

# Use of Vaccine Trials to Estimate Burden of Disease

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## ABSTRACT

Vaccine trials, the most informative way of determining the efficacy of a vaccine, can also provide valuable information about the burden of disease. The burden of *Haemophilus influenzae* type b (Hib) remains a major barrier to the use of Hib vaccines, especially in Asia. Recent studies in Indonesia and Bangladesh have used vaccine-trial designs, with known effective vaccines, to estimate the vaccine-preventable burden of Hib disease in those communities. New vaccines against pneumonia and diarrhoeal diseases are usually directed at only one of various causes of the syndrome. In the case of pneumonia, it is very difficult to determine the aetiology in most cases, so the vaccine trial offers a means of determining the burden of vaccine-preventable diseases. This is particularly important for pneumococcal vaccines as serotype replacement may reduce the effectiveness of the vaccines in the field. This approach would underestimate disease burden if vaccines were found to have an impact on syndromes other than those against which they are directed, and might lead to errors in estimation if there were erroneous assumptions about the efficacy of the vaccine against the condition under investigation.

**Key words:** Vaccines; Morbidity; Disease burden

## INTRODUCTION

Vaccination has been used for the prevention of specific conditions in different parts of the world for centuries, but the 20th century saw the development of vaccination as a highly effective global public-health strategy (1). The proof that a vaccine is effective has traditionally been provided by a vaccine trial, using epidemiological methods that have been developed over the course of the 20th century. Towards the end of the century, there was a dramatic increase in the price of vaccines, largely because their development and production has been taken over by a small number of large pharmaceutical companies (2). Thus, the later years of the century saw the price of vaccine rise from a few cents to over US\$ 50 per dose. This development has

meant that even rich countries must now weigh carefully the costs against the benefits of vaccination. The benefits can be seen as having two components—the burden of the disease that is to be prevented and the effectiveness of the vaccine. These two factors together comprise the vaccine-preventable burden of disease.

This paper discusses the growing use of vaccine trials as a method of measuring the burden of disease, the relevance of burden of vaccine-preventable disease as a concept, and the often unrecognized shortcomings of this approach.

In its simplest form, a vaccine trial can be seen as the introduction of a vaccine leading to the reduction or disappearance of the disease against which the vaccine is directed. In the case of an inexpensive and effective vaccine directed against a common disease, such as measles, this may be sufficient to prove the value of the vaccine to public-health officials and to the general public. However, with vaccines that may not be highly efficacious, or diseases that vary in their intensity from year to year, this approach is inclined to yield misleading results. For example, in sub-Saharan

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Africa and the Middle East, after decades of use against regular epidemics, there are still doubts about the efficacy and duration of protection of meningococcal AC polysaccharide vaccines in young children (3). Another approach is to introduce a vaccine in a manner that leads to only part of the population being vaccinated and then to use epidemiological techniques to compare the likelihood of disease in vaccinated individuals to that in unvaccinated ones. The most commonly-used methods include case-control studies in which the rate of vaccination is compared in diseased versus non-diseased individuals and large-scale modeling techniques in which patterns of disease are related to patterns of vaccine usage (4). The problem with these open approaches is that confounding factors are likely to influence the likelihood of an individual receiving the vaccine, making direct comparisons potentially biased. Such biases are accentuated where the receipt of a vaccine is based on individual choice.

All such methods are inferior to the traditional double-blind, randomized, controlled trial (5). In such a trial, the population under study is effectively divided into compared groups who are equal in every respect, including the likelihood that a case of the disease in question will be detected. In most large trials, this approach avoids the issue of bias, as it can be truly said that the only difference between the groups is whether or not they received the vaccine. Thus, any observed difference in rates of disease, patterns of disease, or mortality can be assumed to be due to the vaccine. If the randomization is undertaken in a 1:1 ratio, it can be assumed that the number of cases in the control group is an indication of the number that would have been found in the vaccinated group in the absence of a vaccine. The number of cases that were prevented by the vaccine can then be calculated, and this presented as a proportion of the total number of cases that would have been expected in the absence of a vaccine. This represents a measure of the efficacy of the vaccine. It is important to note that these calculations do not require that all such cases in the population are detected, just that the methods used for their detection are identical in the two groups. For example, if a trial is conducted for a vaccine to prevent pneumonia, but only half the cases of pneumonia that occur in the study population are detected, the estimate of vaccine efficacy should be the same, although the number of cases upon which that estimate is based will be only half and, therefore, the 95% confidence interval surrounding the estimate of efficacy will be correspondingly wider.

In some cases, vaccine trials are conducted that rely on the use of tests for the detection of endpoint cases that are less than 100% sensitive, less than 100% specific, or both. The impact of these deficiencies will depend on the incidence of the disease outcome in the community under study. For example, the use of a test that is less than 100% sensitive will have a similar impact on the failure to detect a random proportion of cases, provided the test does not perform differently in vaccinated and unvaccinated individuals. The total number of cases detected will be reduced, but the estimate of the proportion that is prevented and, therefore, the estimate of vaccine efficacy should be similar. The cost of the study will be seen in terms of the precision of the estimate and the width of the confidence interval, and will be greater if the endpoint under study is of low incidence. In the pneumococcal field, a number of assays have been proposed for use as endpoints in vaccine trials. Culture-positive pneumococcal disease is highly specific, but as most cases of pneumococcal pneumonia are blood culture-negative, it is very insensitive. In the recent South African trial, in which 39,836 infants were randomized to receive a pneumococcal vaccine or placebo, only 20 cases of proven invasive pneumococcal disease of vaccine serotypes were detected (6). The point estimate of vaccine efficacy (83%) was consistent with previous trials of similar vaccines, but because of the small numbers the confidence intervals were wide (Table 1).

**Table 1.** Vaccine efficacy of 9-valent Pnc-CRM pneumococcal conjugate vaccine in HIV-negative South African infants (6)

| Outcome                                | Vaccinees | Controls | Percentage of vaccine efficacy (95% CI) |
|--|-----------|----------|---|
| Radiological pneumonia                 | 169       | 212      | 20 (2,35)                               |
| All invasive Pnc disease               | 11        | 19       | 42 (28,75)                              |
| Invasive Pnc disease-vaccine serotypes | 3         | 17       | 83 (39,97)                              |

CI=Confidence interval

The use of a test with poor specificity has more severe consequences on a vaccine trial, particularly where the incidence of the endpoint condition is low. Depending on the specificity of the test and how widely it is applied in the study population, a number of false-positive cases will be detected that will be found equally in both vaccinated and unvaccinated individuals, greatly reducing the measured impact of the vaccine and,

therefore, the estimated efficacy. For example, in the South African pneumococcal vaccine trial, the exact number of respiratory infections investigated among trial participants to produce 20 endpoint cases is not stated, but it is likely to be over 2,000. Had an indirect test of pneumococcal disease, such as a pneumolysin immune complex assay (7), been used, it may have a specificity of 95% which seems reasonable. However, such a specificity would add 50 cases to each group, virtually invalidating any measurement of efficacy. The impact of this effect would be less if the test is applied selectively. It must be recognized that this is different from the situation where a vaccine is being used for preventing a specific clinical endpoint, such as radiological pneumonia, where the organism targeted by the vaccine is only responsible for a fraction of those endpoints (Table 1). This will affect the potential efficacy of the vaccine against that endpoint, yet the measures used to identify the endpoint cases could still be regarded as quite specific. The (usually unknown) fraction of radiological pneumonia that is potentially vaccine-preventable represents an upper limit to the potential efficacy of a vaccine directed against that endpoint.

#### Measurement of burden of disease

In vaccinology, disease-burden studies are needed to determine the potential value of a vaccine and, therefore, the need for a government to introduce it. Where a vaccine is inexpensive and safe, it may simply be sufficient to know that the disease exists with sufficient frequency in the community to justify the effort and extra costs involved in its introduction. Thus, in the case of polio, the World Health Organization (WHO) coordinated a large number of 'lameness surveys' to demonstrate the importance of polio at country level to convince governments to include the vaccine in their programmes (8). These were simple, inexpensive studies, but a large number was needed to overcome perceptions that polio was not a condition of great public-health significance in developing countries. The specific clinical picture presented by polio made the estimation of disease burden simple. Indeed, surveillance for the clinical syndrome of "acute flaccid paralysis" has formed the benchmark for the success of the current global polio-eradication campaign.

In the case of vaccines directed against causes of diarrhoea and pneumonia, the disease-burden question is much more complicated and contains a number of conceptual layers. The first level is the overall burden

of diarrhoea or pneumonia. In both the cases, the burden covers the spectrum of the syndrome, ranging from the very common, mild forms to the less common, life-threatening forms, and finally to the burden of mortality attributable to the syndrome. The second level to consider is then the proportion of cases that are caused by the organism against which the vaccine is directed, and this may differ through the spectrum of severity of the syndrome. For example, pneumococcus may cause a small proportion of mild-pneumonia cases, but a larger proportion of severe cases (9). Rotavirus, on the other hand, causes a similar proportion of mild and severe cases of diarrhoea (10). The contribution of these organisms to the mortality burden of pneumonia and diarrhoea remains unknown and may be larger than that inferred from studies focused on severe disease. The third level to consider relates to the strains or serotypes of the organism that cause disease. These may vary in time or space, with the disease manifestation concerned, the severity of the disease, and the age of the individual (11). Cross-protection between strains or serotypes occurs, but this is usually less than the protection offered against the strain or serotype against which the vaccine is directed (12). To further complicate the issue, vaccines directed against the bacterial causes of pneumonia also offer protection against other disease manifestations caused by the same organisms, such as otitis media and meningitis. The level of protection against these other manifestations is also variable and may vary with serotypes (13).

Thus, for vaccines against the causes of pneumonia and diarrhoeal disease, the notion of burden of disease is multifaceted and complex. This is unfortunate as it is these vaccines that are now becoming available at high prices, calling for detailed cost-benefit analyses to guide their introduction. To facilitate this, prospective studies are being undertaken in a bid to provide a composite picture of burden of disease, yet the more complex these analyses become, the more inaccurate the results will be. For example, otitis media is an important component of burden of pneumococcal disease in some settings, yet there are few studies of the burden of otitis media from the developing world, and none that describes burden in relation to aetiology.

It is becoming evident that the most meaningful measure of burden of disease is the burden of vaccine-preventable diseases, and this can only really be measured in the context of a vaccine trial. Furthermore, the trial should be designed with burden of disease in

mind, with as close as possible to complete detection of each disease manifestation to be measured within a known population (14). The size of the population required could be smaller for the more common manifestations, introducing more intense sub-studies into vaccine trials. Where possible, diagnostic tests can be adjusted to maximize sensitivity for the purposes of disease-burden estimates, recognizing that the associated loss of specificity may adversely affect the power of the analysis to determine the efficacy of the vaccine. As a general rule, specificity is more important when trying to determine vaccine efficacy, while sensitivity is more important when trying to assess the burden of disease. Thus, while the South African trial provides valuable information on the efficacy of the vaccine against key endpoints, it provides no information on the burden of preventable disease that did not fall into its strict blood culture or radiological criteria. To achieve this, it should have included a nested study in which all cases of more common but less severe manifestations of pneumococcal disease (otitis media and febrile bacteraemia), and all episodes of acute respiratory infection, as defined by WHO (cough or difficult breathing + fast breathing) were identified. The features of a vaccine trial that enable the estimation of burden of disease are listed in Table 2.

Vaccine trials provide information on the burden of disease by providing a measurable 'vaccine effect', usually the difference in incidence of a syndrome or condition between vaccinated and unvaccinated groups. It is assumed that this difference is due to the effect of the vaccine and that the only effect of the vaccine is to prevent or modify infection due to the organism against which the vaccine is directed. If all the cases occurring in the population are detected, this observed difference translates directly into burden of vaccine-preventable disease. Even if this is not the case, a trial can provide important disease-burden information by showing the proportion of the syndrome being studied that appears to be due to the organism in question. An important assumption in these exercises is the efficacy of the vaccine. If the vaccine efficacy is 100%, the burden of vaccine-preventable diseases will be the true disease burden. If it is less than 100%, the true disease burden will be underestimated accordingly. If the vaccine has an effect on rates of disease other than the infection against which the vaccine is directed, resulting disease-burden estimates will be very difficult to interpret. Where herd immunity is likely to be a factor, cluster

randomization is preferred over individual randomization as it provides maximum vaccine effect (individual protection plus herd immunity) and reduces the possibility that herd immunity will reduce the measured effect by providing some protection for the control group.

**Table 2.** Elements of a vaccine trial required for estimation of burden of vaccine-preventable diseases from the trial

|  |
|--|
| A vaccine of known efficacy (or whose efficacy will be known at the end of the trial)  |
| A valid trial design (usually cluster-randomized or individually-randomized design)  |
| Ascertainment of all disease manifestations that may be prevented by the vaccine   |
| For each disease manifestation, complete ascertainment of cases within a defined population. (This may be a sub-population of the trial population for more common events)   |
| Use of a critical trial endpoint that can be transported into other disease-burden studies or used for monitoring the effectiveness of the vaccine post-introduction         |
| Collection of data that will allow the cost of each recorded manifestation of disease to be estimated to form the basis of an economic evaluation (desirable, not essential) |

A number of vaccines have been developed against the major causes of child death. While it has been fairly straightforward to demonstrate that the disease in question is an important cause of child death and that the vaccine prevents the disease in question, it does not necessarily follow that vaccination will prevent the expected proportion of child deaths. There are two important reasons for doubting this important connection. First, the immunological requirements to prevent a death from, say malaria, may be quite different from those required to prevent illness, as fulminating and fatal disease appears to have a different pathogenesis to milder forms of the disease (15). Second, very little is known about the distribution of deaths from diarrhoeal disease and pneumonia within communities. To prevent such deaths, it will be necessary to introduce the vaccine in such a way that it reaches those children who currently lack the most basic primary healthcare, as this level of care is all that is required to prevent most deaths due to pneumonia and diarrhoea. Thus, prediction of vaccine-preventable mortality may be the most elusive, yet the most important element of burden

of disease. In the following sections, examples will be presented which demonstrate the linkage between vaccine trials and disease-burden estimates.

### **Vaccine studies that have contributed to disease-burden information**

#### ***Neonatal tetanus***

Neonatal tetanus has long been recognized as an important neonatal problem in developing countries, usually attributed to poor management of the umbilical cord during the neonatal period (16). Throughout the developing world, neonatal deaths have been poorly recorded, as most occur at home without birth registration. The idea that neonatal tetanus could be prevented by maternal immunization provoked WHO to embark on a series of studies of neonatal mortality to determine the burden of neonatal tetanus. Such studies were possible because, unlike most other causes of neonatal death, the clinical features of neonatal tetanus are characteristic and dramatic, and so the diagnosis can be made with reasonable accuracy using post-mortem questionnaire. However, it was a large, randomized trial of maternal tetanus immunization undertaken in Bangladesh that confirmed the true burden of that condition (17). In that trial, which was designed to evaluate a cholera vaccine, the controls who received tetanus vaccine and who were later found to have been pregnant at the time of immunization, had a 26% lower neonatal mortality rate, with all the reduction evident in the 4-14-day period (18). This trial provided convincing evidence of both burden of neonatal tetanus and potential impact of maternal tetanus immunization. It also opened the way for future studies of the burden of neonatal tetanus based on 4-14-day mortality rates.

#### ***Haemophilus influenzae type b***

It is now 14 years since the highly effective *Haemophilus influenzae* type b (Hib) conjugate vaccines were first licensed for use in infants (19). During the early years, their use was restricted to a few rich countries due to the high prices charged for the vaccine. Now, with more producers in the market, prices have fallen to \$ 2-3 per dose. This is still prohibitive for many countries, but the Global Alliance for Vaccines and Immunization (GAVI) has now provided funds for the poorest countries to introduce Hib vaccines, provided the burden of disease can be established. Now looming as the main obstacle to the introduction of Hib vaccines in the developing world is lack of understanding of the burden of disease. This is

particularly evident in Asia and is the main reason why, up to the present time, only one Asian country has introduced Hib vaccine as part of its national immunization programme.

Although Hib can cause a wide range of clinical manifestations, most are very rare, and so for practical purposes in developing countries, the burden of disease must be considered as comprising meningitis and pneumonia. Meningitis is an uncommon condition, but the outcome is poor in terms of mortality (20-50% in developing countries) and long-term sequelae (around 30% of survivors in most studies) (20). Pneumonia, on the other hand, is very common, but only a fraction of cases are due to Hib and at an individual level it is very difficult to determine the aetiological agent responsible for a case of pneumonia. To identify a case of Hib pneumonia with certainty, it is necessary to identify the Hib organism from blood culture, or from culture of lung aspirate or pleural fluid. Because it is more easily identified, most studies of Hib burden have focused on detecting cases of Hib meningitis, although it is usually acknowledged that, in the developing world, these cases represent the tip of the Hib iceberg, most cases being the more difficult to identify cases of Hib pneumonia (21).

Over the past decade, a number of studies have been undertaken to establish the burden of Hib in Asia, most supported by the pharmaceutical industry that was looking to Asia as a potentially-lucrative, untapped market for their Hib vaccines (22). However, all studies seemed to suffer the same problems. They were conducted in relatively affluent areas where the presumptive use of antibiotics for childhood illness was very common. Furthermore, meningitis was often treated empirically, without lumbar puncture. The fastidious nature of the Hib organism meant that even when the correct specimen was collected, the organism could still be missed because of minor problems with media preparation or culture technique. As a result, these studies, developed to demonstrate the need for the vaccine, have instead provided evidence to support the hypothesis that there is indeed a very low incidence of Hib disease in Asia. As the global health community drifts towards such a conclusion, two innovative studies (in Indonesia and Bangladesh) have been undertaken in which a Hib vaccine trial was conducted to determine the burden of disease. These studies were built on the experience of trials in the Gambia and Chile where the use of a Hib vaccine (PRP-T) produced a predictable

reduction in the incidence of Hib meningitis (23,24). In the case of the Gambia, the trial also demonstrated that the vaccine had an impact on the incidence of bacteriologically-proven Hib pneumonia. However, the most surprising finding from the Gambia was the 20% reduction in the incidence of radiological pneumonia in vaccinated children (Table 3). Similar results were obtained

be associated with the same radiological features as was evident in the Gambia. There was also a marked reduction in episodes of clinical meningitis in the vaccinated group, consistent with an incidence of Hib meningitis of over 150/100,000 children per year for children aged less than two years. This is a rate similar to that found in Africa and is sufficient to justify the inclusion of Hib

**Table 3.** Episodes of acute respiratory infection by different categories in fully-vaccinated Gambian children who received PRP-T Hib vaccine in infancy and controls (23)

| ARI syndrome  | Hib vaccinees | Controls | Percentage of vaccine efficacy (95% CI) |
|---|---------------|----------|---|
| Cough + fast breathing or lower chest wall indrawing* | 526           | 570      | 7.7 (4.1,18.2)                          |
| Cough + lower chest wall indrawing†                   | 259           | 286      | 9.4 (7.5,23.7)                          |
| Radiological pneumonia                                | 132           | 170      | 22.4 (1.9,38.6)                         |
| Lobar pneumonia                                       | 61            | 72       | 15.3 (20.8,40.8)                        |
| Pneumonia with hypoxaemia                             | 18            | 28       | 35.7 (20.5,66.5)                        |

\* Non-severe pneumonia, by WHO definition  
† Severe pneumonia, by WHO definition  
ARI=Acute respiratory infection  
CI=Confidence interval

from a retrospective analysis of the Chilean data (25). The conclusion of these studies was that, in contrast to prospective pneumonia-aetiology studies that suggested that 5-10% of childhood pneumonia was due to Hib, the true figure may be closer to 20%. This finding had important implications for the use of the vaccine.

The first suggestion to conduct a Hib vaccine trial with the aim of demonstrating the burden of pneumonia came at a meeting on Hib in Asia in Bali, Indonesia, in 1997. Following that meeting, a consortium was formed to conduct a randomized, double-blind trial of a Hib vaccine on the Indonesian island of Lombok. In that trial, 55,000 infants were randomized by village to receive either Hib-DTP or DTP at 6, 10, and 14 weeks of age (26). The primary endpoint was radiological pneumonia and the investigators used the same definition of this endpoint developed by WHO for use in pneumococcal vaccine trials. The trial was conducted in a predominantly rural community with a high infant mortality in which pneumonia is the most important cause of mortality. It was, therefore, surprising to find that the vaccine had essentially no impact on the incidence of radiological pneumonia. There was, however, a small reduction in the incidence of all clinical pneumonia, which was statistically significant due to the large number of events detected. In addition, there was a (non-significant) reduction in deaths due to pneumonia in the vaccinated group. These findings suggest that, in Lombok, Hib pneumonia does occur, but it may not

vaccine, even in the absence of a demonstrable effect on pneumonia. Thus, the trial did, in fact, demonstrate a significant burden of Hib disease, but not the manifestation that the investigators had expected.

A similar study has been completed in urban Dhaka, Bangladesh and is awaiting analysis. Another is being planned as a multicentre study in India. Gradually, the trial of Hib vaccine is becoming the standard for the determination of Hib burden in Asia. The key unanswered question at this time is whether another large trial in East Asia is needed before the Hib in Asia dilemma can be resolved. In the view of this author, such a trial will be needed before Hib vaccine is introduced in much of Asia, particularly China.

#### *Pneumococcal vaccine*

The situation with pneumococcal vaccines promises to be much more complex. The pneumococcus (*Streptococcus pneumoniae*), like Hib, is an encapsulated bacterium in which protective immunity is derived from antibodies directed at the capsule. The range of conditions caused by the pneumococcus is similar to Hib. As with Hib, pneumonia is the most important manifestation of pneumococcal disease, while meningitis is the most severe. Indeed, pneumococcal meningitis is more severe than Hib meningitis, and in most developing-country settings, the mortality is in excess of 50% with many survivors suffering permanent neurological damage (27). Pneumococcus is a major bacterial cause of pneumonia

throughout the world, but as with Hib, it is difficult to prove pneumococcal aetiology in individual cases. Estimates of the global burden of pneumococcal disease range from 1 to 2 million child deaths per year with a similar number of adult deaths. As a cause of disability and death in humans, pneumococcus is substantially more important than malaria and is rivaled only by *Mycobacterium tuberculosis*. One might conclude, therefore, that with such an overwhelming burden of disease, the case for pneumococcal vaccination does not need to be spelled out in detail. In fact, this is quite wrong for a number of reasons.

First, the current price of new pneumococcal conjugate vaccines, around \$ 200 per child for a 4-dose schedule, breaks all records for a routine childhood vaccine. Australia, a relatively wealthy country, recently concluded that the burden of pneumococcal disease is not sufficient to justify the introduction of this vaccine, except for the indigenous aboriginal communities who are at extremely high risk (28) (This decision has recently been reversed). Second, with most pneumococcal disease appearing as pneumonia, estimating the burden of vaccine-preventable pneumonia is an essential, but difficult exercise. To do this, one must first estimate the proportion of pneumonia cases that are pneumococcal in origin and then the proportion that can be prevented by the vaccine. This is extremely complex. Definitively identifying a case of pneumonia as pneumococcal in origin requires culture of pneumococcus from blood or lung fluid, and as this is not possible in many cases, prospective studies are always left speculating about how many cases they missed. The proportion of cases in a series that prove to be pneumococcal depends on the point in the healthcare chain where cases are recruited. Studies conducted at community level typically yield small numbers of pneumococci (9), while

those at hospital level, recruiting more severe cases, see more pneumococcal cases (29). Then there are at least 90 serotypes of pneumococcus that can cause disease in humans (30), although, in most settings, most cases are caused by the serotypes included in the current pneumococcal conjugate vaccine. Some serotypes appear to be more likely to cause bacteraemic disease, while some seem to have a predilection to cause more severe disease, particularly meningitis (11). It is possible that some serotypes are more likely to cause non-bacteraemic pneumonia, but this is very difficult to determine.

These factors and the need to consider other manifestations of pneumococcal disease, such as otitis media and febrile bacteraemia, may lead one to the conclusion that the only way to reliably estimate the burden of vaccine-preventable pneumococcal disease is within a vaccine trial. This may be true, and current phase III pneumococcal vaccine trials underway in the Gambia and the Philippines contain elements designed to estimate components of the overall burden of pneumococcal disease. This can be achieved by ascertaining, within a defined population, the number of cases of each pneumococcal syndrome that are prevented. These syndromes range from relatively mild conditions, such as otitis media, to death. A possible framework for assessing the burden of pneumococcal disease from a vaccine trial is presented in Table 4. This would enable the presentation of, for each 1,000 children immunized, the number of cases of each disease manifestation prevented, the total cost savings, and the number of deaths prevented. For some parameters, the estimates will be crude, and case-fatality rates will need to take account of the likelihood that a child with the condition will not be treated, or will receive inadequate care, in the country concerned.

**Table 4.** A potential framework for assessing burden of pneumococcal disease from a vaccine trial

| Disease manifestation             | Cases prevented in vaccines vs controls | Cases prevented per 1,000 children immunized | Cost per case of disease | Cost saving per 1,000 children immunized | Case-fatality rate | Deaths prevented per 1,000 children immunized |
|-----------------------------------|---|--|--------------------------|--|--------------------|---|
| Otitis media                      | a                                       | b<br>(a.1000/trial size)                     | \$c                      | \$b.c                                    | d                  | b.d   |
| Febrile bacteraemia               |   |  |                          |  |                    |   |
| Radiological pneumonia            |   |  |                          |  |                    |   |
| Other ARIs                        |   |  |                          |  |                    |   |
| Meningitis                        |   |  |                          |  |                    |   |
| ARIs=Acute respiratory infections |   |  |                          |  |                    |   |

Impact on overall mortality has always been seen as the most compelling evidence a trial can produce for the use of a vaccine claiming to improve child survival. Only the Gambian trial has been designed with this endpoint in mind, yet as a result of decisions made in the United States, based on perceptions of the ethical acceptability of the trial, that trial has been stopped with only half the required number of subjects recruited, so it no longer has the power to provide this important information. Data from the Philippines may be difficult to interpret as the efficacy of the vaccine used in that trial (11-valent Aventis pneumococcal conjugate vaccine) is unknown, and no other trials are planned with that vaccine. If the trial does show an impact on incidence of pneumonia, it can be assumed that the observed impact represents the vaccine-preventable fraction of pneumonia, but if the results are negative, it will not be known whether the vaccine is ineffective, or the fraction of pneumonia due to pneumococci in that community is very small. Despite the problems, these trials have the potential to provide substantial information on the burden of pneumococcal disease in those communities yet even these large, expensive studies may yield misleading results.

It has now been shown in a number of studies that children vaccinated with the pneumococcal conjugate vaccine are less likely to be nasopharyngeal carriers of the pneumococcal serotypes they have been vaccinated against, but more likely to carry other serotypes. This phenomenon is referred to as 'serotype replacement' (31). A key question surrounding this whole pneumococcal vaccination strategy is whether serotype replacement will also occur in disease, with vaccination leading to an increase in disease due to non-vaccine serotypes. This has been shown to occur with otitis media, and the U.S. data suggest that it may be occurring there with invasive disease (32), although the numbers are small (as so little childhood disease in the United States is due to serotypes not in the vaccine). It is likely that the same phenomenon will occur in pneumonia cases, but if the 'new' serotypes are less likely to lead to bacteraemia, this may be extremely difficult to detect. It may, however, offset the total number of pneumonia cases prevented by the vaccine, and the lower-than-expected efficacy observed in South Africa, and the U.S. Navajo Indian studies suggest that this may have happened in those trial settings. With a higher proportion of the population vaccinated, the effect will be accentuated by herd effects that will

then increase with time as more children in the community are vaccinated. Thus, when a whole community is vaccinated, the burden of vaccine-preventable pneumonia may move towards zero, despite the existence of a substantial pneumococcal burden and an effective vaccine. Nevertheless, from a public-health standpoint, it is the effectiveness of a vaccine when it is applied to a community that matters, not the efficacy at individual level.

### **Bridging from vaccine trials**

As few countries have the opportunity to conduct a large vaccine trial in their own communities, and the burden of vaccine-preventable diseases is likely to vary considerably between communities, it is necessary to develop mechanisms to bridge epidemiological information from smaller field studies so that conclusions about burden of disease can be drawn. At its simplest level, this will mean prospective studies of the incidence of the main endpoint(s) measured in the context of the phase III vaccine trials. Pneumococcal vaccines present the most complex problem for these bridging studies. Measurement of the incidence in a community of pneumococcal meningitis, radiological pneumonia and otitis media would allow data such as that collected in Table 4 to be used for calculating the burden of vaccine-preventable diseases in that setting. It is probably sufficient to take a key indicator, such as the incidence of radiological pneumonia and to use this to establish a multiplier that will relate the burden of disease in the setting under investigation to that found at the vaccine trial site. Thus, population-based studies of radiological pneumonia, using identical definitions to those used in the vaccine trials, will form the main bridge for pneumococcal vaccines. With rotavirus vaccines, a convenient bridging parameter is the proportion of children admitted with diarrhoea who are infected with rotavirus. The Global Alliance for Vaccines and Immunization has now taken responsibility for this work, so funding should soon be available for these studies in both pneumococcal and rotavirus fields ([www.vaccinealliance.org](http://www.vaccinealliance.org)).

### **Non-specific effects of vaccines**

Recent work from West Africa has provided evidence that certain vaccines have an impact on mortality that is beyond that which can be accounted for by prevention of a specific disease. The authors of the work, published in December 2000, suggest that non-specific stimulation of the immune system, following measles



or BCG immunization, results in a decreased risk of mortality from all causes (33). In contrast, their findings suggest that administration of non-live vaccines, particularly DTP and hepatitis B, results in an increased risk of mortality, presumably due to similar mechanisms. Confronted with this troubling information, WHO's Global Advisory Committee on Vaccine Safety created a special sub-committee to resolve this issue. They commissioned a series of retrospective analyses of old datasets that may be able to address these issues. Initial reports from the group suggest that effects similar to those described in Guinea Bissau have not been found at the other sites, but the studies have not yet been made public, and expert analysis and interpretation of the results is ongoing (34). Meanwhile, in the immunology literature, there is a growing body of evidence to suggest that T-cell-mediated immunity may not be as specific as has been believed (35). Heterologous T-cell immunity may mean that prior antigenic experience could have positive or negative effects on the response of an individual to an apparently-unrelated infection. These findings provide a potential immunological basis for the non-specific vaccine effects described in Guinea Bissau. If this is true in humans, even a small effect could potentially invalidate the vaccine-trial approach to burden of disease. A small effect on mortality could signify a larger, non-specific effect on the incidence or severity of infectious disease. The vaccine-trial approach to disease-burden estimation relies on the assumption that the vaccine only affects disease caused by the organism against which it is directed. If the vaccine has preventative effects beyond that organism, the burden of disease attributed to that organism will be erroneously large. If, on the other hand, the vaccine has negative effects resulting in more illness in vaccinees, the calculated burden of disease will be erroneously small.

### CONCLUSION

As life-saving childhood vaccines become more expensive, governments around the world face agonizing decisions about the incorporation of new vaccines into the routine schedules for their children. Central to this decision-making is an understanding of the benefits that will accrue if the vaccine is introduced. This, in turn, requires an understanding of the burden of disease due to the organism against which the vaccine is directed. The most useful presentation of disease-burden information is the burden of vaccine-preventable diseases,

which is most accurately and practically measured in a vaccine trial. As vaccine trials can only be conducted in a few settings, it is necessary to conduct a series of bridging studies to provide disease-burden estimates at country level that can be used as the basis for economic analyses to support the introduction of vaccine.

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