

The Effectiveness of Evaluating Mumps Vaccine Effectiveness

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(See the article by Peltola et al. on pages 459–66)

In 2006, there were 5783 cases of mumps reported in the United States by October, which was the largest outbreak to occur in the United States in several decades [1]. The disappointing performance of mumps vaccine during the recent outbreak has resulted in a reexamination of its efficacy. Among the factors that have complicated these estimates have been the interpretation of antibody measurement and the occurrence of subclinical cases of mumps. If the objective is to simply decrease clinical illness, the evaluation of cases of mumps parotitis is adequate. If the goal is to interrupt transmission, subclinical cases must also be considered, because individuals with these cases shed virus [2] and presumably are capable of spreading infection. The failure of isolation of patients with mumps to prevent the spread of disease has been attributed to the shedding of virus prior to or in the absence of parotid swelling [2].

If comparisons are made between vaccinated and unvaccinated groups, the effect of prior subclinical infection should not affect efficacy estimates, because the

proportion of individuals with immunity should be the same in both of these groups. This would not be the case if vaccination prevented some clinical cases and converted other cases to subclinical infections capable of spreading disease, as in pertussis [3]. If one compares only clinical cases, the true effect of vaccination with respect to the prevention of infection would be inflated. The subclinical attack rate for mumps vaccinees who are exposed to mumps has not been established. If one were to be satisfied with simply preventing morbidity and not preventing transmission, this would not be a concern. This may be acceptable in a population of heavily immunized individuals, where the possibility of transmission to a susceptible individual is negligible. When there is an accumulation of susceptible individuals who are grouped together in educational institutions or in the military, subclinical infection might play a significant role in spreading infection and perpetuating the epidemic.

It is noteworthy that a significant proportion of the cases in the recent US epidemic occurred among college students, a population in which intimate contact was likely and the chances of transmission increased; the median age of the patients was 22 years. The paucity of cases in younger children, particularly in those enrolled in day care, would suggest that recent vaccinees may be better protected than others [4]. If vaccine-induced immunity is waning, this would be unfortunate, because

the morbidity associated with mumps, as is true of many childhood diseases, is much greater in adults. A significant number of the students who were affected experienced complications (e.g., meningitis and orchitis). Approximately 95% of the students with mumps and one-half of all patients with mumps had previously received 2 doses of vaccine. A second dose, which has been effective in other countries in controlling mumps [5], is now recommended for this group [1].

Evaluation of the results of vaccine trials is dependent on accurate serological testing. Unfortunately, assays for susceptibility generally fail to assure that seronegativity represents susceptibility and that seropositivity represents immunity. In an article by Shehab et al. [6], 49 serum samples from a group of unvaccinated 1-year-old infants who had no history of mumps in a community in which mumps had been eliminated were used to establish a seronegative range for an in-house ELISA. A group of 19 health care workers in a pediatric clinic who were old enough to have had natural mumps served as the putative immune group. There was clear separation in the values for the 2 groups. These serum samples, when tested with a microneutralization test in our laboratory, gave identical results for seropositivity and seronegativity. Using the neutralization test to evaluate the results of prior vaccination in 301 children, the vaccine failure rate decreased from 12% to 7.6% if the amount of challenge virus in this assay was

Received 23 April 2007; accepted 18 May 2007; electronically published 10 July 2007.

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Clinical Infectious Diseases 2007;45:467–9

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1058-4838/2007/4504-0010\$15.00

DOI: 10.1086/520027

increased by one-half of a log [6]. Thus, a neutralization test should not be considered to be the gold standard if the predictive value of the test is not established. The failure rate with the lower virus challenge was similar to that found in our study of mumps vaccinees 15 years previously [7]. These estimates are closer to the current estimates of efficacy than they are to the original estimates [8]. They indicate how the sensitivity of the assay can affect efficacy estimates.

It is essential that those who are evaluating vaccines or reviewing manuscripts insist on estimates of the likelihood that a seropositive test result represents immunity and that the converse also is true. Unfortunately, the statement that an assay is approved by the Food and Drug Administration does not provide this assurance. Serological tests are considered to be devices and are not evaluated as vaccines or drugs are. It makes little sense to insist on meticulous statistical analysis of data that may be faulty.

In the original efficacy estimates, a hemagglutination inhibition assay value of <1:10 was assumed to represent susceptibility and was used to screen enrollees. However, many of the vaccinees responded with values of 1:5 or lower. Therefore, those that had a prevaccine hemagglutination inhibition assay titer of <1:10 underwent additional testing with a neutralization assay, which had been found to be more sensitive. Many of those who did not respond by hemagglutination inhibition assay had neutralizing antibody responses. These included some individuals who had a prevaccination hemagglutination inhibition assay titer of 1:5, which was considered to be nonspecific [8]. The clinical efficacy, comparing vaccinated and control groups, was 95% [9]. Among these mainly school-aged children who had not received routine vaccination, approximately one-third of those with no history of mumps were found to be seropositive at the time of enrollment [8]. One must assume that they had previously experienced subclinical mumps infection during a period

when mumps was prevalent. In our studies, conducted during the same period, the number of seropositive subjects without a prior history of infection increased with age and was ~50% by school entry [7]. These children develop antibody when they are infected, even though they do not experience parotitis [2], and they would not be expected to get mumps if exposed, whether or not they were vaccinated.

If, without accurate pretesting to eliminate those who were immune, one simply determined the rate of mumps among vaccinees, it would be expected to be lower in older studies, performed when mumps was endemic and when a greater proportion of the vaccinees would have been immune prior to vaccination, than in studies conducted at present, when mumps is uncommon. The effect of preexisting immunity was illustrated during an outbreak of mumps in an Inuit community that had not undergone routine vaccination. The attack rate was 74% among the total exposed population and 85% if individuals who had previously been seropositive were eliminated from the calculation and only seronegative individuals were included in the estimate [10].

In any assessment of efficacy, accurate case ascertainment is essential. There are many causes of parotitis in addition to mumps [11], and in epidemic situations, these cases probably are infrequent enough that they do not significantly affect estimates of efficacy. However, an attempt should be made to ascertain the etiology in sporadic cases. We found that only one-half of individuals who developed parotid swelling long after vaccination had cases that could actually be attributable to mumps [11]. Laboratory confirmation has become very important, because clinical experience has probably decreased in the absence of large numbers of cases of mumps. Isolation of mumps virus, as well, is not something with which many laboratories have great experience. PCR testing has not been adequately evaluated, nor have antigen detection assays. The Centers for Disease Control and Prevention rec-

ommends IgM testing, but these tests, too, require careful standardization and experience. These assays are fraught with non-specificity, caused mainly by "rheumatoid factor" or IgG directed against IgM. These commonly occur following most viral infections and are found in serum at levels easily detected by a sensitive ELISA; they are not usually positive for rheumatoid factor in conventional assays. IgM tests usually either remove IgG or use an antibody capture assay. Most removal techniques usually have to be repeated to assure that all of the IgG has been removed. Ideally, removal should be ascertained before the serum sample is tested for viral IgM. The antibody capture technique requires standardization of the anti- μ capture layer, the viral antigen to be used, and the anti-mumps antiserum [12], and most laboratories are unwilling to perform such a complex technique.

In citing the literature on mumps vaccine efficacy, it is important to be certain of the strains used in the vaccines. In comparison studies, at least 1 of the vaccine strains, Rubini, which had been included in many vaccines used abroad, was shown to be inferior to the Jeryl Lynn vaccine strain, which is used in the United States [5].

As Peltola et al. [5] point out in their excellent review, there are many factors to be considered when evaluating mumps vaccine. In less developed countries, the cost certainly is a major issue, and this must be evaluated with respect to other health priorities. In addition, it should be appreciated that efficacy rates that are based on clinical cases alone may yield misleading results. The frequency of mumps in the population may affect certain efficacy estimates if vaccinees are not pretested for immunity. In areas of high disease incidence, subclinical infection may be more of a concern than it is in highly immunized groups. The duration of immunity must be monitored to be certain that a relatively benign childhood disease is not converted into a more severe disease by virtue of waning immunity in

vaccinees. A 2-dose schedule appears to have controlled mumps in several countries, as has been pointed out by Peltola et al. [5]. We should pay particular attention to assuring that our serological tests for immunity truly measure immunity, because their quality will determine the accuracy of clinical trials and surveillance.

Acknowledgments

Potential conflicts of interest. P.B.: no conflicts.

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