

“A Multicenter, Randomized Dose Response Study of the Safety Clinical and Immune Responses of Dryvax® Administered to Children 2 to 5 Years of Age”

I have reviewed the NIAID protocol entitled “A Multicenter, Randomized Dose Response Study of the Safety Clinical and Immune Responses of Dryvax® Administered to Children 2 to 5 Years of Age”, the consent forms, and other supporting documents.

The proposed protocol is well-designed to address the stated objectives. However, this protocol does not warrant approval under 45 CFR Part 46.404, 405, or 406. The protocol does not qualify under 404 because the risk to participants is greater than minimal. It does not qualify under 405 because the anticipated benefit is very small based on the theoretical (and immeasurable) risk of exposure to smallpox from bioterrorism in the participant’s community. The protocol does not qualify under 406 because the risks are more than a minor increase over minimal risk and not commensurate with experiences in the expected medical situations for the healthy children that are proposed for study. This situation could change and the protocol would qualify under 405 if there were more concrete evidence that the children were at risk of exposure to smallpox. In that situation, the potential benefits would outweigh the known risks from the vaccine.

The protocol does warrant approval under 45 CFR 46.407 if some modifications are made to the consent form and additional consideration is given to alternative study designs that would minimize the number of children exposed to the risks from the vaccine.

Is there a justification for performing this study in children when the Dryvax® vaccine proposed for study has been evaluated and found to be highly effective when the vaccine was undiluted, diluted 1:5, or diluted 1:10 in 680 adults? The adult study involved administration with 15 insertions of a bifurcated needle. A new diluent (50% glycerin and 0.21 % phenol in sterile water) was used and response rates of 97% and 99% were obtained with 1:5 and 1:10 dilutions respectively. Thus, the diluted vaccine would be acceptable for use if there was a need for emergency use of Dryvax® within the next few months.

The only pediatric studies with diluted Dryvax® were reported in 1977. When Dryvax® was diluted with 5% peptone (Benenson et al J Infect Dis 1977; 135:135-144) and administered with five bifurcated needle insertions, a 1:10 dilution induced only a 74% “major reaction” rate (Cherry et al J Infect Dis 1977). Possible explanations for the lower response rate in the 1977 study include differences in the diluent, the lower number of bifurcated needle insertions for the earlier study, and differences in definitions of “a response”. The titers of vaccine virus studied in the 1977 pediatric and recent adult studies appear to be identical. There is no biologically plausible reason to expect children 2-5 years of age to respond less well to this or any other live viral vaccine than adults if the vaccine virus and administration methods were the same. Under 15 months of age, passively acquired maternal antibodies can interfere with the immune response to live virus vaccines and the immune response may be somewhat immature as compared to adults; but above 2 years of age there is no impairment of the immune response to any other live viral vaccine as compared to adults and children often respond better than adults. For example, the response to one dose of varicella vaccine is sufficiently greater in children than in adults to recommend one dose for primary immunization of children under 13 years of age and two doses for older persons. There is no impairment in the immune response to measles vaccine, oral polio

vaccine, yellow fever vaccine, mumps, or rubella vaccines in children ages 2-5 as compared to adults.

In order to justify exposing children to the risks associated with smallpox vaccine in the absence of a known risk of exposure to smallpox, all possible explanations for the lower responses to vaccine in the studies done in the 1977 study should be explored in detail. Investigators who conducted the studies in the 1970's should be queried and the manuscripts carefully reviewed to determine if there are any other explanations for the differences in the response rate, such as other methodological issues. My review suggests focusing on the number of insertions, the technique used for the insertions, and the diluent. There was a wide variety of "take" rates at the different institutions participating in the study suggesting variations in administration technique might explain the differences.

Several modifications should be made in the information provided to parents. In the 1st paragraph of the "Dear Parent" letter, the statement "Routine Dryvax® immunization was stopped in 1971 because the world was declared free of smallpox." is incorrect. Routine immunization against smallpox was stopped because of the serious adverse events associated with smallpox vaccine and the very low risk of exposure to smallpox. The last case of naturally occurring smallpox occurred in 1977 and the world was not declared free of smallpox until 1980.

The consent document should provide more complete information and avoid language that minimizes the potential risks from this vaccine. Specifically, on pages 5-6 under item 4, there is no mention that 1/3 of adults who received Dryvax® had sufficient discomfort and/or inability to use their arm that they missed school or work. On the consent form there is a notation of central nervous system "infection" at the bottom of page 6, but there is no mention that severe persistent neurologic sequelae are common in children who develop post-vaccinal encephalitis. Moreover, the consent form implies that treatment with VIG and/or Cidofovir is effective against all complications of smallpox vaccine. This is not the case. There is no known effective therapy for post-vaccinal encephalitis. VIG is not indicated for vaccine keratitis as detailed in the protocol. The consent form should note that Cidofovir is associated with a high rate of renal failure. On page 7, the wording of adverse effects minimizes the risks by using the term "less than" on lines 4 and 7. The rate of post-vaccinal encephalitis was 9.5 per million for children 1-4 years of age (MMWR June 22, 2001), not "less than 3 per million" as noted on page 7.

As part of consent process, consideration should be given to showing photographs of primary takes, robust local responses, and some of the common skin rashes that occur in children.

The potential benefit from developing protection against the smallpox virus is only a benefit if there is a true risk of exposure. The risk of exposure to any one child in the country is close to zero, but the potential for a bioterrorism event is unknown. Many parents incorrectly believe that the risk of potential exposure is very high.

Parent's understanding of the expected adverse events associated with smallpox vaccine would be enhanced if the parents have recently received the vaccine. Consideration should be given to determining if any of the 680 adults who participated in the recently published studies have children and if they would be willing to allow them to participate in a similar trial. Also, children

born to adults who received smallpox vaccine recently because of occupational exposure to vaccinia in laboratories would be good candidates for this study. These parents have recent experience with the side effects from smallpox vaccine so they can better judge the acceptability of giving the vaccine to their children. Also, their children are at some risk of accidental exposure to vaccinia that could be brought home on clothing or other articles from the workplace.

The investigators argue that it is necessary to have children remain out of school or daycare for 30 days after vaccination in order to minimize the risk of transmission of smallpox vaccine virus to their contacts. Do they intend children from having direct contact with all other children during this same time period? The Advisory Committee on Immunization Practices has recently recommended that health care workers can continue to care for patients following smallpox vaccination if the lesion is covered with gauze and a semi-permeable dressing as proposed in this protocol. Given these decisions, reconsideration of the need for children to remain out of school or day care should be undertaken. If it is not necessary for children to remain out of school, then is there a need to bypass studies in children 5-17 years of age which normally would be conducted prior to studying 2-5 year old children?

Since smallpox vaccine is associated with increased risks of serious adverse events and the likelihood of any benefit to the participant is very small, there is an obligation to limit the number of children receiving vaccine to the minimum necessary to answer the primary objective. Most studies evaluating a modification of standard techniques call for comparing the modified approach with the standard approach as is proposed by the investigators. However, for most vaccines there is a direct benefit to the participant and the vaccines being evaluated are associated with a low risk of serious adverse events. Since this is not the situation with smallpox vaccine, consideration should be given to eliminating the study of undiluted vaccine in children because all studies have shown very high "take" rates that can be easily measured. If the investigators administered vaccine diluted 1:5 to 30 children and all 30 develop a "take", then there is a 95% probability that the true "take" rate is greater than 90%. This information would be sufficient for me to recommend widespread use of the 1:5 dilution of this vaccine in the event that smallpox is used in a bioterrorism event and there were inadequate supplies to administer undiluted vaccine to the target population. If a lower "take" rate was observed, additional studies would be indicated.

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