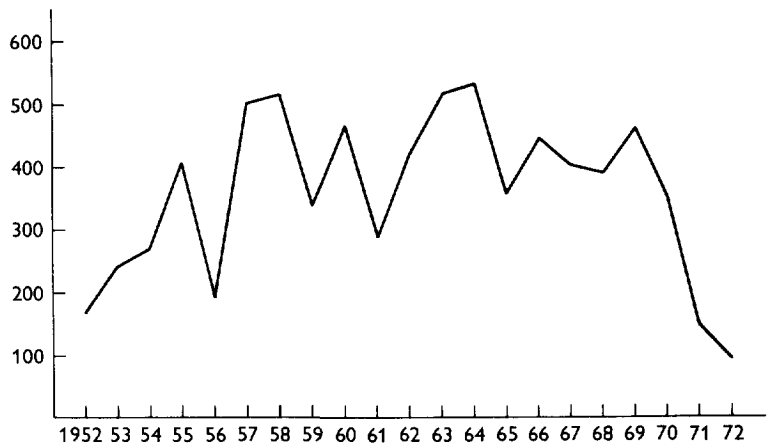

Fig. 6. Measles morbidity rate per 100000 population for the period 1952–72.

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VACCINATION AGAINST COMMUNICABLE DISEASES IN CYPRUS

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The prevalence of communicable diseases in Cyprus, particularly those which are directly related to the environmental sanitation has shown a marked decline in the last one or two decades. The mortality from infective and parasitic diseases accounts for a median proportion of deaths at all ages and all causes of about 2.5 per cent. This is mainly attributed to the rising standard of living of the general population and the improvement of the environmental santitation in particular.

There are, however, certain communicable diseases the prevention of which depends to a large measure on artificial immunisation.

Whereas the general principles of immunisation may be applicable everywhere, it can be said that there is no universal blueprint for vaccination programmes. The nature and the severity of the disease, for which immunisation is intended, vary from country to country, depending on the epidemiological situation in each country; therefore immunisation programmes should match the community hazards of individual countries.

In this respect it is worth mentioning that no disease of high epidemic potential such as the quarantinable and other diseases of international significance occur in Cyprus. Even the common infections, which were dominating our epidemiological picture until one or two decades ago, have nowadays been brought under full control. It is logical therefore that our immunisation programmes may be different from those applied in countries where, for example, smallpox or tuberculosis are prevalent.

The communicable diseases for which immunisation programmes are carried out in Cyprus are: diphtheria–tetanus–pertussis (usually in a combined triple vaccine), poliomyelitis and smallpox.

The basic course of vaccination for these diseases is scheduled to start in infancy. A change has taken place, however, recently with regard to the optimum age at which this basic course should begin. Whereas in the old days the basic course started as from the age of three months, sometimes earlier, the practice now is to delay the starting age until the child reaches the age of six months. This delay was thought necessary to allow time for the antibody-forming system to be fully developed, and also to reduce the risks of reactions to pertussis vaccine which are more serious in early infancy.

Similarly in the case of smallpox the primary vaccination is nowadays deferred to a later age, the reason being to minimise the risks of vaccination reactions,

mainly encephalitis and generalised vaccinia, which are more common and more serious when the primary vaccination is given before the end of the first year of life. The practice in Cyprus is now to begin smallpox vaccination some time in the second year of life. It is admitted that this programme may not be applicable in countries in which smallpox is prevalent. By the way, smallpox vaccination has been included in our immunisation programme simply for the purpose of building up a herd immunity to guard against the challenge of the growing international air travel.

Another important feature in the new vaccination programme has been the spacing of injections to allow time for a durable immunity to be obtained; thus with regard to the triple diphtheria/tetanus/pertussis plus the oral polio vaccines the basic course now adopted is to allow an interval of six weeks between the first and the second injection and of six months between the second and the third.

The recently introduced measles immunisation, with the attenuated morbilli virus, is carried out after the first year of life and well after the completion of the basic course of the diphtheria/tetanus/pertussis plus polio vaccination. It should be noted, however, that because measles is but a minor children's disease in Cyprus, very little use of this vaccine is made. This hesitation, both among the profession and the public, has been prompted by adverse publication in the press and secondly by the unduly severe reactions, particularly of the central nervous system, following vaccination.

Artificial immunisation against typhoid fevers is no longer practised in Cyprus as a preventive health measure, as was the case until two decades ago. The present morbidity rate for typhoid fevers is only 0.5 per 100000 population. Anti-typhoid vaccination is reserved for persons intending to travel abroad to countries where the standard of personal hygiene and environmental sanitation are not sufficiently high. Typhoid, as well as the other enteric infections, is best controlled by improving the environmental sanitation rather than by artificial immunisation.

Similarly, BCG vaccination is not practised as a routine public health measure; the prevalence of tuberculosis in Cyprus is so low as to make this vaccination unwarranted. This is reserved for some selected groups, such as contacts of known TB cases and some hospital personnel who come in contact with patients or their families.

With a view to organising the immunisation services on a co-ordinated and uniform basis, and with a view to ensuring that these services are carried out to the best advantages of all concerned, a schedule of vaccination procedures, in the form of individual booklets, has been prepared and distributed to families. From these booklets the parents may know the optimum dates on which each immunisation including the booster, should be carried out. Further the vaccinations of the infants are checked at the infant welfare centres.

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THE DANISH IMMUNIZATION PROGRAMME

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The Danish immunization programme consists of one compulsory vaccination, i.e. smallpox vaccination, and of some voluntary immunizations recommended by the health authorities.

Vaccination against smallpox has been compulsory in Denmark since 1810. The vaccination is free of charge and is given by the medical officers of health and at Statens Seruminstitut, Copenhagen, according to fixed rules. In case parents want their children to be inoculated by the family doctor they will have to pay a fee.

Pursuant to the law, vaccination must be done before school entrance and the control of it being done, is made by the school authorities.

A possible medical contraindication or religious opposition to vaccination is respected. Approximately 98 percent of the children are vaccinated before school entrance and 99 per cent at the end of their school education.

Besides the compulsory vaccination mentioned, the health authorities recommend a programme of vaccination against diphtheria, polio, tetanus and whooping-cough. This programme has developed during the past 30 years starting with diphtheria vaccination as provided by an act of 1943.

Later the diphtheria vaccine was supplemented with vaccine against tetanus and the children were simultaneously vaccinated against both diseases.

In 1961 the diphtheria/tetanus vaccine was supplemented with whooping-cough vaccine so that a triple vaccine of diphtheria/tetanus/whooping-cough was recommended to be given.

As regards polio vaccination, this was first introduced into the Danish immunization programme in 1955, a Salk vaccine was recommended to be given at the same time as the triple vaccination, but as a separate vaccination.

In 1963 a vaccination campaign was carried out in Denmark advising everybody younger than 40 years of age to receive vaccination with oral polio vaccine Type 1. In March and May 1966 a countrywide campaign was again carried out, offering vaccination of all persons younger than 40 years, first with oral polio vaccine Type 3 and subsequently with Types 1 + 2 + 3.

Since 1968, oral polio vaccination has been part of the general immunization schedule offering 3 oral polio vaccinations to children, first at the age of approximately 2 years, second at about 3 years and the third time at about 4 years.

In the autumn of 1969 the vaccination scheme was changed to the present

form. Whooping-cough is now given as a separate vaccination at an earlier stage than the other vaccinations. Diphtheria/tetanus and polio vaccinations are inoculated as a triple vaccination. The reason for changing the vaccination schedule was partly the wish to protect children against whooping-cough earlier and partly to separate the time of whooping-cough inoculation from the time when infantile spasms most often appear. In this way it is hoped that a possible spontaneous appearance of this condition is not ascribed to the whooping-cough vaccination. The last point was caused by the discussion which has been going on for some years of a possible connection between the whooping-cough vaccination and infantile spasms.

The immunization schedule recommended now is set out in Table I.

Table I. *Present immunization schedule in Denmark*

Age	Vaccination
5 weeks	Whooping-cough
9 weeks	Whooping-cough
5 months	Diphtheria/tetanus/polio mixed
6 months	Diphtheria/tetanus/polio mixed
10 months	Whooping-cough
15 months	Diphtheria/tetanus/polio mixed
Between 1 and 2 years	Smallpox
Approx. 2 years	Oral polio
Approx. 3 years	Oral polio
Approx. 4 years	Oral polio

Considering a possible interference with an entero-virus infection during autumn and also out of regard to the public smallpox vaccinations which are most often carried out during the months of April and May, the oral polio vaccination is offered only in the period 1 December to 15 March. This interval may possibly be extended. All these immunizations are performed by the family doctor and the local government pays the costs involved.

Besides this vaccination programme children who are Mantoux-negative are recommended to have a BCG vaccination. In most counties this vaccination is performed during the first year in school, but a few prefer vaccination in the last year of school. In cases of tuberculosis in the family, babies are vaccinated shortly after birth.

All vaccines with the exception of oral polio vaccine are prepared by the Statens Seruminstitut, Copenhagen.

In connection with the public polio vaccination campaigns in 1963 and 1966 previously mentioned, some claims for damages came up. They were cases where a connection between vaccination and a later disease were claimed. All together eight cases of the sort were accepted by the health authorities and they all received compensation from the State.

Later, demands came up for compensation for diseases contracted – as was

claimed – from the ordinary vaccinations. These cases have mainly concerned cerebral damages in connection with the whooping-cough vaccination. The question of damage arising from vaccination has led to the question of compensation being examined in government committee. A bill was passed in June 1972 on compensation to persons damaged by vaccination. Dr Preben von Magnus will read a paper on this subject this afternoon.

In Denmark there is no programme for vaccination against measles or rubella. The Advisory Board of the National Health Service is at present investigating the need of vaccination against measles. According to information available, it seems that there are few serious complications to measles in Denmark. We are investigating how the disease progresses in children who are not hospitalized. This is done by an interview-survey. The result is due in a few months and we hope then to be able to evaluate the intensity of the disease and how many smaller complications it causes. When this result and the forthcoming evaluation is due a recommendation will be given to the National Health Service.

The problems of rubella vaccination will also be examined in the near future, but we are under the impression that serious complications are scarce.

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VACCINATION PROGRAMMES IN FINLAND: ADMINISTRATIVE ASPECTS

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ADMINISTRATIVE ASPECTS

Previously vaccination, especially against smallpox, was compulsory in Finland, but since 1952, when the present Vaccination Act became valid, the vaccinations have been voluntary for the population. The local authorities (communes, municipalities) have the primary responsibility of organising the services required, and the role of central authorities is limited to co-ordination, finance and health policy problems. The Cabinet (State Council) can make vaccinations compulsory when there are special reasons for such a decision, but generally speaking the highest national authority in vaccination is the National Board of Health. The provincial Medical Officers of Health are responsible for local supervision, and in special organisations such as the army, prisons, etc. the chief medical officer is responsible for the vaccinations.

A general rule is that the physicians act as vaccinators, but the public health nurses and midwives who have gained special training in vaccination may have a licence to act as vaccinators under the control of a physician and licensed by the provincial health officer. The majority of vaccinations are performed by nurses and midwives in local health centres (about 200 at present), and their centralised service units (e.g. MCG centres, about 3500 at present).* About 98 per cent of deliveries takes place in hospitals and customarily the relevant vaccinations are made during the hospitalisation (by midwives). Usual vaccinations are given free of charge. Private physicians can also vaccinate, but normally they charge because the health insurance does not cover such services.

VACCINATION RECOMMENDATIONS: THE PRESENT SITUATION

The vaccination policy has been rather conservative in Finland. The programmes given in Table I are at present recommended.

The military service vaccination programme is interesting. It covers practically the entire male population and consists of smallpox, polio, salmonella, tetanus and mumps vaccination. The mumps vaccination has been practised for 10 years and it has been successful.

Each of the programmes will be discussed briefly.

* Population of Finland: 4.7 million.

Table I. *Present vaccination programmes in Finland*

Age	Vaccination
0–1 months	Calmette
2–3 months	PDT I
3–4 months	PDT II
4–5 months	PDT III
5–6 months	Polio I
6–7 months	Polio II
12–24 months	Smallpox
18–24 months	Polio and PDT booster doses
6–7 years	Polio, Di-Tet booster doses
10 years	Smallpox

BCG VACCINATION

Finland participated in the mass campaigns after World War II and about 900 000 persons were vaccinated in 1945–50. Since then the activities have been rather completely oriented to newborn infants; the vaccinations are mainly done in maternity hospitals and MCH centres. The coverage is about 80–90 per cent of the children. At present the vaccination situation in relation to BCG is interesting (Fig. 1), because the borderline between vaccinated and non-vaccinated is rather clear-cut. The morbidity, mortality and hospital utilisation figures by age reflect very markedly the same dichotomy. The reason is certainly not solely the vaccination, but the available information strongly supports the present vaccination policy.

As the risk of contracting tuberculosis is, relatively speaking, greater in the school-leaving age, the school physicians are admonished to attach special attention to the reinoculation of the pupils in the higher forms of primary schools, when the previous vaccinations are no longer effective. But the present evidence indicates that the protective value of BCG vaccination has a longer duration than previously expected.

Currently, about 60 per cent of the population is BCG-vaccinated.

The 40 per cent non-vaccinated are to a very high degree infected with virulent tuberculosis bacilli.

The vaccinated group consists of age-classes from 0 to 35 years of age and the non-vaccinated of older persons.

The age division is discernible in the current age curves of new cases, utilisation of services and mortality.

Most probably it is incorrect to credit BCG alone with the achievements. Better health services, new drugs, an increased standard of living, and so on, have also had a marked effect.

Vaccination in Finland is performed as a routine procedure in maternity hospitals, and revaccinations, when needed, form a part of routine child and

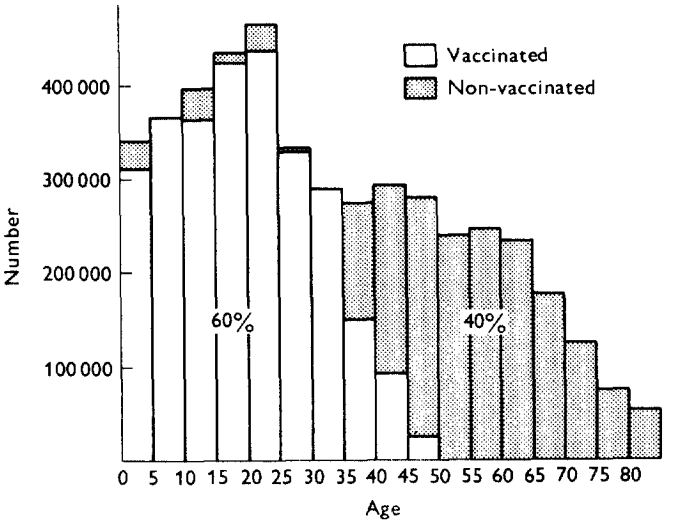

Fig. 1. BCG-vaccinated and non-vaccinated population by age in Finland, 1970. Absolute figures.

school health services. If a stop were made to these activities, no significant savings would be apparent.

Arrangements which would provide the same degree of security as BCG would be very costly, and consume time and effort needed more urgently for other health services.

PERTUSSIS–DIPHTHERIA–TETANUS (PDT) VACCINATION

Children at the age of 3–5 months get three PDT inoculations at about one-month intervals. If the inoculation is for some reason delayed, 'Salk' poliomyelitis vaccine can also be given in connection with the PDT vaccination performed at the age of 6 and 7 months. Combined polio–PDT vaccine may then be used or separate polio vaccine injected simultaneously. A booster dose is given in the latter half of the child's second year of life; not, however, before at least one year has passed since the third PDT vaccination. Often this booster dose can, for several different reasons, be delayed until the third, even the fourth year, whereafter inoculation against pertussis is prohibited and DT vaccine is to be used. In connection with this PDT or DT booster dose polio reinforcement can similarly be given either combined or separately.

At present (1971) the coverage of this vaccination in age-classes less than one year has been estimated to about 90 per cent. The effectiveness of this vaccination seems to be quite obvious, as seen in Fig. 2*a*, *b* and Fig. 3*a*, *b*.

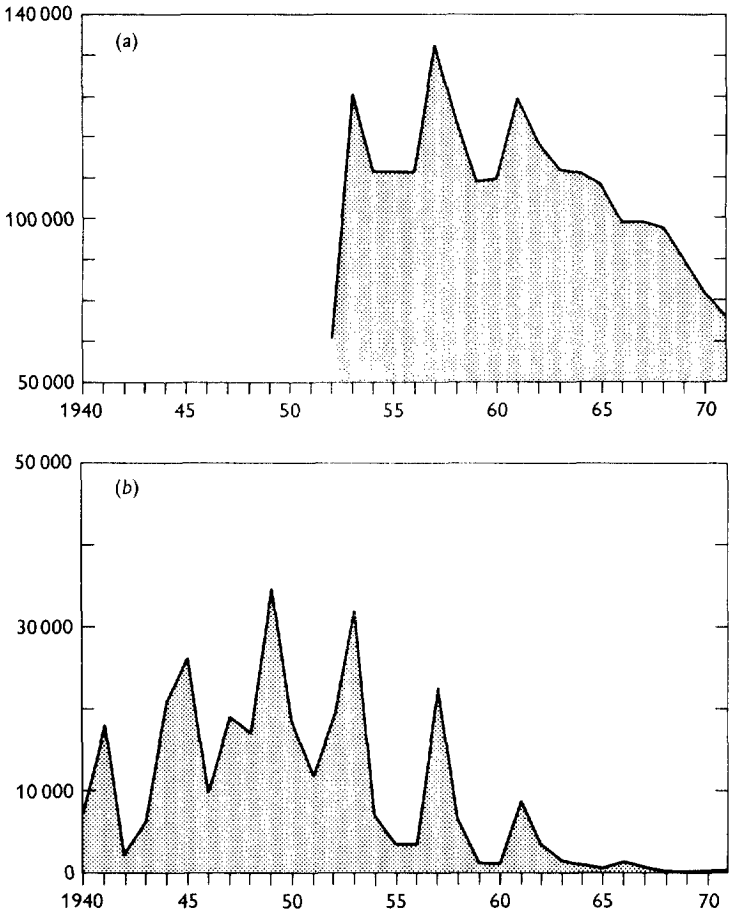

Fig. 2. Pertussis. (*a*) Vaccinations and (*b*) cases in Finland since 1940.

POLIOMYELITIS VACCINATION (SALK)

Vaccination is started when the child is 6 months old. Two polio vaccination doses are then injected at one-month intervals or also combined polio-DT vaccine can be used, as mentioned above. Booster doses are given at the earliest one year after the last vaccination which takes the child to the latter half of the ssecond year of life. It is endeavoured to give a booster dose at the age of 6–7 years when starting school, and about 5–6 years later when leaving school. Boys obtain a further booster dose in the army.

In our country, changing over to the use of live attenuated vaccine (Sabin) has been much discussed. Since, however, Finland has been free from polio since the year 1964, and in connection with the use of Sabin vaccine several polio cases have occurred in many countries, we have been restraining the use of this method.

The effectiveness of polio vaccinations is convincing, as seen in Fig. 4*a*, *b*.

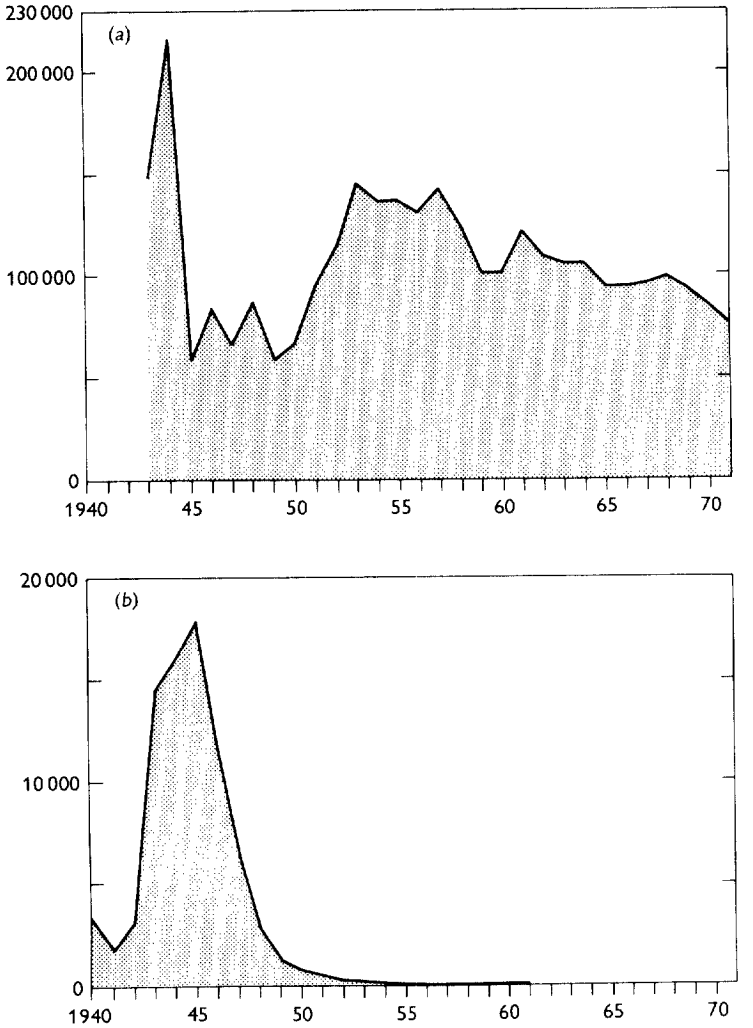

Fig. 3. Diphtheria. (*a*) Vaccinations and (*b*) cases in Finland since 1940.

SMALLPOX VACCINATION

This is performed when the child is 12–24 months old. Smallpox re-inoculation is performed at primary schools at the age of 10 years. The boys are re-inoculated in the army. However, the use of general smallpox vaccinations is seriously disputed, and in the future perhaps only risk groups will be vaccinated.

In Fig. 5 the numbers of vaccinations since 1940 are presented. Two mass vaccination campaigns are clearly seen. If the international anti-smallpox campaign is not effective, there might be situations in which mass vaccinations are needed even in the future. In such circumstances it is difficult to decide whether the omission of routine vaccinations of children would mean any real saving. But

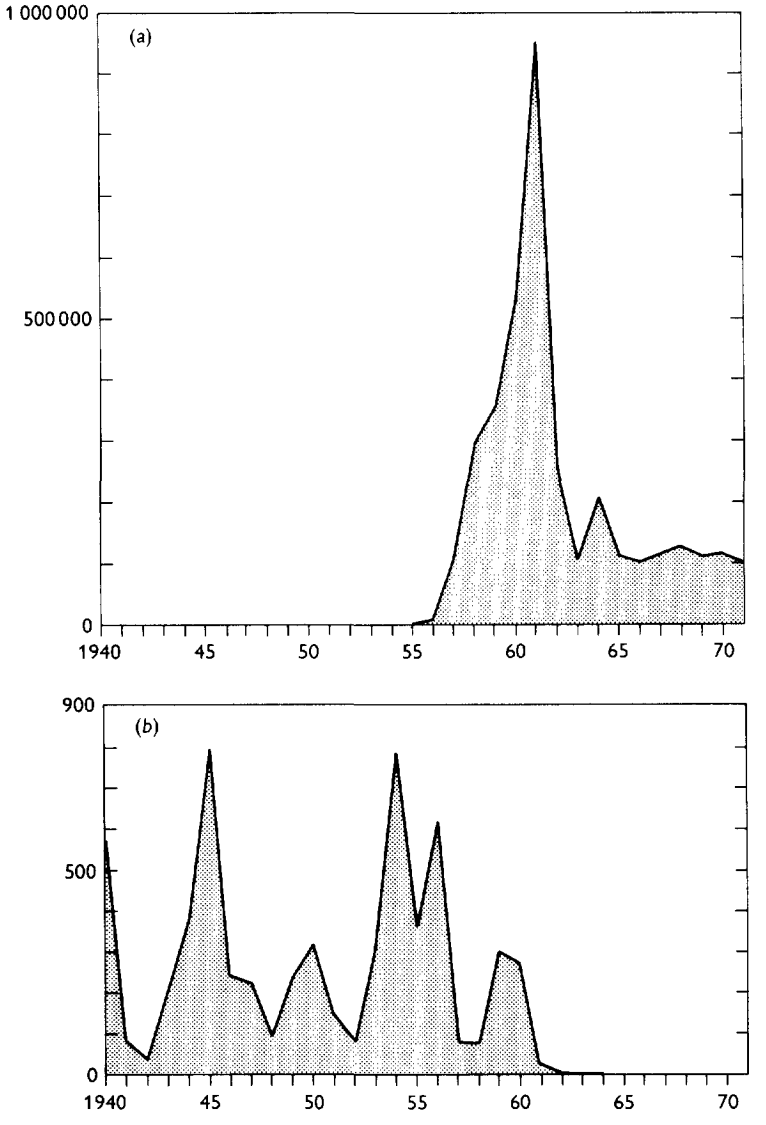

Fig. 4. Poliomyelitis. (*a*) Vaccinations and (*b*) cases in Finland since 1940.

if the eradication of smallpox is successfully completed, the vaccination policy must be adjusted.

TETANUS VACCINATION

This vaccination takes place in connection with PDT vaccination. A booster dose is given to all army conscripts. This dose is also given to all accident cases. It seems that, above all, the immunisation of young cohorts is good enough, because tetanus among them has become a very rare disease indeed.

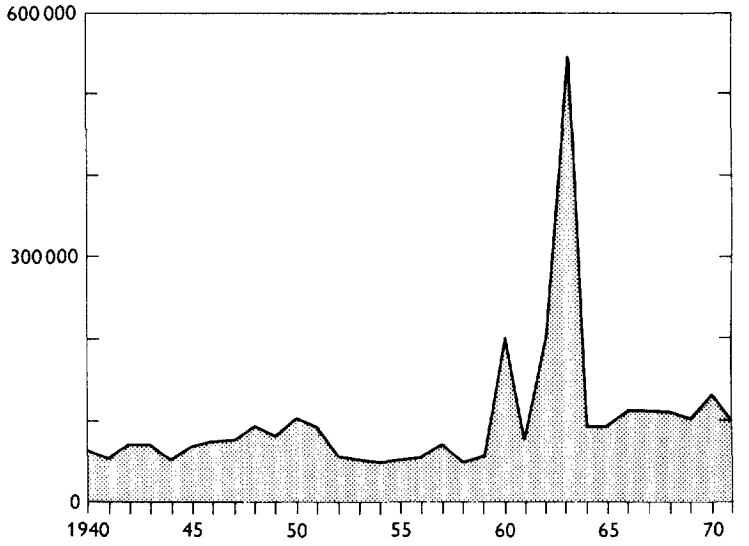

Fig. 5. Smallpox vaccinations in Finland since 1940.

PAROTITIS

Vaccination of all conscripts against parotitis has been considered necessary (2 doses at 2–3 weeks' interval). The vaccine used is produced in Finland.

ADMINISTRATORS' ROLE IN VACCINATION

The vaccinations are a topic where experts have very diverging opinions, and it is difficult to formulate a policy which is unanimously accepted. It cannot be denied that vaccinations are sometimes harmful, even disastrous, and if the risk of disease is minimal, the vaccinations should be omitted. The position of an administrator would be much stronger and much more pleasant if the information services needed for this type of decision were more developed. The following three points need consideration:

(*a*) The efficiency (protective value, duration, side effects, etc.) of vaccines needs systematic control and research. Such studies are expensive and sometimes, if done in one country, biased. Often the most active advocates of vaccination produce the evidence. Internationally organised co-operation would save much money and effort and facilitate the adoption of correct policy.

(*b*) The present statistics on vaccination are, at least in my part of the world, not so exact that one could form a reliable picture on this basis of population at risk, vaccinated population, etc. The minimum requirement would be an information service which gives reliable data on vaccinated persons by birthyear-cohort, by locality and, if relevant, by occupation. A complete register of vaccinated persons might in some circumstances be an exaggeration, but certainly such an approach needs consideration. In my country there are plans to construct

an information system which is based on individual vaccination reports. They will be used as input (optical reader) material for a computerised centralised statistical system. At the first stage only the birth year is registered; later on, the personal identification number will be used.

(*c*) There are some new vaccination procedures (e.g. against measles) which are awaiting the decisions to be introduced. The short-term bonus seems to be well documented and clinical experts are, without hesitation, recommending the procedure. The role of administrator is not pleasant, because he must feel the responsibility in relation to more or less unknown late effects of the procedure. The model of clinically oriented epidemiologists is often too limited in time perspectives. I would like to point out that any such decision needs an evaluation system which also covers all known and suspected late effects of the procedure. Again this is an area where international co-operation would be the only reasonable solution.

(*d*) There are numerous diseases which are notifiable. Some of these are not very important from the administrators' point of view and it might be useful to concentrate on such disease entities which are preventable and for which there exist special programmes (e.g. vaccination). The harmful side-effects especially need proper attention. Without such information the administrator is making his decisions in an information vacuum. Errors in this field are costly both in finances and lives.

Appendix I. *Vaccinations by age of vaccinated persons in* 1971

Vaccination	Age										Total
			Years								
	0–30 days	1–11 months	1	2	3	4	5	6	7–9	10–14	15	
BCG	50 208	3 377	32	12	12	13	9	12	69	93	63	53 900
BCG revaccination	16	61	34	39	76	134	169	249	2 879	3 265	2 051	8 973
												62 873
Diphtheria	56	58 323	2 653	2 276	1 675	1 463	1 114	3 369	4 229	830	2 056	78 044
Pertussis	55	58 216	2 547	1 926	989	661	399	453	488	218	113	66 065
Tetanus	57	58 149	2 794	2 373	1 704	1 506	1 178	3 530	5 187	8 461	34 060	118 999
Smallpox	1	2 305	17 017	9 207	4 754	3 002	2 110	2 900	9 499	17 184	35 305	103 284
Poliomyelitis	55	47 387	9 263	2 610	1 396	1 347	1 364	3 467	6 600	11 928	17 320	102 737
Salmonellosis	—	170	38	10	11	12	13	14	70	120	4 069	4 527
Other	—	63	72	82	118	87	100	93	316	429	26 783	28 143
Total	50 448	228 051	34 450	18 535	10 735	8 225	6 456	14 087	29 337	42 528	121 820	564 672

Combined vaccinations are divided into component parts. Therefore, for example, one combined diphtheria–pertussis vaccination means one diphtheria vaccination and one pertussis vaccination.

Appendix II. *Report on infectious diseases, Finland, December 1972*

Province and cities	Population 1 Jan. 1972	Tuberculosis 010–019	Syphilis recens 091	Gonorrhoea 098.00 098.09	Febris typhoidea 001	Febris paratyphoidea 002	Salm. typhimurium 003	Salmonellosis alia 003	Dysenteria 004–006	Scarlatina et tonsillitis streptococcica 034	Diphtheria 032	Pertussis 033	Poliomyelitis 040–044
1. Uusimaa ...	1 043 368	—	9	444	—	—	4	154	—	384	—	—	—
*Helsinki** ...	*520 042*	—	*9*	*407*	—	—	*3*	*112*	—	*183*	—	—	—
2. Turku–Pori ...	686 123	—	1	71	—	—	18	1	—	95	—	—	—
*Turku**	*158 301*	—	*1*	*45*	—	—	—	—	—	*25*	—	—	—
3. Ahvenanmaa ...	21 325	—	1	1	—	—	—	—	—	6	—	—	—
4. Häme	652 922	—	1	203	—	—	6	9	—	168	—	—	—
*Tampere** ...	*165 008*	—	—	*107*	—	—	*1*	*3*	—	*98*	—	—	—
5. Kymi	348 758	—	—	50	—	—	1	2	—	35	—	—	—
6. Mikkell	218 503	—	—	44	—	—	—	—	—	92	—	—	—
7. Kuopio	258 777	—	—	63	—	1	2	1	—	43	—	—	—
8. Pohjois-Karjala	185 229	—	1	30	—	—	1	—	—	17	—	—	—
9. Vaasa	429 586	—	—	25	—	—	—	—	—	35	—	—	—
10. Keski-Suomi ...	242 521	—	—	31	—	—	1	—	—	24	—	—	—
11. Oulu	411 490	—	—	44	—	—	7	—	—	25	—	—	—
12. Lappi	209 944	—	—	27	—	—	—	—	—	7	—	—	—
Total	4 703 546	412	13†	1 033	—	1	40	167	—	931	—	—	—
Jan.–Dec. 1972 ...		3 664	149	13 850	—	62	1 042	1 126	11	6 263	—	40	—
Jan.–Dec. 1971 ...		3 723	140	13 698	9	54	988	611	156	5 071	—	130	—

Province and cities	Population 1 Jan. 1972	Morbilli 055	Rubeola 056	Varicellae 052	Parotitis epidemica 072	Hepatitis infectiosa 070	Dibothriocephalus 123.40	Tonsillitis acuta 463	Infectio viarum respirat sup. 465	Influenza 470–474	Pneumonia 480–486	Enteritis, diarrhoea 008, 009	Intoxicatio alimentaria bacillaris acuta 005	Tularaemia 021
1. Uusimaa	1 043 368	244	51	148	92	7	29	4 114	11 066	—	418	577	—	—
*Helsinki**	*520 042*	*8*	*18*	*60*	*26*	*2*	*17*	*1 661*	*5 300*	—	*148*	*265*	—	—
2. Turku–Pori	686 123	968	34	265	108	5	14	2 361	6 567	—	336	311	1	—
*Turku** ...	v58 80v	*423*	—	*74*	*23*	*4*	—	*581*	*1 727*	—	*109*	*80*	—	—
3. Ahvenanmaa ...	21 325	3	1	5	—	—	—	72	106	—	23	17	—	—
4. Häme ...	652 922	66	20	175	168	1	12	2 115	6 178	—	287	524	—	—
*Tampere**	*165 008*	*16*	*12*	*43*	*34*	—	—	*454*	*1 317*	—	*116*	*167*	—	—
5. Kymi ...	348 758	322	59	112	78	2	57	1 683	4 017	—	224	279	—	—
6. Mikkell	218 503	57	4	24	20	—	32	692	1 376	—	75	40	—	—
7. Kuopio	258 777	5	8	61	15	—	32	490	1 072	—	77	50	—	—
8. Pohjois-Karjala	185 229	69	5	54	7	2	67	276	483	—	45	30	—	—
9. Vaasa ...	429 586	32	21	40	88	11	7	647	1 750	—	84	133	—	—
10. Keski-Suomi	242 521	53	17	43	49	1	24	1 073	2 138	—	144	105	—	—
11. Oulu ...	411 490	67	12	27	47	—	69	970	2 052	—	172	50	—	—
12. Lappi ...	209 944	38	10	9	9	—	67	426	1 111	—	85	6	—	—
Total ...	4 703 546	1 924	242	963	681	29	410	14 919	37 916	—	1 970	2 122	1	—
Jan.–Dec. 1972		14 159	5 042	7 252	7 895	236	5 307	143 340	299 695	20 277	17 656	25 857	66	—
Jan.–Dec. 1971		20 406	4 584	8 091	22 980	317	7 550	146 845	358 840	74 351	19 109	28 709	—	10

No cases of quarantinable diseases in December 1972.
* The numbers are included in the numbers of the province.
† Of which five were imported cases.

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LES PROGRAMMES DE VACCINATIONS EN FRANCE

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Un grand effort est fait en France depuis quelques années pour codifier l'application des vaccinations courantes. Actuellement la vaccination antivariolique, les vaccinations antidiphtérique et antitétanique, la vaccination anti-poliomyélitique et la vaccination par le BCG sont obligatoires (**8**).* Mais c'est sur un plan tout à fait différent de l'obligation légale que se situent les recommandations, nullement contraignantes, émanant du Ministère de la Santè Publique ou de divers organismes et touchant au 'calendrier des vaccinations' chez le nourrisson et l'enfant. Il s'agit ici d'envisager dans son ensemble le programme des vaccinations les plus usuelles dans une perspective d'hygiène publique: d'où la nécessité de le rendre aussi simple et commode à suivre que possible pour la masse de la population. Les données immunologiques aussi bien qu'épidémiologiques entrent en ligne de compte, ainsi que les risques d'effets secondaires. Nous ne pouvons ici nous étendre à ce sujet.

LES VACCINATIONS DU NOURRISSON

Les 'calendriers de vaccinations' proposés ont pour point commun de faire place à la vaccination anticoquelucheuse (qui n'est pas obligatoire) et de prévoir un cycle de vaccinations primaires commencé de bonne heure et terminé avant l'âge de 1 an puis suivi des rappels nécessaires. Cependant il n'existe pas en France, comme dans d'autres pays, un programme de vaccinations officiel unique. Plusieurs variantes sont suggérées, qui se distinguent surtout l'une de l'autre par les modalités des vaccinations anticoquelucheuse, antidiphtérique, antitétanique et antipoliomyélitique. Pour s'assurer des résultats obtenus avec ces 'calendriers' et pour choisir entre eux, le mieux était sans doute de les mettre à l'épreuve sur le terrain dans des conditions rigoureuses. C'est ce que nous avons cherché à

* *Abréviations:* DT: Vaccin antidiphtérique et antitétanique. C: Vaccin anticoquelucheux. DTC: Vaccin antidiphtérique, antitétanique et anticoquelucheux. DTP: Vaccin antidiphtérique, antitétanique et antipoliomyélitique (virus inactivé). DTCP: Vaccin antidiphtérique, antitétanique, anticoquelucheux et antipoliomyélitique (virus inactivé). PV: Vaccin antipoliomyélitique vivant. VAV: Vaccin antivariolique. VAR: Vaccin antirougeoleux.

faire depuis une dizaine d'années, tout en les adaptant à une situation qui comporte quelques élements nouveaux.*

Les calendriers utilisés sont reproduits, Tableau I. Dans le calendrier I la vaccination anticoquelucheuse est pratiquée isolément vers l'âge de 3, 4, 5 mois et suivie de 3 injections DTP vers 6, 7 et 8 mois. Les résultats obtenus n'ont été satisfaisants que pour le coqueluche et ce calendrier a cessé de figurer dans notre enquête depuis 1966. Sans doute, le vaccin DTP non adsorbé dont nous nous servions n'etait-il pas assez actif. La présence de l'adjuvant minéral semble très nécessaire, pour obtenir une bonne réponse à la vaccination anatoxique primaire, chez le nourrisson de 3 ou même 6 mois car celui-ci n'a pas atteint sa pleine maturité immunologique et la présence d'anticorps d'origine maternelle peut exercer un effet inhibiteur(4).

L'emploi du vaccin quadruple DTCP sert de base aux calendriers II (avec début à 3 mois) et III (avec début à 6 mois). Dans les deux cas, la production d'antitoxines est satisfaisante, grâce a l'effet de l'adjuvant minéral toujours présent en France dans le vaccin anticoquelucheux. En revanche, les résultats de la vaccination antipoliomyélitique ainsi effectuée sont assez médiocres. Dans une étude récente, avec le calendrier II, un mois après la 3ème injection, on trouve 61 % de titre d'anticorps > 1/10 avec le type I, 78 % avec le type II, 70 % avec le type III. Un an après, au moment du rappel, les pourcentages ne sont plus que de 42, 68 et 57 respectivement. Les chiffres s'élèvent 4 mois après rappel mais l'on ne dépasse 90 % qu'avec le type II.

En commencant la même vaccination quadruple à l'age de 6 mois (calendrier III) on fait apparaître un titre d'anticorps antipoliomyélitique > 1/10 chez 81 (type I), 92 (type II) et 83 % (type III) des enfants. Mais la baisse constatée au moment du rappel est très sensible. Après rappel on arrive à des titres > 1/10 chez plus de 90 % des enfants pour les types I et II, 87 % pour le type III. Les résultats observés avec le vaccin quadruple DTCP ne sont, on le voit, pas excellents quant à la protection contre la poliomyélite avant l'âge du rappel.

La superiorité du calendrier III (début à 6 mois) sur le calendrier II (début à 3 mois) est éphémère. Elle s'efface dès avant l'injection de rappel, les résultats que nous avons pu enregistrer 5 ans après la vaccination montrent une assez grande stabilité pour les antitoxines, une diminution assez nette du pourcentage des protégés pour la poliomyélite (par rapport aux chiffres trouvés à la suite du rappel de la 2ème année de la vie) pour la poliomyélite et pour la coqueluche.

Les calendriers IV, V et VI se distinguent des précédents par le recours au vaccin antipoliomyélitique vivant. Les chiffres satisfaisants enregistrés avec le calendrier IV ont déjà été publiés(7). Ceux auxquels on arrive avec les calendriers V et VI sont très voisins (Tableaux II a VII). On notera la baisse assez nette observée entre les prélèvements effectués 1 mois après la 3ème injection et 10 mois plus tard, le jour du rappel. D'autre part, les titres enregistrés après rappel et même 2 ans après sont corrélés à ceux qui ont été trouvés 1 mois après la 3ème injection(4).

* Les titrages d'agglutinines anticoquelucheuses ont été effectués par Madame le Dr F. Herzog, les titrages d'anticorps antipoliomyélitiques par le Prof. Daguet.

Tableau I. *Calendriers utilisés*

Age (mois)	Calendrier I	Calendrier II	Calendrier III	Calendrier IV	Calendrier V	Calendrier VI
1	Groupe A: BCG	Groupe A: BCG	Groupe A: BCG	Groupe A: BCG	—	—
2	C (1ère)	DTCP (1ère)	—	DTC + PV (1ère)	DTC + PV (1ère)	DTC + PV (1ère)
4	C (2ème)	DTCP (2ème)	—	DTC + PV (2ème)	DTC + PV (2ème)	—
5	C (3ème)	DTCP (3ème)	—	DTC + PV (3ème)	DTC + PV (3ème)	DTC + PV (2ème)
6	DTP (1ère)	—	DTCP (1ère)	—	BCG	BCG
7	DTP (2ème)	—	DTCP (2ème)	—	—	—
8	DTP (3ème)	—	DTCP (3ème)	—	—	—
9	VAV	VAV	VAV	VAV	VAV	VAV
10	Groupe B: BCG	Groupe B: BCG	Groupe B: BCG	Groupe B: BCG	—	—
12	—	—	—	—	VAR	VAR
15	—	—	—	—	Rappel DTC + PV	Rappel DTC + PV
20	Rappel DTCP	Rappel DTCP	Rappel DTCP	Rappel DTC + PV	—	—

Tableau II. *Résultats des titrages d'anticorps (calendriers V et VI); antitoxine diphtérique*

Calendrier		Age au moment de la vaccination											
		3 mois (avant vaccination)			6 mois, 1 mois après vaccination			15 mois, rappel			20 mois, 5 mois après rappel		
		Nb. de sujets	Sujets protégés (%)	Moyenne	Nb. de sujets	Sujets protégés (%)	Moyenne	Nb. de sujets	Sujets protégés (%)	Moyenne	Nb. de sujets	Sujets protégés (%)	Moyenne
V	3 injections. DTC + Polio buccal 3–4–5 mois	251	28,3	1,4	208	95,2	3,4	129	80,6	2,7	84	95,2	3,5
VI	2 injections. DTC + Polio buccal 3–5 mois	254	22,0	1,3	215	94,9	3,3	127	67,7	2,2	81	96,3	3,5
	Comparaison		DNS	DNS		DNS	DNS		DS	DTS		DNS	DNS

Tableau III. *Résultats des titrages d'anticorps (calendriers V et VI); antitoxine tétanique*

Calendrier		Age au moment de la vaccination: 3 mois (avant vaccination) Nb. de sujets	Sujets protégés (%)	Moyenne	6 mois, 1 mois après vaccination Nb. de sujets	Sujets protégés (%)	Moyenne	15 mois, rappel Nb. de sujets	Sujets protégés (%)	Moyenne	20 mois, 5 mois après rappel Nb. de sujets	Sujets protégés (%)	Moyenne
V	3 injections. DTC + Polio buccal 3–4–5 mois	252	22,2	1,4	208	95,7	3,3	131	95,4	2,8	84	98,8	3,7
VI	2 injections. DTC + Polio buccal 3–5 mois	254	22,8	1,4	215	97,2	3,4	137	84,3	2,5	81	97,5	3,6
	Comparaison		DNS	DNS		DNS	DNS		DTS	DTS		DNS	DNS

Tableau IV. *Résultats des titrages d'anticorps (calendriers V et VI); agglutinines anticoquelucheuses*

Calendrier		Age au moment de la vaccination: 6 mois, 1 mois après vaccination — Nb. de sujets	Sujets protégés (%)	Moyenne	15 mois, rappel — Nb. de sujets	Sujets protégés (%)	Moyenne	20 mois, 5 mois après rappel — Nb. de sujets	Sujets protégés (%)	Moyenne
V	3 injections. DTC + Polio buccal 3–4–5 mois	198	43,9	3,6	123	30,9	3,0	73	71,2	4,8
VI	2 injections. DTC + Polio buccal 3–5 mois	208	23,1	2,2	122	8,2	1,9	70	62,8	4,3
	Comparaison		DTS	DTS		DTS	DTS		DNS	DNS

Tableau V. *Résultats des titrages d'anticorps (calendriers V et VI). Anticorps antipoliomyélitiques (type I)*

Calendrier		Age au moment de la vaccination: 6 mois, 1 mois après vaccination — Nb. de sujets	Sujets protégés (%)	Moyenne	15 mois, rappel — Nb. de sujets	Sujets protégés (%)	Moyenne	20 mois, 5 mois après rappel — Nb. de sujets	Sujets protégés (%)	Moyenne
V	3 injections. DTC + Polio buccal 3–4–5 mois	163	82,2	3,8	73	75,3	3,0	37	81,1	3,3
VI	2 injections. DTC + Polio buccal 3–5 mois	164	68,9	3,2	77	57,1	2,5	27	74,1	3,1
	Comparaison		DTS	DTS		DS	DS		DNS	DNS

Tableau VI. *Résultats des titrages d'anticorps (calendriers V et VI). Anticorps antipoliomyélitiques (type II)*

Calendrier		Age au moment de la vaccination								
		6 mois, 1 mois après vaccination			15 mois, rappel			20 mois, 5 mois après rappel		
		Nb. de sujets	Sujets protégés (%)	Moyenne	Nb. de sujets	Sujets protégés (%)	Moyenne	Nb. de sujets	Sujets protégés (%)	Moyenne
V	3 injections. DTC + Polio buccal 3–4–5 mois	163	95,7	4,6	73	94,5	4,2	37	97,3	4,2
VI	2 injections. DTC + Polio buccal 3–5 mois	166	96,4	4,6	77	93,5	4,3	28	96,4	4,6
	Comparaison		DNS	DNS		DNS	DNS		DNS	DNS

Tableau VII. *Résultats des titrages d'anticorps (calendriers V et VI). Anticorps antipoliomyélitiques (type III)*

Calendrier		Age au moment de la vaccination: 6 mois, 1 mois après vaccination — Nb. de sujets	Sujets protégés (%)	Moyenne	15 mois, rappel — Nb. de sujets	Sujets protégés (%)	Moyenne	20 mois, 5 mois après rappel — Nb. de sujets	Sujets protégés (%)	Moyenne
V	3 injections. DTC + Polio buccal 3–4–5 mois	163	97,5	4,6	73	94,5	4,3	37	100	4,6
VI	2 injections. DTC + Polio buccal 3–5 mois	166	92,8	4,5	77	92,2	4,1	28	100	4,4
	Comparaison		DNS	DNS		DNS	DNS		DNS	DNS

Le point le plus important est sans doute, que, dans les conditions où nous nous sommes placés, le vaccin PV donne des résultats supérieurs à ceux du vaccin inactivé. Une enquête en cours concerne l'emploi du vaccin inactivé (incorporé dans le DTCP) pour l'injection de rappel lorsque la vaccination a été effectueé la première annee avec le PV.

Il est assez difficile de juger de l'efficacité de la vaccination anticoquelucheuse. Comme on le voit Tableau IV les agglutinines sont loin d'apparaître toujour sà un taux > 1/320, dont il est admis qu'il correspond à une immunité solide. Cependant, le titre des agglutinines ne suffit pas à renseigner. Il est certain que des titres faibles peuvent se trouver chez des enfants efficacement protégés. En l'absence de statistiques de protection valables, on a l'impression qu'en France la vaccination anticoquelucheuse a très bien agi sur la mortalité par coqueluche: les coqueluches graves du nourrisson devenant exceptionnelles. Mais la survenue de coqueluches, généralement benignes, chez des enfants vacines est assez courante.

Tous nos calendriers (Tableau I) comportaient à la même date, vers l'age de 9 mois, la vaccination antivariolique; la vaccination par le BCG étant effectuée à un age variable mais toujours avant 1 an. En définitive, les calendriers IV, V et VI nous ont fourni les chiffres les plus satisfaisants. Nos constatations à cet égard rejoignent celles qui ont été faites en divers pays. L'emploi du calendrier IV est très repandu dans les centres de Protection Maternelle et Infantile et préconisé par beaucoup de pédiâtres. Mais ailleurs, en clientèle privée, le vaccin quadruple demeure souvent utilise. Il arrive aussi qu'aucun calendrier defini ne soit observé. Enfin chez d'assez nombreux enfants des retards importants sont pris avec ou sans raison valable.

La situation en France a été récemment modifiée par un texte reportant à 2 ans l'âge limite pour la vaccination antivariolique obligatoire. Aucun texte ne s'y opposant plus, la primo-vaccination antivariolique au cours de la 2ème année de la vie, déjà pratiquée par quelques médecins (qui jusqu'à présent engageaient ainsi beaucoup leur responsabilité) va sans doute gagner du terrain.

Un autre point qui paraît sujet à révision concerne le nombre des injections de vaccin DT(2). Nous avons pu établir que de très bons résultats pouvaient être obtenus avec deux injections séparées par un intervalle de 2 mois, le rappel étant effectué 1 an environ après (calendrier VI) (Tableaux II et III). Quoique la réglementation continue à prévoir 3 injections, outre le rappel, on pourrait certainement, comme dans plusieurs autres pays, se limiter à 2 injections. Cette simplification n'entraîne aucun inconvénient lorsque la vaccination anticoquelucheuse se trouve inutile (l'enfant ayant déjà eu la maladie), contre-indiquée ou refusée. Mais pour ce qui est de la vaccination triple antidiphtérique, antitétanique et anticoquelucheuse, on hésite à trancher. Si l'on en juge par les taux d'agglutinines après vaccination, il semble préférable de faire trois injections que deux. Quant au vaccin PV, il donne de moins bons résultats avec deux prises (calendrier VI, Tableau I) qu'avec trois mises (Tableaux V–VII).*

* Pour les Tableaux II à VII les sujets sont comptés comme protégés: contre la diphtérie, lorsque le titre antitoxique est ≥ 0,05 UI/ml; contre le tétanos, lorsque le titre

LES RAPPELS ULTERIEURS

La revaccination contre la poliomyélite est généralement recommandée tous les 5 ans environ à partir du premier rappel. On recourt le plus souvent au vaccin vivant, que la primo-vaccination ait été pratiquée avec le vaccin inactivé ou avec le vaccin vivant. Mais le contraire peut se faire éventuellement.

Des rappels périodiques sont certainement nécessaires pour les vaccinations anatoxiques. Quoiqu'ils ne soient pas légalement obligatoires, ils sont conseillés avec beaucoup d'insistance. Peut-être même les rapproche-t-on un peu trop si l'on suit les indications des 'calendriers' recommandés qui en prévoient la répétition tous les 5 ans. En fait, chez les enfants vaccinés avec un bon antigène et ayant recu le premier rappel, l'immunité dure longtemps et une revaccination unique au cours de l'enfance, vers l'âge de 9 ans par exemple, devrait suffire. L'important, surtout pour le tétanos, est de ne pas s'arreter là et de continuer à revacciner tous les dix ans à peu près.

L'indication de la revaccination antidiphtérique chez l'adulte est plus discutée. A notre avis, elle mériterait encore d'être pratiquée a l'âge de 20 ans (elle l'est d'ailleurs dans l'armée). L'emploi de doses faibles d'anatoxine diphtérique peut améliorer la tolerance du vaccin sans empêcher la revaccination d'être efficace. Le niveau de protection n'est pas tres élevé dans la population francaise: ce qui tient au recul de l'infection naturelle, au nombre assez élevé de sujets qui échappent à la vaccination mais aussi, croyons-nous, à l'activité insuffisante de certains vaccins, non adsorbés surtout. En France, pas plus qu'ailleurs, le souci d'un retour offensif de la diphtérie n'est très repandu. On aurait tort cependant d'en exclure l'éventualité et de relâcher l'effort de vaccination.

Un deuxième rappel anticoquelucheux vers l'âge de 5 ans peut être indiqué, notamment dans le but de protéger indirectement un tout petit au foyer familial. Mais ce deuxième rappel anticoquelucheuse doit elle être systématique? L'accord n'est pas réalisé à ce sujet.

En ce qui concerne le BCG, il faut tout d'abord rappeler que la règlementation actuelle permet d'ajourner la vaccination jusqu'à la 6ème année de la vie. Mais, sans vouloir imposer celle-ci toujours dans le 1er mois, il semble raisonnable en France de ne pas attendre au délà de la 2ème annee ou de la 3ème. D'autre part, lorsque les réactions tuberculiniques deviennent authentiquement négatives chez un ancien vacciné, on considère la revaccination comme indiquée(**6**). A l'ecole et au lycée, d'après une circulaire récente, les tests intrade rmiques doivent être pratiqués systématiquement chez tous les enfants de 6 ans (première année de scolarité obligatoire), chez tous les élèves des classes de 3ème et de niveau équivalent (14 à 16 ans), chez tous les élèves de classes terminales et des classes préparatoires aux Grandes Ecoles (17 à 20 ans environ). Les élèves présentant une reaction tuberculinique négative sont vaccinés ou revaccinés.

Quant à la revaccination antivariolique, elle est obligatoire dans les 11ème et

antitoxique est $\geqslant$ 0,01 UI/ml; contre la coqueluche, lorsque le titre des agglutinines est $\geqslant$ 1/320; contre la poliomyélite, lorsque le titre des anticorps est $>$ 1/10.

21ème année de la vie. Il va de soi qu'elle peut à d'autres moments avoir des indications occasionnelles (par exemple lorsqu'un certificat international de vaccination datant de moins de 3 ans est exigé pour un voyage a l'étranger). Mais mous n'envisageons ici que les programmes généraux applicables à l'ensemble de la population.

VACCINATION ANTIROUGEOLEUSE

La vaccination antirougeoleuse, jusqu'à present, n'est conseillée officiellement que chez des enfants atteints de diverses infections chroniques et dans les collectivités d'enfants. Un intérêt particulier s'attache à la vaccination souvent efficace pratiqueé, dans une crèche par exemple, aussitôt après le contact avec un rougeoleux(3). La vaccination systématique contre le rougeole ne fait l'objet d'aucune recommandation des autorités. Elle a d'assez nombreux partisans mais n'est pas encore généralisée actuellement en France (1 enfant sur 6 environ y est soumis). L'obstacle des anticorps passifs paraissant parfois encore sensible jusque vers l'âge de 1 an, la VAR est à pratiquer de préférence dans la 2ème année de la vie, comme dans nos calendriers V et VI (Tableau I). Dans tous les groupes d'enfants où nous l'avons pratiquée le taux de protection, d'après les titrages d'anticorps a dépassé nettement 90 %. La VAR ne modifie pas résultats obtenus avec les autres vaccinations. Un travail est en cours sur les résultats que peut donner la VAR effectuée simultanément au rappel DTC + PV ou au rappel DTCP.

Le programme auquel nous nous arrêterions le plus volontiers (Tableau VIII) comporte donc la VAR. Il est très proche par ailleurs d'un des calendriers qui ont fait l'objet des recommandations officielles celui qui correspond à notre calendrier IV (Tableau I). Mais, en dehors même de l'introduction de la VAR, il en diffère quelque peu, compte tenu des données les plus récentes(5).

VACCINATION ANTIRUBEOLEUSE

La preuve de l'efficacité de la vaccination contre la rubéole n'est plus à faire. Cependant, il n'est pas aisé de définir et d'appliquer une politique lui donnant sa place dans un programme de vaccinations(1). La plupart en France tendent à la pratiquer uniquement chez les filles a l'âge de la puberté, ou plus tard avec davantage de précaution dans la population féminine déjà adulte. La vaccination n'est effectuée qu'en l'absence d'un taux protecteur d'anticorps résultant d'une infection naturelle antérieure.

Des objections ont été faites en France à la vaccination systématique de l'ensemble de la population infantile vers l'âge de 2 ou 3 ans. Ce serait une mesure logique si l'on était assuré que, du fait de l'immunité collective ainsi provoquée dans la population infantile, la maladie avait des chances d'être plus ou moins rapidement éradiquée. Mais, d'après des constatations recentes, la vaccination antirubéoleuse, dans des groupes d'enfants protegés pour le plus grand nombre, n'arrête pas toujours très efficacement la propagation des épidémies(9).

Tableau VIII. *Programme de vaccinations recommandable en France (arrêté à 15 ans)*

Age	Vaccins
1er mois	BCG si accepté
3 mois	DTC + PV (1ère)
4 mois	DTC + PV (2ème)
5 mois	DTC + PV (3ème)
1 an–15 mois	Vaccin antivariolique
15–18 mois	Rappel DTC + PV
Entre 1 et 2 ans	Vaccin antirougeoleux
6 ans	Rappel PV
9 ans	DT
10 ans	Revaccination antivariolique
11 ans	Rappel PV

On envisage enfin, pour des raisons pratiques, de proposer à l'avenir la vaccination antirubéoleuse en même temps qu'une revaccination antidiphtérique et antitétanique.

Pour le moment, ce sont en fait surtout en France des jeunes filles et des jeunes femmes qui recoivent la vaccination en assez grand nombre. Qu'en sera-t-il à l'avenir? Pour le savoir, il faudrait être mieux fixé que nous le sommes sur la durée de l'immunité après vaccination: question d'autant plus importante que, si des revaccinations se montraient nécessaires en période d'activité génitale, elles poseraient des problèmes difficiles à résoudre, en pratique collective tout au moins.

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VACCINATION PROGRAMMES IN ICELAND

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Although the Icelanders wrote many books in olden days there are very few and unreliable sources of descriptions of diseases from that time, especially of repeated epidemics of infectious diseases. This was, of course, due to ignorance and lack of specially trained people. In our sagas there is little told about medical treatment, except for treatment of wounds after a battle.

In the Middle Ages when epidemics from the East began to plague the country, there seem to have been no attempts to cure the sick, as far as we know, and various measures for health maintenance and hygiene, such as sports and baths, that were highly estimated during the Saga Age, had almost disappeared by then.

From descriptions in annals it is known that smallpox was spread through the country many times, most likely in 1240 for the first time, and Plague (Black Death) at least twice, in the beginning and end of the 15th century.

It seems from descriptions that syphilis as an epidemic spread through Iceland in 1500, and at the same time leprosy seems to have become common. Leprosy became a great problem, so serious that the first hospitals in the country were built for the leprous, in 1652. In fact, these were no real hospitals, but only asylums and keeping places where conditions were extremely bad.

THE BEGINNING OF MEDICAL TREATMENT

The first learned physician came to the country in 1760, and from then on various health measures from the official side began to be taken.

The first sign of sanitary measures for foreigners are regulations from 1772 against leprosy and one from 1782 against infectious diseases in general.

The first regulation on smallpox vaccination is from 1802 (6 years after this method was invented, and 4 years after it became generally known).

As mentioned before it is known that smallpox spread at regular intervals, and there is no doubt from descriptions in annals that it was smallpox. This disease proved most fatal in 1707 when almost one-third of all the population died of it.

The first census in Iceland (in fact in Europe) was carried out in 1703. Then the population was little over 50000, or little lower than it is estimated to have been in 930 at the end of the Settlement Age.

During the period 1700–1800 the Icelanders steadily decreased in number. During the decade 1751–60 the average birth rate was 29‰* but the death rate was 40‰. During this period until 1800 it seemed that the nation would die out. It can be mentioned for comparison that in Norway the birth rate was 34‰,

* x‰ = x per thousand.

death rate 25‰, in Sweden 36‰ and 27‰ and Denmark (about 1800) 33‰ and 26‰.

The causes for this situation in Iceland were many, but the epidemics were not the least of them, especially of infant mortality, even though harsh climate, polar ice, volcanic eruptions have also played their part.

There were few general health care measures to be mentioned at the beginning of the 19th century, except for smallpox vaccination and sanitation. Since 1802 the Danish authorities sent vaccine to Iceland and instructions as to its use. These vaccinations were mostly done by ministers and others they taught and entrusted with these activities, because doctors were scarce at this time.

Obligatory vaccination became law in Iceland in 1810 and is still law.

Looking back, one cannot but conclude that it was the vaccination that can be mostly thanked for the change that took place, i.e. that the population stopped decreasing. The nation would not have withstood many epidemics like those in 1707. Still the population increase was slow; in 1850 the Icelanders were 59157 in number, caused rather by an increase in births than a lower death rate, because in 1841–50 the birth rate was 39‰ but the death rate 30‰. The change was most likely brought about rather by better weather conditions during these years than better health situation, since the same epidemic diseases plagued the country during this period, as before. Diseases other than smallpox were: whooping-cough, measles, influenza, scarlet fever and dysentery; these caused many deaths. Diphtheria was a severe disease in children and measles and typhoid fever were common, killing many people yearly. Measles that raged in 1846 killed 2000 people, or 35‰ of the total population. The infant mortality figures are probably the most reliable and at the same time the most dismal proof of the health situation of these times. During the years 1841–50, of all infants born alive, a yearly average of 343‰ died before the end of their first year (at the same time in Sweden 153‰ and Denmark 139‰). The highest infant mortality (654‰) was reached in the year of the measles, 1846.

Of the achievements during these years there can be mentioned the fact that by the middle of the century tetanus, which until then had been epidemic, and most serious in the Westman Islands, had been eradicated. For this the assistance of a Danish doctor, whom the authorities had sent for this purpose to Iceland, can be thanked.

THE HEALTH SITUATION IN THIS CENTURY

During this century the health situation has been steadily improving. This has been caused by many factors: increased understanding of health affairs, more specially trained personnel with extensive technical knowledge and the determination of the authorities to carry out improvements.

Thus at the beginning of the century many determined actions were taken in the field of health affairs, by secure and resolved legislations, e.g. the Sanitation Law and the Law on Vaccination. The fight against leprosy became more active, as a modern hospital for the leprous was built (in fact a gift of the Danish Oddfellows).

Table I. *Iceland's population, births and deaths*

The whole country	1965	1966	1967	1968	1969
Population					
1 December	193758	196933	199920	202191	203442
Midyear	192304	195610	198674	201244	202920
Reykjavík only	78389	79202	80090	81026	81476
% of the population	40.5	40.2	40.1	40.1	40.0
Live births	4721	4692	4404	4227	4218
Live birth rate	24.5	24.0	22.2	21.0	20.8
Still-births	71	57	50	52	47
Still-birth rate	15.0	12.1	11.4	12.3	11.1
Death	1291	1391	1385	1389	1451
Death rate	6.7	7.1	7.0	6.9	7.2
Infant mortality	71	64	59	59	49
I.M. rate	15.0	13.6	13.4	14.0	11.6

Life expectancy 1961–5 was 70.8 years for males and 76.2 for females.

Table II. *Perinatal mortality in Iceland*, 1951–69

	Number	o/oo of total births		Number	o/oo of total births
1951	106	26.1	1961	129	27.8
1952	116	27.9	1962	102	21.4
1953	111	25.7	1963	118	24.1
1954	108	24.8	1964	110	22.7
1955	110	24.1	1965	115	24.0
1956	108	23.1	1966	98	20.6
1957	105	21.9	1967	92	20.6
1958	118	25.1	1968	101	23.6
1959	97	19.8	1969	78	18.3
1960	98	19.7			

By increased hygiene and sanitation control it was possible to diminish the typhoid plagues. It is remarkable how infectious diseases that could not be fought by sanitation or medical treatment (influenza, measles, whooping-cough) gradually become less fatal than before, which is difficult to explain by anything else than generally increased resistance power and higher living standards in general.

But during these years when the health situation of the nation seems to be getting better, a new disastrous disease arrives on the scene – tuberculosis, that for almost all the first half of the 20th century became one of the most common causes of death. The reason for this is not quite clear. In the year 1911 the first complete death certificates were filled out. That year 114 or 1.3‰ died of tuberculosis. In 1918 this rate was 173 or 1.8‰ and was then the cause of almost 14%

Table III. *Causes of deaths (the ten most common) in Iceland,* 1969

	Number	Per 1000 of deaths	Per 1000 of the population
1. Diseases of the heart	426	293.6	2.10
2. Malignant neoplasms	293	201.9	1.44
3. Apoplexy	174	119.9	0.86
4. Accidents (suicides incl.)	117	80.6	0.58
5. Pneumonia (inf. incl.)	115	79.2	0.57
6. General arteriosclerosis	31	21.4	0.15
7. Diseases of infants	29	20.0	0.14
8. Infections of the kidney	23	15.8	0.11
9. Pulmon. embol. infarct	22	15.2	0.11
10. Influenza	21	14.5	0.10
11. Other and unknown	200	137.8	0.98

Table IV. *Causes of deaths per* 1000 *of population* 1965–9

	1965	1966	1967	1968	1969
1. Diseases of heart	1.78	2.04	2.09	1.96	2.10
2. Malignant neoplasms	1.29	1.42	1.47	1.46	1.44
3. Apoplexy	0.86	0.85	0.82	0.97	0.86
4. Accidents	0.68	0.70	0.65	0.57	0.58
5. Pneumonia	0.57	0.57	0.43	0.43	0.57
6. Tuberculosis	0.02	0.01	0.02	0.02	0.02
7. Maternal mortality (acc. to born children)	0.21	0.21	0.0	0.0	0.23

of all deaths. In the year 1921 a certain law was made to prevent the expansion of this diesase, but in spite of all actions the tuberculosis increased and deaths caused by it reached their peak in 1930 when 2.1‰ of all the population died of it and tuberculosis accounted for 20% of all deaths.

During the last 30–40 years the health situation has been steadily improving in Iceland. The infant mortality has decreased, as well as the general death rate and the average life expectancy rate has risen. Tables I–IV show this.

THE VACCINATION PROGRAMMES AT PRESENT

As said before, a regulation on smallpox vaccination was for a long time the only regulation on immunization to be included in the Icelandic law. The first regulation dates from 1802; later there was a law on vaccination from 1901, which was replaced by law of 1 January 1951. This law states the immunizations covered by it. They are the following:

(1) Smallpox.
(2) Diphtheria.

(3) Typhoid and paratyphoid.
(4) Whooping-cough.
(5) Tuberculosis.
(6) Other possible diseases that might come up in the country, if an effective immunization is practicable (e.g. poliomyelitis later).
(7) Other diseases on special occasions, as for instance when people leave the country.

According to the law the health centres, where they are at hand, district physicians and school doctors are to control and carry out immunizations. A general practitioner does not carry out immunizations in Iceland.

Smallpox vaccination is compulsory. Each child is to be vaccinated at the age of 6 months to 1 year. If that is not done, a school physician must vaccinate the child when it starts school at 6- or 7-years old. Moreover all children are re-vaccinated when they are 7–12-years old. Other immunizations are voluntary, but people should submit themselves and their children to immunization against the diseases mentioned in 2–5.

In cases where special precautions are needed, and for those who are most in danger of being infected (sailors, pilots, doctors, nurses, sanitary inspectors), a district physician is to undertake the immunizations.

It is not allowed to confirm a child or marry a couple unless they can show in their vaccination certificates that a smallpox vaccination has been fulfilled; the same applies when entering higher schools.

Nurses and service personnel can only be engaged at hospitals if they get a positive reaction to a tuberculosis test or else submit themselves to tuberculosis immunization.

According to the law the Icelandic State Import of Drugs and Medicine is to provide all vaccine used in accordance with the law.

All expenses caused by the compulsory immunizations are paid by the state.

The Chief Medical Officer of Health has had regulations made on the carrying out of vaccinations. The regulations now in use – from 1969 – are set out in Table V.

Table V. *Vaccination schedule in Iceland*

Age	Vaccination
3 months	Diphtheria, whooping-cough, tetanus
4 months	The same plus poliomyelitis
5 months	All four again
6 months	Smallpox
1 year	Again all four, as in 5 months
2–3 years	Poliomyelitis
7 years	Poliomyelitis
12–14 years	Smallpox and poliomyelitis, but not at the same time

After that people are advised to get poliomyelitis immunization every 5th or 6th year and smallpox every 2nd or 3rd year.

RESULTS OF IMMUNIZATIONS

Table VI. *Children at 2 years of age immunized against diphtheria, tetanus, poliomyelitis and smallpox, Reykjavík, 1971*

	No.	%
Complete immunization	1108	84.6
Irregular immunization	189	14.4
No immunization	13	1.0
Smallpox vaccination		
+	699	53.4
÷	62	4.7
Not certain	67	5.1
Total sp. vaccinations	828	63.2
Not vaccinated	482	36.8

Table VII. *Children at 6 years of age immunized against diphtheria, tetanus, poliomyelitis and smallpox, Reykjavík, 1971*

	No.	%
Complete immunization	1152	86.6
Irregular immunization	167	12.6
No immunization	11	0.8
Total	1330	100
Smallpox vaccination		
+	889	66.8
÷	44	3.3
Not certain	72	5.5
Total sp. vaccinations	1005	75.6
Not vaccinated	325	24.4

These numbers show that 84–86 % of all children in Reykjavík are immunized against diphtheria, tetanus, whooping-cough and poliomyelitis and close to 100% get some kind of an immunization. On the other hand, the smallpox vaccination rate is much lower; in 2-year-old children two-thirds and 6-year-olds approximately three-quarters. This shows that parents (and doctors?) fear smallpox vaccinations more than other immunizations.

In health reports from 1969 and 1970 the figures shown in Tables VIII–XI are given about vaccination for the whole country.

From the available information it can be concluded that between 90 and 100% of all children in Iceland get some kind of immunization in their first year, and that 85 % get complete immunization against whooping-cough, diphtheria,

Table VIII. *Smallpox*

	1969	1970
Primary vaccination	3606	5670
Result	85 %	85 %
Revaccination	3868	2379
Result	67.8 %	74.9 %

Table IX. *Other immunizations during the years* 1969–70

	1	2	3	4	5	Total
1. Diphtheria, tetanus, whooping-cough						
1969	4392	4224	4197	3330	2502	18645
1970	4254	4140	4034	3679	2838	18945
2. Poliomyelitis						
1969	4820	4487	4091	4617	2832	20885
1970	13697	9754	4074	5628	1950	35778

Table X. *Tuberculosis*

	1969	1970
Reykjavík	195	200
Saudárkrókur	1	—
Akureyri	16	2
Total	212	202

Table XI. *Special immunizations (whole country)*

	Influenza	Cholera	Yellow fever	Measles
1969	3306	118	110	926
1970	2665	626	124	225

tetanus and poliomyelitis. On the other hand only 60–65 % get complete smallpox vaccination; 70–75 % have reached some immunization at the age of six.

COMPLICATIONS

There is no available information reliable enough on the complications caused by immunizations in general. On the other hand, it is known that there has been no death caused by smallpox vaccination since 1951.

Since the polio epidemic in Iceland in 1955–6 there has not been known any such case, but there are 1–2 suspected cases.

The last reported diphtheria case was in 1951.

CONCLUSION

In this report I have tried to show how the health situation was in Iceland before immunizations were practised (against infectious diseases), how smallpox vaccination in 1800 has possibly prevented the extinction of all Icelanders and how immunizations against infectious diseases have brought about a complete change in the health situation in Iceland.

Iceland is a good example of the power of vaccinations if they are well organized and utilized. Mortality caused by infectious diseases is very low in Iceland today and is still decreasing. It is being discussed now to take up organized immunizations against measles and rubella, both of which are done now to some extent.

We Icelanders are dependent on others for all vaccine supplies, and we import them mostly from our neighbours, in Denmark, Sweden and England.

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MASS VACCINATION IN THE NETHERLANDS

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The national routine vaccination of infants against diphtheria, pertussis and tetanus started in 1953 with the introduction of DTP vaccine (Fig. 1). It is estimated that at that time about 20% of each age cohort was vaccinated.

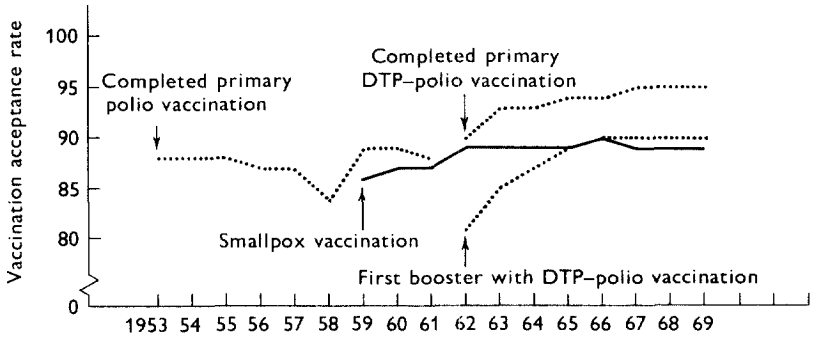

Fig. 1. Vaccination acceptance rates of infants born between 1953 and 1969 for smallpox, diphtheria, tetanus, pertussis and poliomyelitis in the Netherlands.

In the course of 1957–60 all children up to the age of 15 years were offered vaccination against poliomyelitis. Inactivated vaccine (Salk) was and is still to be used. In 1962–3 DTP–polio vaccine was introduced. Vaccination against these four diseases is not compulsory.

Primary vaccination against DTP–polio consists of three injections in the 3rd, 4th and 5th month of age. The first booster is given in the 11th month of age. The second booster with DTP–polio or DT–polio vaccine (from 1973 onwards only DT–polio vaccine will be given) is administered at the age of four. A final booster with DT–polio vaccine is given at the age of nine. The central registration of all the primary vaccinations and of the first booster with DTP–polio vaccine started in 1962. The annual vaccination acceptance rate for the completed primary vaccination against DTP–polio was 90% for the children born in 1962. This vaccination acceptance rate increased to 95% for those born between 1967 and 1969. The vaccination acceptance rate for the first booster with DTP–polio vaccine was 81% for those born in 1962 and increased to 90% for the children born in the years 1966–9.

Table I. *Number of notified cases of diphtheria, tetanus and poliomyelitis and of the mortality of pertussis, absolute and per* 100000 *population* (1950–72)

	Number of notified rates of						Mortality, pertussis	
	Diphtheria		Tetanus		Poliomyelitis			
	Abs.	Per 100000 pop.	Abs.	Per 100000 pop.	Abs.	Per 100000 pop.	Abs.	Per 100000 pop.
1950	2985	29.5	—	—	77	0.8	145	1.4
1951	2765	26.9	20	0.19	568	5.5	130	1.3
1952	2805	27.0	32	0.30	1713	16.5	128	1.2
1953	2714	25.9	18	0.17	167	1.6	81	0.77
1954	1521	14.3	20	0.18	75	0.7	25	0.23
1955	745	6.9	28	0.26	481	4.5	30	0.27
1956	576	5.3	25	0.22	2206	20.3	34	0.31
1957	446	4.0	26	0.23	203	1.8	14	0.12
1958	217	1.9	18	0.16	39	0.34	21	0.18
1959	387	3.4	31	0.27	11	0.09	28	0.24
1960	112	1.0	20	0.17	29	0.25	2	0.01
1961	16	0.13	21	0.18	83	0.71	9	0.07
1962	15	0.12	20	0.16	36	0.30	7	0.05
1963	5	0.04	21	0.17	33	0.27	5	0.04
1964	1	0.01	11	0.09	15	0.12	—	—
1965	2	0.01	10	0.08	3	0.02	—	—
1966	1	0.01	8	0.06	14	0.11	—	—
1967	—	—	14	0.11	2	0.01	—	—
1968	3	0.02	11	0.08	7	0.05	—	—
1969	—	—	7	0.05	16	0.12	—	—
1970	2	0.01	8	0.06	2	0.01	2	0.01
1971	1	0.01	11	0.08	37	0.27	—	—
1972*	—	—	7	0.05	—	—	—	—

* Preliminary data.

Smallpox vaccination of infants is regulated by a special law. The vaccination against smallpox can be refused, however, on religious, principle or medical grounds. Smallpox vaccination had generally been offered in the second month of age. Recently it has been advised to have this vaccination performed at the age of 9–10 months. The annual smallpox vaccination rates fluctuate at 89–90 % for the children born in 1962–9.

The incidence of diphtheria dropped rapidly after the introduction of the mass vaccination against this disease in 1953 (Table I, Fig. 2).

The incidence of tetanus decreases slowly after 1953 (Table I, Fig. 3). In the period 1953–62 an annual average of 22.7 cases were reported against, however, an annual average of 10.7 cases for the period 1963–72. There is also a definite shift to older age-groups among the notified cases of tetanus (Table II, Fig. 4).

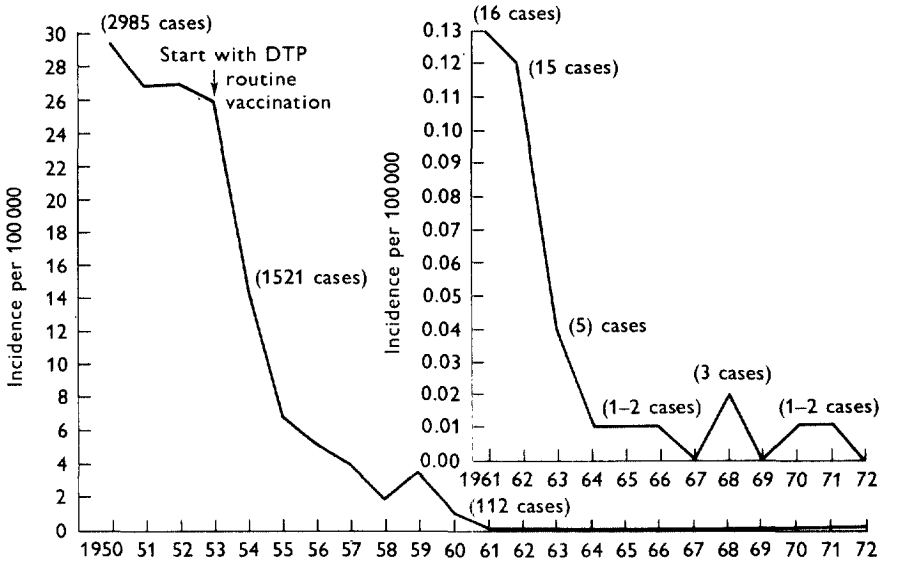

Fig. 2. Incidence of notified cases of diphtheria per 100000 population, the Netherlands, 1950–72.

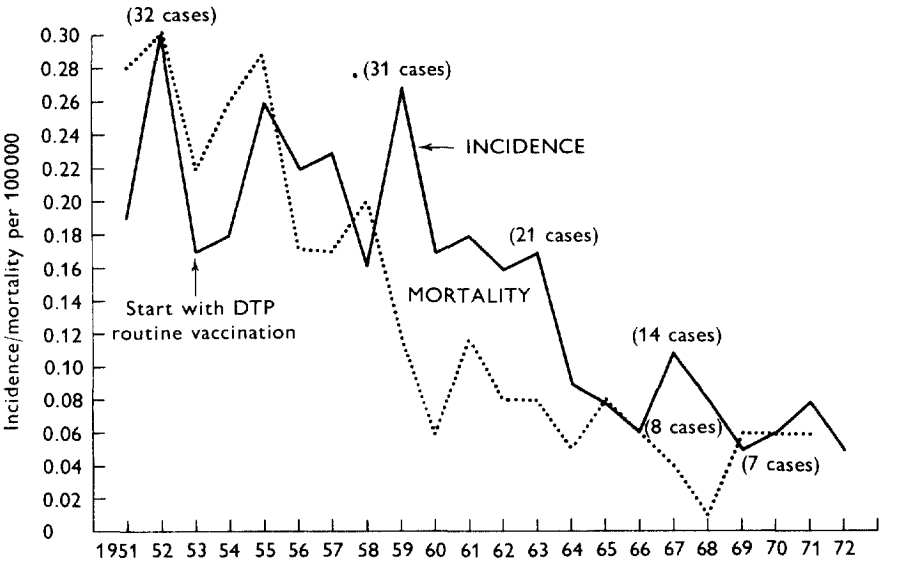

Fig. 3. Incidence of notified cases of tetanus and mortality from tetanus per 100000 population, the Netherlands, 1950–71.

Table II. *Number of notified tetanus cases by age-group and five-year period, 1952–71*

	Age groups							
	0–9 years		10–19 years		⩾20 years		Total	
Period	Abs.	%	Abs.	%	Abs.	%	Abs.	%
1952–6	54	44	25	20	44	36	123	100
1957–61	27	23	34	29	55	48	116	100
1962–6	12	17	13	19	45	64	70	100
1967–71	1	2	5	10	45	88	51	100

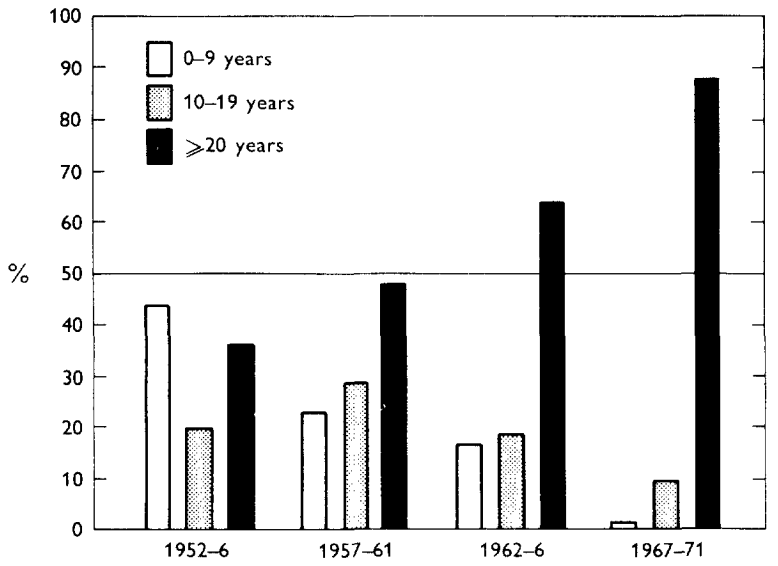

Fig. 4. Notified cases of tetanus by age group and five-year period (in percentages).

Fig. 3 also shows a definite decrease of the tetanus mortality (see also Table III). This figure indicates the under-reporting of tetanus, as sometimes the mortality rates exceed those of the incidence rates. We are now trying to investigate the reported deaths attributed to tetanus in order to have the non-reported cases reported as well.

Pertussis is not notifiable in the Netherlands. The mortality, however, 128–45 deaths annually for the years 1950–2, dropped considerably after 1953 (Table I, Fig. 5). With the exception of two deaths in 1970, no deaths were attributed to pertussis since 1964.

Table III. *Mortality of tetanus*, 1951–71 (*absolute and per* 100000 *population*)

Year	Absolute	Per 100000 population
1951	29	0.28
1952	31	0.30
1953	23	0.22
1954	28	0.26
1955	31	0.29
1956	19	0.17
1957	19	0.17
1958	22	0.20
1959	14	0.12
1960	7	0.06
1961	14	0.12
1962	10	0.08
1963	9	0.08
1964	6	0.05
1965	11	0.08
1966	8	0.06
1967	5	0.04
1968	2	0.01
1969	8	0.06
1970	7	0.06
1971*	7	0.06

* Preliminary data.

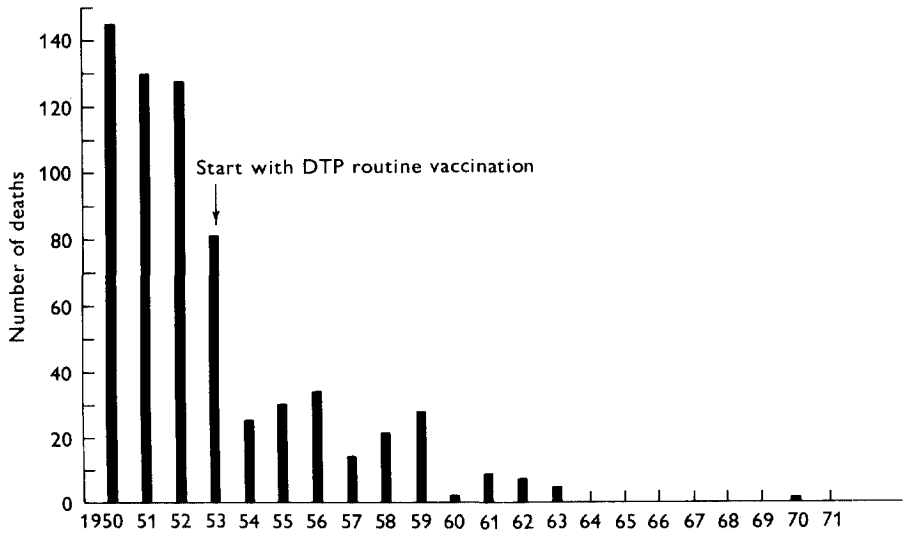

Fig. 5. Mortality of pertussis per 100000 population, the Netherlands, 1950–71.

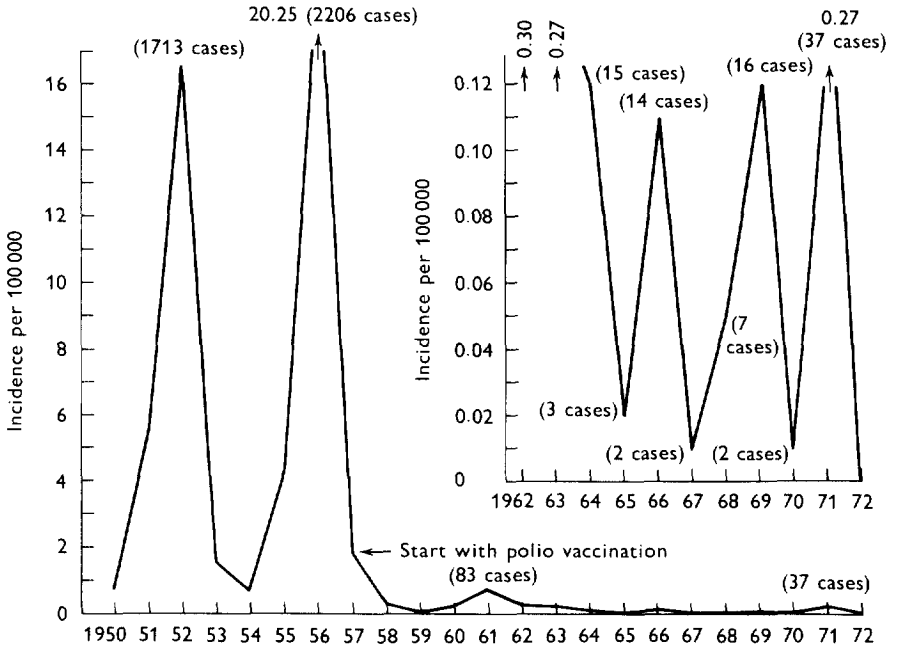

Fig. 6. Incidence of notified cases of poliomyelitis (paralytic and non-paralytic) per 100 000 population, the Netherlands, 1950–72.

The incidence of poliomyelitis decreased considerably after the introduction of the vaccination against polio in 1957 (Table I, Fig. 6). After the epidemic in 1956 with 2206 cases (paralytic and non-paralytic) an annual average of 21.8 cases was reported for the period 1958–72; the highest number (83) was reported in 1961. In 1972 no cases have been reported at all.

We have been confronted since 1961 with small and some bigger outbreaks of polio like the one in Slaphorst in 1921, in areas with a low vaccination acceptance rate (less than 60 %).

One case of polio in an area with an average vaccination acceptance rate of less than 25 % already leads to mass vaccination with monovalent live polio vaccine of the population under the age of 19 in that area. In other areas, with a vaccination acceptance rate of 25 % or more, a 'wait and see' policy is pursued when a case of polio occurs.

Mass vaccination against rubella of all girls at the age of 11 will soon be included in the national vaccination campaigns.

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IMMUNIZATION SCHEDULES IN SPAIN

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From 1963 the immunization of children in Spain has been organized as regular campaigns monitored and sponsored by the Direccion General de Sanidad (General Direction of Health). The vaccines are administered on a voluntary basis and free of charge. The vaccines included in these regular campaigns are triple vaccine (diphtheria–tetanus–pertussis) and oral polio vaccine (Sabin strains). Both types of vaccine are usually administered simultaneously to the children attending the vaccination centres.

Of these vaccines only diphtheria is compulsory for children entering school; the triple vaccine used is an adsorbed vaccine containing 30 Lf of diphtheria antigen, 10 Lf of tetanus antigen and 25 000 millions of *B. pertussis*. Three doses of vaccine are offered to the children with an interval of 6 weeks between the first and second doses and 6 months between the second and third doses; a booster dose is administered one year later.

Oral polio vaccine has been used from 1964 until 1972 as a trivalent vaccine with the following concentrations for each type of polio virus: Type I $10^{5.7}$ $TCID_{50}$; Type II 10^{5}; Type III $10^{5.5}$. Initially two doses of trivalent vaccine was the recommended vaccination schedule. Epidemiological and serological studies showed that in our country two doses of trivalent oral polio vaccine were insufficient in some cases for the full immunization of triple susceptible children.

Therefore three doses were recommended, and in order to immunize the children at a very early age the vaccination campaigns were organized twice every year, in autumn and spring. Generally speaking, the participation of children in the vaccination campaigns is very satisfactory; averages of more than 90 per cent are usually achieved. However, in some districts of some provinces it is more difficult to vaccinate the children with the three-dose programme. For that reason, and taking into account the fact that polio Type I is by far the most frequent paralytogenic agent in Spain, we introduced in spring 1972 monovalent Type I oral polio vaccine as the first doses of the vaccination programme together with the first doses of diphtheria–tetanus–pertussis vaccine; the schedule of primary immunization is completed by two doses of trivalent oral polio vaccine and two doses of diphtheria–tetanus–pertussis vaccine, separating the different doses by an interval of 6 weeks, and 6 months respectively. One year later a booster dose of both vaccines is given simultaneously.

With this vaccination programme a marked reduction in the number of cases has been demonstrated in the two diseases of compulsory notification: diphtheria

and poliomyelitis. In diphtheria the annual average in the years before the start of the vaccination programme was 2057; in the last year only 35 cases have been reported. In poliomyelitis the annual average before the oral vaccine was introduced in our country was 1709, in contrast with the 88 virologically confirmed cases reported in 1972. It has to be noted that the evolution of poliomyelitis in Spain has been considerably better in the last six months after the introduction of the monovalent Type I oral vaccine as the first dose of the vaccination programme.

Tetanus and pertussis are not diseases of compulsory notification; therefore we have no comparative data. However, from the number of hospitalizations and specific mortality by pertussis, a clear reduction in the incidence of the disease must be admitted. Tetanus is today a rarity in children up to 10 years of age in our country, the age group included in the vaccination campaign since birth.

Independently of the campaigns officially organized by the Direccion General de Sanidad that are concentrated in time, the above mentioned vaccines can be received on an individual basis free of charge in the provincial Public Health Services or through the Social Security Services at any time of the year. The vaccination prescribed by private paediatricians and sold in the pharmacies is also a valuable contribution to the child immunization in our country.

OTHER VACCINES

Smallpox vaccine is compulsory in our country for children entering school. Only calf vaccine, liquid or lyophilized, has been until now used. Children are regularly vaccinated during the second year of life, through the Public Health Services free of charge, or through private paediatricians and pharmacies.

BCG vaccine is offered to newborn children in maternity hospitals. Determinations of sensitivity to tuberculin and radiological studies are periodically carried out in schoolchildren, and when needed, BCG vaccine is applied.

Influenza vaccine is used only in selected groups of the population and every winter on an individual basis. Yellow fever vaccine is only used in cases of people travelling to or from endemic areas.

Measles and rubella vaccines have for the moment limited use in our country, but Public Health programmes are under consideration.

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VACCINATION PROGRAMMES IN SWEDEN

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My contribution will consist of a presentation of the official vaccination scheme of Sweden, complemented with some recent experimental work on triple vaccine, particularly concerning pertussis and diphtheria.

The official scheme is as in Table I. I will only make a few comments on some points where the Swedish scheme differs from schemes adopted by most other countries in order to explain the background of the differences.

Table I. *Official vaccination scheme of Sweden*

	Primary vaccination	Revaccination (booster)
BCG	1 week	School age (14–15 years, tuberculin neg. children)
Smallpox	2 months, 7–9 months (compulsory, to be performed before 5 years of age)	Primary school (10–12 years)
DPT	3, 4½ and 6 months	7 years (diphtheria and tetanus)
Polio	9–10 months (2 inject.)	18–24 months (1 inject.), 7 years (1 inject.)
Measles	1–3 years	—
Rubella	Certain hospital staff categories 14 years (girls only, proposal, not yet officially approved)	—

BCG VACCINATION

About 95 % of new-born babies are vaccinated before they leave the maternity wards. Most other countries vaccinate at a considerably higher age, e.g. during primary or secondary school. The main reason for the Swedish method is the organizational advantage. The acceptance is nearly complete, the vaccination is performed in the maternity wards by experienced people at a low cost and the takes can be checked at the child health centres at visits for ordinary health control. Besides, early protection is the probable explanation for the fact that

Sweden has no longer any cases of tuberculous meningitis in children. It should be emphasized that schoolchildren who prove to be negative in the PPD-test with 2 TU during school age are revaccinated.

SMALLPOX

The methods employed differ from internationally current ones regarding the *vaccine* as well as the *age of vaccination.*

The vaccine is prepared on embryonated eggs from chickens tested for freedom of leucosis. Vaccines of two potencies are used: one with a titre of $10^{7.5}$ $TCID_{50}$ per ml for primary vaccinations and for revaccinations after an interval of more than 5 years and another with a titre of $10^{8.2}$ for other types of revaccinations. This method is based on studies performed by Espmark(**2**) on the relationship between potency, rate of takes and reactions with the aim to optimize takes and minimize reactions. The method has been tested for more than 10 years now and has certainly come to stay.

The egg vaccine is, in our opinion, advantageous to the calf vaccine for the following reasons: it can be checked for freedom of leucosis virus, it is easier to standardize and to keep bacteriologically sterile, and the production of it does not cause any animal any suffering.

Vaccination against smallpox during the first trimester of life has been practised in Sweden for more than 10 years. A special investigation, comprising some 145 000 vaccinations in this age group, was performed by Espmark and Rabo(**3**). They found no complications (except secondary single or multiple pocks in 11 cases; Table II) and the take rates were above 95 per cent. As is evident from Table II there were no cases of post-vaccinal encephalitis in this age group whereas an increasing rate of encephalitis was registered in higher age groups.

Table II. *Reported cases of post-vaccinal encephalitis in Sweden*, 1961–71. *Distribution according to age*

Age group	Estimated number of primary vaccinations	No. of cases of post-vaccinal encephalitis
0–3 months	145 000	0
4–12 months	370 000	5
1–4 years	420 000	6 (1 death)
5–14 years	215 000	16 (1 death)
> 14 years	110 000	38 (1 death)
Totals	1 260 000	65

In 1965 the official recommendations as to the age for smallpox vaccination were changed from 1–4 years to 2 months. In the following years a decrease in the rate of encephalitis following vaccination was noted (Table III). This fact might, however, also be due to the change of vaccine strain from the Beaugency to the

Table III. *Number and age distribution of cases of encephalitis after smallpox vaccination in Sweden in relation to changes in vaccine and vaccination policy*

Year	No. year	Age distribution					No. vaccinated (× 1000)		No. vaccine doses distributed	Recommended age for primary vaccination	Type of vaccine	Vaccine strain
		0–1	1–4	5–9	10–20	>20	0–4 years	5–14 years				
1948–57	2.5	0.3	0.5	1.6	—	—	—	—	480	5–7 years	Calf	Beaugency (Belgium)
1958–60	3.7	0.7	2.3	0.3	0.3	—	70	48	460			
1961	7.0	—	2.0	2.0	3.0	—	81	49		From 1958: 1–4 years	Egg	
1962–3	20.5	1.0	0.5	4.0	4.0	11.0	101	44	1120			
1964–5	3.0	1.0	0.5	—	05.	1.0	91	15	565			
1966–8	3.3	0.3	0.3	—	0.7	2.0	106	17	700	From 1965: 2 months		From 1968: Lister-strain
1969–70	0.5	—	0.5	—	—	—	92	15	993			

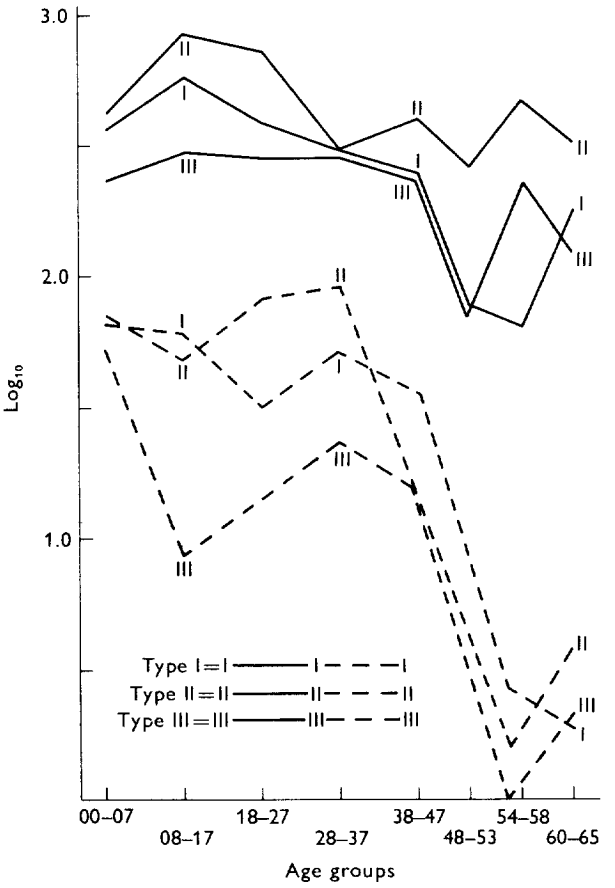

Fig. 1. Mean log titres against polio virus Types I, II and III in vaccinated and revaccinated.

Lister strain. Some countries advise against vaccination during the first year due to an assumed higher risk of encephalitis. It seems as if the differences between our experience and experiences from these countries can be explained on the basis that in Sweden vaccination is performed in the earliest period of life under an umbrella of maternal antibodies, whereas in the other countries it has been performed during the latter part of the first year when the maternal antibodies have diminished or disappeared.

POLIO

In Sweden killed vaccine, produced according to a modified Salk technique, has been used exclusively. The vaccination scheme comprises two primary inoculations 2–4 weeks apart at 9–10 months of age, one booster at 18–24 months and one at school entry (7 years).

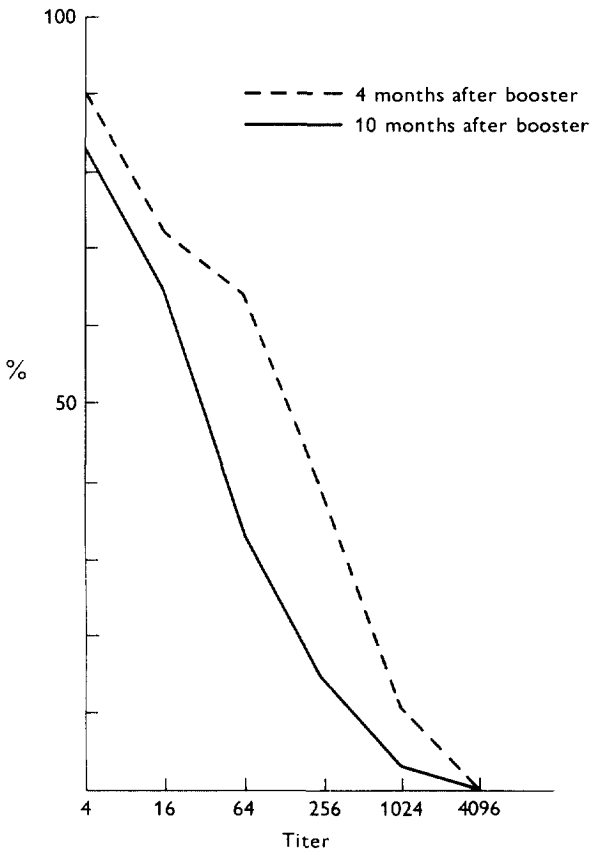

Fig. 2. Accumulated titres against polio virus Type I after booster vaccination of people seronegative to Type I, although previously vaccinated.

In 1971–2 an investigation was made by the National Bacteriological Laboratory of Sweden in order to explore the vaccination and immunity status as to polio in the Swedish population (1). Vaccination histories and serum samples were collected from representative population groups. More than 95 per cent of persons under 30 years of age were reported to have received two or more injections. In the age group 2–19 years 87 per cent were completely vaccinated according to the official recommendations.

Antibodies against all three types of polio virus were found in more than 95 per cent of the sera in all age groups except for those vaccinated in the period 1957–60 (Fig. 1). In the latter groups about 15 per cent were negative to Type I or III. The explanation seems to be that during this period vaccines of a lower potency were used.

The general immunity level was found to be very satisfactory after a vaccination period covering about 12 years. As a safety measure, however, it was con-

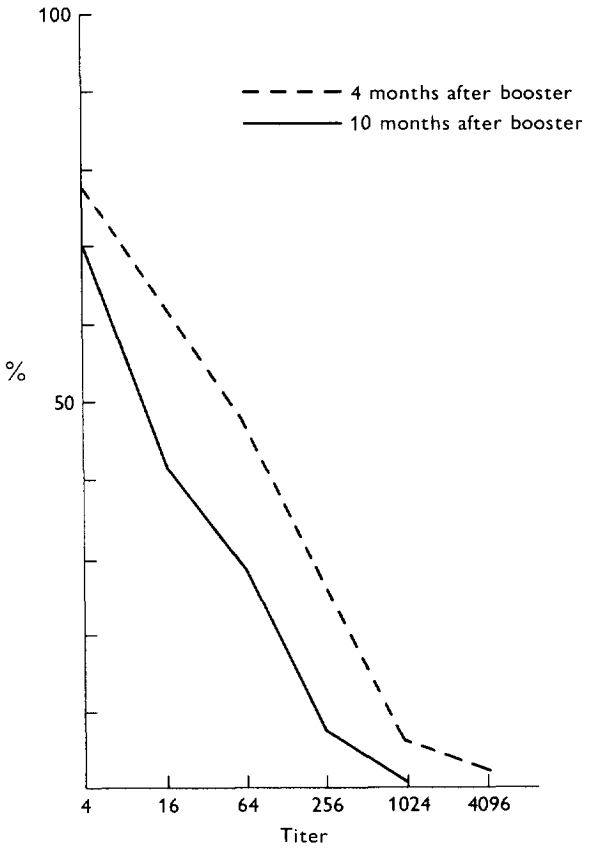

Fig. 3. Accumulated titres against polio virus Type III after booster vaccination of people seronegative to Type III, although previously vaccinated.

sidered desirable to booster the age groups who had received their primary injections in the period 1957–60. Before taking such a step a small study was undertaken to find out whether persons who were vaccinated and in the course of time had become serologically negative actually responded to a booster dose. As is evident from Figs. 2 and 3 a booster reaction was obtained although after 10 months 11 and 31 per cent again lacked antibodies against Type I and III respectively.

DIPHTHERIA, TETANUS, PERTUSSIS (DPT)

Finally a few words about some recent experimental work performed in our laboratory to purify the DPT vaccine.

Diphtheria toxin has been purified with the aid of gel chromatography on a technical scale, to a very high degree of purity. Regular testing of toxoid for two years has not revealed any dissociation or reversion of toxicity. Pertussis bacteria

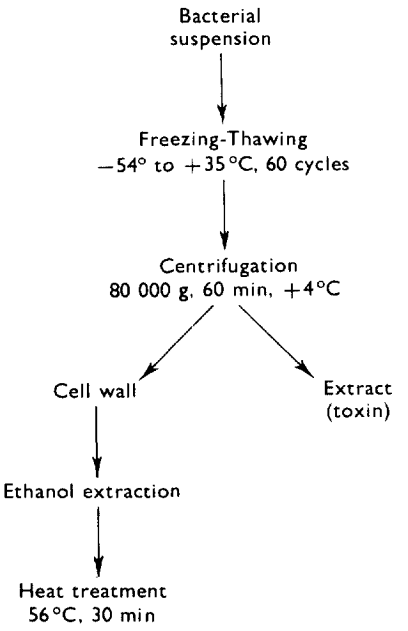

Fig. 4. Fractionation and purification of pertussis bacteria.

Table IV. *Protective, toxic and histamine sensitizing capacity of fractionated and purified pertussis bacteria*

Fraction	Lethal toxin (mice) LD 50 (μg)	Necrotoxin 10 × 10 mm (rabbit) (μg)	Protective effect (mice) PD 50 (μg)	HSF histamindose LD 50 (mg)
Whole cells	7.5	62.5	100 (8×10^8 bact)	6.2
Extract	2.25	3.9	0	—
Cell walls	800	500	20 (1×10^8 bact)	29.6
NaCl control	0	0	0	24.0

Table V. *Adjuvant capacity of fractionated and purified pertussis bacteria*

Pertussis component	Antibody titre	
	Tetanus, IE/ml	Diphtheria IE/ml
Without	0.05	<0.005
With	5.00	>5.000

are cultivated in 200 l batches in a tank with yields of *ca.* 35×10^9 bacteria per ml with no detectable alteration in their serological or immunological properties.

The production procedure comprises disintegration by repeated freezing and thawing in an automatic device and purification through centrifugation and alcohol extraction (Fig. 4). The final product consists of cell walls, has no measurable toxin or histamine sensitizing factor, retains its capacity for inducing protection after intracerebral injection in mice, and is capable of acting as an adjuvant on diphtheria and tetanus toxoids (Tables IV and V). The preparation will be tested in field trials, in co-operation with Dr Cohen in Holland, hopefully in the course of this and the next year.

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LES VACCINATIONS EN SUISSE

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En Suisse, les cantons sont compétents pour décider si une vaccination doit être obligatoire et laquelle doit faire l'objet d'une obligation. Des considérations ethniques, historiques et politiques, en particulier, expliquent cette situation.

D'après la législation en vigueur, les vaccinations contre la variole et la diphtérie ne sont obligatoires, sur 25 cantons et demi-cantons, que dans ceux de Fribourg, Vaud, Genève et Tessin; la vaccination contre la variole seule dans les cantons du Valais et de Soleure et celle contre la diphtérie seule dans le canton de Neuchâtel. La nouvelle loi sur les épidémies qui entrera en vigueur cette année prévoit également que c'est aux cantons, et non à la Confédération, de décider si les vaccinations doivent être obligatoires ou facultatives. En revanche, il est prescrit aux cantons d'offrir à leurs habitants la possibilité de se faire vacciner gratuitement contre les maladies transmissibles dangereuses. Ceci est très important car, dans certains cantons, il s'est révélé que l'absence d'obligation vaccinale pouvait être largement compensée en rendant également gratuites les vaccinations faites par le médecin privé, à son cabinet de consultation. Il est en outre loisible aux cantons, en accord avec le Service fédéral de l'hygiène publique, d'offrir à la population la vaccination gratuite contre d'autres maladies, par exemple contre la rubéole chez les filles à la fin de la période de scolarité. Le danger de la maladie s'évaluera en principe en fonction de son importance pour la collectivité. Par exemple, la fièvre jaune est certes dangereuse pour un voyageur se rendant en Afrique, mais ne l'est pas pour la population suisse. C'est pourquoi la fièvre jaune ne sera pas comprise dans les maladies transmissibles dites dangereuses au sens de la loi sur les épidémies.

Nous savons que la variole, la diphtérie, la poliomyélite, la tuberculose et le tétanos sont des maladies dangereuses contre lesquelles en même temps il existe des vaccins très efficaces. La coqueluche est particulièrement dangereuse pour l'enfant de 1 à 3 ans environ et le vaccin, bien que moins efficace, peut être facilement administré combiné à celui contre la diphtérie et le tétanos.

Il existe un grand nombre de programmes de vaccination, mais il ne peut y avoir de programme passe-partout ne serait-ce que pour des raisons pratiques, car la naissance des enfants s'échelonne au cours de toute une année.

Nous recommandons dans nos Directives, le calendrier suivant, pour les nourrissons et les enfants.

Nous ne déconseillerons officiellement la vaccination contre la variole que lorsque l'éradication de cette maladie dans le monde sera réalisée. En attendant et pour tenir compte de l'accroissement considérable des voyages internationaux

Tableau I. *Calendrier des vaccinations pour nourrissons*

Age	Vaccination
1 à 2 mois	Aucune (BCG en cas de danger de tuberculose)
3 mois	DTP (diphtérie–tétanos–coqueluche) Sabin Type I ou Sabin triple
4 mois	DTP
5 mois	DTP Sabin Type II et III ou Sabin triple
6 à 18 mois	Vaccination antivariolique
1½ à 2 ans	DT(P) (rappel) Sabin triple

Tableau II. *Calendrier des vaccinations pour enfants*

Age	Déjà vaccinés	Non encore vaccinés
5 à 7 ans	DT Sabin triple Vaccination antivariolique (revaccination seulement) BCG (si épreuve à la tuberculine négative)	Deux fois DT à intervalle de 4 à 6 semaines et rappel 1 an plus tard Deux fois Sabin triple à intervalle de 6 semaines BCG (si épreuve à la tuberculine négative)
12 à 14 ans	BCG (si épreuve à la tuberculine négative)	
15 ans	BCG (si épreuve à la tuberculine négative) (revaccination éventuelle) Sabin triple Tétanos (rappel) Vaccination antivariolique (revaccination seulement)	

Toutes les filles avant la puberté: vaccination contre la rubéole.

et du fait que le danger augmente dans nos pays européens en même temps que diminue le nombre des personnes vaccinées, nous continuons à conseiller cette vaccination.

Malgré l'absence de vaccination obligatoire on peut estimer d'après la quantité de vaccin mise sur le marché que près de 300000 personnes sont vaccinées chaque année contre la variole alors qu'il naît 95000 enfants pendant la même période; en 1972, à cause de l'épidémie de variole en Yougoslavie, le nombre des personnes vaccinées s'est élevé à près de 750000.

L'éradication de la poliomyélite en Suisse a été obtenue grâce aux effets conjugués de la propagande de notre Service, de l'Association suisse contre la polio-

myélite et des cantons. Il n'y eut jamais de vaccination obligatoire contre la poliomyélite. Les campagnes de masse ont débuté dans tous les cantons en 1960/61.

Le nombre des cas, qui s'élevait en moyenne entre 1953 et 1956 à 973 et était descendu à 204 en moyenne entre 1957 et 1961 grâce au vaccin de Salk, tomba à 6 en moyenne entre 1962 et 1966 et à 0,6 en moyenne entre 1967 et 1971, grâce aux vaccins de Sabin et de Koprowski. Les vaccins oraux sont en effet les seuls à permettre de tels succès car ils stoppent la circulation du virus sauvage.

Mais comment maintenir à présent les résultats en encourageant la population à se faire vacciner, alors que la maladie absente n'est plus redoutée? Répondre à cette question constituera désormais l'objectif des cantons aidés par la Confédération. Il est certes indispensable de vacciner tous les nourrissons mais il serait en particulier souhaitable d'assurer la coordination des campagnes périodiques de vaccination et de revaccination des enfants et de la population adulte. Il est en tous cas indispensable de continuer, en la renforçant, la surveillance de cette maladie.

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RUBELLA IMMUNISATIONS IN SWITZERLAND

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Switzerland is not only a small country, as you know; it is from the standpoint of health services not even a country but an agglomeration of 25 cantons each having its own health service and its own immunisation programme. That is the reason I cannot give you data from the whole country.

In Basel, in the north part of Switzerland – with a population of about 500000 – a rubella immunisation programme was introduced at the end of 1967 using the Cendehill vaccine strain. For the first year the rubella immunisations were done on an experimental basis, but since the beginning of 1969 as a routine. For the following three groups the rubella vaccine is free of charge, paid by local government.

1. Schoolgirls of the age 13–15 years (20–25 % have no antibodies).
2. Women in the postpartum period (10–15 % seronegative).
3. Adult women in the childbearing age, but only on an individual basis.

In 1967 and 1968 in all groups antibody testing was done before immunisation. Since 1969 rubella antibodies are tested only in the group of adult women vaccinated on an individual basis. Opposite to the American opinion and to Dr Krugman's paper we do not immunise pre-school children. We do not intend to protect children against natural rubella infection but we try to prevent rubella embryopathy. We believe that this can be done best in the future by immunisation of all 13–15-year-old schoolgirls. It is easy to reach schoolgirls in my country; most are immunised by school health department free of charge for parents. We know there is a risk in immunising 13–15-year-old girls because of the possibility of pregnancy, but in Switzerland this risk is a very small one, and – in my personal opinion – if a 14-year-old girl immunised against rubella is pregnant, an abortion should be done.

In Table I may be seen our results of women immunised in 1967/8 in Basel. At the moment I can give you only results from studies done in 1970/1 – 3 years after rubella vaccination. Sera taken 6–8 weeks after immunisation of seronegative ones and 3 years later were simultaneously titrated. In 77 % the titres were the same; a significant antibody decline did not occur. In 12 out of 218 tested we found a significant antibody increase, which can be explained only by reinfection.

Table I. *Comparison of rubella antibody titres*

Second blood: 5–8 weeks after immunisation Third blood: 3 years after immunisation		
Same titre (± 1 dilution-step)	168/218	77.1 %
Antibody decline		
Slight (2 dilution-steps)	3/218	1.4 %
Significant (3 or more dilution-steps)	0/218	
Antibody rise		
Slight (2 dilution-steps)	35/218	16.0 %
Significant (3 or more dilution-steps)	12/218	5.5 %

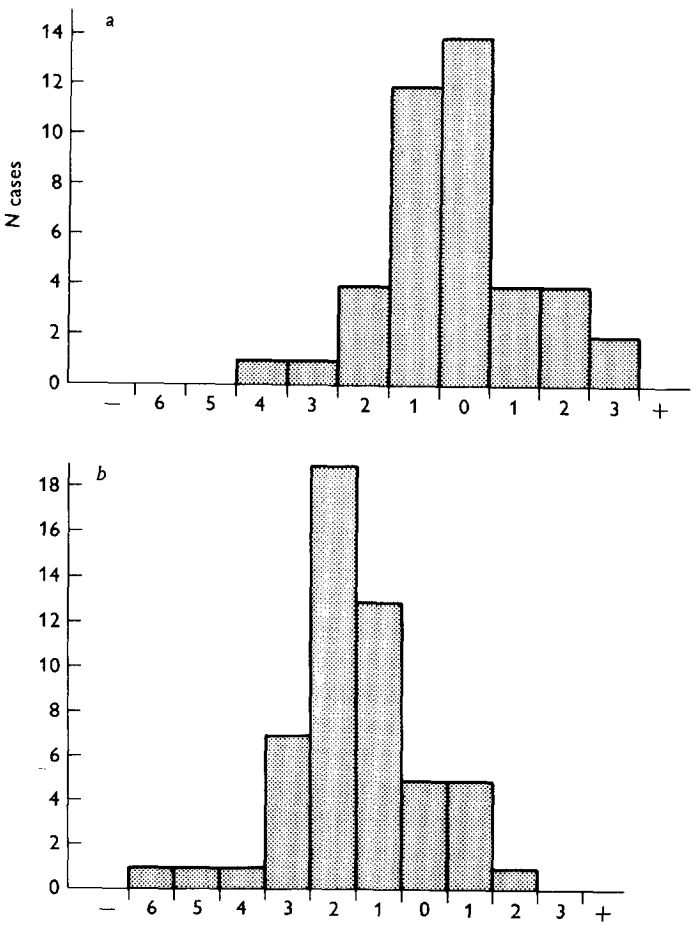

Fig. 1. Long-term study after rubella immunisation with live attenuated virus Cendehill strain. Changes in HI titre 54 months after immunisation. (*a*) 41 subjects seronegative, and (*b*) 53 subjects seropositive before immunisation.

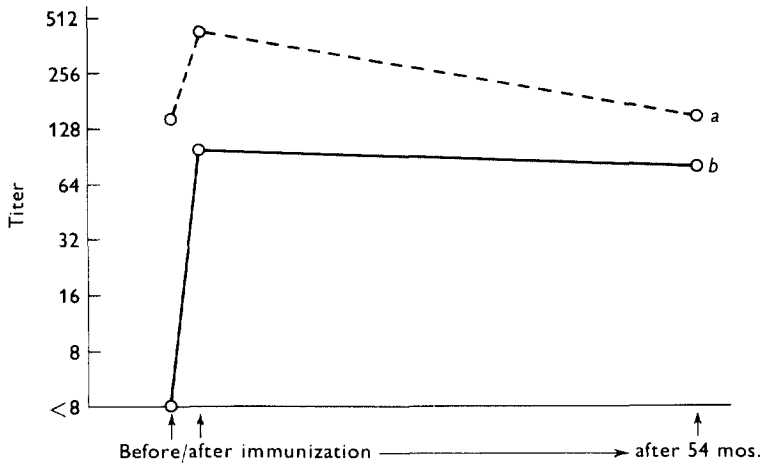

Fig. 2. Long-term study after rubella immunisation with live attenuated virus Cendehill strain. Changes in geometric mean titre (*a*) seronegative, (*b*) seropositive before immunisation.

Professor Hitzig has provided Figs. 1 and 2 showing antibody results from Zürich $4\frac{1}{2}$ years after rubella vaccination. In the group of 41 subjects without antibodies before rubella-immunisation only very little changes in antibody titres are found; only 2 had a more than two-fold fall in the titre (Fig. 1 *a*). In Fig. 1 *b* you see the results of 53 subjects seropositive before immunisation; a drop in titre was not frequently seen.

Calculation of the geometric mean titre shows a slightly lower figure in the vaccinated compared with spontaneously immunised girls (Fig. 2). This value, however, is practically constant during the whole observation period of $4\frac{1}{2}$ years.

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VACCINATION PROGRAMME IN YUGOSLAVIA

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NATIONWIDE COMPULSORY VACCINATION

1. *Smallpox, tuberculosis, diphtheria, tetanus* and *whooping-cough* All persons of a particular age.

2. *Rabies* All persons bitten by rabid animals, or animals suspected of being rabid.

3. *Cholera, smallpox and yellow fever* All persons travelling to a country in which one of these diseases exists, or to a country requiring vaccination against such diseases.

4. *Typhoid fever* In particular areas when required by the epidemiological situation.

In three of our republics vaccination against *measles* is compulsory for persons of a particular age.

Vaccination against *influenza* is not compulsory, but is widely applied.

There are also legal provisions concerned with the conditions and ways in which compulsory immunization including persons who have to be vaccinated, contraindications, vaccinators, types of vaccine, techniques of vaccination, etc.

Depending on the development of the health service of individual areas, vaccination is effected continuously or seasonally.

Vaccination is considered successful if at least 70 per cent of persons envisaged for vaccination are properly vaccinated.

SMALLPOX VACCINATION

The vaccination and revaccination programme covers all the children at the first, seventh and fourteenth years of age. Medical personnel and persons serving in international traffic are revaccinated every three years. The mean annual coverage in the past 15 years amounted to 77–83 per cent of those planned for vaccination. In spite of this a hypothesis persisted that this does not provide a stable and lasting general immunity of the population, an immunity that could prevent the spread of disease if imported into the country.

The following contraindications are legally recognized: febrile condition, communicable diseases at an acute stage, and convalescence, acute digestion

disturbances, leukaemia and severe anaemia, severe forms of rickets or diabetes, nephritis or pyelitis, heart failures with decompensation, cachexia, allergy to any vaccine ingredient.

In addition to these common contraindications to vaccination against any disease, there are some specific contraindications, such as: active tuberculosis, skin diseases and conditions, scabies, or other diseases accompanied by purulent changes of the skin and external (visible) mucosa, pregnancy throughout term, illnesses or impairments of the central nervous system (tetany, spasmophilia, encephalopathy, epilepsy, intracranial bleedings, convulsive conditions, etc.).

The smallpox outbreak which hit Yugoslavia in March and April, 1972, confirmed the hypothesis held with regard to the insufficient general immunity of the population.

Of the total of 124 patients in the Province of Kosovo, 65 had been previously vaccinated. The largest number of affected was found in the age group over 15, i.e. 59, while in the group 5–14 there were only 6 cases. There was no case of smallpox in the age group below four, among the children who had been previously vaccinated. On the contrary, most of the 55 patients who had not been vaccinated before, were in the age group below four – 20 of them – and 36 cases in the age group up to 15.

Of the total number of patients (175) during the outbreak 100 had old vaccination scars, while 73 had not been vaccinated before the epidemic. In two cases it was impossible to find out whether they had been vaccinated before or not. The case fatality rate in the previously vaccinated was 9 per cent, and in the non-vaccinated 35 per cent.

VACCINATION AGAINST DIPHTHERIA, TETANUS AND WHOOPING-COUGH

Compulsory vaccination against diphtheria and tetanus was introduced in 1951, and against whooping-cough in 1961.

Primovaccination against diphtheria, tetanus and whooping-cough takes place in the first year of life and 3 doses are administered of combined vaccine within 4–6 weeks intervals. The first revaccination takes place after a year, the second in the seventh year of life – and this only by DI–TE vaccine – and the following revaccination in the 14th year, while in the 19th year only antitetanus vaccine is administered.

Both vaccination and revaccination cover annually about 72–82 per cent of those planned for vaccination, but the percentage varies considerably from area to area. There are areas in which the coverage regularly amounts to over 85 per cent, contrary to those where it is less than 70 per cent; this because of the inadequately developed health service.

In the period 1959–71 morbidity due to diphtheria fell from 3015, or 16.3 per 100000 population, to 118, or 0.6 cases per 100000. Mortality also decreased by ten times in the same period.

The number of those affected by tetanus decreased from 701, or 3.8 per 100000 population, to 316, or 1.5, while mortality decreased by three times in the period under review.

The number of whooping-cough patients decreased in 1961–71 from 15522, or 83.7 per 100000 to 6079, or 29.7, while mortality decreased by more than three times. Prior to the compulsory vaccination, in 1958, for example, the number of cases amounted to 41537, or 228.3 per 100000 population.

These data clearly illustrate the impact the programme of vaccination had on the incidence. Considering the regions, we find differences which are quite significant. Thus in Slovenia, for instance, not a single case of diphtheria has been registered in the past four years.

Vaccination against polio was introduced in 1961, and the annual mean number of vaccinated and revaccinated is about 80 per cent of those planned for vaccination. The number of cases already decreased in the first year of vaccination by more than ten times, in comparison with the previous year, i.e. 1960, as in that year the number of notified cases was 1686 and 99 fatal cases, which fell to 122 cases with 9 deaths in 1961. In 1971 the total of 23 cases were notified, or 0.1 per 100000 population, with only one fatal case.

Vaccination against *measles* has reached a large scale in the past few years. The Institute for Immunobiology and Virology, Belgrade, and the Immunology Institute of Zagreb obtained good pre-test results encouraging a wider application. Their investigations showed that the incidence was nine times lesser in those vaccinated and a relatively small percentage of them (20 per cent) developed a higher temperature as a reaction to the vaccination.

The application has had a considerable impact also on the reduction of the infant mortality in the underdeveloped areas.

SOME MORE IMPORTANT PROBLEMS AND EXPERIENCES WITH THE VACCINATION

The most important problems arising in the application of the programme of vaccination are primarily resulting from the inadequately developed network of the health institutions, because of which the vaccination acquires the character of a campaign in the less-developed areas. The coverage in these areas is also smaller and the success less checked.

Another important problem is posed by the migration.

Administration and recording makes a complex problem, especially where the information of parents is concerned in the areas where this activity takes the form of a campaign.

Some signs have been noticed suggesting insufficient knowledge of correct vaccination techniques.

Co-operation of the health institutions plays an important role where the success of the programme of vaccination is concerned.

Often the problem of remuneration, especially in the areas where vaccinators have to cover large areas, hilly regions and inaccessible localities, has to be

taken into account. As a rule, it is in such areas which are not covered by the vaccinators that epidemics occur.

Our vaccination programme has yielded significant results in the control of diseases for which it is applied. This is why this measure has a special place and role within the framework of common steps applied to prevent and control communicable diseases. This will continue to be so for some years to come, bearing in mind the insufficiently high standard of living, inadequate knowledge of health, etc.

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LA VACCINATION EN MONACO

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Je vous remercie de m'avoir donné la parole. Cela me permettra, d'une part de vous dire toute la satisfaction que j'éprouve devant la haute tenue des travaux de ce congrès, d'autre part de faire le point du problème des vaccinations dans notre Principauté de Monaco, bien que, et vous le comprendrez, facilement, notre position n'a rien de comparable à celle des orateurs qui m'ont précédés et qui vont suivre.

Une seule vaccination est chez nous obligatoire: c'est la vaccination antivariolique, suite à la loi n° 15 du 18 Juin 1919. Mais dans les années qui suivirent, devant les succés indéniables des vaccinations, après la mise en place progressive du calendrier des vaccinations en France et en Italie et dans tous les états européens, le besoin s'est fait progressivement sentir d'une réorganisation de ces actes médicaux de prévention.

C'est ainsi que le Docteur Boeri, mon prédécesseur, délégué auprès de l'OMS, s'est penché sur ce problème, et moi-même, en maintes occasions, j'ai demandé d'avancer dans cette voie. Le Gouvernement princier enfin a mis en chantier un projet de loi qui qui fut voté le 29 Mai 1970, en vertu de laquelle sera rendue obligatoire la vaccination contre la variole, la diphtérie, le tétanos, la poliomyélite et la tuberculose. En outre, pour certaines professions, seront aussi exigées les vaccinations contre la typhoïde, les parathyphoïdes et enfin la rubéole.

En droit malheureusement, cette loi n'est pas encore applicable. Je le regrette d'ailleurs, jusqu'à ce que les textes d'application soient publiés. Il reste des questions administratives encore à discuter. Fort heureusement, la quasi totalité des enfants de la Principauté sont vaccinés par les médecins des familles. Celles-ci se sont rendues compte depuis longtemps de l'efficacité de la prévention contre les maladies contagieuses qu'apporte la vaccinothérapie.

En terminant, Monsieur le Président, permettez moi deux observations:

Il est évident tout d'abord que je souhaite personnellement que cette loi sur la vaccination prenne corps le plus vite possible et soit appliquée rapidement.

Peut-être aussi, sommes-nous dans un pays trop imbus des libertés individuelles et les pouvoirs publics ont peut-être trop le respect de la personne humaine pour imposer quoi que ce soit à nos concitoyens, avec en conséquence les avantages mais aussi les inconvénients que cela peut comporter.

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THE PROGRAMME OF VACCINATION AGAINST COMMUNICABLE DISEASES IN GREECE

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The question of vaccinations is undoubtedly a manifold one, affected as it is by numerous factors and requiring a continuous, exhaustive and unprejudiced investigation of existing and of constantly arising problems.

The expression, therefore, *a priori* and in a general way, of distrust in their expediency would only provide a grave disservice to the community as a whole, while, conversely, their acceptance in principle and the carrying out of further research for their adjustment to the ever-changing conditions of each particular area will lead to an improvement of methods and the consequent increase of the effectiveness and expansion of vaccination programmes for the ultimate purpose of eradicating, as far as possible, the communicable diseases.

In Greece, certain prophylactic vaccinations are legally compulsory, others are voluntary.

COMPULSORY VACCINATIONS AGAINST:

1. Smallpox (vaccination and re-vaccination)
   Emergency Law 171/1936
2. Diphtheria
   Law 1658/1951
3. Poliomyelitis – Sabin (trivalent)
   E1c/8835/4-8-64 (Sanit. Regulation)
4. BCG for children over 7 years.
   Law 4053/1960

VOLUNTARY VACCINATIONS AGAINST:

Measles
German measles
Parotitis (in early childhood)
TAB

IN COMPLIANCE WITH THE INTERNATIONAL SANITARY REGULATIONS

Cholera
Plague
Yellow fever
Typhus

During the last six years, 1967–71, vaccinations were carried out as reflected on Tables I and II.

Table I. *Compulsory vaccinations from* 1967 *to* 1972

Year	Number of vaccinated persons				
	Smallpox	Triple	Double	Sabin	BCG
1967	199 293	79 348	491 717	402 798	108 071
1968	169 960	112 566	329 274	2 550 908	28 457
1969	305 527	107 625	364 804	495 807	44 769
1970	680 097	128 917	357 503	469 047	53 950
1971	327 597	91 001	337 978	445 024	36 381
1972	2 031 092	46 892	125 099	260 948	
Total	3 713 566	566 349	2 006 375	5 093 579	271 628

Table II. *Vaccinations, voluntary or performed in compliance with the International Sanitary Regulations from* 1967 *to* 1972

Year	No. of vaccinated persons against:					
	Typhoid–paratyphoid	Cholera	Yellow fever	Tetanus	Plague	Typhus
1967	70 605	13 901	2 520	26 135	16	55
1968	53 792	9 801	2 127	14 925	2	317
1969	52 201	20 474	2 406	131 285	35	173
1970	33 582	2 188 331	0	181 138	0	0
1971	33 178	1 522 258	2 828	96 026	0	0
1972	11 326	100 061	1 592	17 009	—	—
Total	254 684	3 854 826	11 473	466 518	53	545

No serious side-effects were observed as a result of the vaccinations set out in Tables I and II.

In April 1972, owing to the smallpox epidemic that had broken out in the area of Kossovo, Yugoslavia, a total of 2477671 persons were vaccinated to provide protection against the disease. The number of postvaccinal encephalitis cases caused by the above vaccinations amounted to 49 or 1.9 per 100 000.

The periods involved in performing compulsory vaccinations are as follows:

(*a*) Poliomyelitis (Sabin). Administered from the 3rd month in three doses at 45 days intervals.

One year after the first dose a fourth dose is given, and three years later the fifth dose.

(*b*) Diphtheria–whooping-cough–tetanus (triple) D. TEPER. It is injected from the 3rd month, at 15-, 20- or 30-day intervals (according to the instructions provided by recognised manufacturers of biological products), duly interposed over the period of polio vaccine administration.

The first (booster) dose is injected a year after the last (third) dose, and the second at the age of 4.

(*c*) Smallpox. This is performed within the first 14 months, especially at the age of 8–9 months, when the danger of postvaccinal encephalitis is, under prevailing conditions in this country, almost non-existent.

Smallpox re-vaccination is performed on the registration of children for admission to the 1st class of elementary schools (6th year of age), also during military service.

(*d*) BCG. On persons, aged from 15 days to 6 years, living away from home or in a tuberculous environment.

As regards the time of performing non-compulsory vaccinations, this is as follows:

(*a*) Measles: between the 9th and 12th month.

(*b*) German measles: after the 12th month.

(*c*) Epidemic parotitis: after the 12th month.

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COMPULSORY VACCINATIONS IN HUNGARY

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In Hungary immunobiological products are subjected to a three-fold control (the third is the state control). The laboratory tests are practically the same as in other countries. In case laboratory control has proved the suitability of a vaccine for mass immunization (including every charge), reactogenicity and efficacy are tested on adequate groups of human subjects. Reactivity of DPT vaccine is, for instance, tested in the course of primary immunization of about 300 infants. Two to four weeks after the last injection the serum antibody level of 50 infants per charge is determined.

If the control for reactogenicity and efficacy has yielded satisfactory results the charges are authorized for mass immunization. The number of charges is limited, thus field trials have to be conducted with not more than 1 to 3 preparations yearly.

The following vaccinations are compulsory in Hungary:

Vaccination	Year started
BCG	1953 for infants 1959 for 4, 6, 10, 13, 17 year olds
DPT	1953 (diphtheria 1938)
Poliomyelitis	1957 (Salk) 1959 (live)
Smallpox	1887
Measles	1969

Continuous field trials of preparations used for mass immunization and done in the past 20 years have yielded a great number of immunological and epidemiological data on the potency of vaccines. Accordingly, modifications were introduced in the composition, antigen content and time of vaccination, further in scheduling the intervals in the case of serial injections.

Table I illustrates changes of DPT and DT vaccines and immunizations for the period 1953–73. The changes have contributed to more satisfactory immunity and to reduced reactivity. Table II demonstrates the vaccination calendar as based on experience in the continuous control of vaccination efficacy (over 60000 blood tests). Table III shows the number and intervals, the minimum intervals between the different vaccinations, and the vaccines which may be given simultaneously if necessary.

Table I. *Changes of DPT and DT vaccination in Hungary*

	DPT primary immunization					DPT booster I					DPT booster II					DT booster III			
		Antigens/dose					Antigens/dose					Antigens/dose					Antigens/dose		
Year	Age (months)	Di. Lf	B. pert. ($\times 10^9$)	Te. BU	Adsorbent	Age (months)	Di. Lf	B. pert. ($\times 10^9$)	Te. BU	Adsorbent	Age (years)	Di. Lf	B. pert. ($\times 10^9$)	Te. BU	Adsorbent	Age (years)	Di. Lf	Te. BU	Adsorbent
1953	6–11†	30	10 extract§	10	$Al(OH)_3$	18–23†	30	10 extract§	10	$Al(OH)_3$	—	—	—	—	—	11†+*	—	12.5	Alum
1954	—	—	—	—	—	18–23*	—	—	—	—	6†	30	10 extract§	10	$Al(OH)_3$	—	—	5	—
1956	—	15	22.5 whole-cell	5	—	—	15	22.5 whole-cell	5	—	—	15	22.5 whole-cell	5	—	—	—	—	—
1958	—	—	—	—	$AlPO_4$	—	—	—	—	$AlPO_4$	6*	—	—	—	$AlPO_4$	—	—	—	—
1961	3, 4†	—	—	—	—	12*	—	—	—	—	—	—	—	—	—	—	—	—	—
1963	3, 4, 5‡	—	—	—	—	—	—	—	—	—	—	—	—	—	—	11*	5	5	$Al(OH)_3$
1964	—	—	—	—	—	—	—	—	—	—	—	7.5	11.25 whole-cell	2.5	—	—	2.5	2.5	—
1965	—	—	—	—	—	18*	—	—	—	—	—	—	—	—	—	—	—	—	—
1966	—	—	—	—	—	24*	—	—	—	—	—	—	—	—	—	—	—	—	—
1969	—	—	15	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1971	—	—	—	—	—	36*	—	—	—	—	—	—	—	—	—	—	—	—	—
1973	—	—	—	—	—	—	7.5	11.25	2.5	—	—	—	—	—	—	—	—	—	—

* Single inoculation. † Two inoculations, interval of 4–6 weeks. ‡ Three inoculations, intervals of 4–6 weeks. § Grasset-type extract.

Table II. *Compulsory mass immunization in Hungary* 1972

Age of vaccinees	Vaccination	Time of vaccination
3–42 days	BCG (Pasteur strain)	Continuously
3 months	Diphtheria–pertussis–tetanus I/a (adsorb.)	
4 months	Diphtheria–pertussis–tetanus I/b (adsorb.)	
5 months	Diphtheria–pertussis–tetanus I/c (adsorb.)	
6 months	Tuberculin testing refers only the babies, who don't have any sign of BCG local reactions. Revaccination of tuberculin-negative subjects	
12 months	Smallpox I (Lister strain)	
36 months	Diphtheria–pertussis–tetanus II (adsorb.)	
9–21 months	Measles vaccination (live L. 16 strain)	Apr., Sept.*
3 months to 3 years	Poliomyelitis (live) type 1, 3, 2	Dec.–Mar.
6 years	Diphtheria–pertussis–tetanus III (adsorb.)	May–June or Sept.
6–7 years	Tuberculin testing. BCG revaccination of tuberculin-negative subjects	Mar., Apr.
10 years	Tuberculin testing. BCG revaccination of tuberculin-negative children except those who have had BCG vaccine in the last 5 years	Mar., Apr.
11 years	Diphtheria–tetanus (adsorb.)	Sept., Oct.
12 years	Smallpox II	Apr., May
13 years	Tuberculin testing. BCG revaccination of tuberculin-negative subjects	Mar., Apr.
17 years	Tuberculin testing. BCG revaccination of tuberculin-negative subjects	Mar., Apr.
18 years (for recruits only	Smallpox III	
	Typhoid/aceton killed and dried/tetanus/plain	—

* From Oct. 1974 on, continuously for 10-month-old babies.

As a number of tests on diphtheria and tetanus toxoids, further on pertussis vaccine, indicated that several months or years of interval between the first and second, or the second and third vaccinations did not affect immunity, the repeated injections of primary vaccination were not restarted but continued with the previous vaccinations taken into account.

Table IV illustrates the morbidity data of important infectious diseases that can be controlled by vaccination, for the period 1952 to 1971. As a result of immunizations a significant decrease in incidence can be observed.

Doctors performing vaccinations have to report to the Department of the Control of Immunobiological Products, National Institute of Public Health, all cases developing post-vaccination complications and vaccination accidents. Experts in laboratory and clinical medicine investigate every case. From 1973 on, the State takes the responsibility for every injury caused by vaccinations.

Table III. *Some prescriptions for vaccinations in Hungary*, 1972

Vaccine	Interval (weeks)	Injections
A. Interval between the injections of vaccines		
DPT (adsorb.)	4–6*	3
Tetanus	4–6	2
Poliomyelitis (live)	4–6	1, 3, 2 type
Scarlet fever (adsorb. toxin)	2	3
Mumps (adsorb. inactivated virus)	6	2
Paratyphoid (plain)	1	3
Typhus exanth. (plain)	2–3	3
B. Minimal interval after different vaccination		
After DPT vaccination (except polio) (between DPT and polio 2 weeks)	4	
After smallpox	4	
After measles	4	
After scarlet fever	4	
After polio (live)	2	
C. The possibility of simultaneous vaccinations, if necessary		
BCG–polio (live)		
BCG–DPT		
Polio (live)–DPT		
Smallpox–DPT		

* If, for any reason, the interval is longer, whole schedule has not to be repeated but continued.

Table IV. *Morbidity of some infectious diseases in Hungary*, 1952–71
(*per* 100000 *inhabitants*)

Year	Diphtheria	Tetanus	Whooping-cough	Poliomyelitis	Measles	Tuberculosis new cases	
						<14 years old	>14 years old
1952	21.8	5.8	199.2	5.3	248.9	—	—
1953	18.9	5.2	594.2	3.3	566.7	227	417
1954	15.1	4.1	194.6	12.1	380.6	229	352
1955	11.0	3.8	96.4	6.3	510.5	218	337
1956	9.0	3.3	91.3	11.2	374.7	217	327
1957	6.9	2.6	155.8	23.8	383.6	221	306
1958	4.6	2.6	129.7	1.7	493.9	236	335
1959	4.1	1.9	27.1	18.3	339.1	184	334
1960	2.9	1.7	18.8	0.4	518.5	136	329
1961	2.2	1.3	45.8	0.06	262.2	93	314
1962	1.4	1.2	64.3	0.01	571.9	57	286
1963	0.7	1.1	15.9	0.04	385.6	32	285
1964	0.8	1.3	3.1	0.03	378.1	23	239
1965	0.3	1.1	5.7	0.06	388.3	17	197
1966	0.3	1.1	21.7	0.06	477.4	13	175
1967	0.4	0.9	2.0	0.02	490.1	12	160
1968	0.2	1.0	1.5	0.07	242.1	10	152
1969	0.02	0.8	2.1	0.02	517.3	10	134
1970	0.02	0.8	3.4	0.02	72.3	8	120
1971	0.01	0.8	0.5	0.03	32.4	5	113

GENERAL DISCUSSION

CHAIRMAN There is now about 20 to 25 minutes for discussion, I wonder if I might start perhaps by asking Dr Sievers whether he has any idea how much compensation for immunization reactions has cost the Government in Denmark?

SIEVERS (Denmark) Not yet. We have only had the eight cases I mentioned who have actually received compensation, and I do not know how much.

CHAIRMAN I believe that Monaco also pay compensation for reactions, but they have a casino here and perhaps they can afford it, I do not know.

MAURIN (France) What is the prophylaxis of measles in Belgium owing to the fact that there is no anti-measles vaccine allowed in Belgium? What is the prophylaxis against measles in the nurseries for children?

LAFONTAINE (Belgium) The Council of Hygiene has maintained until now a careful position. The main reasons were that to its knowledge the problem of the danger of measles in young children is not in Belgium a very important one, that the reactions to the first vaccines were not always mild and that doubts remained about the duration of the immunity. That last question was the most important one: to avoid measles in childhood to carry it into the adult life cannot be a reasonable solution.

Progresses in present knowledge may be at variance with the findings of rhe past. On the other hand, it may be real that the non-compulsory report of the cases of measles do not give an exact measure of the disease in the country: a more critical approach appears necessary. That attitude explains how until now the vaccination has not been recommended and that no vaccine has been accepted in Belgium, although the Belgian authorities do not prohibit the importation of measles vaccines from abroad if it is prescribed by the doctor for his own patients and if the pharmacist in charge of the execution of the recipe announces the importation to the Inspection of Pharmacy.

VON MAGNUS (Denmark) On the question of the compensation paid to the polio-associated cases, people were paid according to their disablement up to an amount varying from somewhere around $7000 to $20000. The total amount paid in damages was, I think, about $80000 to $100000.

CHAIRMAN Would this affect your cost effectiveness, Dr Sencer?

NETTER (France) I have one question to Dr Smith and some others to Dr Relyveld.

First, to Dr Smith, you say that few countries have adopted influenza vaccine in their policy. Is there any which has adopted a policy except for a selected population group?

CHAIRMAN Dr Netter asks if any country has adopted influenza vaccination other than for selected population groups. I believe that in the United States people are concentrating on the elderly, and in the United Kingdom we allow vaccination primarily for people at special risk, people with bad chests for example. Has anybody any observation to offer on this?

SCHILD (UK) I believe that widespread vaccination with live attenuated vaccines is practised in the USSR, and although I do not think this is compulsory, it is strongly encouraged.

CHAIRMAN Is this still on an experimental basis perhaps?

SCHILD (UK) I think it has gone past the experimental stage.

VASSILOPOULOS (Cyprus) I should like to ask Dr Henderson whether the firms manufacturing prophylactic vaccine or sera have to comply with WHO standards and requirements as to their potency or efficacy.

HENDERSON (WHO) Might I suggest that this question be put to Dr Outschoorn, who is head of the Biological Standards Division of WHO.

OUTSCHOORN (WHO) There is no single answer to that, but there are many countries that are making a valiant effort to improve the quality of the control of preparations. I can quite categorically state that the position today is much better than it was say 10 or 15 years ago, and many products are made available, produced in the countries themselves, which do meet the requirements published by WHO and which are taken over by the countries themselves according to their own conditions. So the answer is yes, but not numerously so.

KRUGMAN (USA) In regard to pertussis, it is clear that it is impossible to protect those infants who acquire the disease prior to two or three months of age by modifying the immunization schedule. We have occasionally/seen pertussis in infants as young as 4 weeks of age. Consequently, it would seem more rational to concentrate our efforts on the immunization of the siblings of the infants. Well immunized siblings are less likely to introduce pertussis organisms into the family.

CHAIRMAN I believe the policy in the United States is to immunize in very early infancy.

KRUGMAN (USA) The recommended schedule for active immunization of normal infants is as follows: diphtheria and tetanus toxoid combined with pertussis vaccine and trivalent oral polio vaccine at 2, 4 and 6 months of age, at 1½ years of age and just before admission to school at 4 to 6 years of age. Pertussis has been an extremely rare disease in populations of children who have been immunized according to this regimen. Pertussis has occurred chiefly in unimmunized children and in infants who have been exposed to their unimmunized siblings.

MEYER (USA) I should like to comment about measles and rubella. There is such a wide variation in the interpretation of the same data, and I recognize that there are many reasons for this. I would wonder whether all the data which could be brought to bear on decision-making have indeed been brought to bear.

Thinking specifically of measles, for example, American pediatricians are perhaps more concerned about measles than some pediatricians from other countries. This is because of two types of demonstration. One is a rate of encephalitis of 1 per 1000, but this is confirmed in smaller studies by electro-encephalographic evidence of abnormality in 50 per cent of all children with uncomplicated measles. Measles is unique among childhood diseases in this high frequency of micro-encephalographic abnormalities. I wonder whether any of the European groups have addressed themselves specifically to looking at encephalographic abnormalities in supposedly uncomplicated measles. I am not aware of such studies.

My second point concerns rubella. The comment is made that congenital rubella is not recognized here, and there is a problem. If one has done serologic surveys on women in their child-bearing years in any country, and if one has found a proportion of such women rubella-susceptible, I suggest one should look at the evidence very closely to see that congenital rubella was not a problem in such a country.

CHAIRMAN I wonder if perhaps Dr Griffith might comment on Dr Meyer's first point concerning measles encephalitis.

GRIFFITH (UK) Studies carried out in Britain certainly show that changes in the EEG with measles are very common indeed, amounting to 80 or 90 per cent of children. This

is a slowing of the EEG, and there is no evidence that we know of that these changes in the EEG are related to any ill-effects afterwards, and certainly they are not related to whether or not the child will develop encephalitis afterwards. It is a separate phenomenon altogether.

LUNDBECK (Sweden) We had to know the frequency of EEG complications after vaccination as well, and I remember seeing rather high figures published, although I could not recall exactly what they were. They were not very far from the figures in natural measles.

JUST (Switzerland) We published a paper a few years ago on measles encephalitis in Switzerland, and we had about 1 case in every 2000 cases of measles. We did work on EEG changes after natural measles and we had about the same number. We had about 25 to 30 per cent of changes in uncomplicated measles. Then, with about 300 vaccinated children, we had only 3 or 4 cases of such EEG changes after vaccination.

NETTER (France) I should like to ask Dr Relyveld why, in his survey, he chose the age of 2 to 6 for immunization in Africa, because for measles immunization that seems late, even for BCG.

RELYVELD (France) The children in the first group were between 1 and 5 years, not between 2 and 6. The aim was to find an easy way to vaccinate against the five diseases. As you know, it is very difficult to vaccinate big populations in these countries, so if you can vaccinate children between 1 and 5 years against the five diseases it is easier than vaccinating at 3 months and again at 6 months. We were looking for a practical solution.

WITTE (USA) This is a comment in regard to Dr Lundbeck's question or comment, and that is that it is very important to look at risks associated with vaccine as well as risks associated with disease. We have recently completed a review [*J.A.M.A.* (1973), **223**, 1459–62] of all reported episodes since licensure in 1963 of central nervous system (CNS) illness which occurred within 30 days after measles vaccine administration, and we compared the frequency to CNS illness associated with naturally occurring measles. With the latter there is 1 case of encephalitis per 1000 cases. Following measles vaccine there is roughly 1 case per milllion of rather diffuse and diverse central nervous system disease. This is a temporal association; how many, if any, are related to the vaccine *per se* is hard to say. However, even if they all were, I think the difference between 1 in a million and 1 in 1000 is very striking.

HENDERSON (WHO) I should like to make a comment to supplement Dr Meyer's observations. I wonder whether, in evaluating risks and problems in respect of many diseases, we really have adequate information. In Ethiopia in 1970, only 500 cases of smallpox were reported. It was said at that time that the disease was not a major problem, but when a surveillance programme was implemented the following year, some 26000 cases were discovered and we know that still all cases were not reported. I am sure that in Europe you have a more accurate measurement of disease incidence, but I should like to recall just one episode in a country that you, Mr Chairman, and I know quite well. Ten years ago I came to this country and inquired about a disease called hepatitis, which we in the United States were troubled about. I was informed at that time that this was not a problem in the country concerned. It was also pointed out that it was not a notifiable disease. Five years later, however, the situation was quite different; epidemiological studies showed that hepatitis was widely prevalent and it had been included in the list of notifiable diseases. It was recognized to be a problem not dissimilar to that in the United States.

Not only in the developing countries but in Europe I query sometimes whether, in fact, we really have looked carefully to see what the problems are in respect to a number of diseases. With measles, for example, I have a feeling that perhaps in Europe the situation is not so different from what it is in the United States, where it is generally acknowledged to be a problem.

Not only is it important to assess accurately the extent of the problem, but also to monitor the immunization programmes as they progress, to know among which groups the cases are persisting. If one has an immunization programme and one continues to record cases of the disease in question, there are, obviously, failures or at least weaknesses in the immunization programme. One can monitor a programme in this way and perhaps redirect it to vaccinate those who are failing to be immunized for one reason or another.

CHAIRMAN I think this is a very important point, Dr Henderson.

VASSILOPOULOS (Cyprus) I should like to mention a case we had last year in Cyprus which developed encephalomyelitis with complete paralysis of the lower limbs and incontinence of urine and faeces, 10 days after she had had her primary smallpox vaccination. We have attributed this complication to the late age at which she had the vaccination.

I should like to know whether the experts here agree with us that this complication is related to the late age of vaccination, or whether they think that some other factor was involved.

CHAIRMAN Thank you for bringing that point up. May I suggest that you discuss it with one of the experts in the tea-break because time is getting on?

VON MAGNUS (Denmark) In reply to Dr Henderson's remarks, I can inform you that we are now carrying out an investigation of 'normal measles' in Denmark. We have been stating for a long time that measles in Denmark is less severe than it is claimed to be in, for instance, the United States, but we wish to know more about this. That is why we are now having a survey for which families have been chosen by computer. There will be personal interviews in each home where there has been a case of measles during the last year. These interviews will be rather detailed and will be conducted by a specially trained nurse. So before the summer vacation we shall be able to tell whether measles is severe in Denmark or not. At present we only know about encephalitis cases, and the rate is about 1 in 3000.

KRUGMAN (USA) As a pediatrician I feel that I must speak up in behalf of infants and children. If children could be given the option to choose between an attack of measles characterized by 6 days of high fever, cough, coryza, conjunctivitis and just plain misery or an immunization characterized by no symptoms or possibly a transient fever, their choice would be obvious. Moreover, the usual complications of measles–otitis media, laryngotracheitis, pneumonia and encephalitis are extraordinarily rare in association with measles immunization. As physicians we are obliged to think about the comfort of children as well as the more severe complications.

CHAIRMAN Thank you very much, Dr Krugman, for bringing this point up so that we can bear it in mind.

UNGAR (Switzerland) I have a question to ask Dr Relyveld. In his table he showed a number of antigens he is preparing for study in the French part of West Africa. I wondered why he did not mention the pertussis antigen. In West Africa my experience is that, next to measles vaccine, pertussis is a killer for young children. I should be very glad to know the policy of Dr Relyveld in leaving out the pertussis antigen from his table as an important component in his study.

RELYVELD (France) We have studied pertussis in other programmes. We had a programme in which we studied DT–pertussis, yellow fever and measles. We found that the results were not very good for measles, we think because of the presence of endotoxins, as we saw also with yellow fever and cholera.

The object of this programme was to study a combination of the five antigens. Because we knew that pertussis would have given a lowering of the measles and probably of yellow fever titres we did not include it in this programme. However, after the results I have given, you can understand that it is quite possible to imagine a programme giving tetanus

and pertussis in the first month of life and then the other antigens as I have shown after one year, and a booster for tetanus at the same time.

PECENKA (Czechoslovakia) I have a question for Dr Levy. If the polio vaccine used in France is a live one, is it trivalent?

NETTER (France) Monovalent polio vaccines are licensed in France and also trivalent polio vaccine. I think that in the particular study done by Dr Levy he was using monovalent.

LEVY (France) No, it was trivalent.

SENCER (USA) I should like to ask Dr Bijkerk what he recommends for travellers from the Netherlands who are going to areas where polio is either endemic or epidemic.

BIJKERK (The Netherlands) We advise them to be vaccinated with the killed vaccine, preferably the DTP–polio vaccination, so that travellers will also be protected against these diseases.

CHAIRMAN I gather, Dr Bijkerk, that you have not used BCG in Holland at all, except perhaps for exposed people; is that right?

BIJKERK (The Netherlands) Yes, you are right. BCG vaccination is not carried out and has never been applied in the country and, therefore, the tuberculin reaction has become an important tool in the hands of the epidemiologist. Actually we had in 1946 an incidence of 160 cases per 100000, including relapsed cases of TB. Since then the incidence has dropped considerably and, in 1971, the lowest incidence ever of 19 per 100000 was found. We have sampled children by previous testing, or we shall carry that out from this year onwards, with 10-year-old children in a surveillance programme for tuberculosis. This has replaced the mass X-ray examinations in the age group under 15 years.

CHAIRMAN I know that we are fortunate in having with us Dr Gilliland, who is from Pretoria in South Africa, and it might be interesting if he would come and say something about immunization programmes in South Africa, because so far we have only heard about one tropical part of Africa.

GILLILAND (South Africa) Mr Chairman, I do not want merely to recite a list of vaccination programmes. Therefore I would like to stress the differences that we have in South Africa.

We have only two compulsory vaccinations – that is legally compulsory. The first is smallpox, and everybody must be vaccinated within 13 months of birth. We have had encephalitis reactions in 1 in 100000 cases, and to date we have a percentage vaccination of the whole population of about 90 per cent. For poliomyelitis vaccination the oral attenuated vaccine is given, and three doses are recommended within the first year of life.

Religious and other conscientious objectors can get exemption from smallpox vaccination, and when we drew up the poliomyelitis regulations we left this out and no one raised any objection, so you cannot get exemption from polio vaccination.

At present we are busy introducing legislation to prepare for the mandatory vaccination with BCG for all new-born children, and again, after tuberculin testing, for children before they go to school. We do have a tuberculosis problem in South Africa. The latest figures we have indicate that we had 46000 cases notified in 1972.

Vaccines that are supplied free via the State Health Department, but are not legally required, are DPT and, to all at-risk patients, measles and influenza. Typhoid and paratyphoid are still used, though of doubtful value I think, and rabies is supplied for cases requiring it therapeutically.

International travel requirements are yellow fever, cholera and smallpox. Then, available but not free, are rubella and mumps.

I should like to say just two words about the documentation or recording that we have

introduced. This has helped us. You must remember that we are a developing country, and we have introduced an immunization card which is printed on a double linen-backed base and is fairly durable, and on this all the immunizations of the baby are transcribed. We hope very soon to introduce a Book of Life for a child in which all this information will be displayed. At the age of 16 all these vaccinations are transcribed into the adult Book of Life, and this Book of Life, of course, contains every single certificate you need in South Africa from possessing a firearm or a driving licence to the final page where there is a copy of your death certificate.

The Department of Health finances all mandatory immunizations, whereas advisory immunizations are financed seven-eighths by the State Health Department and one-eighth by the municipal clinical departments. All vaccines are manufactured in South Africa except influenza, which we import.

CHAIRMAN Thank you, Dr Gilliland.

One of the aspects of this session that has struck me has been the frequency with which legislation is used by various countries to promote their immunization campaigns. In the United Kingdom no vaccine has been mandatory since 1948 when smallpox vaccination was stopped as a compulsory measure. It is interesting to hear that in many countries, and many states in the United States, vaccination programmes are compulsory. In the United Kingdom I think it would be very difficult to get the population to accept mandatory vaccination and there would be a lot of reaction against it, but it obviously goes very well in many countries.

GRIFFITH (UK) It is quite interesting that in Britain the smallpox vaccination rate was 40 to 45 per cent during the 1940s when vaccination was compulsory, but went up by 10 per cent after it ceased to be compulsory in 1948.

CHAIRMAN That must say something about the English character I think!

PECENKA (Czechoslovakia) Mr Chairman, is it at all pertinent to speak about 'the campaigns' in European conditions when we speak about immunization? I think this is, in fact, 'a regular systematic immunization' and the term 'campaign' should be left for a rush programme.

HOFMAN (The Netherlands) In our country, where smallpox vaccination is compulsory and other vaccinations against diphtheria, tetanus, polio and pertussis are not, we have a much higher acceptance rate for the latter group of vaccines. During the Staphorst outbreak in March 1971 there were suggestions in our country about imposing this vaccination by law, but it was abandoned because many people thought that this compulsory vaccination would not be feasible because people would object for acceptable reasons which had already prevented them from taking the vaccinations.

Now I come to a third question which I put to Dr Sencer about the vaccination in some states of the United States. I understood that some of these states knew compulsory vaccination against polio as well as for some other diseases, whereas other states did not. The question I should like answered is, is there any difference in acceptance rates between these states. Has enforcement by law had any advantageous influence on this vaccination rate?

SENCER (USA) I should very much like to answer this, because I personally do not believe in the mandating of immunization by law. I think that frequently we have put reliance on that and allowed children to go until they are 5 years of age before they are immunized. This was particularly true in the past with smallpox vaccination, when this was being recommended in the United States. You would see a sudden jump to around 95 per cent of children being immunized between the ages of 5 and 9, whereas before, in the age group 1 to 4, it would be down to around 60 to 65 per cent. So I think there is danger in making it mandatory for immunization at school entrance, because people will begin to think that this is the time to get their children immunized.

I do not believe that we could document any difference between our states in the United States, as between those which have laws and those which do not. There may be a lag of a year. In a state which passes a law, if a vaccine were introduced in 1968 the children might be immunized by 1970, whereas in a state where it was voluntary it might be 1971. I do not think the laws really contribute.

CHAIRMAN Perhaps the laws are not pursued very vigorously in the different states.

SENCER (USA) There is no way in which the laws can be enforced if the individual wishes to decline vaccination. There was one state which made it a crime not to be immunized by the age of one, but I defy anyone to figure out how to enforce it.

BIJKERK (The Netherlands) I should like to clarify one remark made by Dr Hofman. Smallpox vaccination as such is not compulsory. It is regulated by law, but the only compulsion is either to declare that a child has been vaccinated or to make an objection to that vaccination.

Moreover, the Health Council will soon be reconsidering the policy of routine smallpox vaccination in our country.

HENNESSEN (Germany) I think there is some misunderstanding about the law and vaccination in some countries. To talk about law and vaccination does not always imply that the vaccination is compulsory. For instance, in Germany the law regulates vaccinations which are not at all compulsory. As a matter of fact, we have the highest participation in those vaccinations which are not compulsory, while we have lower participation rates in the compulsory vaccinations.

It is a matter of compensation for the vaccinee and it is a matter of cost. The Government can take over the cost of vaccination. This and the compensation are not questions of a vaccination being made compulsory.

UNGAR (Switzerland) I should like to put two questions to Dr Gilliland. I was very interested when he mentioned that he still had about 20000 to 40000 cases of tuberculosis. Can we please be told the age of those who have contracted tuberculosis. Is it young individuals? Is it the middle-aged?

Secondly, do you still use isoniazide(INA)-resistant BCG?

GILLILAND (South Africa) The answer to the first question is that there were 46000 cases in 1972. Approximately three-quarters of these were young children and the others were reactivated cases. We have had no INA-resistant cases to date.

GRIFFITH (UK) Returning to the question of compulsory vaccination, I believe that when a state makes vaccination compulsory it implies and accepts responsibility for promoting the belief that vaccination undoubtedly is to the benefit of the subject. Voluntary vaccination allows the state merely to recommend vaccination. There is a difference. Once it becomes a statutory requirement that a person undergoes a procedure, then the state must be certain that it is in the person's benefit and must accept responsibility for any adverse reactions that may occur as a result of that procedure.

CHAIRMAN One gets the impression that in many of the Eastern European countries the vaccination programmes have been extremely successful, perhaps in part through compulsory vaccination. I do not know whether Dr Rangelova would care to comment. Is there not compulsory vaccination in Bulgaria?

RANGELOVA (Bulgaria) We have mass immunization, but it is not compulsory. If someone refuses to be vaccinated we do not take any measures. However, we have free mass immunization and a lot of people are willing to be immunized, and to immunize their children.

SENCER (USA) If I could take issue with Dr Griffith, he said that it had to be to the benefit of the individual to be immunized, but many of the immunizations we are using

today are not so much for the benefit of the individual as for the benefit of the community. We are asking the individual to take a minimal risk to do a maximal job of protecting the community. That is why I think that programs such as Professor von Magnus described in Denmark are so essential. In immunization programs where we are asking the individual to take a minor risk for the good of the community, the community should be willing to take care of that individual if he suffers as a result of helping to protect the community.

GRIFFITH (UK) Dr Sencer stated that the individual was asked if he would be vaccinated, but when legal powers are used the person is being compelled to accept the minimal risk involved. This is why we should endeavour to achieve 100 per cent voluntary acceptance rather than order a person to accept a minimal risk.

CHAIRMAN Dr Sencer is probably in agreement with you there, Dr Griffith.

GEAR (South Africa) I think it should be pointed out that the problem in Africa in regard to multiple vaccinations is not so much the combination of vaccines – although obviously it is reasonable to combine as many antigens in one vaccine as possible – as the reduction of the number of visits to a minimum. The minimum number of visits which is possible is three. We worked out a programme under which at 3 months they got DPT, BCG and a first feed of polio virus. Then at 6 months they got DTP, variola and polio virus second feed, and at 9 months they got DTP, polio virus third feed and MMR. Several of the MOHs of the larger centres have pointed out that whooping-cough when it does cause trouble causes it between birth and 6 months of age, and this programme is not adequate to cover these patients.

I should be very grateful to anyone who would like to say whether he feels that this programme is inadequate in its protection against whooping-cough.

The second question I should like to ask, particularly perhaps of people from Britain, is what vaccinations do they recommend for visitors going to, let us say, Bangladesh or other countries in the East. This is an increasing problem with the increasing number of visitors, and if you are going to diminish some of the vaccinations in early age you will increase the number necessary later.

RELYVELD (France) As I said, there are many difficulties. The first difficulties are epidemiological in nature. There are many diseases against which you have to give protection – smallpox, measles, yellow fever, diphtheria, tetanus, polio and pertussis. These are problems in Africa and so you have to protect against all of them. During the last year another disease has come up and that is cholera. So the programmes have to be designed to protect against all these diseases. That is the first difficulty.

The second difficulty is one of organization. First of all, the sanitary organization in the countries in which we are working is inadequate. There is not much money and there are not many doctors. For instance, in some countries all the injections and vaccinations are given not by doctors but by a male nurse or nurse. In many African countries, after a birth the mother and the child receive an injection of tetanus antitoxin given by a nurse. So most of the public health work is done by nurses if they are available. So it is a question of money and a question of skilled people.

Another problem arises from the infrastructure of the population. Populations are very widespread and it is difficult to bring them together. Moreover, these are rudimentary populations, and they tend to think that if you have given them one injection with one vaccine they are protected against all diseases. They have no idea about diseases.

So you have to look for very simple programmes, and the first solution is a reduction in the number of injections, because it is impossible to send doctors into the country on 1 January, let us say, and send them back on 1 February and again on 1 March. Generally in these countries there is not enough equipment, nor enough vaccine. What you can do is to send vaccine over from the producing countries, but you have to do it at the right time to avoid storage. With the people and equipment you have you can go once a year to a region and vaccinate, but you cannot do it again one month later. So we have to look for

a reduction of injections. We try also to combine our vaccinations so that we can vaccinate against as many diseases as possible in one or two trips by the medical staff. The problem is to discover the best combination, and that is the aim of our programmes. We have found that if we vaccinate very young children in Africa, antibodies of maternal origin can decrease the immunological response to many diseases.

So you have to know what you are going to inject and at what age. We now know that we can give tetanus toxoid to very young children, and this makes it possible to devise a programme and give an injection of tetanus toxoid eventually, associated with pertussis vaccine and BCG and then, a year later, inject all the combinations of which I have spoken today.

CHAIRMAN I wonder if we might perhaps answer the second question which Dr Gear raised. This was the question of vaccination for travellers. I think I am right in saying that Dr Gear thought that with the stopping of smallpox vaccination in some countries, vaccination of travellers may become more important. I wonder whether Dr Cockburn would care to say something about this.

COCKBURN (WHO) This question of the vaccination of travellers certainly is very important, and of increasing importance. One has to look at it in two ways. There are travellers coming from endemic countries who may introduce infection, and the prevention of this introduction is essentially the responsibility of the national government to which the person is coming. There is also a more important problem in some ways, and that is the movement of people from non-endemic countries into endemic areas. I think that the medical profession have a very great responsibility to ensure that travellers – tourists, commercial travellers and so on – are protected against the diseases they are likely to come into contact with in these other countries.

One of the most important perhaps is poliomyelitis, but of course there are others. I agree with Dr Gear that this is a matter which will increase in importance as time goes on.

CHAIRMAN One particular group of international travellers are likely to be the military. They may have to travel to endemic areas quite rapidly and operate under conditions where hygiene is difficult to maintain. I believe that General Sachs might be prepared to say something about immunization in military establishments.

SACHS (UK) One of the problems is that soldiers may have to proceed overseas at short notice. Therefore we always ensure that they are fully immunized.

In some recruits we find that the information given of previous immunization history is very often incorrect and often incomplete, so we have the problem of starting *de novo*. The immunizations that we have to carry out are against the enteric fevers poliomyelitis, diphtheria if Schick-negative, tetanus, smallpox, BCG to tuberculin-negatives and, when necessary, cholera, yellow fever and sometimes typhus. This is a fairly hefty immunization programme and we are always at loggerheads with commanding officers who need to train the men, and they dislike incapacity which is inflicted by the doctors. Some commanding officers are very rude about it!

The soldiers also have wives and children. The children we hope will be immunized in accordance with civilian practice, but the wives do create a problem. They are not so amenable to military discipline as their husbands!

In England an army laboratory prepares a number of special vaccines for the different procedures, like intradermal injections, and also cholera vaccine.

I think that that is all one need say about the soldiers, but I should like to reinforce something that Dr Cockburn said about this mass movement of populations, particularly during the holiday period. It involves well over two million people and that is a problem. There is an increasing demand from people going to certain countries in North Africa for inoculation against typhoid, and very often there is not enough antityphoid vaccine readily available.

The group that I think one has to look at carefully are those who live rough. In the last few years I have had two cases of tick-borne relapsing fever and one of typhus.

A problem in the army and elsewhere is the tremendous increase of Sonne dysentery and Salmonella infections. I have no idea what the true figures are for Sonne dysentery, some mild, some severe, the greater majority never coming to the laboratory. Perhaps we suffered from the disease known as 'desoxycholitis' when we diagnose many cases.

These are the points that I feel have not been quite covered. Of course, as mentioned, you do get politicians travelling, and on one occasion I had to immunize a Very Important Person very urgently when he was flying off somewhere and could not remember whether he had had yellow fever, or not. They usually come the night before they travel and then you suddenly get a comment that the technique was rotten, that he had a high fever and was incapacitated for 48 hours. It is always just the night before they are going that they wake up to the need to have something done.

SENCER (USA) I recognize the need of the military to be prepared for any occurrence, but I would hope that in civilian populations we could approach the immunization of travellers on a more cautious epidemiologic basis.

Last summer, for example, Mexico experienced a major epidemic of water-borne typhoid fever. There were literally thousands and thousands of American tourists going into the area and we only had three confirmed cases of typhoid fever imported back into the United States.

I think that of more concern to travellers to many of the areas, particularly the areas that Dr Gear mentioned like Bangladesh and South-East Asia, is a need which we have not mentioned, for prophylactic gamma globulin against hepatitis which I think in many respects is a greater risk than typhoid fever.

BIJKERK (The Netherlands) With military personnel you can space your vaccinations in order to be prepared for special events, but, apart from the compulsory vaccinations like smallpox, cholera and yellow fever, we advise our travellers to be vaccinated or re-vaccinated against diphtheria, tetanus and polio, as well as typhoid fever. When going to tropical countries, and primitive areas, as well as camping in the subtropical areas we emphasize the need for an injection of gamma globulin against infectious hepatitis, and we should not forget prophylactic measures against malaria.

The point is that so many people are travelling within a short period of time, and we need some advice. It is very difficult to establish a dose for a rush programme. What is the optimum? I have discussed this with Dr Cockburn and he has advised us to start with the virus vaccines and, a week later, go on to the bacterial vaccines. I think that that would be the easy way of doing it, and then we have about 5 weeks to finish the whole schedule. We can give at least two injections with a 4-week interval against DTP and also against typhoid fever.

However, I should like to hear other advice or suggestions pertaining especially to rush programmes for travellers going abroad.

SCHUMACHER (Germany) We have a second problem group besides the tourists; that is our foreign workers, and especially the families. Out of our 14 cases of polio in 1972, we could isolate the virus in 13 cases, and 9 of those cases were imported by the children of our foreign workers.

I should like to put a question to Dr Lundbeck on the effect of killed vaccine. I suppose that there have been investigations on the circulation of the virus, for instance in sewage, but has the circulation of the virus been interrupted in Sweden?

LUNDBECK (Sweden) I should have dealt with that. Since 1963 there has been no domestic case in Sweden, and the circulation of the virus in patients, so far as can be established, has been interrupted. We have found in the past few years a few positive isolations in a mass investigation of sewage, but since the beginning of the 1960s we have

not been able to isolate the virus from people. There are between 6000 and 7000 specimens a year sent in, and there were plenty of positive specimens before the introduction of the vaccination programme against polio. There is very little circulation, if any, in the community of wild virus.

HALONEN (Finland) I should like to add to what Dr Lundbeck has said. In our countries, Sweden and Finland, we have not only eradicated poliomyelitis but have also eradicated the live virus. Now, when we do not have any cases, it does not necessarily mean that our whole population is immune. We have no challenge virus to test the immunity. It is therefore very important for travellers from our countries that they should be vaccinated, or given a booster vaccination, against poliomyelitis. We have strongly recommended that all travellers going to tropical countries and to the southern European and Mediterranean countries should follow this course.

CHAIRMAN That is a booster of killed vaccine, is it?

HALONEN (Finland) Killed, yes. Of course it is different in countries which use a live poliomyelitis vaccine where one may get some kind of booster from vaccinees, but of course that does not happen in our countries.

PECENKA (Czechoslovakia) What Professor Halonen has told us is a very strong statement – 'we have eradicated poliomyelitis.' This also comes into the summary of Dr Griffith's paper which is printed in the booklet. Are we really sure that we have eradicated the infection? It seems to me that we have eliminated it as a public health problem only. At least, in Czechoslovakia we have had no clinical cases of poliomyelitis since 1960, but we do sometimes find the wild polio virus in sewage waters. Therefore, I do not think we can yet speak about the eradication of the infection.

The same might be true of diphtheria, which was also mentioned in Dr Griffith's summary. In the Czech Republic there are very few, perhaps two or three cases in a year, especially in teachers in the kindergartens, but the *Corynebacterium diphtheriae* might still be found in communities of children. They are fully immunized so that the agent might circulate, without any pathogenic effect unless a susceptible host enters such a community.

I think that we should be a little careful in the way we use and misuse the word 'eradication'; it is not good that we should be too self-satisfied.

Referring to the previous part of the discussion when mention was made of what is compulsory and what is not, in Czechoslovakia most of the immunization is compulsory. Polio immunization is also compulsory, but at the present time we are happy if we have 80 per cent coverage, which means that 80 per cent of the mothers come with their children to the immunization or vaccination centres. At the time of the last polio epidemic these mothers were only 8- or 10-year-old girls, so they do not have the fear – as their mothers had 15 years ago – that their children could be paralysed for their whole lives.

I think that we must increase everything possible, and we must never forget our vigilance to maintain surveillance of all these infections in all of their forms, even the invisible ones.

CHAIRMAN Thank you very much. I believe that most European countries are involved in surveillance, but perhaps Dr Griffith might like to take up that point particularly.

GRIFFITH (UK) The term 'eradication' referred to a few countries which have not reported cases of diphtheria during the last 10 years. It does not apply to Britain. In Britain I believe there are about 200 isolations of polio virus in a year through the public health authorities, so poliomyelitis has not been eradicated. In other countries, however, there have been no reports and no isolations during the last few years. I am not suggesting that these diseases have been eradicated in Britain but some Scandinavian countries have been free of these infections for some years.

LAFONTAINE (Belgium) I should like to refer to the problem of immigrants. We found in 1971 54 cases of polio strains mostly in immigrants coming from North Africa and from Turkey. So we must be careful about such people who may import wild strains. A similar problem may arise from persons from ones own country going abroad.

So far as diphtheria is concerned, we are asked to check whether it is toxigenic or not, because we found a lot of *Corynebacterium* diphtheria which were not toxigenic.

I should like to ask a question of those who can answer it about the effectiveness for travellers of gamma globulin against hepatitis.

SENCER (USA) I cannot quote numbers, but we have extensive experience with gamma globulin in Peace Corps volunteers and in missionaries, where we have had groups who have not received gamma globulin in the same areas. It is extremely effective in these groups who are living out in the back country.

KRUGMAN (USA) It has been well documented that gamma globulin is effective for the prevention or modification of viral hepatitis, type A (infectious hepatitis). Accordingly, its use has been very beneficial for Peace Corps volunteers and other personnel who live in areas where the disease is highly endemic.

However, in recent years it has become clear that viral hepatitis, type B (serum hepatitis) can be transmitted orally and by contact as well as by inoculation. It is also clear that standard gamma globulin which is so effective for the prevention of viral hepatitis, type A, has little or no effect for the prophylaxis of viral hepatitis, type B. Consequently, in areas of the world where hepatitis B infection is highly endemic, the use of gamma globulin will have limited value.

In a recent report [*New England J. Med.* **288** (1973)] we described preliminary studies which indicated that specific hepatitis B gamma globulin was effective for the prevention or modification of viral hepatitis, type B. At the present time a nationwide controlled study to evaluate hepatitis B immune serum globulin is being sponsored by the Veterans Administration and the National Heart and Lung Institute of the National Institutes of Health. If these studies confirm the efficacy of this preparation, it will be licensed for use in the United States.

CHAIRMAN It is difficult to see big supplies of anti-B gamma globulin being available.

KRUGMAN (USA) I doubt very much that it will be possible to collect an adequate supply of anti-B gamma globulin. Gamma globulin for hepatitis A virus infection prophylaxis can be obtained from any adult donor. Plasma for hepatitis B gamma globulin would have to be provided by the limited number of donors who have high levels of hepatitis B antibody in their blood.

COCKBURN (WHO) I support very much what Dr Krugman has said. There is another point which occurs to me, and this arises from a paper which came from Colindale. It was a survey of the use of gamma globulin in people who had spent some time abroad. My recollection is that there was a quite distinct reduction in incidence in the first six months, but that after that period there was an increase which more or less brought the total incidence up to the levels which had existed earlier. In other words, the protection was very much a temporary phenomenon. If you were going to be abroad for several years, or if you were going to be going abroad very frequently, either you would have to have repeated injections of gamma globulin, or you would have to take the risk of its occurring.

JUST (Switzerland) I have nothing to add on hepatitis, but I should like to address a question to our Swedish and American colleagues. The Swedes are doing re-immunization against diphtheria and pertussis at the age of 7 years, and the Americans are doing it in the second year at the age of about 2 years. Does Dr Krugman have data to show that such re-immunization has to be done at the age of 2 years?

CHAIRMAN I do not think I have the question clearly, Dr Just. Do you want to know if,

in the American experience, the diphtheria vaccine gives a good immunity level with the schedule they use? Is this right?

JUST (Switzerland) Yes.

KRUGMAN (USA) First I should like to clarify what the schedule is. Three inoculations of diphtheria, tetanus and pertussis are given in the first year. It is recommended that it be given at approximately 2, 4 and 6 months of age. A booster inoculation is given in the second year, usually at approximately 15 months of age. An additional booster is given at the time of entry into school, which may be anywhere between 4 and 6 years of age. After this booster, approximately 10 years later, only adult-type diphtheria toxoid and tetanus is given. So that the total number of inoculations of diphtheria would be three in the first year, one in the second year and one before school.

This is a programme that has been used for many years and, in well immunized groups there has been no problem so far as diphtheria is concerned. There have been isolated outbreaks in certain areas involving almost exclusively children who had never been immunized.

LUNDBECK (Sweden) You may remember that a couple of the slides I showed here indicated that we have a good booster response with killed vaccine. Has anybody any information about live vaccine, that is the efficiency of live vaccine, as a booster? We should not take it for granted that live vaccine is always effective as a booster.

CHAIRMAN There have been some studies about this which are in the literature. We have a study on this going at the moment, but we have no results yet. None of the Australian workers concerned in the most recent study are here, are they?

Unfortunately time is going on, and perhaps we might have the last point from Dr Relyveld. If he has any experience of boosters of oral polio perhaps he might mention it.

RELYVELD (France) We know at the moment that post-vaccinal reactions to diphtheria are due to impurities of the toxoid. I should like to ask Dr Krugman why in the United States, manufacturers are still going on using no crystalline or very pure toxoid, and preparing an adult dose with less toxoid.

KRUGMAN (USA) I do not know whether I can comment about that. Diphtheria toxoid which is being used for children and the adult-type diphtheria toxoid have not been associated with any significant reaction.

As to why we do not have the other preparation – I really do not know the answer to that question. Perhaps either Dr Witte or Dr Meyer might have some comment about that.

CHAIRMAN I think there has been a long American experience of purified diphtheria toxoids showing that the hypersensitivity reactions are often due to the diphtheria antigen itself. This accords with our own experience of tetanus vaccine, and I do not think that purification will necessarily stop all hypersensitivity reactions. Obviously this is a point for further discussion and we have no time now, unfortunately. It is a great pity to have to draw this discussion to a close, but we must stop now.

SESSION VIII

SAFETY: RISKS AND RESPONSIBILITIES

Chairman: Dr F. T. Perkins (UK)

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COMPENSATION FOR INJURIES POSSIBLY RELATED TO IMMUNIZATION

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It has been known for many years that immunization procedures entail a certain risk of adverse reactions. This problem was thoroughly reviewed some five years ago by Sir Graham Wilson in his book *The Hazards of Immunization* (2). Minor reactions are quite frequent but they are mostly temporary and of little importance. In rare cases, however, serious ill-effects occur which may result in permanent disablement or in death. Adverse reactions have in recent years become of increasing concern not only for the medical profession and producers of vaccines but also for the population in general. There are several reasons for this. One of the most important may be that the adverse reactions stand out more clearly with the reduction or even disappearance of the disease which the vaccines are intended to prevent. Under such circumstances persons or dependents of persons who suffer injuries, in particular in connection with recommended or enforced immunizations, may feel entitled to compensation. This has resulted in malpractice suits and claim for damages against the manufacturers in various places.

In a few instances adverse reactions may be due to faulty production or administration of a vaccine. If such faults are obvious, and can be proven, the responsibility and liability to pay damages should not be a great legal problem. However, serious complications do occur which can be ascribed neither to the producer nor to the vaccinator, and in such cases, which with our present knowledge are unforeseeable, nobody can be held directly responsible for the injury.

Most immunization programmes are carried out not only to protect the recipient of the vaccine but also to prevent spread of infection in the population and they are consequently advantageous for the community in general. It seems reasonable, therefore, to establish a system that will spread the costs of unavoidable injuries to all who benefit and to create a system of indemnification of those unfortunate individuals who happen to be the victims of serious accidents. It would seem logical that a compensation system of this kind should be public since most of the immunizations in question are either sponsored or recommended by the Health Authorities or may even be compulsory. This problem was discussed by some of the participants in the International Conference on the Application of Vaccines in Washington 1971.

A public compensation system has been in effect in some European countries and in Japan for some years(1) and, as mentioned by Dr Sievers, a bill concerning this problem has recently been passed by the Danish parliament. In the following I shall briefly discuss the provisions of this Act, which is named 'The

Indemnification for Injuries Caused by Vaccination Act of 7 June 1972'. An unofficial translation of the act into English is printed as an appendix to this paper.

The *first section* prescribes that the Treasury shall pay compensation for loss or reduction of economic capacity caused by disablement or for loss of supporter if the cause with reasonable probability can be ascribed to immunizations which presently are enforced or recommended by the Danish Health Authorities.

It will be noted that the chief point of view is the economic loss due to disablement or death. Damages are not paid for minor adverse effects of a few days duration, nor for pain, suffering, etc. On the other hand, the Treasury is liable in damages regardless of whether the injury is due to fault or neglect or it must be considered an unforseen contingency. The injured person can thus claim compensation without trying to evaluate this problem and will obtain compensation provided the injury with 'reasonable probability' has been caused by the inoculation. The delimitation of vaccine-induced injuries and coincidental diseases of different origin may, of course, cause considerable difficulties, but the intention of the wording is that definite proof of causal connection with the vaccination is not required to obtain compensation.

This evaluation problem will be handled by the Directorate of Industrial Insurance as prescribed in *Section III and IV*. This Directorate has experience in a similar field since it has for several years handled causal connections in question of damages in occupational diseases under the Industrial Insurance Act. Its judgement will, for each case, be based on expert opinions and an evaluation of all existing circumstances.

Section V prescribes that it is the duty of medical practitioners to notify the Directorate about all cases of severe injuries which may be vaccine-associated.

Section VI prescribes that the Act shall be administered in accordance with a series of regulations which are contained in another law, i.e. the 'Indemnification to Injured Servicemen Act'. Of the 10 items listed, most are technical and presumably of little general interest. It should be noted, however, that *item* 2 establishes the right of the Treasury of recourse against anybody who can be considered liable in damages in connection with the injury, for instance in the case of faulty production.

According to *item* 8, the compensation for vaccination injuries is calculated in the same way and is of the same order as compensation to Injured National Servicemen; this, however, is somewhat modified in the following section. In *Section VII* it is thus specified that the compensation can be paid at the earliest when the injured person has reached the age of 15 years. In order to understand this provision it must be remembered that the chief point of view of the Act is compensation of loss in earning capacity. A child below the age of 15 is not considered to have an earning capacity and is accordingly not eligible for compensation until this age has been reached.

However, under existing Danish social laws (in particular the Public Assistance Act), any disabled child is entitled to considerable financial support from public funds. It may be treated in institutions free of charge or, if it stays at home, the parents are entitled to recover the additional expenses they incur from

public funds. This support is paid regardless of the economic status of the family and covers not only treatment and medicine but also, for instance, special furniture or other special arrangements which are necessary for keeping the child at home. It is also possible to obtain subsidies for payment of outside assistance to look after the child and for payment of transportation, etc.

Section IX and X deal with the basis for the calculation of the compensation. For persons between 15 and 21 years of age the amount is calculated in accordance with the provisions in the Industrial Insurance Act, and for persons above 21 years of age according to the Indemnification of Injured Servicemen Act. In both cases the amounts are price-regulated.

I shall not enter into details about the rather complicated calculations but only give some indication of the compensation provided for persons above the age of 21 years.

The disablement benefit will depend on the degree of the disablement and will usually be paid as a cash sum if the disablement is less than 50 per cent. The amount will also to a certain extent depend on the age of the person in question. For instance, the compensation for a 25-year-old person with a disablement of 35 per cent, will be about 106000 kr. ($17700) and for a 50-year-old about 97000 kr. ($16000).

If the disablement is 50 per cent or more, the compensation will be paid as an annuity which for 100 per cent disablement will amount to about 35000 kr. ($6000) annually. This is about 12000 kr. ($2000) more than could be obtained under the Industrial Insurance Act for disablement due to other causes.

The legislation on indemnification of persons who have suffered injuries in connection with enforced or recommended immunizations was passed only a few months ago. We have, therefore, so far no experience as to how well it will work. It should be emphasized that the chief point of view has been to compensate for loss in earning capacity and that benefit is paid only from the time when the condition has become stationary and at the earliest from 15 years of age.

With this law the government has taken over the responsibility for injuries caused by recommended vaccinations and the Act should accordingly abolish the need for costly litigation of personal injury claims in relation to immunization. Furthermore, it may be hoped that the fact that there is no provision for any immediate benefit in the form of a capital sum, will alleviate the drama often associated with unfortunate accidents of this kind. Exaggerated journalistic treatment of accidents may cause undue anxiety in the public and thus be harmful for the general acceptance of desirable immunization programmes.

It should, however, be pointed out that the Act to a very large extent is tailored to Denmark's social laws and is therefore not applicable in countries with other social welfare and health practices.

REFERENCES

(1) KONO, R. (1971). *Proc. International Conference on the application of vaccines against viral, rickettsial, and bacterial diseases of man*, p. 500. PAHO, Washington, D.C.

(2) WILSON, G. S. (1967). *The hazards of immunization*. The Athlone Press, London.

UNAUTHORIZED TRANSLATION

ACCOUNT OF THE PROVISIONS OF THE DANISH INDEMNIFICATION FOR INJURIES CAUSED BY VACCINATION ACT OF 7 JUNE 1972

I

The Treasury shall pay compensation for loss of or reduction in economic capacity caused by disablement and for loss of supporter and for funeral expenses if disablement or death with reasonable probability can be considered to be caused by inoculations performed in this country against smallpox, diphtheria, whooping-cough, polio or tuberculosis and also against tetanus if the tetanus vaccine is given together with one or more of the above mentioned vaccines.

II

The Minister of the Interior may make provisions that other vaccinations shall also be covered by this act.

III

The Directorate of Industrial Insurance shall administer all cases concerning benefits according to this act.

IV

Notification to the Directorate of injuries, which may entail compensation according to this act, must be made as soon as possible and not later than one year after the first certain symptoms of the injury have been noted. The Directorate can, however, deviate from this time limit if exceptional circumstances make this indicated.

V

It is the duty of any physician who in the practice of his profession learns about injuries which may entail compensation according to this act to report on this to the Directorate of Industrial Insurance.

The cases under this act are administered in accordance with the regulations in the VI Indemnification to Injured National Servicemen Act concerning:

(1) the injured person's aiding and abetting the occurrence of the injury,

(2) recourse against person(s) causing the injury,

(3) payment of medical certificates,

(4) the means which can be employed by the Directorate for elucidating the case,

(5) the rights of the Directorate to make certain demands on the injured person or his dependents after the occurrence of the injury,

(6) transference and legal proceedings of claims against the injured person,

(7) aids and invalid chairs for the injured person including physical rehabilitation and medical treatment,

(8) calculation, capitalization and payment of disablement compensation or contribution towards funeral expenses and compensation for loss of supporter (cf. however, VII–VIII),

(9) increase, decrease or withdrawal of the benefits listed under item (8), and

(10) the rights of the Directorate to supervise the annuitants.

VII

Compensation for disablement is paid with effect as from the time when the condition of the injured person can be considered stationary but at the earliest when the injured person has reached the age of 15 years. As regards the cases mentioned in IV, last sentence, the Directorate decides from which time compensation shall be paid.

VIII

Compensation for loss of supporter is paid also in cases where the deceased consort has acted as supporter by working in the home.

IX

The annualincome which shall be used as basis for calculation of the compensation cannot be fixed at a higher amount than the highest annual income according to the Indemnification to Injured National Servicemen Act such as this amount is regulated at the time for the first compensation payment.

X

For persons below 21 years of age the annual income shall be fixed according to the regulations in the Industrial Insurance Act §44 item 6, last sentence.

XI

The decision of the Directorate can, within 4 weeks after the notification to the person or the guardian concerned, be submitted to the Council of Industrial Insurance, whose administrative settlement is final.

XII

The Minister of Social Affairs may establish rules regarding the payment of an annuity, including its complete or partial withdrawal, if the injured person is institutionalized under the Care of Handicapped Persons or in another way is provided for by public funds.

XIII

This act enters into force on its announcement in the Gazette (*Lovtidende*).

XIV

This act is applied to vaccination injuries when the first certain symptoms are noted after the coming into force of the act.

XV

This act is furthermore applied to vaccination injuries when the first certain symptoms have been noted before the coming into force of the act provided that they are notified to the Directorate not later than one year after the coming into force of the act.

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CONTRIBUTION TO DISCUSSION

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I want to say a few words about risks and responsibility, mostly in relation to live polio vaccine prepared from Sabin's attenuated strains, though the underlying principles are applicable to all biological products.

A WHO advisory group has estimated on the basis of published data that there may, under some circumstances, be a risk of the order of 0.06–1.05 to 1 million of the development of paralytic illness in association with the ingestion of trivalent oral polio vaccine. With monovalent vaccines the risk may be higher under some conditions. These are probably overestimates, since in arriving at the figures no account has been taken of the passage level of the vaccine used in relation to the original material distributed by Sabin as starting seed. It must also be remembered that the association has been only a circumstantial one, and while virus isolated from the faeces of the subject may on occasion have been shown to be vaccine-like in its serological markers, this is only what one would expect in the recent recipient of oral polio vaccine. It would indeed be difficult, if not impossible, to obtain proof positive in the majority of cases as it is well known that many vaccinees excrete virus of increased monkey neurovirulence without apparent ill-effect, and one has to fall back on 'reasonable probability', although the legal and scientific definitions of this may differ at times.

That, then, is some measure of the order of risk and it would seem unreasonable to ask the vaccine producer to accept responsibility for the occurrence of a recognised potential problem occurring as a result of prophylaxis with a vaccine produced according to the standards of the relevant licensing authority and approved batch-wise by that authority.

It seems to me that there are two major responsibilities of the vaccine producer and these apply to all biological products. The first is to ensure that each batch of vaccine is manufactured and tested in strict accordance with the regulations laid down, not only in letter but also in spirit. It is equally, and under the same heading, his responsibility to ensure that only batches of vaccine which have satisfied those requirements and have been released by the licensing authority are released into commercial use.

The principle of strict liability or absolute responsibility can surely only be applied to a preparation which is defective and proven to be so. It is hard to see how this can be done in the case of a vaccine which has been produced according to official standards and checked to see that it meets those standards by the licensing authority involved.

The second area of responsibility is the responsibility to warn. This is a fair

and reasonable one. One must assume that not all of those responsible for initiating vaccination campaigns or administering vaccine to individuals will be as fully aware of any potential risk as is the manufacturer or the licensing authority to whom much more information is available. Any potential risk associated with the use of a vaccine should certainly be drawn attention to in the package insert distributed with the material. Of course many, if not most, physicians are aware of the risks of smallpox vaccine and of pertussis vaccine and it is surely the responsibility of those individuals to balance risk against benefit not only for the individual but also for the community.

In some law suits arising out of polio vaccine associated cases there has been advocated the absolute responsibility to warn not only the local authority or physician who has recommended the prophylactic use of the vaccine, but also the recipient or in the case of a minor, the responsible parent or guardian. This warning, it has been suggested, should be communicated not only through mass media such as the press, television and general advertising, but must be directed personally to each individual receiving the vaccine.

This surely is a ridiculous and impractical standpoint. Can one imagine the situation in the event of a mass immunisation campaign, perhaps necessitated by an impending epidemic? On the one hand, public health authorities would be urging the population to be vaccinated and on the other each individual would be bombarded by messages from the vaccine manufacturer warning of the risk involved.

The situation in the United States has recently gone even one step further in that an individual has not only received a substantial settlement from a manufacturer, but has also conducted a successful case against the government on the grounds that the licensing agency was negligent in releasing the batch of vaccine involved. Dr Witte told us yesterday that in many states of the USA immunisation is a condition of school entry. Who is to be responsible for accidents under these circumstances – the manufacturer, the State or the Federal Government? These are problems to which there may be no quick or easy solution, but it seems to me that Denmark, Germany, and the other countries mentioned by Professor von Magnus, have taken the right step in accepting governmental responsibility for the recognised hazards of immunisation.

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CONTRIBUTION TO DISCUSSION

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Nowadays when most of the infectious diseases have been gradually conquered, in which immunization has played no small part, the problem of the safety of vaccines becomes more important. Every case of accident or complications occurring in immunization causes not only in the medical profession but also in the whole of society a great deal of anxiety. What do we understand by a 'safe' immunizing agent? In making it's judgment on the safety of a drug, the Food and Drug Administration of the United States regards the effectiveness and safety as being completely interwoven, any consideration of safety involving weighting the therapeutic value against the possible toxic effects as well as against the risk, and effectiveness of other available agents. This conception of safety is likewise to be found in a World Health Assembly Resolution inviting the member States to communicate with the WHO any decision to restrict the availability of a drug 'if the decision is taken because of lack of substantial evidence of effectiveness – in relation to its toxicity and the purpose for which it is used'. I think that the same parameters may be applied also to immunizing agents. Immunization, as with any other medical intervention, involves some hazards, small though they may be. However, these hazards should not approximate to the incidence or the danger of the disease against which the immunization is applied, because any immunization is justified only if its advantage – even with some risks – exceeds many times the disadvantages of the disease for the individual and the community. The causal correlation of the injury following immunization with the vaccination may be stated only on the basis of cautious investigations; particularly the extreme and exclusive estimate of the coincidence in time – *post hoc ergo propter hoc* – may be misleading. Injuries following immunization can be classified as post-vaccinal reactions and post-vaccinal complications. The two categories, however, cannot be sharply differentiated. Post-vaccinal reactions can be considered as post-vaccinal pathologic symptoms which appear in all or in a considerable portion of the immunized persons, and which can be attributed to the toxicity of the immunizing agent or, if it is a live vaccine, to the multiplication of the micro-organisms. In healthy persons the post-vaccinal reactions must not be more severe or as severe as the disease to be prevented by immunization and must not cause lasting injury to health or endanger life. Post-vaccinal complications are not inevitable or regular consequences of immunization. They may be due to: (1) inadequate quality of the immunizing agent; (2) faulty innoculation technique; (3) abnormal reactivity of the inoculated persons.

More important than such a classification is the difficulty of deciding whether a given complication is the result of the vaccine or only coincidental. How, for instance, is it possible to tell whether six cases of neurological damage occurring after the vaccination of $2\frac{1}{2}$ million people are to be ascribed to the vaccine? Without a control group it is often impossible to say. Exact diagnosis particularly when supported by histological findings or autopsy may help; but only too often, particularly with neurological lesions in children, an exact diagnosis is lacking. In Hungary each post-vaccinal complication must be reported to the Department for the Control of Sera and Vaccines of the National Institute of Public Health which checks every case very carefully. According to the Hungarian sanitary law issued in 1972, if as a consequence of compulsory immunization or other compulsory sanitary measure, a citizen becomes damaged in his health, and is disabled, or he dies, the State compensates him or the relatives supported by him. In order to prevent accidents and complications of vaccinations, persons entrusted with the preparation, control and application of immunizing agents must in particular be careful to maintain constant vigilance as a single error may be disastrous. Over-confidence must be avoided, as expressed by Shakespeare:

> And you all know, security
> Is mortals' chiefest enemy.

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VACCINATION AGAINST POLIOMYELITIS: VACCINE-ASSOCIATED CASES

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The incidence of paralytic poliomyelitis in Norway was on the average more than 700 cases from 1950 to 1955. From 1956 to 1965 the inactivated poliomyelitis vaccine was used, and approximately 100000 children were vaccinated per year. During this 10-year period the incidence of poliomyelitis decreased to about 70 cases per year.

In 1965 the inactivated vaccine was replaced by trivalent live oral vaccine. The main reasons for switching to live vaccine were:

(*a*) New regulations for production of inactivated vaccine resulted in vaccines having a lower antigenicity.

(*b*) Immune surveillance indicated a low level of antibodies against polio viruses. About 50 per cent of the children tested on entry to elementary school had no antibodies against Type I and Type III although they had been vaccinated as infants.

(*c*) An epidemic occurred in the northern part of Norway with 10 paralytic poliomyelitis cases. The epidemic was evidently brought to an end by mass vaccination with the live oral vaccine.

Seven million doses of live poliomyelitis vaccine were distributed from 1965 to 1972. As most children were primarily vaccinated it is judged that about 300000 children were vaccinated each year. The age groups recommended for vaccination were 6–12-month, 7-year and 14-year cohorts.

Since the introduction of live vaccine and up to 1972, 11 cases of paralytic poliomyelitis have been traced. Four cases were caused by wild polio viruses and seven cases associated with vaccination. During the last six years only vaccine-associated cases have occurred, except for one case where the infection by wild virus evidently was acquired abroad.

Of the seven vaccine-associated cases five were adults and two children. The adults had severe disease with extensive paralyses. Most interesting is the fact that five or six cases were contact vaccine-associated. All three polio virus types were involved, but four cases were caused by Type II, two cases by Type I and only one case by Type III.

In conclusion the rate of vaccine-associated cases is rather high, one per million distributed doses, i.e. approximately one case per 300000 vaccinated children. It should be stressed that the trivalent live poliomyelitis vaccines employed were the same as those used in the UK and USA. The reason for the high incidence may be that the tracing of cases is more easy in a small and homogenous population.

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CONTRIBUTION TO DISCUSSION

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Prophylactic vaccinations are today more necessary than ever. The more the elimination of communicable diseases is crowned with success, the less will be the possibility for our children, in a natural way to acquire antibodies for overcoming infectious diseases. This must accordingly be achieved by vaccinations – if a renewed increase of the cases of communicable diseases is to be avoided.

On the other hand, the more communicable diseases are eliminated, the more in public opinion and discussion is the remembrance of the disease substituted by the very few vaccination accidents.

A vaccination does not only offer protection to the vaccinees; it is also of considerable benefit to the public. The more people are vaccinated in a country, the more speedily any chains of infection discontinue, the better therefore is the protection of the population against propagation of an epidemic. A pre-requisite of adequate collective protection due to vaccination is the individual readiness for vaccination. Promotion of this readiness is one of the tasks of national health policy. It includes, last and not least, appropriate compensation for damage arising from post-vaccinal reactions.

Therefore, in my country, legislation on compensation was included in our law on prevention and control of communicable diseases as early as 1961, and after ten years of experience it was improved last year (1972). According to this legislation any person suffering damage due to vaccination shall, on the grounds of the consequences to health and economy arisen from the vaccination damage, receive a compensation in appropriate application of the regulations of the federal law on pensions. This applies to those vaccinations which were either prescribed under statutory regulations recommended in public by a competent authority and carried out in its area or carried out pursuant to the implementing Ordinances under the International Health Regulations. The last mentioned group shall only apply to persons who were vaccinated for the purpose of re-entry into our country after an international journey to certain parts of the world.

A compensation shall also be due to a person who, as a German national, suffers damage from a vaccination carried out abroad, if he had been liable to this vaccination by law when staying at home.

The surviving dependents of a person damaged due to vaccination shall receive a pension in appropriate application of the regulations of the Federal Law on Pensions, but only if at the time of death the damaged person had completed his 18th year of life. Damage due to vaccination shall be regarded as any damage to

health exceeding the usual extent of a post-vaccinal reaction. A vaccination damage shall also be deemed to exist if a vaccination was carried out by means of live vaccine and any other than the vaccinated person suffers damage to health by means of such pathogens being excreted by a vaccinated person.

For the acknowledgment of a damage to health as a post-vaccinal reaction, the probability of the causal relationship shall suffice. If such probability does not arise solely on account of the fact that in medical science the cause of the ascertained disease cannot be stated with certainty, a pension may be granted in the same way as for vaccination damage.

GENERAL DISCUSSION

CHAIRMAN The subject is now open for discussion.

SENCER (USA) I should like to ask Professor von Magnus what administrative mechanisms they have for determining the reasonable probability.

VON MAGNUS (Denmark) As a matter of fact, we do not know yet. The cases we have had so far have been submitted to our Council of Forensic Medicine, and they have called in professors in paediatrics and often specialists. About a year ago there were about 20 claims for damages. Of these, some were encephalitis after smallpox, and this I believe is a fairly well established complication occurring in time relationship to the vaccination.

As for the polio cases, they occurred in time relationship to the vaccination, and the vaccinations were carried out during the time of the year when wild polio is not prevalent in Denmark.

The difficult cases are those believed to be caused by the pertussis antigen. According to the literature – particularly Anglo-Saxon literature – it is claimed that infantile spasms may well be caused, or at least provoked, by a pertussis vaccination. I think that the infantile spasms in most of the cases where there are claims for damages after pertussis vaccination really present a tough problem. Some of the clinicians in our country believe in a relation between pertussis vaccination and infantile spasms.

HOFMAN (The Netherlands) I should like to ask Professor von Magnus something about the law in Denmark in this respect, which I think is filling a lack which exists in many countries where vaccinations are required or advised by governments. Do I understand correctly that under this system it is no longer possible to go to the civil courts in the case of an individual claiming that the damages according to income are higher than is provided in this law? Also, is it possible to take out extra insurance with a private company if you think you might need more money if you were to sustain damage?

The third question is, what is the responsibility of the individual physician who administered this vaccine which, in a particular case, resulted in damage? Is the responsibility taken by the government, or is there a risk for him, too, against which he should insure himself? This is a question which I would ask Dr Schumacher.

VON MAGNUS (Denmark) I understood the first question to be whether additional damages could be claimed from companies, manufacturers. I would say not, because the Treasury takes over all the legal problems in the matter. If there is a fault in the production which can be proved – and that would probably be very difficult – the government can have recourse to sue the manufacturer, but the individual who has been injured cannot.

The medical practitioner is also out of the picture, because again the State has taken over the full responsibility as well as the right to recover its expenses in the case of demonstrable neglect.

Of course all the problems of pain, suffering, etc. can be brought into the courts, and people can try to see whether the courts will give them additional damages. Any administrative decision can of course be brought to a court hearing, but it is unlikely that the courts will award any additional compensation.

CHAIRMAN It is a very difficult problem, as you all appreciate, but what a wonderful lead is being given by Denmark. I really feel that the Danish Government should be congratulated on taking such a far-reaching step for the first time.

SCHUMACHER (Germany) The regulations in my country are nearly the same. There is no possibility of making additional claims. Of course people can go to the courts if they think that the compensation is not appropriate to the law, but there can be no additional claims.

As to the responsibility of the vaccinator, the compensation does not depend on that, but the provincial government which has to pay the compensation may ask the doctor if there is any fault on his side. However, I do not remember a single case where this has been done.

SENCER (USA) I think there is another situation that we shall have to face in the future, if not at the present time. Professor von Magnus said that compensation could be paid in case of faulty production, but I think we shall have to face up eventually to faulty regulation, too. Frequently we shall find that the regulations of 1960 were not appropriate due to subsequent experience, and I think that this is going to be another litigious situation in the future.

MATSANIOTIS (Greece) I should like to ask what happens if the victim is an immune-deficient individual. If both the vaccinator and the vaccine were all right, but the vaccinee was deficient, who is responsible?

CHAIRMAN Do you mean that the immune-deficient individual has not been detected?

MATSANIOTIS (Greece) If you vaccinate in the early months of life it is probable that he will not be detected. We all know that all BCG fatalities during the last 20 years were due to a host deficiency, not to the vaccine.

CHAIRMAN Of course it is a contraindication for vaccination, but this situation would arise only in a person with an undetected immune-deficient state.

Do you say anything about that, Professor von Magnus? Have you legislated for those occasions?

VON MAGNUS (Denmark) No, because I think this belongs to the unavoidable problems. Of course it is a fault if you know about it, and in this case all doctors have their insurance. If a very strong fault is proved against them, of course the Treasury can claim recourse from their insurance companies. This will again be a matter between the Treasury and the insurance company.

WITTE (USA) This raises another issue, and that is the question of perhaps wrong decisions being made by the judiciary. Dr Stones in his presentation showed considerable restraint in relating the current mood of the judicial branch of our Government. One of the cases that I believe he was alluding to was a child who received polio vaccine in an epidemic control program several years ago and, three or four days later, developed a paralytic illness. A wild-type polio virus was recovered from the stool, but this was adjudged to be a vaccine-induced case and a large settlement was awarded to the family. The case is now in the Court of Appeals. I think to have some knowledgeable scientific body reviewing these types of cases, as Professor von Magnus has indicated, has great merit.

COCKBURN (WHO) May I ask Professor von Magnus and Dr Schumacher whether these regulations apply in any way to experimental vaccines?

VON MAGNUS (Denmark) In the Danish law it is specified which vaccinations are covered by the law. The Minister of the Interior can decide that other vaccinations can be included, but I do not think that anyone has mentioned the use of experimental vaccines so far. If such vaccines were recommended by competent authorities they might be included.

SCHUMACHER (Germany) Experimental vaccines are excluded because they cannot be prescribed by law and they cannot be recommended to the public. That is one of the

prerogatives. So there is no compensation for damages during, say, field trials on an experimental basis.

HENNESSEN (Germany) I should like to mention something with regard to experimental vaccines. As I understand it, among several of the big European insurance companies, especially Swiss and German companies, there is some negotiation about coverage of damage due to experimental vaccines and experimental pharmaceutical products under test in certain individuals after they have been accepted – not registered – by some national authority. This is supposed to be being solved during the year 1973.

CHAIRMAN This has been a lively discussion, many seeds have been sown and I hope they have fallen on very fertile ground.

SESSION IX

FIELD TRIALS

Chairman: Dr F. T. PERKINS (UK)

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THE FIELD TRIAL OF VACCINES

A. BRADFORD HILL

In judging the value of a vaccine against a communicable disease we inevitably need a standard of comparison. Under defined circumstances we must measure the incidence of the disease in vaccinated persons compared with the incidence in the unvaccinated. This automatically implies that the two groups that we compare, the vaccinated and the unvaccinated, are, except in their vaccination status strictly comparable in all such characteristics as will, or might, influence the incidence of the disease.

In practice it is usually easy enough to ensure that the groups are comparable in such clear-cut factors as age and sex (though the latter is perhaps not so clear cut in the present epoch of long hair and 'genes' of both varieties). It is not so easy deliberately to make them comparable in less well defined but even more essential features – such as the likelihood of the individual being exposed to infection, his, or her, existing antibody status or relative immunity to that exposure; and so on.

RANDOMISATION

With ill defined and immeasurable characteristics our only hope of achieving that equality is by *randomisation*. There are various ways in which individuals can be randomly allocated to the defined groups; it is not my intention to discuss such detail now. I merely want to emphasise that it is only with randomisation rigorously applied to large enough numbers of persons that we can be reasonably sure that we have constructed equivalent groups. Much experience in the clinical trial of treatments and in the trial of prophylactic agents confirm this. Thus we have as our starting point groups which will allow us effectively to measure the results of our particular intervention in one, or more, of them.

The next step is to keep them under observation, record the illnesses that take place, and calculate the incidence of those illnesses. We ought, however, to be clear in our minds what exactly we are measuring in those incidence rates.

ATTACK RATES

What ideally they would show are the incidence rates in vaccinated and unvaccinated persons *who have been effectively exposed to infection*. But usually we do not know who has been exposed to infection. We have rates which result from the combination of *two* probabilities, viz. the probability of an individual being exposed to infection and the probability, in that situation of his succumbing to that exposure.

Table I. *Vaccination against influenza*

	Epidemic 1		Epidemic 2	
	Unvac.	Vac.	Unvac.	Vac.
No. of persons	1000	1000	1000	1000
No. exposed to infection	100	100	600	600
No. attacked	90	30	540	180
Attack rate (per cent):				
Attacked/exposed	90	30	90	30
Attacked/all persons	9	3	54	18

Table I shows two (imaginary) epidemic situations. In one exposure was infrequent, in one it was widespread. In each case the attack rate in the unvaccinated was very high – 90 per cent succumbed. In each case it was reduced by vaccination to only 30 per cent. (We must, of course, envisage an equal number of exposures in the two groups; this is inherent.) It seems to me that it is these rates that we would like to measure. But it is not what we have, as I previously said, to compound the risk of succumbing with the risk of exposure. And so in the epidemic 1 situation we record attack rates of 9 per cent against 3 per cent; in the epidemic 2 situation we record 54 per cent against 18 per cent. These rates still show us correctly the *relative* efficacy of the vaccine (66 per cent protection). But I wonder whether we would all draw the same conclusions from them?

We might well, and justly, say in epidemic 1 that the risk of being attacked is so small that it is not worth vaccinating. But if we knew this 90 per cent attack rate in the unvaccinated when exposed to infection we might equally think vaccination was worthwhile in vulnerable or important groups, e.g. doctors and nurses. In epidemic 2 we would probably conclude that vaccination was generally worthwhile in view of the high attack rate. But I suggest we should keep in mind this aspect of our results, the underlying rate of attack, when we come to interpret them.

RANDOM UNITS

Sometimes, however, we may not be so interested in this very precise measure of the value of a vaccine in exposed persons. We may know from past experience that the vaccine is likely to be effective. Yet we may properly ask ourselves, is widespread vaccination worth all the work, use of manpower and cost that it must involve. How much shall we save by it? This is the question that we are asking in some of the current influenza vaccine trials under the British Public Health Laboratory Service.

In one of our approaches to the problem we are randomising not persons but *units*. Thus, with the co-operation of the Post Office, we have taken nearly 200 places of work (telecommunication centres and the like). These places of work we have divided up by geographical situation and within that geographical

situation we have randomly allocated the units to the offer of vaccination to all workers or none.

Within the units this offer was taken up by varying proportions of the work people. And so we have the figures of Table II.

Table II. *Vaccination rates (influenza) in Post Office units*

Vaccinated (%)	No. of units	No. of persons
60 or more	17	2 846
50–59	16	5 194
40–49	25	6 580
30–39	16	6 240
Under 30	14	5 457
Total	88	26 317
		42 %
Control Units	98	25 202
		0 %

In total only 42 per cent of the work people chose to be vaccinated. This 42 per cent is, of course, a self-selected population; we can make no comparisons between them and any other group. What we can do validly is to say we have a population of 26 317 persons of whom 42 per cent were vaccinated.

Is the incidence of influenza in these 26 317 persons materially less than in the 25 202 persons none of whom were vaccinated? There is no selective bias in that. Going further we might seek at what point on the percentage vaccinated scale was the incidence of influenza altered to a worthwhile extent.

In doing this it is vital to note that we must not compare these subgroups directly with one another as with the *total* control group. For all the subgroups are self-selected. Maybe, for instance, a large percentage volunteered for vaccination because they had experienced influenza recently, did not like it and did not want it again. Clearly this might bias their current experience. In fact we do not know what leads to this selection giving high or low acceptance rates.

However, *within* each subgroup we have strictly comparable vaccinated and unvaccinated units because they were originally randomised. We can, therefore, validly compare these 17 units with more than 60 per cent vaccinated with their own randomised control units. And this we can do at each level on the scale of acceptance. With the ratios of vaccinated to unvaccinated at each point of the scale we may see, so to speak, a biological gradient. We may see how much vaccination is necessary before it becomes worthwhile in terms of reduced sickness absence from work due to influenza. We hope by these means to solve a very practical problem.

BIOLOGICAL GRADIENT

I now digress to pontificate gently upon the general nature of evidence in trials in preventive medicine, I believe that today too much emphasis and too much reliance is placed upon the isolated test of significance. More weight should be given to trends and to consistency.

I take, for example, some figures derived from the enquiries of the British Committee on Safety of Medicines into the contraceptive pill – that Achilles heel of all such Committees. If we had found that more cases of thrombosis had occurred in women on the pill than in women not on the pill, then whatever the test of significance denoted, I should personally have been unconvinced of cause and effect. The nature of the woman on and not on the pill might have differed and have been related to their risk of thrombosis. But we were able to go further than this. Table III shows briefly our result.

Table III. *The contraceptive pill*

Dose of oestrogen (μg)	No. of cases of thrombosis		
	Observed	Expected	O/E (%)
150	74	37	2.0
100	415	345	1.2
75/80	80	102	0.9
50	343	436	0.8
Total	920	920	—

We could itemise the pills actually in use according to their oestrogen content. We had figures to show the frequency of use of each kind of pill in the women of Great Britain. And so, on the numerical basis, infrequency of use – we could divide up the 920 reported cases of thrombosis, i.e. presuming that the risk of thrombosis was exactly the same for all pills. Finally we could compare these figures of equal risk with the actually observed figures. We end up with a clear gradient of risk from highest to lowest oestrogen content.

One has still to consider what bias could produce this gradient. For myself I find it much more difficult to think of one. In other words, the gradient gives strong support to the cause and effect interpretation.

CONSISTENCY

Continuing this digression into another field of prophylaxis, I take as example a diet study of some 10 years' duration in mental hospitals in Finland. During half this period the inmates took the normal diet. During the other half they took a diet constituted to reduce the blood cholesterol and so, it was hoped, the incidence of coronary heart disease. I show in Table IV my own calculations from the published results.

Table IV. *Standardised death rates (‰) in Finnish diet study*

	Coronary heart disease	All other causes
Hospital N, males		
Diet years	5.7	28.8
Control years	13.0	25.8
D/C (%)	44	112
Hospital K, males		
Diet years	7.5	27.6
Control years	15.2	25.0
D/C (%)	43	110
Hospital N, females		
Diet years	4.0	27.1
Control years	7.7	24.4
D/C (%)	51	111

The table shows the experience of men and women (separately) in one hospital and of men in another. (The population of women in the second hospital was materially altered during the 10 years by the removal of the more chronic cases to another hospital. I, therefore, regard it as useless in providing evidence.)

I am myself reluctant to add these three groups together. I prefer to regard them as three distinct experiments and to look for consistency of result. The percentage changes do, in fact, show a remarkable consistency. The 'all other causes of death' arose slightly in the special diet years – 112, 110 and 111 per cent. The coronary heart disease deaths fall substantially – 44, 43 and 51 per cent. Though I would like to know more about the changes at ages and in time, I do find this consistency much more impressive than any P value of, say, 0.001.

RECORDING

An extra point that arises in this example is the benefit to be derived from observing and recording much more than the one variable with which you are primarily concerned. Table V shows some figures from the British Medical Research Council's trial of whooping-cough vaccine. (Remember when I show these past events that to copy from one book is plagiarism, to copy from three is research.)

With nearly 4000 children in each group, vaccinated and control, the discrepancy in the incidence of whooping-cough is impressive. But it is even more impressive, I submit, when one sees the equality in the frequency of some other diseases. This is evidence that the two groups were similar in their exposures to communicable diseases. The extra work entailed in observing and recording these other diseases is well worthwhile.

More generally, in this observing and recording of illness there are simple things that we should remember in designing a field trial.

Table V. *Vaccination against whooping-cough*

	Vaccinated	Control
No. of children	3801	3757
No. of cases during trial:		
Whooping-cough	149	687
Measles	920	891
Chickenpox	289	280
Bronchopneumonia	95	94

BIAS IN DIAGNOSIS

Firstly, should the diagnosis be biased then that bias will almost certainly be to the advantage of the vaccinated. If we tend to think 'I doubt whether this is a whooping-cough as I doubt whether this is really influenza' because we know the patient was vaccinated, and tend to accept it as a whooping-cough or an influenza when the patient was unvaccinated, then we *must* be exaggerating the efficacy of the vaccine. Such difficulties in diagnosis may particularly arise if the vaccine sometimes modifies an attack, rather than preventing it. Built into the design of the inquiry, if at all possible, should be a 'blind' diagnosis, that the doctor should not know the vaccination status of the patient confronting him. It would be better if the patient also did not know what vaccine he had received. That raises difficult problems which none-the-less should be closely examined.

ERRORS IN DIAGNOSIS

Secondly, we should remember that if *unbiased errors* of diagnosis occur then these will denigrate the vaccine – they will make it appear less efficient than it actually is.

To take a simple example, suppose that we have 50 cases of influenza in the unvaccinated group and only 10 in the vaccinated. The vaccine gives 80 per cent protection. Clinically, however, we cannot invariably distinguish influenza from other diseases of the respiratory system. The vaccine will obviously give no protection against these other diseases; it is not formulated to do so. These other diseases will therefore occur with equal frequency in the vaccinated and unvaccinated groups. Thus instead of 10 cases against 50 we might have through wrong diagnosis 10+15 and 50+15, or 25 against 65. The apparent efficacy of the vaccine is now only 40 per cent or half its real value. The amount of error in the ratio will clearly depend upon the frequency of errors in diagnosis.

Here once more we may be somewhat helped if we demand records of other illnesses. Such a demand may make the doctor more conscious of his diagnosis, in considering the different labels and weighing the symptoms in the patient. In these days one might, I suppose, feed them to the computer and let it come up with the most likely answer. Leaving that apart we shall benefit by being able to see what is happening within these other categories.

Table VI. *Vaccination against influenza*

	Vaccinated	Control
No. of persons	6340	6370
% attacked with		
Influenza	3.0	4.9
Febrile cold	3.4	3.8
Febrile sore throat	1.4	1.4
Other respiratory diseases	2.1	2.3
Non-respiratory diseases	4.0	3.3

In the example shown in Table VI we can see a fair advantage to the vaccinated group in what was diagnosed as influenza as about 40 per cent protection. There is a suggestion of a slight advantage in the other respiratory illnesses. This one would anticipate if, due to errors in diagnosis, some small part of the illness includes some influenza. The vaccine protects against that small part. But on the whole, though the 40 per cent protection value is still probably an understatement, we do get a more useful picture by our knowledge of these other diseases.

It has been alleged that statisticians are persons who deliberately set out to make simple questions appear difficult. This has certainly not been my aim, now or ever. The concepts of the field trial are simple and can be kept quite simple. But it needs careful planning, careful execution, simple sums and logical deduction. As I noted a great many years ago the conquest of typhoid fever did not hinge upon a Latin square nor call for the analysis of variance.

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SOME ASPECTS OF VACCINE ASSESSMENTS IN ENGLAND

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Field trials of immunising agents are now commonplace in many countries throughout the world. In England such investigations are made by various different bodies. These include the manufacturers, the Medical Research Council, and individual workers in universities and hospitals. Nowadays, however, field trials of vaccines are often organised by the Epidemiological Research Laboratory in collaboration with the Medical Research Council's Immunological Products Control Laboratory, and with Medical Officers of Health. At the Epidemiological Research Laboratory we are also concerned to some extent with the field surveillance of vaccines.

Vaccines are assessed in three main situations:

1. The first of these is when a vaccine which is not in routine use in England is tested. This was the position with the trials of pertussis, BCG and measles vaccines and with our current studies of influenza vaccines.

2. The second arises when an immunising agent which is already in routine use requires to be reassessed. Pertussis vaccine, normal human immunoglobulin (to prevent rubella in pregnancy) and antivaccinia immunoglobulin have all been reassessed recently.

3. The third situation is when vaccines previously tested and in routine use are kept under surveillance to try to ensure that standards of safety and efficacy are maintained.

These three situations dictate the type of investigation required.

FIELD TRIALS

In the first instance – the introduction of a new vaccine – the investigation is usually a controlled field trial, i.e. the type of study in which a vaccinated group and a similar unvaccinated control group are followed up to compare the incidence of the disease in each. In this type of study an attempt is made to observe four main criteria:

(1) The participants are allocated by an effective random method.
(2) The potency of the vaccine and the technique of vaccination are adequate.
(3) The vaccinated and control groups are followed up with equal intensity.
(4) The diagnosis of the patients is unbiased.

A key feature in the validity of a vaccine assessment by field trial is the simi-

larity of the groups, but similarity which is easy to arrange at the outset is often difficult to maintain throughout the period of observation. Moreover, environmental changes over which the investigator has no control may invalidate the findings.

More than twenty years ago, for example, the MRC began a field trial of BCG vaccine. At the outset about 60000 schoolchildren were allocated by an effective random method to receive a potent tuberculosis vaccine, or to remain unvaccinated as a control; thereafter both groups were followed up with equal intensity.

During the follow-up – a period of 15 years – tuberculosis rates in England fell rapidly. Moreover, the follow-up which had been very intensive for about half this period declined in intensity. These two factors reduced the number of cases found to a point which rendered invalid estimates of the relative efficacy of the vaccine at different intervals after vaccination. (At the outset the annual incidence in the control group was more than 2 per 1000 and 0.4 per 1000 in the vaccinated. After 10 years the corresponding figures were 0.3 and 0.1). The investigation, while providing incontrovertible evidence of the efficacy of BCG over a relatively short period, gave less reliable information about the maintenance of the initial degree of protection over a long period.

Comparisons between vaccinated and control groups may be invalidated by circumstances other than a decline in the disease. Eight years ago with the Immunological Products Control Laboratory we began a field trial of measles vaccine which included about 35000 young children aged between 10 months and 2 years. These children were allocated by a random method to receive one of two vaccination regimes, or to an unvaccinated group, and an equal and intensive follow-up of all three groups was begun.

To enlist the co-operation of the parents and medical officers of health, it was arranged to offer vaccine to the control group if and when the trial showed that the vaccine was safe and effective. In the event a pronounced reduction in measles incidence in the vaccinated as compared with the control group was obvious within the first year. Although not all parents accepted the agreed offer of vaccination, sufficient did so to affect the number and similarity of the control group. This alteration in the control group greatly reduced its value as a valid measure of the relative degree of efficacy of the vaccine at varying intervals after vaccination.

REASSESSMENTS

When a vaccine is already in routine use it is not possible to allocate participants to a control group and thus deprive them of a vaccine generally understood to be beneficial. In these circumstances comparisons of incidence between groups which are not allocated by a random method, and which are in consequence not necessarily similar, have to be made. We can of course try to demonstrate the character and extent of the dissimilarities and judge how far they are likely to bias the comparison, but it is not usually possible to obtain conclusive evidence from such investigations considered in isolation; we have to rely more or less

heavily on supplementary evidence such as the biological likelihood of the findings and of course collaborative evidence from other sources.

In England and Wales immunoglobulin is distributed by the Epidemiological Research Laboratory. Some time ago we made a small investigation to try to determine the efficacy of immunoglobulin prepared from British sources in preventing infectious jaundice in travellers from England to endemic areas overseas. At the time of the investigation immunoglobulin was already in routine use and for this and other reasons a controlled trial would have presented considerable difficulties. However, each year about 1000 young people leave England to work for about 18 months in many of the developing countries. When immunisation was begun it was therefore possible to compare the incidence of infectious jaundice in the group immunised during the first year with the incidence among those who had gone abroad – unimmunised – during the year preceding. A check showed that the participants in the immunised and in the unimmunised groups tended to go to the same countries and to stay abroad for about the same time; to this extent the groups were therefore similar. In the event the incidence of infectious jaundice was about the same in each group, but there was a striking difference in the time at which the disease became manifest in each. In the unimmunised group jaundice began to occur soon after leaving England. In contrast, the immunised group – with a solitary exception – remained free of jaundice for 8 months after leaving England; in this group jaundice began to be reported only after that period. These findings of course suggest that immunoglobulin prevented infectious jaundice in these travellers initially, but that its effect had declined about 6 months after it was given. It will be appreciated that this conclusion is based less on the demonstrable similarity of the two groups than on the fact that the immunoglobulin was known to be effective in preventing infectious jaundice in England. In consequence it might be expected that it would also be effective in other environmental circumstances. Moreover the relationship of the development of jaundice to the period since immunisation suggested a good but brief protective efficacy against infectious jaundice. These conclusions were thus based on observation and not on statistical data.

SURVEILLANCE

The surveillance of the continuing safety and efficacy of vaccines used in England is by no means comprehensive, but four main methods are used.

1. Family doctors are asked to report vaccination reactions to the Committee on Safety of Medicines. Standard record forms are supplied to family doctors for this purpose. Such reports are necessarily incomplete since not every doctor reports; moreover, they take account only of reactions which occur soon after vaccination and are obviously related to it. We have at present no means of evaluating any suspected association between an individual immunisation procedure and the development of a complication occurring after a long interval (the development of neurological or malignant disease, for example). Such long-term surveillance would require accurate individual immunisation records which

would have to be stored for many years and made readily available for instances of disease which might be related to immunisation in childhood. Such a system is doubtless possible, but would require much time and effort to introduce in England.

2. To check the persistence of antibody after vaccination, surveys of circulating antibody are made from time to time and in future it is hoped to monitor the persistence of vaccination-induced rubella antibody after vaccination in childhood. Rubella vaccine is currently offered to girls aged 10–12 years, and within the next few years the first girls included in the scheme will begin to enter universities. A sample of the students will be tested to determine the proportion with antibody and the vaccination history of a sample will also be checked.

The vaccination reactions and tuberculin responses of a sample of the batches of BCG vaccine which have undergone laboratory tests at the Immunological Products Control Laboratory are examined routinely under standard conditions in two areas.

3. With some infectious diseases which are now very infrequent – notably poliomyelitis, diphtheria and tetanus – a different approach is employed. The circumstances of each instance of these diseases are investigated and an attempt made to check the vaccination history.

4. Finally, it is sometimes necessary – as with pertussis vaccine – to make special studies. At intervals of six months, about twenty medical officers ofhealth send the Epidemiological Research Laboratory details of the number of children in their area of each year of age up to 10 years; the proportion of these who have received three doses of pertussis vaccine; and the number of notifications in vaccinated and unvaccinated children. These data provide an indication of the relative incidence of notified pertussis in vaccinated and unvaccinated children and this general approach is supported by more intensive studies in a few areas.

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NOTE ON VACCINATION IN THE NETHERLANDS

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My colleagues Cohen & Bijkerk have already presented the overall situation in the Netherlands in relation to the vaccination against some infectious diseases. I would just make some remarks on a closer examination of the situation especially for poliomyelitis. Fig. 1 presents the overall situation, shown already by Dr Cohen. A national average of the acceptance rate of almost 95 per cent might suggest that all problems have been solved. However a more detailed examina-

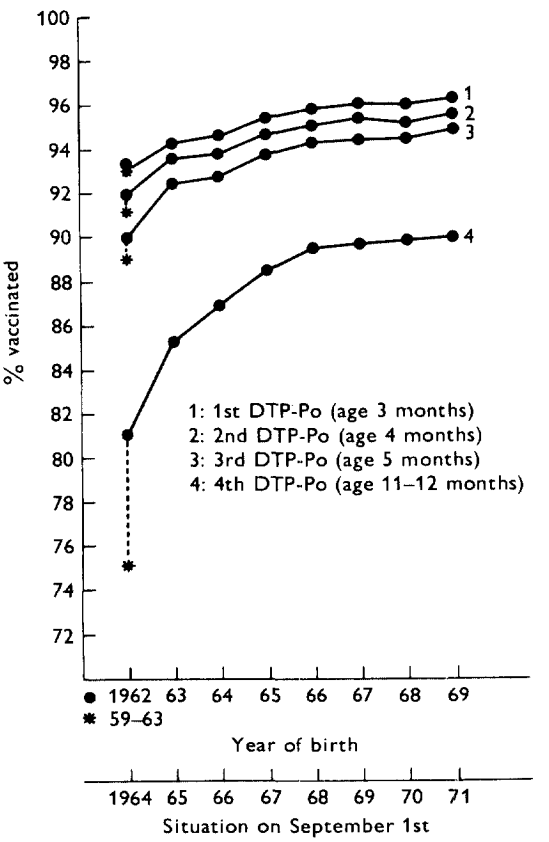

Fig. 1. Diphtheria, tetanus, pertussis and poliomyelitis (DTP-Po). Vaccination status in the Netherlands of infants and children as to year of birth.

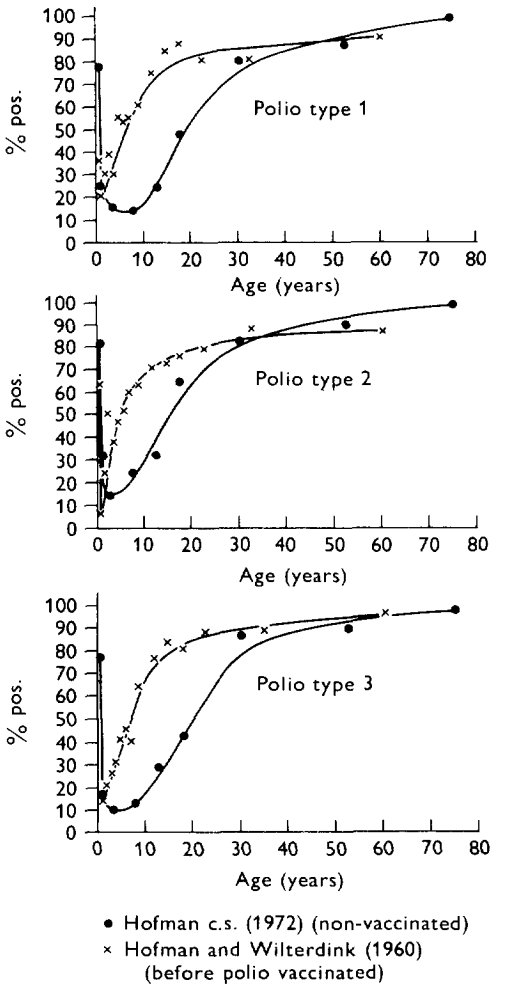

Fig. 2. Sera with antibodies against polio as to type and age.

tion of these rates shows that they are unevenly distributed over the country, particularly in older children. For the younger age groups the overall situation is somewhat less unsatisfactory, but the discontinuous pattern remains.

From several unvaccinated subjects in different parts of the country sera were examined for the presence of polio antibodies (Fig. 2). These results were compared with those of an earlier study carried out before polio vaccinations started in 1957. The unvaccinated in the younger ages are now in a much worse situation as to polio, and most probably to diphtheria and pertussis. This picture adds to the evidence that inactivated polio vaccine played its part in decreasing polio virus circulation.

Insofar as these unvaccinated subjects live in areas with high acceptance rates

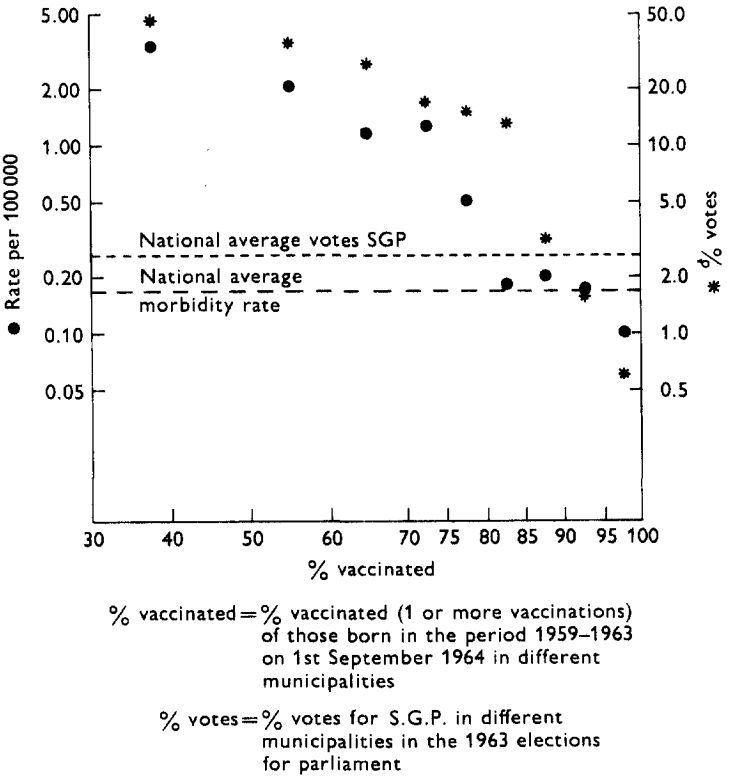

Fig. 3. Paralytic poliomyelitis, 1958–9. Relationship between average yearly morbidity, percentage vaccinated and percentage votes on S(taatkundig) G(ereformeerde) P(artij) as to municipalities.

(more than 80 per cent), they are sufficiently diluted, but in the badly covered regions, where they are more clustered the risks may not be neglected. In these regions religious objections against vaccination are responsible for the low coverage. Fig. 3 shows you this relationship. Those refusing and opposing vaccination find these and other ideas represented in a small orthodox Calvanistic party. And from Fig. 3 you see that it was in these regions where polio struck. The local outbreaks of polio in these regions were responsible for the majority of cases since 1957 (1961, 1963, 1969, 1971). Cases only occurred in the non-vaccinated. This was particularly striking in the last outbreak in 1971 in Slapshorst, where 37 cases occurred. About 40 per cent of the children were vaccinated and none showed signs of polio under the extreme pressure in this small community. Considering this pattern we can offer virtually 100 per cent protection to vaccinated subjects, but we may expect more outbreaks in the future in the areas mentioned. Every year a group of non-vaccinated children is added to the population, which increases the vulnerability of these communities to polio and probably diphtheria. It is not a matter of quality of vaccine or of organisation of the vaccination programmes, but of specific sociological circumstances, which need approach of other disciplines than medical.

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FIELD TRIALS

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In his opening remarks Dr Cockburn expressed concern over the future plight of 'field trials', or perhaps more accurately stated, the future of experiments utilizing human volunteers. I believe that this problem is serious enough to take a few minutes of this meeting, since this meeting has in attendance the three groups most concerned with the organization of such experiments, namely, the developers, the controllers (licensers) and the authorities responsible both for the welfare of volunteers and the usage of the products developed (the Ministries of Health).

Whether all agree or not, there is growing public and professional concern over the circumstances under which drugs and biologics are tested in human beings. This is particularly acute in the US but I am sure that we are not alone. It is becoming increasingly difficult to develop new products, and even more so to develop field information on modifications of existing agents.

Dr Perkins listed on Table I potential new viral vaccines: RS virus, cytomegalovirus, hepatitis, possibly cancer virus. If these vaccines are to be field tested we must be prepared to meet standards of professional conduct that will satisfy not only scientists concerned with validity of tests but also of lay people who are concerned with general ethical considerations.

This will entail having protocols reviewed by non-involved parties to assure, among other things, that adequate safety testing has been accomplished to assure that the individuals in the field trial will receive appropriate medical supervision, and to assure that participants understand and agree to the procedures and follow up.

If we wait for criticism to arise we will never be able to counteract it, no matter how complete has been the preparation. Before any field trial is undertaken full disclosure of the protocol review process and the informed consent process should be made to appropriate bodies, even the public if the trial is large enough. Is it within the purview of the International Association of Biological Standardization to take the leadership in developing such a program?

GENERAL DISCUSSION

CHAIRMAN Could we have any comments that you would care to address to Sir Austin Bradford Hill or Dr Pollock, and then perhaps we can spend a few moments discussing the remarks of Dr Sencer.

COCKBURN (WHO) If no one else has anything more important to say, I should like just to ask Professor Bradford Hill a question. He said something at the end of his paper about typhoid vaccines and that the early men had got the answers without all the elaborate field studies which are now used in these circumstances. But surely the problem was that, though they were right, they had not shown that they were right. It took forty years before the final answers were obtained.

BRADFORD HILL (UK) I think that was fair comment. I was not, in fact, emphasising that our predecessors did not use elaborate field trials; they did use acute observation, of course. My meaning was that the results do not invariably need a great deal of statistical handling. Our predecessors drew from their data very clear logical deductions without all the paraphernalia of significance testing. I think these trials are simple in concept and can be kept simple. I know that tests of significance have a useful place and make us all say the same thing, but I think that their importance is exaggerated at this present time.

SACHS (UK) With regard to that first typhoid trial, which lasted 5 or 6 years at the time, to introduce it there were very strict and stringent rules in India, and it had to have the personal sanction of the Commander-in-Chief, who was at that time Lord Kitchener. It is rather interesting that everybody who took part in the trial had to be a bachelor and a volunteer.

When one assessed the results, the incidence varied in different areas. A point that has not been mentioned is the question of the infecting dose. If you are going to drink pure sewage – we had not all the water purification equipment then – in one place you would find a higher incidence of infection, no matter what the state of protection was, when compared with somewhere else, say in the hills, where there was less chance of pollution.

When I was Consultant Pathologist to the Army, I had to mount two trials requiring the participation of Service volunteers. One had to follow a procedure similar to that outlined by Dr Sencer. A carefully prepared protocol, giving details of any risks or ill-effects, had in the first instance to be approved by the Director General of Army Medical Services. He had to submit this, if he approved, through the Adjutant General, under whose jurisdiction the Army Medical Services came, to the Service Chiefs for their final decision. It has always been the practice that soldiers must be volunteers and those who were inoculated had to be carefully supervised.

UNGAR (Switzerland) I have one question to Dr Pollock regarding the trial with BCG by the Medical Research Council. If I remember rightly, there was one group of subjects who were tuberculin-positive. I think what was stressed in the final report was that there were those also with a certain low degree of tuberculin positivity and they seemed to be slightly but not fully resistant to BCG vaccination; nevertheless there was a certain degree of protection. It would be of great interest to us to know what was the distribution or infection rate between the two groups 5 or 10 years later. So far no one has commented upon such an observation.

POLLOCK (UK) I think that this question of tuberculin sensitivity was a very interesting one in the vaccines trial and, of course, I did not touch on that at all today. However, it is

quite true as Dr Ungar says that the children who were tested when they came into this investigation and were found to have only a very weak degree of tuberculin sensitivity, that is those who were tested with 3 tuberculin units and, if they were negative to 3 tuberculin units, they were re-tested with 100 tuberculin units, these latter children did appear to have a considerable degree of protection against tuberculosis. So far as the present figures have gone, this protection seems to have been maintained and is of almost the same order as that which has been produced by BCG.

CHAIRMAN Are there any other questions about the field trials?

I should like to ask Dr Sencer a question, if I may. One of the biggest problems we have come up against in the United Kingdom recently in field trials is this question you mentioned of the need to give a full explanation to the participants. The problem is, can a parent volunteer the participation of a child who as yet has not reached the age of consent, or in fact probably cannot even speak? Has that problem been overcome?

SENCER (USA) I think that is a question more for the lawyers than for me. It would be a matter of individual law in the country. In the United States parental consent is obtained and it has stood up as an acceptable method.

COCKBURN (WHO) I do not think that applies in many other countries. So far as I can make out the legal situation, a parent may offer his child for study, but if anything untoward happens to that child I think it is quite likely that the authorities, either the investigators or someone else, might be in a very difficult position in law. Simply because the parent has said that it is all right does not destroy the child's rights and privileges.

CHAIRMAN In your eradication programme, Dr Henderson, have you come across any problems of this kind? Your programme is not strictly a trial, but you do have people volunteering for mass vaccination programmes. Have the countries involved accepted this at government level and thereafter the question of consent has not been a problem to you?

HENDERSON (WHO) The question of consent has essentially posed no problem. Smallpox is, of course, a problem potentially affecting all in the community. A high level of immunity retards or prevents its spread. Thus, when the community, effectively the government, decides upon a vaccination programme, individual consent is not specifically sought.

May I make one other comment, going back to a previous point? I should like to emphasize a point that I believe Dr Pollock brought up – the need for surveillance, an activity which is seriously neglected in many areas. Specifically, if one has cases of diphtheria, or pertussis, or tetanus, or polio, why does one have such cases? Analysis of the characteristics of these cases can provide very helpful information which may permit constructive redirection of a programme. I think that this was illustrated by the experience reported in Holland. Once a problem group has been identified, there is the possibility that something specific may be done to improve its vaccination immunity.

This approach has been particularly of value to us in the smallpox programme where, for example, we found, much to our surprise, that in Africa and South America, 97 per cent of all smallpox cases occurred in individuals who had never been vaccinated. Consequently the emphasis of the programme was redirected toward primary vaccination, and revaccination only in the immediate area of outbreaks. This vastly simplified the entire programme. There are many other illustrations but I have a feeling that if we were to carefully examine the characteristics of cases of other diseases such as diphtheria, polio, tetanus, we could determine the frequency and courses of vaccine failures and also identify particular groups at risk which would permit the development of more effective vaccination programmes.

GEAR (South Africa) While we are discussing the legal aspects, there is another point, the reverse aspect. Parents who deliberately refuse to have a child vaccinated against

poliomyelitis, for example, are responsible to that child. After the child has grown up with, let us say, a withered limb as a result of poliomyelitis he might theoretically have an action against the parents. Yesterday we were talking about compulsion, and a good case can be made out for compelling parents to have their children vaccinated.

BIJKERK (The Netherlands) I am very glad to hear this remark, because I would have put this question myself. I remember during the Staphorst polio outbreak in 1971 in the Netherlands a child of 17 years of age with a quadriplegia who exclaimed, 'Why did my parents refuse to have me vaccinated against polio?' I wonder what would happen if such a child were to sue his parents.

MEYER (USA) I had the opportunity to discuss some of this with Dr Sencer before he brought the subject up, and it is obviously a subject that is discussed widely in the United States as well as abroad.

In listening to the discussion here today I believe it has diverged slightly from Dr Sencer's main interest. I find that most people are addressing themselves to the strictly legal interpretations, and in essence there is no ultimate answer to the legal interpretations whether the subject is a child or an adult, whether he gives his consent or not; there is still the possibility that he can legally sue later. I think that what Dr Sencer is really addressing himself to is the ethical considerations – should there be, and can there be, broad agreement between countries as to what or what does not constitute a reasonable ethical basis for a clinical trial.

CHAIRMAN Yes, I am sure you are quite right, Dr Meyer.

STONES (UK) I was really going to say almost exactly what Dr Meyer said, that we seem to be wandering away from Dr Sencer's point.

I think this is a very important one, and an organization such as ours should be able to address itself to the problem and should do so as a matter of some urgency, because this is not something that is going to happen in five years time, but later on this year. It is going to be happening next year and is going to be a recurrent problem as new vaccines or even improved ones are developed. I think we should deal with this proposal as a matter of great urgency.

CHAIRMAN I wonder, then, if it would be an imposition to ask Dr Sencer if he would draft something between now and tomorrow morning so that, at our Summary and Conclusions session he could present this to us. We can report this in the book of the Conference and this, at least, would be a start. It would be a lead to the governments of the various countries to take the matter up and discuss it at a national level.

SESSION X

ORGANIZATION AND EXECUTION OF PROGRAMMES

Chairman: Dr F. T. PERKINS (UK)

International Symposium on Vaccination against Communicable Diseases, Monaco 1973; *Symp. Series immunobiol. Standard, vol.* 22, *pp.* 367–375. *Printed in Great Britain*

ORGANISATION AND EXECUTION OF VACCINATION PROGRAMMES

G. CUST
Medical Director, Health Information and Research Unit, Health Department, Hertfordshire County Council

Hertfordshire is a county situated 20 miles north of London. It has a population of 930000, of whom 80000 are aged between 0 and 4, and 158000 aged 5–14 years. The birth-rate is falling, the 13500 live births in 1972 being the lowest since the 1930s. The county contains no very large towns (the largest has a population of 78000), but it contains a number of new towns and other urban areas which have been extensively developed since the end of the last war. Being so near to London, the county has been influenced by the development of London and the migration to the south-east in the last 25 years. About 20 per cent of the working population commute daily to London to work. There are, however, many rural areas still left in the county. The Health Department of Hertfordshire County Council is responsible for the 'public health' services, including protection against communicable diseases. The staff of the Health Department includes 45 doctors and 500 nurses. There are 390 general practitioners in the county.

The scheme of routine vaccination carried out in Hertfordshire is the standard scheme of the Department of Health and Social Security (DHSS) and is shown below.

Normal schedule

Age of child	Vaccine
6 months	1st combined whooping-cough, diphtheria, tetanus. 1st oral polio
7½ months	2nd combined whooping-cough, diphtheria, tetanus. 2nd oral polio
13 months	3rd combined whooping-cough, diphtheria, tetanus. 3rd oral polio

As some general practitioners prefer to start protection at an earlier age, an alternative schedule as follows is also used:

Alternative schedule

Age of child	Vaccine
3 months	1st combined whooping-cough, diphtheria, tetanus. 1st oral polio
4½ months	2nd combined whooping-cough, diphtheria, tetanus. 2nd oral polio
11 months	3rd combined whooping-cough, diphtheria, tetanus. 3rd oral polio

Measles vaccination is given at 15 months of age. At 4½ years, a few months before the child begins school, a booster dose of diphtheria/tetanus vaccine and oral poliomyelitis vaccine is given.

No further routine vaccination is carried out until the child is 13 years, when during that year BCG vaccine is given to tuberculin-negative children. Girls aged 13 are vaccinated against rubella.

Booster doses against tetanus and poliomyelitis are given to children in their 15th year, the year that the majority of them leave school.

In 1972 we began to vaccinate adult women in special at-risk groups – school teachers, nurses, nursery nurses, etc. against rubella.

Health education about vaccination is continuous. The major campaigns in recent years have been to improve the level of acceptance of measles vaccine. All mothers attending ante-natal classes receive information about vaccination; health visitors discuss vaccination with all mothers of new babies, and there are posters or displays in the health centres and in general practitioners' premises. The health visitor, in combination with an efficient system of administration using the computer, are the major methods by which we attempt to keep the vaccination status of the child population at a high level.

A computerised scheme was introduced in July, 1967, to manage the routine vaccination of children under five. All the local health authority clinics and 67 per cent of general practitioners take part in this programme. There is an extensive child health computer scheme producing information on births and birth statistics; on 'at-risk' children, congenital abnormalities, handicapped children, child development and the vaccination programme. After a child is born the Health Department of the County Council is notified within 36 hours on the birth notification form C.H. 1.* This form is used as an input document to produce a child health file on card random access memory (CRAM). The computer then produces for each child a set of forms:* C.H. 2 (the health visitor's record card); C.H. 3, a consent form for vaccination, and C.H. 4, the child's personal health record card. All the identification details of the child are printed by the computer on these forms. On the health visitor's card various other data from the birth notification are also printed. This set of cards is sent to the health visitor who will be looking after that child. In Hertfordshire all health visitors are attached to general practitioners – the health visitor looking after all 'her' G.P.s patients. When she receives this set of forms the health visitor tears off C.H. 2 (her record card for the child) and puts this in her files. She visits the mother and among other things discusses vaccination and gives the mother the consent form, which after signing by one of the parents is returned to the health visitor. The consent rate to triple immunisation is 94 per cent and to measles vaccination 70 per cent. The consent card is used as an input document to create a computer vaccination file. The child's personal health card (C.H. 4) on which is recorded details of vaccination and a plastic envelope to keep it in, is kept by the parent.

All the health department clinics and the offices of the general practitioners taking part in the computerised scheme have been given a treatment centre number and the days and times of the vaccination sessions at each centre are also held on a computer file. Once a week the computer scans the vaccination file and picks out those children who are due for vaccination. It then prints out:

* See Appendix.

(1) An invitation to the parent asking that the child be taken along to the selected treatment centre for vaccination, and

(2) A list of appointments for children who are to be given vaccination at each treatment centre. (This form is shown in the Appendix.) This list is sent to the doctor at the treatment centre.

When the child attends at the treatment centre it is given the appropriate injection and the doctor puts a tick alongside the child's name on the appointment sheet. If the child does not attend, the doctor puts a tick in the appropriate column. The doctor also adds the batch number of the vaccine. The only other thing he has to do is to sign the form. This treatment centre appointment list is then sent back to the computer section who input the information to update the computer file. If a child misses two appointments without an excuse being given, the computer is programmed automatically to print out this information which is sent to the health visitor who can then visit and find out why. When children are aged 21 months and 5 years of age, the general practitioner is sent a print out of the vaccination history of the children in his practice. In cases where the vaccination is incomplete this serves to remind the doctor of this fact. The computer also generates from the treatment centre appointment list, a list of the injections done by each doctor. This list is sent to the Executive Council who then pay the doctor the fees due to him for carrying out vaccinations. The general practitioner gets the following benefits from taking part in the computerised scheme:

(1) All administration is done for him.

(2) The County Health Department pays the potsage on the card asking people to come for vaccinations.

(3) The doctor has only to put a tick, write in the batch number, and sign his name once for each vaccination session.

(4) He has not to make special billings to obtain payment for vaccinations given – the computer does this for him.

(5) Copies of the vaccination status of his patients at 21 months and 5 years of age are sent to him for his records.

He in return has to accept one of the two schedules and the discipline of filling in the treatment centre appointments form in a specified way.

Not all general practitioners take part in the computerised scheme – of the 33 per cent who do not, many are in small rural practices with only small numbers of patients to vaccinate and some do not carry out vaccinations, preferring that the children in their practice are vaccinated by health department staff at health clinics. Those doctors who do carry out vaccinations but are not in the computer scheme claim payment from the Executive Council on Form E.C. 73. This form is then passed to the vaccination section of the County Health Department so that the vaccinations can be entered into the child's records.

The other great advantage of the computerised system is that accurate up-to-date statistical information can be easily obtained. The County Health Department each year has to make returns to the DHSS on the number of completed courses of vaccination given and on the number of reinforcing vaccinations given.

These include details of type of vaccine used by ages of people vaccinated. To give information on the vaccination status of the child population to the medical officer of health of each county district, a quarterly and annual print-out of statistics is prepared. A sample of the annual statistics is shown in Table I.

Table I. *Vaccination statistics by County District at* 31 *December* 1971

County District	Born in 1970, triple vacc., 2 injection (%)	Born in 1969		No. of 1969 born children
		Completed triple (%)	Measles (%)	
Hertford M.B.	92.2	90.7	75.1	394
Bishop's Stortford U.D.	78.2	81.0	64.2	341
Cheshunt U.D.	87.3	85.8	68.0	804
Hoddesdon U.D.	93.3	90.3	69.6	504
Sawbridgeworth U.D.	81.9	81.9	67.4	138
Ware U.D.	81.3	86.6	45.5	255
Braughing R.D.	92.3	91.7	74.6	205
Hertford R.D.	85.3	88.0	66.2	207
Ware R.D.	86.7	83.1	66.7	231
Baldock U.D.	94.2	97.7	83.5	85
Hitchin U.D.	77.1	73.4	59.0	497
Letchworth U.D.	87.0	86.6	65.1	522
Royston U.D.	83.9	91.2	78.8	170
Stevenage U.D.	81.8	78.9	56.1	1367
Hitchin R.D. etc.	80.6	81.1	58.5	386
Highest percentage	94.2	97.7	83.5	—
Median percentage	85.1	84.2	66.7	—
Lowest percentage	76.9	73.4	45.5	—

In Table II, cumulative percentages of children under 4 vaccinated against measles, and in Table III, vaccinated against diphtheria, are shown as examples of information produced.

Detailed print-outs of the vaccinations carried out on the pre-school children in each county district showing number of children vaccinated by type of vaccine, e.g. whooping-cough, diphtheria, tetanus, or diphtheria, tetanus, is also produced. From time to time reaction to the whooping-cough component of triple vaccination is alleged to occur and doctors replace the triple vaccine by a diphtheria–tetanus vaccine in the case of these children. Naturally, the medical officer of health gets worried if this happens in too many cases.

In those areas where the vaccination rate is below the median, the medical officer of health is sent a print-out showing percentage of consents, the performance of each treatment centre in his district, and the number of vaccinations

Table II. *Cumulative percentage of children vaccinated against measles*

At year end	Year born							
	1965	1966	1967	1968	1969	1970	1971	1972
1968	12.2	13.9	12.5	0.2	—	—	—	—
1969	—	27.4	31.0	15.2	0.1	—	—	—
1970	—	—	41.9	49.9	42.4	0.1	—	—
1971	—	—	—	54.4	66.7	40.9	—	—
1972	—	—	—	—	68.8	66.8	40.1	0.1

Table III. *Cumulative percentage of children immunised against diphtheria*

At year end	Year born							
	1965	1966	1967	1968	1969	1970	1971	1972
1965	38.6	—	—	—	—	—	—	—
1966	81.2	38.7	—	—	—	—	—	—
1967	83.5	83.0	42.6	—	—	—	—	—
1968	83.8	86.2	84.5	45.4	—	—	—	—
1969	—	85.5	95.3	83.0	0.6	—	—	—
1970	—	—	94.0	93.5	68.4	0.4	—	—
1971	—	—	—	93.8	91.5	66.5	0.5	—
1972	—	—	—	—	91.7	90.4	66.2	0.7

carried out by general practitioners not in the computer scheme. He can then make more detailed investigations as to why his district is below the median.

There are a number of problems which occur in the execution of a large vaccination programme:

(1) Doctors as a group are notoriously poor at form filling and special efforts have to be made to improve this if records and subsequent statistics are to be correct and if the computer scheme is to be run properly.

(2) Alterations in schedules of vaccination occur from time to time on the advice of the Joint Committee on Immunisation and Vaccination, and lead to a great deal of work in changing the computer program, in persuading general practitioners to change established habits and explaining to parents why the timing of their children's 'jabs' have been changed.

(3) There is a small number of doctors who modify the schedule for various reasons, e.g. give a half dose for the first vaccination, or complete triple immunisation with diphtheria–tetanus vaccine, etc.

(4) Problems inherent in the vaccine cause difficulties from time to time. The reactivity of whooping-cough vaccines a few years ago led to large numbers of children not completing courses of triple vaccine and thus not getting adequate

protection against whooping-cough. At the present time this occurs in 2 per cent of children. There is also the problem of the efficiency of whooping-cough vaccine. The reactivity, or fear of the reactivity, of measles vaccine has kept consent rates for this vaccination to 70 per cent, 24 per cent lower than the consent rate for triple vaccine.

(5) The introduction of new vaccines always gives a few administrative problems. When rubella vaccination of 13-year-old girls was introduced, it was thought the best way to give this vaccine was at the schools and we had to persuade our head teacher colleagues to allow us to encroach again on their already busy time-tables. Rubella vaccination in 'at-risk' women which was introduced in 1972 posed a number of special problems – serological testing, problems of ensuring the women are not pregnant when vaccinated, informing the general practitioners of the results of serological testing, etc.

(6) The mobility of parents with young children is very high – these people are in an age-group where they change employment frequently or receive promotion and consequently change their house as their prospects improve. Most of them, however, do not move very far and inform the clinic, health visitor or general practitioner and are easily traced.

Protection against the communicable diseases other than smallpox began in Hertfordshire in 1934, though the number of children protected was not noted in the Annual Report of the County Medical Officer of Health until 1942, when 3773 children were protected against diphtheria. In 1942 there were 102 cases of diphtheria (4 deaths), 1044 cases of whooping-cough (7 deaths), 2571 cases of measles (1 death – in a non-epidemic year), 3 deaths from poliomyelitis and 271 deaths from tuberculosis.

In 1972, 12280 children received primary courses of diphtheria, whooping-cough and tetanus vaccination, and 13427 children received booster diphtheria injections. 12526 children received primary vaccination with oral poliomyelitis vaccine, and 18000 children received booster doses of oral poliomyelitis vaccine. There has been no case of diphtheria in the county since 1961; no case of poliomyelitis since 1964; the pattern of measles occurring in the county changed from large epidemics (14000 cases) every other year to the lowest figure ever in 1972 of 2500 cases (no deaths); there were only 68 cases of whooping-cough notified (no deaths), and 12 deaths from tuberculosis in 1972.

Though vaccination is not the only cause of this great reduction in communicable disease, it has certainly played a large part and great credit is due to the combined efforts of immunologists, vaccine manufacturers, the national and international standards institutes, public health specialists, general practitioners, health visitors, public health administrative staff, and the parents who so regularly bring their children for their protective 'jabs'.

APPENDIX

C.H.1

HERTFORDSHIRE COUNTY COUNCIL
HEALTH DEPARTMENT

NOTIFICATION OF BIRTH

Child No. _____
FOR OFFICE USE

Surname (in CAPITALS) Mother's Forename

01

02
03
04
05 } Home address in CAPITALS

06 Hospital code..... OR Write "Home" or other confinement address here

07 grams
OR } Birth weight
08 lb. oz.

Estimated gestation _____ weeks

09 Date of birth

Time _____ a.m./p.m.

10 (M)ale or (F)emale

C.D.H. test performed? Yes/No

Congenital malformations:

11 Stillbirth? (Y)es or blank

12 Illegitimate? (Y)es or blank

Confinement normal? Yes/No.
If no, give details: _____

13 Mother's age in years

14 Total previous births (including stillbirths)

15 } MULTIPLE BIRTHS ONLY — No. of babies at this confinement

16 } MULTIPLE BIRTHS ONLY — Position of this baby in birth order

G.P's name: _____

Attending midwife's name: _____

17 G.P. booked? (Y)es or blank

18 G.P. present? (Y)es or blank

Name of person notifying (if neither of above):

19 'At Risk' codes (see overleaf)

FOR OFFICE USE

20 Cong. Malf. codes

21 G.P.

22 Midwife

23 Birth area

24 Residence Area

25 Health Visitor

Surname and Forenames

Address:

HEALTH VISITORS RECORD

HERTFORDSHIRE COUNTY COUNCIL

Child No.

Midwife: H.V.

Sex Date of birth Born at: Weight Grams Mother's Age Parity C.P.

At risk: Con. Malf:

Routine Test	Hips	Phenylketonuria	Hearing
Date			
Result	Normal: Yes/No	Satisfactory: Yes/No.	Satisfactory: Yes/No.

Prophylaxis	DATES COMPLETED Primary	Booster
Diphtheria		
Whooping Cough		
Tetanus		
Poliomyelitis		
Smallpox		
B.C.G. Vaccination		
Measles		

Illnesses and Injuries—give dates			
Wh. Cough		Scarlet Fever	
Measles		Rubella	
Mumps		Jaundice	
Other-specify			
Injuries/Operations—specify			

Dev. Test	1 month	3 months	6 months	9 months	12 months	15 months	18 months	2 years
Date								
Result								

Landmarks (Give dates).	Sits up (no support):	Stands holding on:	Walks without support:	Uses two or three words correctly:

Significant family history:

Occupation—Father: Occupation—Mother: Fireguard: Yes/No.

Date	Source	Visitors Notes	Initials

C.H.2

C.H.3

HERTFORDSHIRE COUNTY COUNCIL — HEALTH DEPARTMENT

PROTECTION AGAINST INFECTIOUS DISEASES

Name: .....
Please insert Forename(s) if not shown

Address: Sex: Sequence: (Twin-births)

Date of birth:

Name of Family Doctor and surgery address .....

I hereby consent to the vaccination/ **immunization** of my child, named above, against diphtheria, whooping cough, tetanus, poliomyelitis and measles.

Appointments should be made for my child to attend:

EITHER *a) the County Council clinic at: .....

OR *b) my family doctor whose surgery address is given above.

*(Please delete whichever does not apply)

Signature: ..... Date: ..... Relationship: .....

Child Number	Forenames	G.P.	Treatment Centre	Consent
	01	21	30	31

VACCINATION & IMMUNIZATION

It is important that your child should receive protection against infectious diseases. This can be achieved by means of immunization according to the following timetable.

The ages shown below are those at which most computer appointments are made. Some family doctors prefer, however, to begin at three months of age. The intervals between the first three stages are important and are the recommended minimum; it does not matter if they are exceeded by a few weeks.

Approx. Age	*Vaccine/antigen*	*Date given*
6 months	TRIPLE (Diphtheria, Tetanus and Whooping Cough) POLIOMYELITIS	
7½–8 months	TRIPLE POLIOMYELITIS	
13 months	TRIPLE POLIOMYELITIS	
15 months	MEASLES	
School entry	DIPHTHERIA AND TETANUS (booster) POLIOMYELITIS (booster)	
Other (specify)		

HERTFORDSHIRE COUNTY COUNCIL
HEALTH DEPARTMENT

CHILD'S PERSONAL HEALTH RECORD CARD

..... (Surname) (Forenames)

Your Health Visitor may be contacted at:

.....

.....

Telephone .....

TETANUS IMMUNIZATION

In cases of accident or injury this card should be shown to your family doctor or hospital doctor as he may wish to refer to it before giving further injections.

C.H.4

Vaccination and Immunisation Appointment List

Dr. SMITH, 26, Manor Close, Hadham

Treatment Centre No. 641

HERTFORDSHIRE COUNTY COUNCIL
HEALTH DEPARTMENT
COUNTY HALL, HERTFORD, HERTS.

If you have any query, please telephone
HERTFORD 4242 Extn.

APPOINTMENTS MADE			STAGE	GIVEN	NOT GIVEN	NOTES		FOR OFFICE USE ONLY
	Triple and Polio							
10.00	CARTER,	Donald	1				71 110114 CA	
10.00	JAMES,	Maureen	1				71 11903 JA	
10.00	TURNER,	Victor	1				71 112047 TU	
10.15	STRINGER,	Mary	1				71 113214 ST	
10.15	COWEN,	David	2			2nd appointment	71 115950 CO	
10.15	RIGBY,	Joe	3			2nd appointment	71 115999 RI	
10.30	PINES,	Jack	3				71 113125 PI	
	Measles							
10.30	SMEE,	Sara	1				70 129236 SM	
10.30	SMEE,	Horace	1				70 129237 SM	
10.30	TAYLOR,	William	1				70 134161 TA	
	Diphtheria/Tetanus and Polio							
10.45	ROE,	Colin	4				68 110246 RO	
10.45	FORD,	Bernard	4				68 113241 FO	

CLAIM FOR PAYMENT/CERTIFICATION

I hereby certify that I have carried out treatments as shown on this form and claim payment accordingly.

Signature_____

If locum, on behalf of_____

EXCESS
5

GENERAL DISCUSSION

CHAIRMAN Thank you very much, Dr Cust, for that most interesting presentation of how you tackle your immunization schedules and programmes.

Would anyone from another country wish to say a few words about his own programme, or are there any questions for Dr Cust to answer?

HENDERSON (WHO) I have a very simple question. What is the incidence of diphtheria, pertussis, tetanus and measles in Hertfordshire, and is this information used in any way in the guidance of your immunization scheme?

CUST (UK) We have had no case of diphtheria since 1961, we have had no case of poliomyelitis since 1964, the measles figure for 1972 was the lowest ever with 2500 cases. In the old days when we had an epidemic in alternate years we used to have about 14000 cases in an epidemic year and about 5000 cases in a non-epidemic year. We had 68 cases of whooping-cough last year.

So far we have not used this information to guide us in our vaccination programmes because we are part of a national scheme and we do follow the central guidance that we get from the Department of Health about our vaccination schedules.

LAFONTAINE (Belgium) I should be glad to know the cost of such control.

CUST (UK) I thought someone would ask that very nasty question. So far as Hertfordshire is concerned, I cannot tell you, but thinking that someone would ask that question I have got a copy of a paper from West Sussex who have carefully costed their computerized vaccination scheme, and I think the best thing for me to do is to pass a copy of this over for Professor Lafontaine to have a look at. We cannot cost our vaccination computer scheme because it is tied up with so many other things which are tremendously valuable. For example, we are involved in monitoring congenital abnormalities which we get through this system, we are involved in child health development programmes for which we need the basic computer child health file, so it is all very much tied up and I cannot answer that question.

CHAIRMAN Dr Cust, many people believe that this is an extremely expensive operation, but I imagine that Hertfordshire would not go back on the grounds of cost now that they have established it. The benefits that you are getting from the system, expensive though it may have been to set up initially, you feel are worth while. Is that correct?

CUST (UK) It is correct; we would not go back to any other system. We have 5 hours of computer run each week. We run it with a small computer section of five clerks, who also look after deaths and death returns, and infectious diseases returns. We have got rid of the clerks in our divisional offices who used to be involved in laborious clerical work filling in cards by hand. Perhaps I ought to finish by mentioning West Sussex, who had a look at the cost if their system were applied to the whole of Britain, and they said that the costs of immunization and vaccination would be 22 per cent less in Britain if their computerized scheme were used nationwide. As part of the reorganization of the National Health Service the Department of Health has a team working on setting up a standardized computer system for the whole of England.

So I think that the cost benefits, though I cannot prove it for Hertfordshire, are probably good.

WITTE (USA) We had a rather varied experience using computerized systems as a way of following up live births and attempting to get children immunized in a relatively large number of states during the late 1960s. In some of the states they were quite successful in raising immunization levels the way you have. In other areas, despite great expenditure of time, effort and money, there was no impact on the immunity status of the children. On examining the data more closely, it would seem that the less populated areas, and more rural states, did a better job than some of the larger states. Then on further examination it was found that those areas that followed up the notifications to the parents that the computer sent out with a home visit, having a public health nurse or health visitor actually go to the home and discuss this with the parent, were the areas that had the good results. So I would hope that as you extend this you will make every effort to use the computer well, but also to follow it up with home visits.

CUST (UK) In reply to that, I think that some of the rural areas in England have very good results without the use of a computer. The health visitor is very much a part of our computer system. She takes the consent form and gets the consent form back. If a child is sent for vaccination and does not attend twice at a treatment centre without an excuse being given, the computer prints out automatically a note to the health visitor saying, 'This child should have been for vaccination on two occasions, has not turned up, will you please find out why?' In other words, the computer reminds the health visitor to monitor what is happening.

HALONEN (Finland) We have a non-computerized vaccination programme in Finland resulting in an almost 90 per cent vaccination rate, but we are not satisfied with our central record-keeping indicating accurate vaccination rates of each age group, complication rates, etc. That is one of the main reasons why we have been looking for ways to computerize the system. A model like this will be of great help to us.

May I ask Dr Cust one small detail which is causing a lot of problems in our well baby clinics with vaccination appointments. Appointments are made, as your computer has shown here, but in about 30 per cent of cases the baby has respiratory symptoms, or something else, which make vaccination impossible. What type of problem does this cause in a computer system?

CUST (UK) This makes for some difficulty in that you do get people who are scheduled for appointments, but because the children are ill, or some other child in the family is ill, or the mother is ill, the mother does not turn up. We have had a look at our treatment centres and, in fact, the best achievement we have is 85 per cent of scheduled attendances. We also do get a number of unscheduled attendances. So it does cause problems. However, we have had a look at what used to happen in the old days and the same sort of thing used to go on; we had doctors sitting in clinics and patients not turning up. I think it is just one of the problems of having to deal with young children who do get ill and cannot come.

GORDON (UK) I find it necessary to say something about Scotland as Dr Cust has talked about England and not the UK. The first point I should like to make is that the schedule which he said was most commonly used in Hertfordshire is in fact the schedule that the health departments of England, Wales, Northern Ireland and Scotland recommend.

So in Scotland the schedule we use is exactly the same, and the percentage of children immunized that we get is very much on a par with what happens in Hertfordshire. We have not managed to cover the whole country with a computerized system yet, but we do have the large City of Glasgow, with about a million population, on a computer system. Although it has not been going very long, it does not appear to be the complete answer to ensuring that a high percentage of children are immunized against the diseases covered by the schedule.

I should like to support Dr Witte in his remark that there is still a need to follow up

these children who are not taken to the clinic for vaccination on the first appointed date, the second appointed date, or perhaps a third.

As to results we have had little diphtheria in this country for the last 20 years. In fact, during that period there have only been some half-dozen cases and most of these occurred in one episode in 1968. Poliomyelitis is down now to one or two cases a year since the last outbreak in 1962 and whooping-cough is at its lowest ever. The only failure is with measles where the situation is patchy. In some areas there has been a good response to measles vaccination, in others not. For example, there are two cities in Scotland with similar populations each of about ¼ million and during this winter when we have had a moderate outbreak of measles in some parts, the incidence of the disease in these two cities has been quite different. One is having practically no cases of measles, only one or two per week, and the other is having over 100 per week. The picture regarding their vaccination figures is reversed.

JUST (Switzerland) How many health visitors do you have, or do you need, and what is the educational level of these women?

CUST (UK) We have 175 health visitors and, of course, they have many jobs other than the vaccination scheme, on which little of their time is spent. Health visitors in Britain are State Registered Nurses, and they have done a special course in public health nursing and social aspects of disease. This course lasts nine months. So that they are highly qualified public health nurses, but they do have many other jobs.

Our health visitors in Hertfordshire, though we do pay them and they are employed by us, i.e. they are on our staff, are attached to general practitioners and work very closely with general practitioners. They deal with a lot of the medico-social problems in those practices. It is very nice, of course, that these two people do work closely together because, if there are any problems with things like vaccination, the health visitor can easily sort these out with the general practitioner.

GEAR (South Africa) Mr Chairman, my question is not exactly relevant to the theme under discussion, but we have not had a chance of sorting out the difficulties. I am referring to the schedule of immunization. Yesterday we discussed the time of giving whooping-cough vaccine. Most deaths from whooping-cough occur before the age of 6 months and, if one is to protect against these deaths, one will have to arrange the vaccine programme accordingly. I know the solution is to immunize the possible contacts of these young infants, but this cannot always be done.

I have a second question also referring to the schedule following on Dr Lundbeck's presentation this morning. I am thinking of the change in the timing of smallpox vaccination from 6 years or so back to 2 or 3 months, when it was done under cover of maternal antibodies. I recall, I think, that the first outbreak of encephalitis following smallpox vaccination occurred in Holland just after World War I, and one of the features was that the vaccination had been given to infants aged from 5 to 7 years instead of in the infancy period of under 1 year. This was blamed for the encephalitis.

I wonder if we can sort out these two questions briefly.

CHAIRMAN In the United Kingdom the reason why the schedules were changed from 3, 4 and 5 months to 6 months, 7½ and 11 – something of that nature – was because of the increased antibody response of the older child. Although it is true that the deaths due to whooping-cough do occur in children under 6 months, they are so rare that the argument was used that one should not jeopardize the better response by the majority for the few who are going to succumb to the disease in the early stage of life.

COHEN (The Netherlands) May I ask whether these were adsorbed vaccines or non-adsorbed vaccines?

CHAIRMAN No, at the time they were all particulate, non-adsorbed vaccines.

COHEN (The Netherlands) That might be the reason for the failure.

GRIFFITH (UK) We have compared the efficacy of vaccination by the old British schedule of immunization at 3, 4, 5 and 18 months with the new schedule of immunizing at 6, 9 and 15 months using both plain and adsorbed vaccines. The results of these studies showed that the ultimate diphtheria and tetanus antitoxin titres were similar, irrespective of the schedule or type of vaccine used.

HOFMAN (The Netherlands) The motivation in Holland for the schedule starting at 3 months with the quadruple vaccine has been that the death toll from pertussis was heavy in the first 6 months. At this moment we have proceeded many years according to this schedule and many older children have been protected against pertussis. It is known that babies of 6 months and younger are not exposed to pertussis unless their older siblings have it. So that could be a reason for changing the schedule to older children and to carry it out at the age of 6, 7 and 9 months. However, in Holland we should then run into difficulties with our first booster injection, which has to be done in the first year because children only show up in well baby clinics in the first year. It means that there are different arguments for keeping at this schedule as time proceeds.

SENCER (USA) In trying to answer Dr Gear's first question, I think perhaps we spend too much time worrying about the optimal schedule for immunization. You have to take into account the epidemiologic situation in the area with which you are concerned, the resources available and so on. If smallpox is still a threat and is epidemic, I think you should forget whooping-cough if you do not have enough resources to do both. I do not think a cook-book schedule is practical. Everyone has to look at his own epidemiologic situation and adapt his resources to meet it.

KRUGMAN (USA) I should like to add one more comment. It is well known that the older an infant is the less likely it is that the mother will bring her child for immunization. She is more apt to come at 2, 4 and 6 months of age than toward the end of the first year. In evaluating a better immunologic response, 'better' may be just slightly better or there may be no significance at all. When we add up the number of infants and children who receive vaccine, we may immunize many more if we start earlier.

CHAIRMAN Yes, that is perfectly true.

GEAR (South Africa) I should like to get back to the theme under discussion and to ask Dr Cust what happens when mothers, as they often do, bring their infants unannounced? Is this card which the mother has the evidence of immunization?

CUST (UK) If the mother turns up unscheduled – for example a mother may come a few weeks before 6 months, or a general practitioner may feel that that child should be done – the general practitioner enters this on to the treatment centre form; this comes back to the computer and is entered into the file. We have no problem really about entering these unscheduled vaccinations.

CHAIRMAN Perhaps Dr Henderson could answer the smallpox question.

HENDERSON (WHO) The question of the optimum age for primary vaccination against smallpox is a cloudy one. The data from various areas are contradictory and difficult to interpret. In the first year of life, for example, a certain number of cot deaths occur and, variably, some of these are ascribed to smallpox vaccination.

The studies of vaccination in the United States suggest that vaccination between one and four years is safer than when vaccination is performed between 9 and 12 months of age, the usual age of primary vaccination in the United States. The relative risks of complications among older children and young adults is most uncertain as the numbers given primary vaccination are so small and serious complications are so infrequent (in all age groups) that meaningful rates are difficult to calculate.

In the endemic regions, vaccination at birth is increasingly common and there is now a considerable experience accumulating. In areas where there is satisfactory follow-up, this seems to be a very safe period indeed.

In brief, the answer is not very clear as to what is the optimal age for beginning vaccination. We do have the sense that vaccination at birth is at least as safe as vaccination at a later period, but comparative data regarding the risks of vaccination say, at 2 months, 3 months, 6 months, and 9 months are not available.

GEAR (South Africa) If I could just come back to the question, I think Dr Lundbeck's point was that under 6 months of age the infant is vaccinated under cover of its maternal antibodies, whereas if the mother has no antibodies this cover will be lost. We see quite a number of primary vaccinations in young adults who have a severe reaction, and I presume this is general experience.

HENDERSON (WHO) I should like to refer to the studies that were done in the United States, in regard to the question of the relative risk of complications in young adults. Records of those in the military who had been vaccinated at the time of entry into military service were examined. By survey, it was determined that between 5 and 10 per cent of those entering military service had not previously been vaccinated. In reviewing all medical records back to 1945 it was found that there were no deaths attributed to complications of smallpox vaccination and, as I recall, no cases of post-vaccinal encephalitis. The total number of primary vaccinations estimated ran into the hundreds of thousands.

This was a surprising finding and contrary to the conventional concept that adults are very susceptible to complications following primary vaccination. These data, on the one hand, suggest that primary vaccination in young adults is associated with minimal risk while studies in several European countries indicate an increased risk of complications among older age groups.

The data I find to be puzzling and contradictory, making it impossible to provide a clear-cut answer.

WITTE (USA) Dr Henderson is quite right in saying that there were no cases of encephalitis, as I remember, and I think the number of primary vaccinations approximated a million.

CHAIRMAN I think that we have had a very full discussion and we must now draw it to a close.

SUMMARY AND CONCLUSIONS

Dr Cockburn opened the symposium by discussing the major problems in ensuring that populations are protected against the major infectious diseases. The controversial question of the discontinuation in the use of some vaccines was mentioned, especially where the disease had been reduced to a very low incidence. Compensation for the rare occasions in which a serious reaction occurred was a major issue.

Dr Griffith showed that DTP and polio vaccines used in good immunization programmes were very effective. There was little information, however, on the precise contribution that BCG vaccine made in routine vaccination programmes. In those countries in which the vaccine was used, the incidence of the disease in the vaccinated community was markedly decreased. In several communities with an increase in hygiene, and a consequent decrease in the disease, it was now necessary to vaccinate ten thousand children to prevent a single treatable case of tuberculosis. The continuation of the use of this vaccine therefore, was being questioned but it was difficult to know what criteria should be used in deciding whether routine vaccination of infants or adolescents should be discontinued. The argument put forward for continuing the use of BCG vaccine was the number of new cases of tuberculosis attributable to atypical 'mycobacteria' which are not sensitive to antituberculosis drugs.

As far as smallpox vaccine was concerned the discussion also concerned the possible relaxation of immunisation in European countries. It was felt that as long as there was a risk of a case of smallpox entering a country vaccination should continue. In considering the cost benefit analysis in support of the continued use of established vaccines it was pointed out that the global expenditure on smallpox eradication, for example, was about 30 million dollars. The first mention of cost benefit went as far back as 1917 when the late Professor Winslow showed that the cost of immunization against diphtheria was about one-tenth that of hospitalization of infected cases. It was emphasized that the assessment of any cost benefit should include the future earning capacity of people who, if incapacitated, would be seriously affected, or perhaps die as a result of the disease. It was pointed out also that in developing nations the usual factors used in the calculation of cost benefit analysis was unacceptable because of negative benefits, but the savings in the limited medical resources were certainly worthwhile.

There was some concern about the potential dangers of giving smallpox vaccine to young adults entering the military, a situation that may arise 15–20 years after a country had discontinued routine vaccination in infancy. It was pointed out, however, that smallpox may be eradicated by then, in which case vaccination in adult life may not be necessary, and furthermore in the United States it

had been shown that the risk of primary vaccination in adults is not as great as some people believe it to be. In any event it was considered important to protect all hospital staff against the disease. Dr Henderson mentioned that an unforseen economic benefit of eradication is the reluctance of families to participate in family planning programmes until all the major endemic killing diseases in childhood had been controlled.

The third session was devoted to a discussion of the use of newer vaccines (measles, mumps, rubella). Krugman and Meyer discussed the experiences of the United States where 50 million doses of live attenuated measles vaccine, 11 million doses of live mumps vaccine and 45 million doses of live rubella vaccine have been used.

The extensive use of measles vaccine since 1963 had been associated with a significant decline in the incidence of reported cases of measles and a similar decline in the incidence of measles encephalitis. It has been shown that the antibodies have persisted for the 11 to 12 years during follow-up period.

When the vaccine was licensed the problem of febrile reactions in the early stages of its use was cause for concern. Furthermore, the possibility that the use of the vaccine, as with the natural disease, might be complicated by a temporal association with acute encephalitis and subacute panencephalitis (SSPE) was closely followed. The development of more attenuated vaccines, which have been in use since 1965, has solved the problem of excessive febrile reactions, but during the past 10 years there has been an incidence of acute central nervous system disease occurring in approximately one per million subjects inoculated with vaccine. This figure must be compared with an incidence of 1 per 1000 associated with naturally acquired measles. The pathogenesis of SSPE and its association with measles immunization is not clear. The survey by Jabbour in the USA has identified 400 cases of SSPE of whom 40 occurred in vaccinated subjects but there is no suggestion that they are vaccine-associated. The data to date, therefore, indicate that the risk of a central nervous system complication is far greater following a natural measles infection than following attenuated measles-virus infection.

Experience during the past 10 years has revealed that live attenuated measles vaccines are safe, immunogenic and highly effective. It is likely that immunity will be long-lasting.

Mumps vaccine, used since 1967, has been well tolerated and reactions have not been observed. The antibody responses have been excellent, exceeding 90 per cent, but the levels of antibody are low. The question of persistence of immunity was raised and it was shown that a six-year follow-up revealed persistence of both antibody and protection.

The immunization programme against rubella in the United States since 1969 has had two major objectives: (i) the routine immunization of all children, one to twelve years of age, and (ii) the selective immunization of girls post-puberty as well as women of child-bearing age. In the first objective the aim was to decrease the incidence of rubella, and the dissemination of rubella virus, thereby preventing the expected epidemic of rubella anticipated between 1970 and 1973.

This indirect approach was reinforced by a direct approach of selective immunization of women (*a*) who have been shown to be seronegative, and (*b*) who have been urged to avoid pregnancy for at least two months after vaccination. The use of approximately 45 million doses of rubella vaccine has progressively reduced the incidence of rubella and congenital rubella.

The approach to immunization against rubella in the United Kingdom and some other European countries, however, differs markedly from that of the USA. As rubella is not a troublesome disease to children no attempts have been made to prevent them from obtaining immunity by natural infection. The vaccine is being given to selected groups of females to prevent rubella in pregnancy and all schoolgirls between their 11th and 14th birthday are being offered vaccine. Any female older than 14 may have vaccine provided that a serological test shows that she is seronegative and that she understands the risks involved in becoming pregnant for 6 to 8 weeks after having been given the vaccine.

The main questions that caused concern to some about rubella immunization included: (1) communicability, (2) clinical reactions such as joint manifestations, (3) possibility of waning immunity, and (4) the significance of reinfection. However, experience has shown that: communicability has not been a problem; severe joint manifestations were associated with the dog-kidney-adapted HPV-77 strain, which is no longer available, whereas vaccines made from the rubella strains HPV-77 in duck embryo, Cendehill in rabbit kidney and RA 27/3 in human diploid cells (WI-38) have been well tolerated. The very small incidence of mild and transient joint manifestations associated with these three vaccines is much lower and less severe than that following natural rubella infection. The 'potential' problems of persistence of immunity and reinfection are currently under study. In the meantime it is reassuring that antibody has persisted for 7 years, the current period of follow-up, and viraemia has not been detected during reinfection.

In discussing the vaccines for limited use it was reported that the influenza A virus produced recurrent epidemics of disease of considerable impact on a worldwide scale in terms of both morbidity and mortality. The recurrence of epidemics was closely related to antigenic changes in the two surface antigens of the virus, namely the haemagglutinin and the neuraminidase. Such changes give rise to problems in the control of influenza by vaccination in that vaccines are effective for a limited number of years before becoming redundant when changes in the antigenic composition of the prevalent strains occur. This necessitates replacement of the vaccine strains by more up-to-date ones which is accompanied by a delay of several months. The WHO influenza programme of surveillance and research is aimed at the early detection of new viruses and at minimizing this delay. The influenza B virus produces a smaller impact than influenza A and epidemics tend to be localized.

In most countries prophylaxis of influenza is based on the use of inactivated vaccines that usually contain influenza A and B components. Until now such vaccines have had only limited acceptability because of their relatively low levels of efficacy and purity and their frequent association with reactions. These

disadvantages can now be minimized by the use of zonal-centrifuge purified preparations as well as by the use of recombination techniques in the development of high-yielding strains.

Advances in influenza technology have recently led to methods which enable the preparation of highly purified (crystalline) preparations of influenza haemagglutinin and neuraminidase proteins. Such preparations, because they are free from materials which are irrelevant to immunity (i.e. viral internal proteins and nucleic acid) have a considerable attraction as potential vaccines for future use. They have been shown to protect experimental animals from influenza when administered together with adjuvants but studies in man have been disappointing so far.

Live, attenuated influenza vaccines are in experimental use in some countries. They have the advantage of ease of administration and they are relatively inexpensive to produce. Previously it was necessary to carry out long term serial passage of viruses in order to obtain an attenuated strain, but recent advances in virus genetics have enabled the rapid attenuation of newly isolated variants by recombination with a standard 'parent' strain known to be avirulent for man. This offers the possibility of a considerable reduction in the time necessary to prepare potential vaccine strains when new variants occur in nature. Experiences during the next few years will evaluate the potential advantages of the use of living influenza vaccines.

The standardization of influenza vaccines presents considerable technical problems. New advances which may be relevant to providing improved criteria for quality control are the use of polyacrylamide-gel electrophoresis in the qualitative identification of influenza virus specific proteins and the use of single-radial-immunodiffusion methods for the accurate assay of virus antigens (haemagglutinin and neuraminidase) and antibodies.

In discussing the benefits that were given by the incorporation of vaccines in emulsions, Dr Hilleman emphasized that the reactions that had occurred with the use of Freund's adjuvant could be eliminated by using chemically synthesized pure components in the emulsion, as well as using a vegetable oil (peanut oil) as had been done in adjuvant 65. A particular benefit was the higher antibody response to a broader spectrum of antigens for the influenza virus when the vaccine was incorporated in such an emulsion. Of many thousands of inoculations none had given rise to an abscess and at most there was no more than a local transient reaction. Similar sorts of benefits were achieved by the adsorption of antigens onto mineral carriers but most of these gave a nodule at the inoculation site, some of which persisted for a long time, but they were not giving rise to complications.

Combination of several bacterial vaccines had greatly decreased the actual number of injections necessary in protecting against the bacterial diseases. Although not used on a wide scale some countries were still using the killed polio vaccine combined with DTP vaccine with good results.

There was some concern about the persistent screaming that sometimes follows the use of a vaccine containing a pertussis component. There were no data to

correlate the incidence of screaming with any biological test that could be applied in the laboratory and more work was urgently needed in order to determine the cause of the screaming and to eliminate such causative agents from pertussis vaccine.

The use of bivalent and trivalent combined living virus vaccines that contain measles, mumps and rubella attenuated viruses carefully adjusted so that the response to all vaccines is satisfactory, is also meeting with great success. There is no evidence of interference and the antibody responses, as well as persistence of antibody is as good as when the vaccines are given separately. There is no increase in clinical reactions when the vaccines are combined. Care must be taken, however, in making combined vaccines that the combination of the particular virus strains are compatible and are in such concentration that none would dominate the immune response. Combined live measles and smallpox vaccine has given satisfactory results also without reducing the antibody response to either virus and without reducing the dermal reaction. In one study combined measles, rubella and smallpox vaccine was found to be satisfactory. Giving other live vaccines simultaneously such as yellow fever, smallpox and even BCG vaccine, had been studied. Good antibody responses, without any increase in the incidence of untoward reactions, have been observed.

There was a feeling that the simultaneous inoculation of living virus vaccines with bacterial vaccines containing endotoxin was not entirely successful and Dr Hilleman pointed out that endotoxins were extremely efficient interferon inducers and this may explain the suppression of the responses to the living virus vaccine when given at the same time. When live vaccines are given the appearance of interferon is delayed for some days after the virus is replicating in the vaccinee. There was some concern about the simultaneous administration of too many vaccines and giving MMR, for example, with DTP has not been evaluated. Immunity after giving killed whole virus measles vaccine lasts for only a short time. Concern was expressed about the use of subunit measles vaccine since, in Swedish studies, it had been shown to induce haemagglutinin-inhibiting antibody but did not protect against the disease. A lack of antibody production against the measles haemolysin was noted.

The developments that have taken place in the manufacture of vaccines have been as a result of a growing understanding of the nature of antigens, the progress in technology, the improvement in standardization methods and the use of reference preparations, etc. Some vaccines available today are almost at the limit of the highest possible purity.

In order to take advantage of the improvements in vaccine manufacture made during the last few years it is essential that the conditions necessary to maintain their potency and efficacy are fully appreciated by all who handle the vaccines. Stability studies and storage requirements are not infrequently reduced to those for temperature and light, disregarding the interdependence between stability and other factors of the multivariant system contained in one ampoule. Known and even undetected risks in handling are often taken during distribution, particularly when poorly informed personnel, including the medical profession, abuse the acceptable storage conditions.

Much effort was going into the quality control of vaccines in order to ensure that safe effective and stable vaccines were provided to the physician for immunization. A great deal of this effort is wasted, however, if insufficient attention is paid to the correct storage conditions of the vaccines by health authorities or physicians. Although instructions concerning the storage and the use of the vaccines are included by manufacturers in the leaflet accompanying the products, not enough attention was being paid to these. It would be a great help if WHO would draw up suggested recommendations for the distribution, storage, and use of vaccines as they have done for the manufacture of vaccines.

It was clear that an immunization schedule represents a practical compromise between the recommendations of epidemiologists and immunologists and of the administrators who must put the programme into operation. Moreover, the scientific background upon which to base a schedule of immunization is often incomplete. Consequently, the choice of vaccines to be used in different countries, and their timing and spacing, are liable to differ, even when those countries are in close proximity to each other and possess similar epidemiological patterns of infectious disease.

The routine vaccination programmes adopted by the countries represented at the conference were considered in detail. Almost everywhere routine vaccination against diphtheria, tetanus, pertussis and poliomyelitis is practised. In addition, most countries recommend immunization against smallpox in infancy, although in both the USA and the UK routine smallpox vaccination has recently been discontinued. On the other hand, BCG vaccination is not practised everywhere, partly because in some areas of the world it may not be very effective, and partly because the incidence of tuberculosis has been decreasing in most countries without the use of BCG. Measles vaccination has been adopted for routine use in many areas. In some countries rubella immunization has been used mainly for girls in early adolescence while in others, such as the USA widespread immunization of pre-adolescent children is being used. Live mumps vaccine has found wide acceptance only in the USA but in Finaland, where protection of all military recruits is considered necessary, killed vaccine is being used.

Influenza vaccine has not so far been incorporated into routine programmes except for the protection of high-risk groups in a few countries. Enteric fever vaccines also are routinely given in only a few limited areas, and with improving hygenic precautions their use should diminish.

The age at which immunization is begun, and the number of doses of the different vaccines recommended, differs in only minor respects in most of the countries under consideration. However, an interesting exception is the current practice in Sweden of giving primary smallpox vaccination at the early age of 2–3 months and as a consequence, the Swedish experience has been that adverse reactions are less commonly seen.

Few countries make acceptance of all vaccines compulsory, although in many areas smallpox vaccination is mandatory. It was considered that, in the absence of appropriate legislative power, vigorous efforts should be maintained to ensure that high acceptance rates continue to be secured.

Immunization for travellers was discussed briefly, and was acknowledged to be a difficult and pressing problem – particularly in view of modern, rapid travel and the large numbers of people crossing national frontiers, whether immigrants, holidaymakers, businessmen or migrant workers. On the one hand, travellers from endemic areas may transmit infection to non-endemic areas and, on the other hand, people entering endemic areas may encounter infectious diseases against which they possess little resistance. More consideration will need to be given to these questions in the near future by all countries.

Immunization of the Armed Forces could not be discussed in detail at the Conference. Much interest was invoked, however, by the need to maintain the health of soldiers who could be regarded both as travellers, who are often required to operate in circumstances where disease control may be difficult, and also as recruits who are subjected to acute respiratory and other infections.

Although immunization programmes in developing countries was not part of the present Symposium the Conference heard the impressive experience of French workers on the use of various simultaneous vaccination programmes in Africa. The findings suggest that many vaccines might be effective when given simultaneously and that such combinations will prove of great value in prophylaxis of infectious disease in the developing countries and for travellers, provided that the efficacy of each combination has been evaluated. As more experience of simultaneous immunization is gained, benefits for immunization schedules in all countries should follow.

The problem of adverse reactions and legal responsibilities for injuries caused by immunizations was discussed by Dr Preben von Magnus. Severe side-effects are rare but are known to occur, even when the vaccine has been prepared according to regulations and has been administered correctly. Under such circumstances it is difficult to place the responsibility, but malpractice suits and claims for damages against the manufacturers have occurred in various countries.

In view of the fact that most immunizations recommended by National Health Authorities are of benefit not only for the recipient of the vaccine but for the community in general, some countries in Europe and Japan have established a public compensation system under which the Governments have accepted responsibility for the recognized hazards of immunization. Reports were presented on the legislation concerning this subject in Denmark and in the Federal Republic of Germany. The laws enacted in both countries provide for compensation from public funds to persons suffering damage from vaccinations which are prescribed or recommended in public by the competent authorities. In both countries a reasonable probability of the causal relationship between the immunization and the injury is regarded as sufficient for payment of damages. In Germany damages are paid as a pension and this is also the case in Denmark, provided that the disablement is 50 per cent or more. If the disablement is less than 50 per cent, damages are usually paid as a capital sum. Children, however, receive their compensation only after they have reached an age of 15 years. Below this age financial aid can be obtained from public funds under the general social laws.

The *primary* responsibility of the manufacturer and the *ultimate* responsibility of the State were emphasized. The manufacturer has two major responsibilities – to ensure that each batch of vaccine is manufactured and tested in strict accordance with the regulations, and to warn about any potential risk which may be associated with the use of the vaccine in question. It was argued that if these obligations were fulfilled, and the vaccine had been administered correctly, the responsibility for accidents should rest with the authorities responsible for initiating vaccination campaigns, for instance by the acceptance of governmental responsibility for the recognized hazards of immunization.

The problem of responsibility in case of injuries in connection with the use of experimental vaccines was briefly discussed. Neither the German nor the Danish law provide for compensation under such circumstances. However, section II in the Danish Act authorized the Minister of the Interior to decide that other vaccinations may also be covered by the Act. Although the intention has been to make it possible only to extend the law to cover other routine vaccinations (e.g. rubella, measles) an experimental vaccine might possibly be covered also by this provision.

In discussing the assessment of immunizing agents by field trials, Sir Austin Bradford Hill drew upon an unrivalled experience of these investigations and reminded the Conference of the importance of effective random allocation in the creation of similar vaccinated and unvaccinated groups. He considered that too much attention was often paid to tests of statistical significance and too little to consistency in results to trends which often provided convincing evidence of association between prophylactic agents and the occurrence of the disease concerned. Among the other important points made was that prophylactic agents were usually highly specific. One way of assessing the validity of findings in vaccinated and unvaccinated groups was to compare not only the incidence of the specific disease concerned but also of those other diseases not affected by the agent and which, if the comparison is to be valid, should remain similar in both groups.

Dr Pollock dealt with some of the practical aspects of field trials. Controlled field trials were often an unsuitable means to evaluate the duration of protection of vaccines because the long follow-up involved led to practical difficulties of administration and assessment. Dr Pollock also gave a brief outline of the present state of vaccine surveillance in England. No comprehensive scheme was in operation but some information was obtained from a recording system of reaction by antibody surveys and by closely following up cases of three diseases, polio, tetanus and diphtheria, whose prevalence was small enough to make this approach possible.

There was a brief discussion covering several points but perhaps the most important of these was the question of the ethics of field trials. Dr Sencer introduced this subject and felt that the time had now arrived when it was essential to consider codes of practice for controlled trials and moreover to make sure that the general public knew both that such codes existed and that advances in disease prevention would be hindered if field trials were made more difficult to perform.

In considering how best to reach the majority of children in a community, one of the computerized systems of the administration of vaccination schemes in Britain was described. The scheme which had now been running for 5 years is a part of a comprehensive child health information system. The advantage of such a scheme was that the dual effort needed by both the administrative staff and the doctor giving the vaccine has been reduced. As a result of this the rates of vaccination to DTP and poliomyelitis had increased from 65 to 94 per cent.

The discussion ranged over the problems of introducing computer systems in other countries – the problems of large open areas with a highly mobile population, difficulties in recruiting public health nurses (who are an essential part of the schemes in England) and difficulties in pilot schemes in Finland, where there was a low attendance rate at clinics to which children were invited for vaccination. As with immunization schedules each Health Authority must apply the system best suited to the community but efforts should be made in all countries to increase the acceptance rates for all vaccines.

A 'CODE OF CONDUCT' FOR CLINICAL TRIALS

During the discussions on the risks inevitably taken in the immunization of subjects it was emphasized that there will be a continued need for field trials. New vaccines as well as improvements in existing vaccines will be developed, some of which may require reassessment, and each will require tests in man to prove the efficacy of the product. There was a growing anxiety that it was becoming increasingly difficult to carry out field investigations and the situation may be partially relieved if a 'code of conduct' was drawn up and known to both the participants and investigators for such future trials. Dr D. Sencer produced the first draft of such a 'code' which stimulated much discussion. The main causes for concern were the advisability of inclusion of placebo material and the nature of such material. The time at which the controls may be offered the vaccine or drug and the need for long-term studies were critical. The improbability of being able to use the same 'code' in all countries unless couched in the most general terms was mentioned, as was the inadvisability of attempting to produce such an important document as a 'code' in a short time at this meeting.

It was agreed that the drafting of such a 'code' needs much careful thought. It was known that many health authorities were involved in writing such regulations and these authorities should be consulted. Accordingly the IABS was asked to organize an international meeting in order to draw up a code which may find international agreement in the future. Nevertheless there was some urgency in this matter and it was suggested that the proposals of Dr Sencer, suitably modified, should be reported as part of the proceedings of the Symposium. The modified statement reads as follows:

'The participants in the Conference on Vaccination against Communicable Diseases recognize the future needs for properly conducted field trials which will test the efficacy and safety of new and/or improved immunizing agents.

"Properly conducted" field trials are those conducted not only with scientific integrity, but also conducted in a manner that safeguards the rights as well as the health of the individuals involved and preserves the dignity of the individuals.

To accomplish this the following recommendations are proposed as a basis for discussion.

1. All investigators periodically review the Helskinki Declaration.

2. National governments establish and enforce realistic guidelines for investigations after consultation with the experienced investigators and set up a procedure to ensure that the guidelines are observed.

3. Investigators from countries with such guidelines working in countries

where such have not been established collaborate with the government to ensure that acceptable standards of the investigators are met.

4. Guidelines should include as a minimum (*a*) the process for ensuring protocol review, (*b*) the process for obtaining informed consent if required by the Government in the country, and (*c*) the measures to supervise trials and to protect the health of the participants.

5. All field trials should be openly discussed with the persons concerned before institution, explaining the randomization process if such is to be used, the benefits of the study, the known side-effects of the agents, if any, and the need for and the nature of a control substance as well as its action.

6. If an agent or drug has been under study for a sufficient period of time to have been found to be of benefit, those who did not receive it during the study should be given the opportunity, upon completion, to receive it.

7. Appropriate international organizations should evaluate their role in stimulating uniform high standards of ethical experimentation.'

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INTERNATIONAL MEETINGS
of the
Permanent Section of Microbiological Standardization

I. Première rencontre européenne de standardisation biologique

Lyon 1955 (22–25 juin) (Documents multicopiés)

Diphtheria Toxoid – Tetanus Toxoid – Tuberculins in Human Medicine – Tuberculin in Veterinary Medicine – Poliomyelitis Vaccine – Gamma Globulin.

II. Atti del secondo congresso internazionale di standardizzazione immuno-microbiologica

Roma 1956 (10–14 settembre) (Ed. Technica graphica, Via Gallia 150, Roma 1957)

Lactobacilli and Lactic Ferments – Pertussis Vaccine – Polio Vaccine – Smallpox Vaccine – Typhoid Vaccine.

III. Proceedings of the Third International Meeting for Biological Standardization

Opatijà 1957 (2–6 September) (Ed. Tiskara, Jzdavaćkog zavoda, Jugoslavenske akademije, 1958)

The Use of the Tissue Cultures *in vitro* in the Control of Sera and Vaccines – Influenza Vaccines – Combined Vaccines – Brucellosis Vaccines – Sterility Tests of Sera and Vaccines – Round Table Communications and Discussions – Tetanus – Typhoid.

IV. Proceedings of the Fourth International Congress for Biological Standardization

Bruxelles 1958 (24–30 juillet) (Ed. Imprimerie de Charleroi, Charleroi 1959)

Staphylococcal Vaccines – Pyrogens and Their Control – Control of Phage's Products – Control During the Production – Control of Vaccines in Veterinary Medicine – Vaccinations for Children – Tuberculin – Live Vaccines – Sterility – Documentation and Bibliography – Conclusions and Resolutions.

V. 5th International Meeting for Biological Standardization

Jerusalem 1959 (13–20 September) (The Weizmann Science Press of Israel, Jerusalem, 1960)

Standardization of Prophylactics and Diagnostics in Human Virus Infections – Standardization of Prophylactics in Zoonoses and Antropozoonoses Caused by Viruses – Inactivated Poliomyelitis Vaccines – Living Poliomyelitis Vaccines – Combined Vaccinations – General Problems, Precaution and Safety Tests – Standardization of Prophylactics and Diagnostics in Leptospirosis – Precipitation in Agar Gels – Standardization of Bacterial Prophylactics and Diagnostics – Antigens of Parasitic Origin – C-Reactive Protein – Passive Haemagglutination – Antivenomous Immune Sera – Conclusions

VI. **Proceedings of the 6th International Congress for Microbiological Standardization**

Wiesbaden 1960 (5–10 September) (H. Hoffmann Verlag, Berlin-Zehlendorf 1961)

Polio Vaccine, Oral – Combined Polio Vaccines – Measles – Germ Counting – Disinfection – Veterinary Matters

VII. **Proceedings of the 7th International Congress for Microbiological Standardization**

London 1961 (28 August–1 September) (E. and S. Livingstone Ltd., Edinburgh and London 1962)

Biological Standardization – The Use of Standards – International Standards – Adventitious Agents in Tissue Cultures – Diagnostic Sera for Viruses – Sterility Testing – Toxicity Testing – Tuberculin Problems – Staphylococcal Antigens and Antibodies – BCG Vaccine – Field Investigation in Relation to Standardization – Antiviral Agents – New Antiviral Vaccines – Helminth Vaccines – Reports Participants.

VIII. **Proceedings of the 8th International Congress for Microbiological Standardization**

Bern 1962 (18–21 June). Vol. 1 of the Progress in Immunobiological Standardizations (S. Karger, Publishers, Basel 1964)

Opening Session – Standardization of the Antibiogram and its Reagents Used – Standardization of Diagnostic Methods in Rheumatic Diseases – Standardization of Reagents in Virology – Standardization of Microbial Antigens – Standardization of Sterility Tests (Round Table) – Control of Biological Products Performed by Official Laboratories (Round Table) – Standardization of Reagents in Allergy (Round Table) – Standardization of Enzymes in Immunology (Round Table) – Standardization of Methods of Disinfection (Round Table) – Problems Concerned with Live Poliomyelitis Virus Vaccine (Round Table) – Summary of the Subjects, Conclusions and Resolutions.

IX. **Proceedings of the 9th International Congress for Microbiological Standardization**

Lisbon 1964 (1–5 September). Vol. 2 of the Progress in Immunobiological Standardization (S. Karger, Publishers, Basel 1964)

Purification of Antigens – Adjuvants of Immunity – Tetanus Prophylaxis – Standardization of Mycotic Allergens – Standardization of Typhoid Vaccines – Preparation and Control of Vaccine against Respiratory Diseases of Poultry – General Papers and Round Table on Diphtheria Carriers, Foot-and-Mouth Disease. African Swine Fever.

X. **Proceedings of the 10th International Congress for Microbiological Standardization**

Praha 1967 (19–23 September). Vol. 3 of the Progress in Immunobiological Standardization (S. Karger, Publishers, Basel 1968)

Recent Development in Viral Vaccines: Extraneous Agents and their Detection: Oncogenic Viruses – Viral Genetics – Modern Trends in Research and Use of Tissue Cultures – Methods of Concentration, Purification and Inactivation of Viral Vaccines – Development, Production, Control and Use of Viral Vaccines – *Recent Development in Bacterial Vaccines*: Production Methods (Cultivation Procedures, Purification of Antigens, etc.). Laboratory and Chemical Testing of Reactivity (Side Effects) and Efficacy of Vaccines – Special Problems Relating to Pertussis Vaccine – *Other Actualities.*

XI. **Proceedings of the 11th International Congress for Microbiological Standardization**

Milan 1968 (16–19 September). Vol. 4 of the Progress in Immunobiological Standardization (S. Karger, Publishers, Basel 1970)

Immunoglobulins: Biochemistry, Immunochemistry, Molecular Biology, Preparation, Control, Assays and Standardizations; Special Ig; Antilymphocytic Ig; Anti-D Ig – *Local Immunity*: Enterovaccines and Oral Immunization – *Immuninochemistry of Enzymes* – *Free Papers*: Biochemistry, Pharmacology, Antivenom Sera, Immunology, Tuberculins, Toxoids, Bacteriology, Virology.

XII. **Proceedings of the 12th International Congress for Microbiological Standardization**

Annecy 1971 (20–24 September). Vol. 5 of the Progress in Immunobiological Standardization (S. Karger, Publishers, Basel 1973)

Developments with Hepatitis – Developments with Marek's Disease – Developments with Virus Vaccines – Tests for Oncogenicity of Viruses – Anti-viral Agents – Virus Pneumonia Vaccines for Calves – Developments with Bacterial Vaccines.

SYMPOSIA
of the
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1st Symposium, Opatijà 1959:	International Symposium of Immunology.
	Edited by Dr D. Ikić, Tiskara Jzdavaćkog zavoda, Jugoslavenske akademije, Zagreb.
2nd Symposium, Opatijà 1960:	International Symposium of Microbiological Standardization.
	Edited by the Direction of the Institute of Immunology, Zagreb.
3rd Symposium, Lyon 1961:	Production et contrôle du vaccin buvable contre la poliomyélite (Sabin).
	Duplicated.
4th Symposium, Lyon 1962:	Symposium international de virologie vétérinaire: Pestes porcines et fièvre aphteuse.
	Edited by the "Office International des Epizooties (OIE)" and the "Association Internationale des Sociétés de Microbiologie (AISM)".
5th Symposium, Prague 1962:	Pertussis Immunization.
	Duplicated.
6th Symposium, Lyon 1962:	Vaccination antivarioloque (smallpox).
	Edited by the Institut Mérieux, Lyon.
7th Symposium, London 1963:	Méthodes consacrées aux épreuves de stérilité.
	Duplicated.
8th Symposium, Opatijà 1963:	The Characterization and Uses of Human Diploid Cell Strains.
	Edited by the Direction of the Institute of Immunology, Zagreb.
9th Symposium, London 1964:	Tuberculins.
	Publication under consideration.
10th Symposium, Paris 1964:	Désinfectants.
	Publication under consideration.
11th Symposium, Lyon 1964:	Antigènes et vaccins pour la sérologie et la prophylaxie de la rougeole et de la rubéole.
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* Published by Blackwell Scientific Publications, Oxford and Edinburgh, January 1970, 292p. Obtainable from our Office in Geneva.

† Published in 'Laboratory Animal Handbooks 4', London, Laboratory Animals Ltd., November 1969, 268p. Obtainable from our Office in Geneva.

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(Permanent Section of Microbiological Standardization)

1st Meeting	Zagreb, Institute of Immunology, 12–13 October 1964 (Duplicated)
2nd Meeting	Geneva, Hôtel Métropole, 26–27 May 1965 (Duplicated)
3rd Meeting	Philadelphia, Wistar Institute of Anatomy and Biology, 18 May 1966 (Printed)
4th Meeting	London, National Institute for Medical Research (Hampstead Laboratories), 16 September 1967 (Printed)
5th Meeting	Philadelphia, The Wistar Institute, 27 November 1968 (Printed)
6th Meeting	New York, Albert Einstein College of Medicine, 30 October 1969 (Printed)
7th Meeting	Geneva, Institute of Hygiene, 14 September 1970 (Printed)
8th Meeting	Chatham Bars, Massachusetts, October 1971 (Printed)

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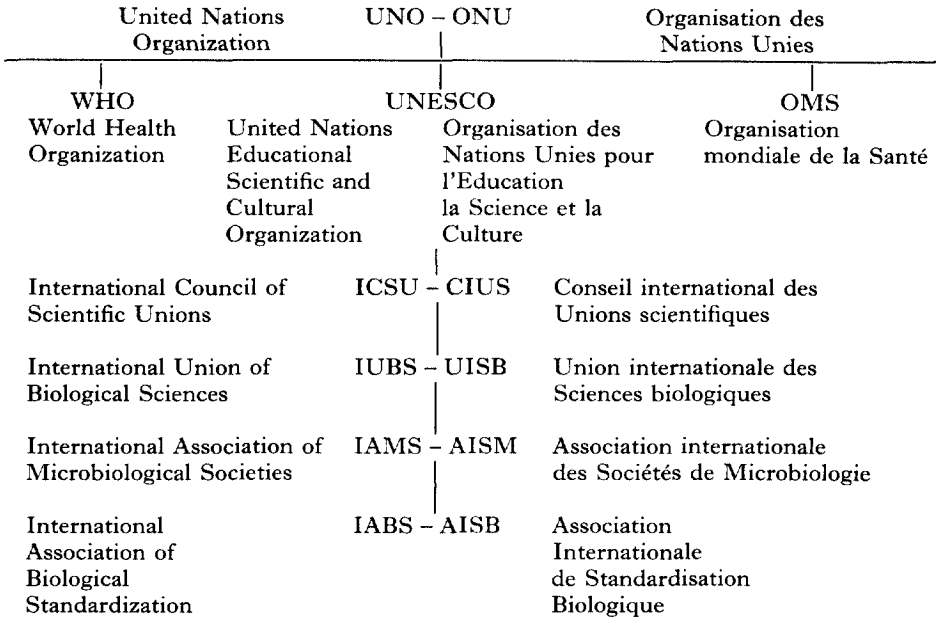

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