cultural and socioeconomic settings more akin to developing countries. The efficacy of PRP-OMP against invasive Hib disease among Navajo infants was 95%, and the protection began with the first dose administered (7). At the same time, PRP-D administered to Alaskan native infants scarcely raised anti-PRP antibody concentrations after two doses and did not protect significantly against invasive disease (9). Nonetheless, protein conjugate Hib vaccines were licensed for infant use in 1990, and with widespread introduction, invasive Hib disease has almost disappeared from the industrialized world (10,11).

To achieve similar success in the developing world appeared more complex. The incidence of Hib disease and the prevalence of nasopharyngeal carriage were higher in developing countries, and the disease occurred in younger children, with half of all cases occurring before the age of eight months (12,13). In addition, Hib was a significant cause of pneumonia in developing countries, and it was unclear whether the systemic antibodies induced by vaccine would diffuse sufficiently into the lung to prevent cases of pneumonia, particularly those that came about by direct spread of the pathogen from the upper to the lower respiratory tract.

The first evidence of postlicensure vaccine effectiveness outside the industrialized world came from Chile, where existing epidemiological studies had confirmed a significant burden of Hib disease (14). As part of a strategy to determine country-specific policy toward the new conjugate vaccines, the 71 vaccine health centers of Santiago city were divided into two approximately equal groups and randomly assigned to administer either DTP (diphtheria-tetanus-pertussis) vaccine alone or DTP with PRP-T in the routine immunization schedule. National census data were used to define the populations served by the two sets of health centers and the numbers of cases of invasive Hib disease occurring in the two sets of areas were compared to establish vaccine effectiveness. Approximately 46,000 infants were served with vaccines by each of the two health center sets. The vaccine effectiveness was 90.2% (95% CI, 74.5–100%) for invasive Hib disease, and it did not vary by age at onset of disease. The effectiveness against Hib pneumonia (80%) was lower than that against meningitis or other invasive Hib syndromes (91–100%) but the number of culture-proven pneumonia cases was small (15).

The first randomized controlled efficacy evaluation of PRP-T was conducted in The Gambia between March 1993 and March 1996 (16). The only previous evaluation of PRP-T was an open study comparing the incidence of Hib disease in four districts of Oxfordshire, United Kingdom, where PRP-T had been offered simultaneously with DTP, against the incidence in four districts where PRP-T had not been offered (8). In The Gambia, 42,848 infants were randomly assigned to receive either PRP-T mixed with DTP or DTP alone. PRP-T was given on three occasions at a median age of 11 weeks, 18 weeks, and 24 weeks. The primary endpoints of the study were (*i*) protection against proven Hib pneumonia after two or three doses of vaccine and (*ii*) protection against all invasive Hib disease after three doses of vaccine. There were 10 eligible cases of proven Hib pneumonia among the controls and none among the vaccinees who had received two or three doses, giving a vaccine efficacy of 100% (95% CI, 55–100%). There were 19 eligible cases of invasive Hib disease among the controls and one among the vaccinees who were fully vaccinated giving a vaccine efficacy of 95% (95% CI, 67–100%). The point estimate of efficacy against invasive disease after one dose of vaccine was 44%, but this had little precision (95% CI, −85%, 85%).

On the basis of culture of blood and lung aspirate material, several previous studies of pneumonia etiology in The Gambia had suggested that Hib was responsible for approximately 7% of cases of severe pneumonia (17–20). The estimate of vaccine efficacy was also obtained predominantly from cases of pneumonia with blood cultures positive for Hib, although in two cases Hib was isolated from lung aspirate cultures. However, for the first time the question of nonbacteremic Hib pneumonia was also examined in detail in this study (16). In the trial, 1821 episodes of pneumonia were investigated among study participants, and the protective efficacy of the vaccine was estimated for different case definitions irrespective of confirmatory etiologic data. Using the sensitive but poorly specific WHO-defined clinical criteria for pneumonia (cough with fast breathing or lower chest wall indrawing), vaccine efficacy was 4.4%; among the subset who required admission to hospital (with lower chest wall indrawing), the vaccine efficacy was 6.5%. Neither of these estimates could be distinguished statistically from a null effect. However, the vaccine efficacy against radiologically defined pneumonia was 21.1% (95% CI, 4.6–35%) and against radiologically confirmed lobar pneumonia or pneumonia with effusion it was 25.2% (95% CI, 0.24–44%) (16).

For a clinically defined endpoint like pneumonia, which can be caused by numerous different etiologic agents, the observed vaccine efficacy estimates in themselves do not define any precise biological parameter. Rather, they help to establish limits to the parameters of which they are composed. The observed vaccine efficacy is equal to the product of two measures: (*i*) the true vaccine efficacy against all Hib pneumonia and (*ii*) the proportion of all cases meeting the clinical case definition that have been caused by Hib. If the true vaccine efficacy against Hib pneumonia is 100%, that would imply that 21.1% of all radiologically defined pneumonia cases are caused by Hib. Equally, if the true efficacy of the vaccine against Hib pneumonia is closer to the observed estimate (0.80) among bacteremic Hib pneumonia patients, this would imply that 26.4% (21.1/0.8) of all radiologically defined pneumonia is caused by Hib. These deductions suggest that Hib contributes considerably more to the etiology of severe pneumonia than had previously been anticipated.

The analytical approach of using vaccine as a ''probe'' to estimate disease burden has become a useful tool in Hib and pneumococcal epidemiology. For example, to test whether Hib causes ~20% of radiologically confirmed pneumonia in other populations, the clinical data and radiographs of the Chilean PRP-T effectiveness study were reexamined. The incidence of radiologically confirmed pneumonia was calculated for children aged 4 to 23 months who received at least two doses of conjugate Hib vaccine and compared against the incidence among children from control areas. Clinical and radiological confirmations were abstracted from the in-patient records of children admitted to the three public hospitals in the area on the basis of a screen of discharge diagnoses. If the radiological report was insufficiently precise to distinguish pneumonia, the original radiograph was retrieved and classified by a radiologist blinded to the child's vaccine status. Vaccine status was inferred from residence in one of the vaccine intervention areas or one of the control areas. Although the study size was inadequate to define precisely the efficacy of vaccine against radiologically confirmed pneumonia (consolidation or effusion), the point estimate of 22% (95% CI, −7%, 43%) was very similar to that obtained in The Gambia trial (21).