
Technical Afterword

Policy decisions regarding influenza rest on judgments about the behavior of the virus, the impact of the disease and our ability to interdict its course. But the virus is capricious, the disease elusive, and our remedies imperfect. The technical dilemmas discussed in this Afterword reflect what we know, what we think we know and what we do not know. They run from matters of definition, to matters of measurement, to matters of substantive understanding. We hope they convey the nature of technical limitations in contending with the influenza problems.

Influenza Virus and Disease

The term influenza applies both to a particular virus and to a clinical disease, consisting of fever, headache, muscle aches, prostration and, frequently, cough, watery eyes, nasal stuffiness. The influenza virus can cause this syndrome, although not always exactly the same symptoms, and the severity of the disease ranges from very mild to fatal; death usually comes from rapidly progressive pneumonia.⁸⁹

Many other infectious agents, mostly viruses, can produce illness resembling that caused by the influenza virus.⁴⁰ Influenza-the-virus certainly predominates as a cause of influenza-the-disease during epidemic periods, but other viruses are relatively more prominent as producers of year-in and year-out influenza-like illness. Persons who are vaccinated and protected against the influenza virus remain susceptible to "flu" when caused by other organisms.

Public understanding thus is constantly at risk. To virologists and influenza experts, "influenza" means the influenza virus and only the disease produced by that virus. To members of the public, "flu" is the disease regardless of viral cause. Many people also speak colloquially of "intestinal flu," a misnomer to the specialist since influenza is not a gastrointestinal ailment.

For public policy, therefore, the problem of influenza-the-disease is analytically distinct from problems produced by the influenza virus. This applies to any assessment of the health and economic magnitude of the "influenza" problem, to the development of short and long term strategies

to address the "influenza" problem, and to the presentation and promotion of "influenza" programs.

The significance of influenza-the-virus to national health is substantial, but the measures used to assess its importance have many limitations. The medical consequences of illness can be described in terms of mortality, or deaths, and morbidity, or discomfort and disability. In estimating the morbidity and mortality due to influenza virus, two main difficulties arise. First, because of the overlap in clinical symptoms produced by different infectious agents, estimates of influenza-like illness would overstate the effects of the influenza virus. (The degree of exaggeration depends on the relative prevalence of other viruses at the time the estimate is made.) Second, influenza viruses not only cause death directly and in association with bacterial pneumonia, but very often may contribute to death in patients with other, serious primary illnesses, such as heart, lung and renal disease. In fact, during a typical year, the "influenza-related" deaths due primarily to other diseases are believed to outnumber those directly due to influenza and pneumonia.⁴¹

In order to detect the occurrence of influenza epidemics and to capture their full impact on mortality, the CDC has for years relied on a derived index, called "excess mortality." Mortality rates normally show a regular year-round fluctuation, highest in winter and lowest in summer. The CDC currently receives weekly mortality counts (total deaths and those attributed to pneumonia and influenza) from 121 urban centers around the country, comprising about 30 percent of the U.S. population. The CDC compares the observed mortality with the "normal" curve, which is based on a composite of several years' experience. If the reported mortality exceeds a certain threshold for two consecutive weeks, this is considered indicative of an epidemic. CDC sums the number of excess deaths reported by the 121 cities during the flu season (usually 2-3 months), computes an "excess mortality" rate per 100,000 population covered, and then extrapolates to the entire population to derive a total number of excess deaths in the country.⁴²

Computation of excess mortality is a sensitive way to identify the occurrence of an epidemic, but it may be an inaccurate indicator of influenza's importance as a national health problem. First, urban centers, having relatively dense concentrations of people, would be more likely to experience epidemic outbreaks; extrapolating from 70 million city dwellers to the entire country may therefore exaggerate national experience. Second, restricting the excess death counts to the influenza season fails to correct for those patients who would have died shortly (within the year) without any influenza. One old study concluded this effect was present, but small, and that most excess deaths occurred in people who

were not just about to die anyway.⁴³ A recent comparison of CDC's calculated excess mortality with annual mortality data compiled by the National Center for Health Statistics (NCHS) suggests that CDC's excess mortality estimates have tended to be too high in recent years.⁴⁴

In addition to possible inaccuracies of this sort, the number of deaths is an incomplete measure of the importance of influenza virus as a cause of death. For purposes of setting priorities among health programs, a vital, supplementary measure is the "years of life lost" due to disease.⁴⁵ This is a function both of mortality rate and age at death. Everyone is going to die, and what is important is not the fact of death, but its prematurity, the number of years of life expectancy foreclosed. This could be calculated from age-specific death rates compiled on an annual basis. But so far as we know, the calculation has not been done by CDC. Therefore, its attributions of mortality cannot be adjusted in this way. Elderly persons make up such a high proportion of influenza deaths that the adjustment could reduce flu's relative importance as a cause of death in this country.

A further limitation to the CDC's "excess mortality" measure is its inability to reflect the extent of *non*-fatal influenza. No mortality measure, even if otherwise perfect, can do that. The extent of temporarily disabling influenza can be decidedly important to employers and school superintendents alike, also of course to the patient. This, too, is an aspect of influenza's standing among national health problems. Indeed, the NCHS does count in its weekly household surveys the number of influenza-like illnesses in the population.⁴⁶ But that is just the difficulty. These measures cannot distinguish flu from other things that have the same effects on people. Catch-22!

The extent and severity of illness caused by the influenza virus appears to depend on characteristics of the virus, of people at risk of infection, and of the environment. Scientific understanding of the contribution of each is incomplete.

The influenza virus contains eight genetic fragments. This arrangement of genetic material into separate segments is unusual among viruses. When the influenza virus invades a host cell its genes commandeer the cell's machinery and synthesize seven proteins incorporated into the virus and a couple which are left in the host cell.⁴⁷ Two of those virus proteins are internal antigens, by which the virus can be typed as A, B, or C (in descending order of importance to humans). Two are the surface antigens, H (Hemagglutinin) and N (Neuraminidase), which undergo the major "shifts" and minor "drifts" that camouflage the virus to a host's antibodies. Shifts are attributed to the reassortment of gene segments from

two different influenza viruses. This primitive form of sexual reproduction results in a recombinant virus which has some properties of each parent. Drifts are believed due to mutation in a single gene.⁴⁸

As a matter of convention, influenza viruses are named according to a system adopted by the World Health Organization in 1971. The strain designation includes the antigenic type (A, B or C), the species from which the strain was first isolated (if non-human), the country or city where it was first found, its laboratory strain number and the year of isolation. In addition, for type A viruses, its specific H and N antigens may be cited, usually in parentheses following the strain designation. The swine flu virus, for example, was formally named A/New Jersey/8/76 (HswIN1).⁴⁹

Each antigenic shift to a new H or N antigen, or both, produces a new subtype of the virus. Type A subtypes now active include H1N1 (A/Russian) and H3N2 (A/Victoria). Within each subtype, there may be further variations caused by antigenic drifts. A/Texas, for example, drifted from A/Victoria; both are H3N2 viruses. For simplicity, we have used only place names in our narrative. There we deal only with type A flu, since that type alone is believed to cause pandemics.⁵⁰

Regarding the flu viruses, little is known about the determinants of infectivity (ability to invade cells and cause illness), mobility (ability to spread from person to person) or virulence (ability to cause serious disease and death). To further complicate matters, the greater the number of virus particles to which a person is exposed at one time, other things equal, the more likely is illness to follow. Attempts to test a new virus strain in human volunteers can give misleading results because laboratory passage of the virus may have attenuated its virulence.⁵¹

Different individuals are differently susceptible to infection and to complications from infection. Individual resistance to infection is related to a person's level of antibodies to the infecting virus. School-age children, especially age 5-14 years, are most commonly affected by influenza. Patients debilitated by other medical conditions are more likely to die from influenza than are healthy persons. Infants and the elderly are likelier to die than young adults (although the great pandemic of 1918 also killed many of them). These likelihoods rest on statistical associations and call for close scrutiny. Since so many flu-related deaths involve other diseases, either the virus has profound effects on healthy tissue outside the lungs or other illnesses contribute in a major way to deaths "from" influenza. Thus the statistical association of those deaths with age may actually reflect not years as such, but rather other illnesses common among

the elderly. A healthy oldster may be little or no more likely to die from flu than a healthy young adult.

Death from influenza is rare overall (less than 0.1 percent of cases), but mortality from a nationwide epidemic can be in the tens of thousands because of the enormous numbers afflicted. The large number of deaths attributed to the Asian flu in 1957 (more than 60,000) is probably due to the very high attack rate, and not to any unusual virulence of the virus.⁵²

Environmental effects, including biological, physical and social factors, can also alter the course of influenza. For reasons which are not understood, epidemic influenza is a seasonal illness in temperate climates.⁵³ Concomitant bacterial infection in individual patients can produce serious complications. A closed setting, such as a boarding school, nursing home or military base is conducive to the spread of disease. Indeed, experience at Fort Dix in 1976 emphasizes the hazards of projecting to the general community observation of viral spread in a closed community, where crowding and stress prevail.

One additional phenomenon is worth noting here: the second wave of a particular virus sub-type occasionally causes more deaths than the first wave. This was true of the 1918 pandemic worldwide, of the 1968-70 Hong Kong epidemics in Europe, and possibly of the 1889-90 Asiatic influenza.⁵⁴ It is not clear whether a particular virus may attain increased infectivity or virulence over time, whether some people become sensitized and overreact to subsequent infection or whether there is some other explanation.

Predictions of the severity and extent of influenza-the-virus in any given year are very shaky. In particular, speculations about periodicity of influenza pandemics rest on a slender factual base. Epidemiologists are largely confined to natural experiments, to the observed occurrence of influenza epidemics in the human population. Only since the 1930's have we had techniques for isolating and identifying viruses. Recognition of influenza subtypes came later. Since then there have been only a few influenza pandemics, a few observations with a relatively long time to discuss them and to theorize about them. Serological evidence can extend knowledge of previous epidemics back to the births of living individuals, but this offers at best a few more observations.

Long reflection on a limited number of observations has given rise to such conventional dogmas as the cyclical appearance of pandemics every decade or so.

Influenza pandemics are worldwide occurrences of disease, while epidemics are lesser but still wide-spread outbreaks. One careful historical review identified ten definite pandemics and ten possible pandemics in the past 250 years (not including this year's Russian flu).⁵⁵ The intervals between definite pandemics varied from 10 to 49 years, 24 years on average, and the intervals between all twenty definite or possible pandemics varied from 3 to 28 years, a 12-year average. Thus, pandemics have occurred at very irregular intervals, and the average interpandemic period has been between 12 and 24 years.

In addition to the questionable theory of regular pandemic cycles, there is a separate theory that influenza A has a limited number of subtypes which recycle through the human population.⁵⁶ This theory holds that subtypes reappear every other generation as those immunized by previous exposure die off, leaving a huge pool of susceptible people. The regularity of reappearance is questionable.⁵⁷ Old viruses can turn up again—witness this year's Russian virus, the same subtype as the virus prevalent (with minor drifts) from 1947 to 1957. Sadly for the theory, and maybe for the virus, it returned in just one generation.

Circumstantial evidence supports the idea that antigenic shifts in human influenza are due to recombinants of animal and human viruses.⁵⁸ The theory is that a human core gains animal surface antigens. Such a recombinant event, producing an antigenic shift, is believed prerequisite to worldwide pandemic. This is among the reasons why swine flu was taken so seriously when it reappeared in humans after many years in pigs.

Epidemic extent and severity (as measured by excess mortality) do not correspond in any simple way with antigenic changes in the virus. Experience with the Fort Dix virus reconfirms a few earlier observations that new antigenic strains isolated in humans do not necessarily take hold in the population.⁵⁹ We do not yet know enough to predict which new strains will take hold and which won't. Since viruses were first isolated in the 1930's, the only universally acknowledged antigenic shifts with wide effects on people came in 1957 (39 years after 1918), 1968 (11 years after 1957) and in 1977-78 (9 years after 1968). The 1947 virus is considered a shift by some and the product of a sequence of drifts by others.⁶⁰ Since the mid-1930's, the greatest "excess mortality" in the United States attributed to influenza occurred in the years 1937, 1943, 1953, 1957 and 1960, only one of which (1957) was also the year a shift occurred and pandemic ensued. In 1968, also a year of antigenic shift, there was less mortality than occurred in the other years listed.⁶¹

The lack of correspondence between antigenic shifts and excess mortality punctures a traditional piece of conventional wisdom. The new

conventional wisdom, becoming current since the swine flu affair, is that flu mortality is not alone or even mainly a problem of pandemics.⁶² It is now seen to center in the frequent epidemics, which occur every one to three years.

Prevention and Control

There is no completely effective and safe way to guard a population against influenza virus. The principal means which have been proposed are vaccines and drugs.

Traditional teaching in medicine's antibiotic era has been that bacterial disease is treatable, but there are no good drugs against viruses. This is no longer true, at least not for all viruses. The drug amantadine appears to be effective in preventing type A influenza, and some believe it will also shorten the course of illness.⁶³ A few physicians advocate its use during flu season, especially for high-risk patients.⁶⁴ However, it is dismissed as an "impractical" intervention by others in part because of questions regarding its efficacy and in part because of side effects.⁶⁵ These side effects are mainly mild central nervous system reactions such as dizziness, insomnia and confusion, and while uncommon at recommended dosages, occur more often in the elderly. Some physicians have extensive experience with amantadine, but it has not been used on a scale large enough and time period short enough to detect unanticipated, very rare side effects. To be an effective preventive, amantadine must be used daily and would cost approximately 50 cents per day or roughly the same as a single dose of vaccine good for an entire season. Despite its uncertainties and drawbacks, amantadine deserves serious consideration, at least as an adjunct measure, in planning for influenza epidemics.⁶⁶

Research is also underway on other antiviral agents, such as interferon, a naturally produced substance which inhibits viral invasion of cells. As additional information accumulates, and possibly as new drugs are identified, reliable antiviral agents are likely to become more important weapons to counter influenza in the future. If and as they do, the roles of the FDA and private sector probably will increase relative to those of CDC and the state health departments. Tensions may impend in and among agencies, to say nothing of researchers with different agendas.

Naturally acquired influenza stimulates many of the body's defenses against subsequent infection: local defense cells gear up, secretory antibodies coat the respiratory tract and serum antibodies circulate in the blood. Vaccination, by contrast, primarily produces a rise in specific, circulating antibody. This is sufficient to provide some protection, but the quality of immunity differs from that following natural infection.⁶⁷

Both anti-hemagglutinin and anti-neuraminidase antibodies contribute to resistance from infection. However, the former is much more protective than the latter.⁶⁸

Vaccination strategies differ for different diseases. In smallpox eradication, for example, the idea was to contain disease by vaccinating people in the immediate vicinity of any new cases. In another instance, children are vaccinated against rubella (German measles) so they will not carry disease to their pregnant mothers. Some vaccination programs aim at herd immunity, achieved by vaccinating enough people to suppress epidemic spread in a population. Some have advocated this approach for influenza.⁶⁹ However, herd immunity does not seem reliable for influenza at achievable levels of immunization in the population.⁷⁰ Outbreaks have spread in boarding schools, even when more than 95 percent had been vaccinated.⁷¹ Therefore, advocates of influenza vaccination usually stress protection for the individual against the virus and its consequences, without regard for herd effect. This was the prevailing view at CDC in 1976 and is so now. Civilian immunization programs typically focus on the groups at increased risk of death, for example, the elderly and the chronically ill. Military forces try to prevent illness in large numbers of their troops at the same time.

Both live and killed virus vaccines are used in different countries to prevent influenza. Live vaccine has certain theoretical advantages, including protection more akin to that from natural infection and lower volume of virus required for immunization, but questions about its dependability, safety and acceptability (it must be inhaled) have thus far discouraged its use in the United States.⁷² Over the near term, killed virus vaccine will probably remain the key element in programs to control influenza in the United States.

Insofar as scientists can more quickly produce more potent vaccines against a broader spectrum of strains, longer-lasting and with fewer side effects, we will strengthen our hand against the influenza virus. No strategy against the virus, no matter how successful, copes with the whole "influenza" disease problem.

In the remainder of this section, we will touch upon vaccine production and side effects, both highlighted in the swine flu story, and then discuss technical issues related to vaccine effectiveness.

Producing vaccine entails a series of connected steps.⁷³ The first two are isolation of the virus and preparation of recombinant strains. Kilbourne pioneered recombinant technique.⁷⁴ His laboratory still sets standards and has customarily prepared recombinant strains for vaccine production,

as with swine flu. The next steps are seed lot preparation, growth of vaccine (in enough embryonated eggs), inactivation, purification and concentration in bulk. This is where the manufacturers paused in the summer of 1976. The last steps are dilution to required strength and packaging.

What matters in production is not only the time until the first dose of vaccine is ready for testing, but also the rate and volume at which vaccine is produced thereafter. Technical improvements in any stage may speed production of the first dose, but the volume of output can be rapidly expanded only by widening a choke-point. That point, we are told by laboratory specialists for one manufacturer, is the purification process. Research to prepare for intensive production in the future should focus on such points. They, not facilities in general, limit production.

Rare side effects can be detected only by a comprehensive and sensitive surveillance system. These are unlikely to reveal themselves during field trials. Whether side effects such as Guillain-Barré syndrome are related only to swine flu vaccines, or to any influenza vaccine, or to any vaccine of any kind, is not now known.

The effectiveness of flu vaccines in the general population remains uncertain. Despite administration of millions of doses of vaccine, there have been no direct measures of the extent to which immunization reduces mortality. In terms of ability to prevent disease, the measured effectiveness of influenza vaccines has ranged in different studies from zero to 100 percent.⁷⁵ The expert consensus is that present influenza vaccines would be about 60 to 80 percent effective in the general population.⁷⁶ By this is meant that compared to an unvaccinated group, 60 to 80 percent fewer people in a similar but vaccinated group will contract influenza.

There are many determinants of vaccine effectiveness and of differences in measured effectiveness.

One of these is variability in the amount and potency of antigen in supposedly equivalent vaccines. Up until this year, the standard vaccine content was measured in CCA (chick cell agglutination) units. However, CCA directly measures only the biologic activity of one viral protein and not its immunologic activity, nor does it reflect the amount of antigen in a dose of vaccine. This shortcoming is well recognized, and work has been done at NIAID and BoB to develop a better standard of measurement for antigenic amounts. The question of antigenic potency (ability to stimulate antibody response) for a given amount of antigen is particularly important because of the different types of killed vaccine produced by different manufacturers—some using whole viruses and some using

chemically split viruses. Whole virus preparation and split virus vaccines both have their advocates, the first because of potency and the second because of lessened reactivity. Other, more subtle differences in manufacturing technique may also affect vaccine potency.

Healthy persons will differ in their antibody response to equally potent doses of vaccine, depending on age and previous exposure to this or similar antigens. There will also be normal biologic variation in antibody response among persons of similar age and antigenic history. In persons who have never been previously exposed to a particular viral antigen, often the case with children, it may take two separate injections, the first used as a "priming" dose, to stimulate adequate antibody response.⁷⁷

In general, resistance to influenza virus increases as specific antibody level rises, but level of antibody is not the sole factor in protection from the virus.⁷⁸ Changes in the infectivity of the virus, differences in numbers of invading organisms, alterations in the biological, physical or social environment can all affect the likelihood of illness in an individual who has a given level of circulating antibody.

Antibody is most reactive with the specific antigen which prompted its production. However, there is often some degree of cross-reactivity with similar antigens. To the extent that influenza viruses in the field undergo antigenic drift, or that the seed virus preparation and vaccine production alter the antigenic content of the vaccine, immunization effectiveness will be compromised.

Variation in the interval between vaccination and exposure to the virus will also affect the degree of protection. Two or more weeks must pass before a person produces adequate antibody to an injected antigen. The duration of protection from a shot of influenza vaccine is controversial, but there probably is some decline in protection after about six months.⁷⁹ Part of the reason for disagreement is that those who believe in longer term protection attribute rising attack rates to antigenic drift in the virus.

Different methods for assessing vaccine effectiveness can produce differences in apparent efficacy. These include methods of testing and surveillance as well as the criteria for diagnosis.⁸⁰ All ways to assess vaccine depend on differences in disease rates between vaccinated and unvaccinated. Thus the incidence of influenza must reach a rather substantial level before differences can be detected. Testing and surveillance wait on that. Problems with diagnosis are related to the fact that flu-like illnesses may not be caused by influenza viruses. If the clinical syndrome alone is considered indicative of influenza, the apparent efficacy of vaccine will decline; infection by other agents, unaffected by the vaccine, will be

counted against it. Laboratory identification of the influenza virus would solve that, but isolation of the virus is too inconsistent among cases to be useful in assessing vaccine effectiveness. Clinicians often rely on a four-fold rise in antibody level, from before to after illness, to show infection by a particular agent. But the usual antibody rise in response to infection may be stifled by recent vaccination. Hence, persons genuinely ill from flu soon after getting shots might not be counted as cases of influenza; apparent vaccine efficacy then would rise higher than it was in fact.

Finally, observed vaccine effectiveness in one population may not apply to others. Findings in the military may not apply to civilian populations; findings in nursing homes may not apply to the elderly living on their own; and findings in one age group may not apply to another.

Taken together, the foregoing comments elaborate, selectively, the five features of influenza we set forth in Chapter XII: first, a capricious virus; second, short-lived (and partial) protection against it; third, attribution to it of assorted other ailments; fourth, a mimicking by others of its symptoms; and as a consequence, the fifth, entanglement of influenza-the-virus with influenza-the-disease, causing confusion in the measurement of impact. These are the features that, taken together, give influenza standing in our eyes as an extremely slippery phenomenon.

Regarding swine flu, one question remains to be asked. In 1918, something extraordinary happened: Why? What accounts for the most devastating influenza pandemic history records? Why were young, healthy adults carried off as surely as the elderly and infirm? Epidemiologists have debated for sixty years. Theories abound, but nobody knows. Perhaps concomitant bacterial or other infection played a major role, perhaps the stress of war or other environmental factors made a difference. If so, well and good, for the times have changed and today we have potent antibiotics. But conceivably a large part of that pandemic mortality was due to some intrinsic feature of the virus, a characteristic that may be harbored even today on a gene fragment somewhere in the animal kingdom, a gene that could just possibly combine with human virus.

Despite impressions left by the swine flu affair, this remains a possibility. Ford could not accurately predict the killer and was thus severely limited in seeking to guard everyone against it. Mathews, Cooper and Sencer could not do so either. Neither could their scientific advisers. Nor can anyone in 1978. Only research, perhaps, someday will manage that.