Evaluation of Vaccines to Prevent Childhood Pneumonia: Lessons Relevant to Planning Tuberculosis Vaccine Trials

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Bacterial pneumonia in children is usually caused by one of the two leading pathogens, Streptococcus pneumoniae (pneumococcus) and Haemophilus influenzae, either type b (Hib) or nonencapsulated types. Hib conjugate vaccines suitable for use in infants have been available for about a decade, and experience with a trial of one of these vaccines in Africa showed that the vaccines can prevent Hib pneumonia, as well as other manifestations of Hib disease. It also showed that vaccine trials can provide useful estimates of the role of Hib in childhood pneumonia. Trials of pneumococcal conjugate vaccines that are currently under way have been designed to estimate disease burden and efficacy. A major risk of vaccine trials that use bacteriologic end points is that the vaccine may affect the diagnostic test itself, creating a misleading impression of efficacy. Trials of future tuberculosis vaccines are discussed in light of these experiences. It is important that the trials are designed to measure the effect on all clinical disease, as well as strict microbiological end points. The existence of bacille Calmette-Guérin (BCG) complicates future trials, and such trials should take into account possible nonspecific effects of BCG in addition to its effect on tuberculosis.

Bacterial pneumonia is the most important cause of child deaths in the world [1]. Vaccines against the 2 main bacterial causes are now available or under development. This article briefly describes the evaluation of these vaccines in developing countries and draws on this experience to help design trials of future tuberculosis vaccines.

The 2 leading causes of bacterial pneumonia are Streptococcus pneumoniae (pneumococcus) and Haemophilus influenzae type b (Hib) [2, 3]. Vaccines to protect young infants from invasive Hib disease became available in 1990 after several Hib conjugate vaccines (capsular polysaccharides conjugated to a protein “carrier”) had been shown to protect against invasive Hib disease, mainly meningitis, in studies in the United States and Finland [4, 5]. Protection against pneumonia had not been demonstrated, and because pneumonia is the most important manifestation of Hib disease in developing countries, a trial was planned to evaluate the efficacy of one Hib conjugate vaccine in a developing country.

The vaccine chosen was Hib polysaccharide–tetanus toxoid conjugate (PRP-T; Act-HIB, supplied by Aventis Pasteur, Lyon, France). The site was the Gambia, a small country in West Africa, where several studies of pneumonia etiology had been conducted in the past. The study objectives were to evaluate the efficacy of PRP-T for the prevention of Hib pneumonia (proven by blood or lung-fluid culture), all invasive Hib disease, and Hib carriage. More than 42,000 infants were enrolled in a double-blind trial in which they received either diphtheria-tetanus-pertussis vaccine (DTP) alone or DTP mixed with PRP-T, at 2, 3, and 4 months of age. All vaccines were given in government health centers, and surveillance for pneumonia and meningitis was undertaken at the 3 hospitals in the study area and at the larger health centers. A detailed description of the study is available elsewhere [6].

After 2.5 years of enrollment and nearly 3 years of surveillance, the study was terminated. The number of children enrolled and investigated in the two groups is shown in table 1. The primary end points, as laid out in the analytical plan, were strictly microbiological outcomes. Efficacy against Hib pneumonia, as defined above, was estimated at 100% (10 cases were identified, all in placebo recipients), whereas efficacy against all invasive Hib disease was 95% (PRP-T recipients, 1 case; placebo recipients, 19 cases). Protection against Hib carriage in the second year of life was 60% (PRP-T recipients, 4%; placebo recipients, 11%).

Despite these results, doubts remained about the effect on pneumonia. Further analyses were conducted in which 2 definitions of pneumonia were used: one highly sensitive (cough with fast breathing) and one highly specific (definite alveolar consolidation evident on a radiograph). These analyses (table 2) showed that the incidence of pneumonia with definite alveolar consolidation was reduced by 21% among the PRP-T recipients, demonstrating both the ability of the vaccine to prevent pneumonia and the contribution of Hib to the total pneumonia burden. The latter point was in sharp contrast to the findings of earlier studies, in which investigators had estimated
the contribution of Hib to the burden of pneumonia to be 5%–10% [7].

In this study, it was the clinical end point that provided the information needed to determine the public health use of the vaccine in developing countries. This is an important lesson, relevant to any vaccine trial in which a large proportion of actual cases are not detected because of insensitivity of the diagnostic test.

Pneumococcal conjugate vaccines have been developed along lines similar to the Hib conjugate vaccines and are ~10 years behind in their development. The pneumococcus is a more difficult target than Hib, because it causes disease throughout life, from the neonatal period to advanced age, and there are 90 serotypes capable of causing disease. Pneumococcal conjugate vaccines currently under investigation cover 9 or 11 of the most important serotypes. Three phase III trials are under way in the United States, Finland, and South Africa. Another trial in the United States is complete, and 4 others are in advanced stages of planning. The completed trial, in northern California, showed a high degree of efficacy against the bacteriologic end point evaluated, but it also demonstrated that the vaccine prevented a substantial number of respiratory tract and ear infections that were not blood-culture-positive (H. Shinefield, Kaiser Permanente Vaccine Study Center, Oakland, CA, personal communication).

Investigators in one of the ongoing pneumococcal trials, conducted in the Navajo population in the United States, are employing a novel system of randomization, cluster randomization. In this study, the unit of randomization is a community unit, so that all children in a given community are assigned to the same choice of vaccine or control group. This design may be relevant to trials of new tuberculosis vaccines. The advantages and disadvantages of this system are listed in table 3.

Cluster randomization provides a measure of the sum of individual protection and the herd immunity that results from living in a community where many individuals have received the vaccine. Thus, it provides the best approximation of the expected effectiveness of large-scale introduction of the vaccine. There is some loss of power, but this can be minimized, provided sufficient units of randomization are used. The main risk of cluster randomization is that viral epidemics may disproportionately affect a small number of clusters, producing a bias in estimates of the effect of the vaccine on all-cause pneumonia. Another disadvantage, one particularly relevant in developing countries, is the possibility that variability in access to care will lead to case-ascertainment bias. Despite these risks, this is a suitable design for evaluating a vaccine that can be expected to have a significant herd effect.

The potential for microbiological end points to provide misleading results was demonstrated in a study of the efficacy of pneumococcal polysaccharide vaccine in South African gold miners [8]. In that study, 1523 miners received the vaccine, and 3171 served as control subjects. Vaccine efficacy was apparently 80%, as only 10 cases of blood-culture-positive pneumococcal pneumonia were detected among vaccine recipients, whereas 50 would have been expected on the basis of the incidence in the control group. However, the difference between the total number of pneumonia episodes detected among vaccine recipients and the number that would have been expected (given the rate in the control group) suggested that the number of pneumonia episodes prevented was actually less than the 40 blood-culture-positive episodes that appeared to have been prevented.

This finding suggests that some of the blood-culture-positive pneumococcal pneumonia episodes that appeared to have been prevented were actually converted from bacteremic cases to nonbacteremic cases. Thus, the measured vaccine efficacy of 80% was probably misleading, whereas the clinical end point gave a better indication of the true value of the vaccine. The use of an insensitive bacteriologic end point that could itself be affected by the vaccine is a major risk for this sort of trial and could also be a problem for future tuberculosis vaccine trials.

Pneumococcal conjugate vaccine trials currently under way are designed with microbiological end points, but there is a growing awareness of the importance of identifying the end points relevant to the public health impact of the vaccine. In addition, new vaccine trials in developing countries will be designed to yield information on the disease burden attributable to the organism, in addition to vaccine efficacy. This information will then be usable in the context of future smaller

Table 1. The number of children enrolled and investigated in the Gambian *Haemophilus influenzae* type b (Hib) vaccine trial.

| Variable                        | PPR-T recipients | Control subjects |
|---------------------------------|------------------|------------------|
| Enrolled                        | 21,490           | 21,358           |
| Investigated for possible Hib disease | 1272            | 1342             |
| Chest radiograph obtained       | 616              | 653              |
| Lumbar puncture performed       | 173              | 192              |
| Percutaneous lung aspiration performed | 71               | 75               |

NOTE. Data are no. of children. PPR-T, Hib polysaccharide-tetanus toxoid conjugate.

Table 2. The number of episodes of pneumonia in the 2 groups of subjects in a *Haemophilus influenzae* type b (Hib) trial. Two definitions of pneumonia were used, one highly sensitive (cough and fast breathing) and the other highly specific (alveolar consolidation).

| Definition of pneumonia      | No. of episodes among | Vaccine efficacy, % | No. of episodes prevented |
|------------------------------|-----------------------|---------------------|--------------------------|
|                               | PRP-T recipients      | Control subjects    |                          |
| Cough and fast breathing<sup>a</sup> | 873                   | 913                 | 4                        | 40                        |
| Alveolar consolidation<sup>b</sup> | 198                   | 251                 | 21                       | 53                        |

NOTE. PRP-T, Hib polysaccharide-tetanus toxoid conjugate.

<sup>a</sup> Respiratory rate >50 breaths/min for children 2–12 months of age and >40 breaths/min for children ≥12 months of age.

<sup>b</sup> Evident on chest radiograph.
Implications for the Design of Tuberculosis Vaccine Trials

Despite persistent problems with quality control and inconsistent efficacy data, there is general agreement that BCG vaccine protects children against tuberculous meningitis and miliary tuberculosis [9]. Although the value of infant BCG vaccination for the prevention of adult tuberculosis is unclear [10], it does appear to provide effective protection against leprosy [11]. The existence of an imperfect and variable but effective vaccine poses a special challenge for the conduct of future tuberculosis vaccine trials. It would be unethical to include a placebo arm under such circumstances, so although infant trials could be conducted to compare a new vaccine with BCG vaccine in the hope of detecting an improvement, studies of the vaccine given later in life would need to be done with the assumption that all participants had received BCG vaccine in infancy.

Therefore, only infant studies could provide the information to allow a new vaccine to eventually replace BCG vaccine. Assuming this is the objective, such studies should form part of the initial round of studies with a new vaccine. On the other hand, to have an impact on the substantial burden of tuberculosis in young adults in developing countries, a new vaccine will need to be effective when given to adults who have received the BCG vaccine in infancy. It would be ideal for both objectives to be addressed simultaneously in the first round of studies of a new vaccine. If the studies go well, then the next step would be to evaluate the vaccine among young adults who did not receive BCG in infancy. It is essential at the outset to define what will be expected of a vaccine under evaluation and to design trials with this in mind.

When a vaccine is given in infancy, the objectives are to prevent development of clinical tuberculosis in childhood, to prevent development of pulmonary tuberculosis in later life, and, if tuberculosis does develop, to reduce its severity and infectivity. Of these objectives, the prevention of childhood tuberculosis is a necessary prerequisite if the vaccine is to eventually replace BCG. In an infant trial, the definitions of clinical outcomes might be difficult, since many cases of presumed childhood tuberculosis are not proven, particularly in developing countries. Children presenting with progressive weight loss or unresolving pneumonia are frequently treated for tuberculosis without confirmation of the diagnosis.

A particularly interesting aspect of a successful trial of a new tuberculosis vaccine will be its impact on these difficult syndromes, which might reveal a hitherto unsuspected burden of tuberculosis presenting with nonspecific malnutrition. This picture could be further complicated by the nonspecific effect of BCG on the immune system, which may improve infants’ immunity to infections other than tuberculosis. This would be important information, so it is essential that such a trial evaluate other disease events, such as pneumonia and diarrheal disease, in addition to episodes of possible tuberculosis. It is not impossible that a new tuberculosis vaccine could offer improved protection from childhood tuberculosis, but this could be offset by reduced protection against other bacterial disease.

These points argue strongly for the use of a double-blind trial design. However, in such a trial the use of BCG in one group raises difficult issues with regard to blinding. These will need to be taken into account in the design.

The second potential use of a new tuberculosis vaccine that should be evaluated at the same time is for young adults who have received the BCG vaccine. Here the objective would be to prevent pulmonary tuberculosis and, if it occurred, to reduce its severity and infectiousness. With a BCG-vaccinated population, it would be acceptable to compare the vaccine with a placebo among young adults. Although herd immunity would not be an important consideration in an infant study (as most cases are acquired from infected adults), it would be an important consideration in a trial of young adults.

Therefore, serious consideration should be given to designs that employ cluster randomization for studies of efficacy in young adults, although population mobility may make this difficult in practice. Such a study could be done in the entire adult population of a high-risk community or even among high-risk individuals in an institution like a prison. Although the main outcome measure would be clinical pulmonary tuberculosis with sputum positive for acid-fast bacilli, it would also be important to measure the incidence of syndromes that could be compatible with tuberculosis, given the theoretical risk that a new vaccine could affect the outcome test but not the clinical

### Table 3.

| Variable                          | Individual randomization | Cluster randomization               |
|----------------------------------|--------------------------|-------------------------------------|
| Potential bias(es)               | Herd immunity            | Variable access to care; potential for clustering of pneumococcal or other respiratory disease (e.g., influenza) |
| Power                            | May be slightly reduced by the effect of herd immunity | May be slightly reduced by the design (depending on the no. of clusters) |
| Accuracy of the measure of protection | Maximal for individual protection | Measures the combined individual and herd protective effects |
| Practical value of results       | Predicts individual impact only | Predicts the effect of vaccine use in community, including the impact on antimicrobial-resistance rates |

Studies designed to estimate the vaccine-preventable burden of pneumococcal disease in various communities.
syndrome (i.e., reduce the number of acid-fast bacilli in the sputum but not reduce the number of cases).

A third potential use of a tuberculosis vaccine would be in cases of confirmed tuberculosis, as an adjunct to chemotherapy. There the objective would be to improve the outcome, in terms of morbidity and mortality, and to simplify and possibly shorten the duration of chemotherapy, thereby improving compliance and reducing the cost of therapy. In contrast to the other 2 uses, trials of this type would resemble drug trials and would be relatively simple to perform: they could be based in a treating institution and would require a sample of only moderate size.

Conclusion

Studies of the efficiency of vaccines for the prevention of bacterial pneumonia in children in developing countries provide useful insights for the planning of trials of new tuberculosis vaccines. It is essential that studies be designed to yield the information that will be needed for future decisions about the use of these vaccines in developing countries. When microbiological end points are used, they should be supported by evidence that the vaccine also reduces the total number of clinical episodes. A new tuberculosis vaccine may (1) prevent childhood tuberculosis as well as or better than BCG vaccine, (2) prevent adult tuberculosis when given to young, BCG-vaccinated adults, and (3) modify the course of established clinical tuberculosis. These issues need to be thought through carefully before any trials are begun. If possible, the different potential uses of the vaccine should be addressed simultaneously.

References

1. Garenne M, Ronsman C, Campbell H. The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries. World Health Stat Q 1992;45:180–91.
2. Adegbola RA, Falade AG, Baldeh I, Greenwood BM, Mulholland EK. The aetiology of pneumonia in malnourished and well nourished Gambian children. Pediatr Infect Dis 1994;13:975–82.
3. Shann F. Etiology of severe pneumonia in children in developing countries. Pediatr Infect Dis 1986;5:247–51.
4. Mulholland EK, Hilton S, Adegbola RA, et al. Randomized trial of Haemophilus influenzae type b-tetanus protein conjugate vaccine for prevention of pneumonia and meningitis in Gambian infants. Lancet 1997;349:1191–7.
5. Santosham M, Wolff M, Reid R, et al. The efficacy in Navajo infants of a conjugate vaccine consisting of Haemophilus influenzae type b polysaccharide and Neisseria meningitidis outer-membrane protein complex. N Engl J Med 1991;324:1767–72.
6. Eskola J, Käyhty H, Takala AK, et al. A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive Haemophilus influenzae type b disease. N Engl J Med 1990;323:1381–7.
7. Greenwood BM. Epidemiology of acute lower respiratory tract infections, especially those due to Haemophilus influenzae type b, in the Gambia, West Africa. J Infect Dis 1992;165(suppl 1):S26–8.
8. Smit P, Oberholzer D, Hayden-Smith S, et al. Protective efficacy of pneumococcal polysaccharide vaccines. JAMA 1977;238:2613–6.
9. Rodrigues LC, Diwan VK, Wheeler JG. Protective efficacy of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. Int J Epidemiol 1993;22:1154–8.
10. Fine PEM. Variation in protection by BCG: implications of and for heterologous immunity. Lancet 1995;346:1339–45.
11. Karonga Prevention Trial Group. Randomized controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for the prevention of leprosy and tuberculosis in Malawi. Lancet 1996;348:17–24.