J HEALTH POPUL NUTR 2004 Sep;22(3):246-256
ISSN 1606-0997 $ 5.00+0.20

Introducing New Vaccines in Developing Countries: Concepts and Approaches to Estimating Burden of *Haemophilus influenzae* Type b-associated Disease

Paul E. Kilgore and Batmunkh Nyambat

Division of Translational Research, International Vaccine Institute, PO Box 14 Kwanak, Seoul 151-600, Republic of Korea

ABSTRACT

In the past 30 years, great strides have been made in immunizing infants and children routinely in developing countries under the Expanded Programme on Immunization. Despite this, the introduction of *Haemophilus influenzae* type b (Hib) vaccines has progressed rather slowly compared to previously-introduced vaccines for infant immunizations. This slower uptake has been attributed partly to the need for data on the burden of invasive Hib disease. To understand this need, conceptual underpinnings and prerequisites were explored for Hib disease-burden studies. Methodological approaches were also reviewed for conducting Hib disease-burden studies that may be considered in developing countries. Potential studies span a range of designs that provide varying levels of clinical, laboratory and epidemiologic evidence of the burden of invasive Hib disease. Carefully-conducted studies can lay the foundation for complementary studies of long-term disability due to invasive Hib disease, national economic analysis, and field evaluations of vaccine. Studies done in collaboration with national agencies and clinical investigators will maximize study value and provide critical data for national decision-makers who make choices regarding the introduction of Hib vaccines.

Key words: *Haemophilus influenzae*; *Haemophilus* vaccines; Meningitis; Vaccine; Morbidity; Mortality; Epidemiology; Developing countries

INTRODUCTION

During the past several decades, a number of new vaccines have been introduced into the routine immunization programmes of developing countries starting with the earliest efforts of the World Health Organization (WHO) in the global smallpox-eradication campaign and the establishment of the Expanded Programme on Immunization (EPI) (1). During the 1970s-1980s, as developing countries introduced routine infant immunizations, there was little doubt among international health officials and national public-health decision-makers that the basic childhood vaccines, already available in developed countries for 20 or more years, were desperately needed to reduce morbidity and mortality among infants and children (2,3).

Following the development and routine introduction of new vaccines for hepatitis B and *Haemophilus influenzae* type b (Hib)-associated disease in developed countries, the use of these new vaccines in developing countries was felt to be a natural next step (4,5). However, the introduction of these vaccines has lagged behind their introduction in developed countries by more than 10 years (6). A number of countries still do not use hepatitis B vaccine as a routine immunization, and a good number of developing countries have yet to begin Hib immunization. In the case of hepatitis B vaccines,

Correspondence and reprint requests should be addressed to:
Dr. P.E. Kilgore
Division of Translational Research
International Vaccine Institute
PO Box 14 Kwanak
Seoul 151-600
Republic of Korea
Email: pkilgore@ivi.int
Fax: (822) 872-2803

a number of factors associated with delayed introduction have been identified, including problems with knowledge of disease burden, cost of vaccines, supply of vaccines, and immunization programme logistics of delivering an increasing number of vaccines to infants (7).

The experience over the past 20 years with hepatitis B and Hib vaccines has underscored the need for understanding the degree to which new vaccine-preventable diseases are a problem for a given population. This knowledge allows decision-makers to place a given disease in the overall context of national public-health problems. This process of understanding the extent of a particular disease problem requires effort to establish the burden of disease.

BURDEN OF DISEASE

In general, the burden of disease is represented by the sum total of outcomes that include both morbidity and mortality associated with a particular pathogen or disease (8). Thus, the burden for a number of pathogens, such as Hib, requires consideration not only of potential outcomes, e.g. hospitalizations, but recognition that Hib is capable of causing different disease manifestations (9). Thus, to account for the impact of Hib in children, we consider moderate or severe manifestations of invasive Hib disease, e.g. meningitis, pneumonia, and sepsis, that may lead to emergency visits, hospitalizations, clinical sequelae, or death (10).

Prior to the introduction of Hib vaccine in developed countries, Hib-associated deaths were frequent (11). In developing countries where access to healthcare is limited, Hib-associated mortality is thought to be high. Previous studies in several countries have shown that the highest number of Hib-associated deaths occur among children aged less than five years, especially among children aged less than two years (12,13). In addition to death, children who survive serious disease, such as Hib meningitis, are often affected by lifelong disability due to permanent damage of the central nervous system that leads to neurologic deficits (14). Such disability may lead to physical or cognitive deficits. Other severe manifestations include meningitis, pneumonia, and sepsis, and may require emergency department treatment or hospitalization.

Because of these severe disease manifestations and their associated outcomes, accurate estimation of the burden of invasive Hib disease in studies can provide important insights for health policy-makers who must make important choices regarding public-health interventions that will be financed with public or international donor funds. Appropriately-conducted burden-of-disease studies often provide previously unavailable data that show the relative importance of diseases. Results of burden-of-disease studies may also be used for projecting or modelling what might be the impact of a given vaccine when used in a routine immunization programme (15). In this way, data from baseline Hib disease-burden studies, conducted prior to the introduction of Hib vaccine, provided valuable information for later comparisons.

Since 1993, global organizations, including World Bank and WHO, have developed the concept of disability-adjusted life years (DALY) (16). DALYs are a parameter used for quantifying the burden of disease that incorporates measures of both years of life lost and years of life lived with disability. The use of DALYs is particularly useful when comparing benefits, costs, and outcomes prevented with alternative public-health programmes, such as a new vaccination programme. Estimation of DALYs associated with invasive Hib disease can incorporate information on morbidity and mortality collected in the course of Hib disease-burden studies.

Initially, one might think that disease-burden studies provide few insights into the importance that other key opinion leaders, such as clinicians, attribute to a given disease (17). However, in some cases, those who are conducting disease-burden studies often communicate with national agencies and staff who can directly use and disseminate disease-burden data. In this way, collaborative studies that involve clinicians, laboratory scientists, national public-health officers, and other national public-health workers can provide intangible benefits beyond the valuable data that such studies generate by themselves.

CONCEPTS IN MEASURING BURDEN OF DISEASE

Value of disease-burden information

Early childhood immunizations were typically introduced into routine national schedules in the absence of formal epidemiologic or clinical studies or surveillance information on the rate or number of cases of a given disease, e.g. pertussis (18,19). Why has the public-health

environment changed and why are the disease-burden data now needed? In part, this trend results from a growing number of public-health challenges that are either new, e.g. severe acute respiratory syndrome, or re-emerging diseases, e.g. tuberculosis. Another factor for lower-income countries has been the demand on the part of donor agencies that local agencies show evidence that a given disease is worthy of substantial investment (20). An additional factor may relate to the higher cost of new vaccines. The first EPI vaccines could be purchased at a substantially lower cost than new vaccines against Hib. As a result, the addition of a Hib vaccine in a national immunization programme represents a greater national financial commitment compared to previous vaccine introductions (21).

In earlier efforts to define the burden of invasive Hib disease, investigators conducted studies designed to estimate the population-based incidence of Hib and other diseases (22,23). These studies were typically conducted over a defined period to enable the calculation of annual incidence rates and used data collected either prospectively or retrospectively (24). Data from such studies have been used in conjunction with population census data for directly estimating the total number of children expected to suffer from Hib disease. Population-based studies, while often considered to provide the highest-quality data, are also more challenging due to the effort required for comprehensive case detection in large populations (25-28).

A number of Hib studies have been conducted in single hospitals or networks of hospitals over a wide geographic region (29). Such studies allow determination of the proportion of meningitis due to Hib but are less well-suited to providing estimates of Hib incidence (30,31). Nonetheless, hospital-based studies, conducted in a network of hospitals simultaneously or in a number of different hospitals over time in a given country, may provide stronger data compared to data from a single hospital-based study (32,33). Such may be the case when studies are done in ethnically- or geographically-diverse populations within a given country.

Increasingly, investigators globally are gaining experience in conducting more rigorous disease-burden studies relating to invasive Hib disease. In Africa, 26 countries initially participated in a laboratory-based surveillance system for paediatric invasive bacterial meningitis (34). In such systems, data are collected in systematic surveillance with laboratory-based testing that provides confirmed diagnoses using microbiologic culture methods. Surveillance systems such as this may provide the first and only Hib data for national decision-makers. As a result, these data may provide the foundation for later disease-burden estimates.

More recently, efforts have been made to obtain indirect estimates of burden of invasive Hib disease using retrospective reviews of hospitalizations and laboratory records of cerebrospinal fluid and blood cultures positive for Hib (35). These indirect estimates also take advantage of previous studies in which the proportion of meningitis or pneumonia due to Hib has been ascertained either through prospective laboratory-based surveillance for Hib or in Hib vaccine studies in which the proportion of pneumonia or meningitis prevented by Hib vaccine is used for estimating the proportion of disease due to Hib (36,37). This approach has led to the development of a tool to rapidly assess the burden of Hib disease (38). While still relatively new, this approach offers an alternative for countries where it is not feasible to conduct either large-scale population-based studies or sustained laboratory-based hospital studies.

Although not typically considered in the category of disease-burden studies, case reports of invasive Hib disease may be the only evidence that Hib is a cause of illness among children (39-42). While such data may be useful to local doctors when considering individual treatment decisions, they provide little evidence that Hib is more than just a sporadic disease. As such, case reports should be considered only as evidence of the presence of invasive Hib disease in a given location where it may be impossible to conduct either a rapid disease-burden assessment, hospital-based or population-based surveillance.

Local capacity for studies

Prior to initiating disease-burden studies to assess invasive Hib disease, it is crucial to evaluate the national capacity that exists to support epidemiologic surveillance and microbiologic laboratory diagnosis of Hib. If surveillance or a disease-burden study is contemplated in a province or district, attention must first be directed to understanding the ability of local clinicians and laboratory workers to identify children with bacterial meningitis (43,44). If the local capacity does not exist or exists for one aspect of surveillance, e.g. epidemiology, but does not exist for another, provisions must be established to

ensure that adequate training is conducted among workers who will be responsible for surveillance. In general, the more complex the study, e.g. population-based surveillance, the greater the need to ensure that adequately-trained personnel are in place to conduct surveillance.

The microbiologic laboratory capacity must exist or be developed prior to starting studies where investigators will use laboratory-confirmed outcomes. In many countries, the local microbiology laboratory capacity may vary greatly. Thus, in some settings, it is necessary to adapt laboratories to use less technology-intensive methods (45). In addition, investigators should have a clear documentation of local laboratory procedures before the start of formal microbiology laboratory training begins (46). Such information will be critical to design appropriate laboratory training and follow-up inspection schedules. Local laboratories must demonstrate accurate and consistent identification of invasive bacterial pathogens, including Hib, *Streptococcus pneumoniae*, and *Neisseria meningitidis*.

Timing of disease-burden studies

The choice of when to conduct Hib disease-burden studies may be crucial and, whenever possible, should be carefully deliberated with local and national public-health leaders. Because the capacity to conduct the surveillance of invasive Hib disease often requires clinical and/or laboratory training programmes and novel surveillance procedures for local staff, it is helpful if there are few diversions or other major public-health programmes that are initiated at the same time and in the same location where Hib surveillance is likely to take place. While this might be the ideal situation, it is not uncommon for public-health emergencies to develop that demand the involvement of local health workers who also might be involved with Hib surveillance. Similarly, other events, such as work stoppages by employees of hospitals or clinics, may also place stresses on surveillance for Hib. In other cases, conflicts may arise within communities or countries that are conducting Hib surveillance. In many situations, while it may be impossible to change the stressful circumstances having a negative impact on surveillance, development of contingency plans may be possible to mitigate the impact on surveillance and the detection of invasive Hib disease.

Involvement of key stakeholders

Stakeholders for Hib disease-burden studies will include individuals or groups that have an interest in data to be generated from studies on Hib. Stakeholder groups typically include donor agencies, vaccine advisory committees, paediatricians, parents, and public-health leaders within national agencies responsible for making decisions regarding the introduction of new vaccines. Thus, prior to initiating surveillance, it is valuable to know what audience will receive the Hib study data. In this way, study investigators can help ensure that results are communicated to stakeholder groups in an appropriate and timely fashion.

APPROACHES TO BURDEN ESTIMATION

Measurement of outcomes

Studies of the burden of invasive Hib disease focus on identification of children suffering from manifestations of severe disease, such as meningitis, pneumonia, and sepsis. Studies also detect children who die in hospital with confirmed Hib disease. Often, disease-burden studies will detect children who suffer clinical sequelae at the time of discharge or transfer from the hospital. Because additional effort or resources are needed to follow children several weeks or months after discharge from hospital, relatively few recent studies have described long-term clinical sequelae associated with Hib.

Options for study design

Choosing an appropriate design for Hib burden investigations is crucial, but resource limitations should not prevent moving forward with limited studies when there is national commitment to gaining information on invasive Hib disease (Appendix). Thus, even with limited resources, studies can be initiated to collect disease-burden data. Financial resource-limited studies should not be equated with reduced intellectual rigour or reduced efforts on the part of lead investigators to be vigilant and maintain close attention to details of conducting the study. In this sense, it may be more prudent to start small-scale studies, e.g. surveillance in a single hospital, and ensure that all children with suspected invasive Hib disease enter the surveillance system.

In the case of prospective study designs (e.g. hospital-based or population-based), an essential element of surveillance are those methods used by clinicians and epidemiologists that help ensure that all children with suspected Hib disease do, in fact, undergo evaluation within the surveillance system. If incidence rates of invasive Hib disease are expected to be low or moderately low (e.g. <10/100,000 or 10-25/100,000 children <5 years

respectively), clinicians must take great care to conduct parent/guardian interviews and physical examinations of all children who present with signs and symptoms of invasive bacterial disease. Such children must, whenever possible, undergo appropriate examinations and collection of laboratory specimens. Depending on the study duration, sufficient efforts must be expended in sustaining attention of clinician to systematic evaluation and collection of CSF, blood, or other clinical specimens.

In the case of retrospective hospital-based studies or when using the rapid disease-burden assessment, epidemiologists and laboratory workers have the greater responsibility to identify hospitals with laboratories where adequate microbiological testing has been performed over a sustained duration (47). In these studies, careful and comprehensive review of the existing computerized or paper hospital records is of paramount importance. An intimate knowledge of the laboratory operating procedures can be valuable when activities involve reviewing logbooks to identify the number of CSF or blood cultures that grow Hib. Collaboration and frequent discussions with senior microbiologists are essential to ensure that all culture results are reviewed for a given study period.

Bias considerations

Those conducting Hib disease-burden studies and those who use study findings may be able to anticipate characteristics of the study population, surveillance hospitals, and characteristics of the health system that could introduce potential biases that ultimately influence either the number of patients with Hib disease identified or the calculation of incidence rates, or both. These biases may result from inadequate consideration of healthcare-seeking behaviours or healthcare institutions where parents bring children for care of serious or life-threatening diseases. They may also stem from inadequate knowledge of study clinicians regarding the signs and symptoms of disease that require prompt medical attention, evaluation, and collection of laboratory specimens. Other biases may include partial or complete absence of patient referral whereby local doctors, e.g. private clinics, choose to evaluate and treat patients with suspected invasive Hib disease rather than to participate in surveillance by referring patients to a nearby hospital where CSF and/or blood can be collected for microbiologic culture. Other potential sources of bias may limit the detection of fastidious Hib organisms when specimens are not transported or processed within a relatively short time.

Analysis

Plans for analysis of surveillance data may be easily overlooked when one is in the planning stages or early phases of surveillance. However, establishing an analytic strategy is essential to ensure that appropriate data are collected and that weekly or monthly reviews of data are focused on ensuring that complete and accurate data are recorded. Incomplete data discovered at the end of a study or surveillance period may preclude analysis of valuable data on one or more key outcome(s) for the disease-burden study. Time must be taken to plan how data will be presented in both periodic interim reports and the final report. If appropriate to the study design, methods for the calculation of incidence rates of invasive Hib disease should be described and understood by study investigators. Increasingly, performance indicators are being used in surveillance and disease-burden studies. Such indicators help monitor the progress of data collection and the quality of surveillance activities. Statistical comparisons of surveillance indicators from month to month provide valuable feedback to clinicians, laboratory workers, and epidemiologists who perform day-to-day surveillance activities.

Integration of outcome studies

National leaders with responsibility for decision-making may view invasive Hib disease from different perspectives. Some may value the calculation of incidence rates and the fact that these can be used for estimating the annual number of expected patients with invasive Hib disease. Some may value the fact that studies yield credible data on the number of children who may die as a result of invasive Hib disease or the case-fatality rate among children with serious Hib disease. Other decision-makers may wish to know the proportion of children who suffer long-term or even lifelong disability due to invasive Hib disease. Finally, other decision-makers may wish to compare the burden of invasive Hib disease based on DALYs (48). Such diverse needs can be met by anticipating that study results from different time periods, populations, or that were derived from different methods should be integrated into a package of Hib-burden information that is easily digested by national decision-makers with or without a clinical or laboratory background.

Reporting study results

In the planning stages of a burden study, simple tabulations and sample figures can be created to illustrate

how data will be reported. Reports should be brief and written in a relatively simple language to allow understanding by readers with varying backgrounds. Outcomes of epidemiologic studies, e.g. incidence rates, can be 'translated' into a simpler language to maximize understanding among readers. One approach that may be used involves showing the risk of disease in terms of percentage risk (e.g. x children out of every 10) or may convert risk into language where the risk of a given outcome is placed in terms that use a "lowest common denominator" (e.g. 1 child in every 8 will develop Hib disease). Finally, in using these simpler approaches to quantifying outcomes of Hib-burden study, it is useful to consider quantifying risk over a defined period or age group (e.g. 1 in every 20 children will be hospitalized for Hib disease each year). Alternatively, investigators may express the outcome as a cumulative risk of an outcome event (e.g. 1 in every 8 children will develop Hib disease by the age of 5 years).

IMPLICATIONS OF HIB-BURDEN STUDIES

Economic analyses

Hib disease-burden studies provide data that can be critical for sound economic analysis of Hib-prevention programmes. Data inputs with respect to Hib-associated disease-incidence rates, mortality rates, case-fatality, and the occurrence of clinical sequelae may come from a number of different sources, including published scientific articles, government reports, or personal communications from experts in the field. The quality of data used in economic analysis of Hib-prevention programmes is also important to understand and consider prior to initiating economic studies. Thus, one rationale for conducting high-quality Hib disease-burden studies is that they can provide data for use in making optimal cost-effectiveness or cost-benefit calculations for Hib disease-prevention programmes.

Evaluation of vaccine

Evaluation of Hib vaccine in the context of a large-scale vaccine-demonstration project is often considered to address policy uncertainties (49). Evaluation of Hib conjugate vaccines (vaccine-effectiveness studies or so-called vaccine 'probe' studies) following the introduction of vaccine may also be considered to evaluate the programmatic impact of Hib immunization (50). In the latter case, national health agencies may have ongoing active surveillance systems in which laboratory-confirmed Hib disease is identified (51). As such, disease-burden studies in which active or passive surveillance is conducted for laboratory-confirmed Hib-associated disease can take on added value when such systems are used for evaluating the impact of Hib immunization as Hib vaccine uptake increases (52,53). In other cases, passive reporting of Hib-associated cases is used for estimating the population impact of Hib immunization over a defined period (54). In still other situations, infants may be randomized by group or individual to receive Hib vaccine or another vaccine while all children are monitored in ongoing surveillance for Hib-associated disease (55,56). Hib disease-burden data, e.g. cases of meningitis, can also be evaluated retrospectively or prospectively to evaluate the impact of Hib immunization (57). In this study design, cases may be matched with controls to compare those children who received Hib vaccine with those who did not receive Hib vaccine (58-60).

Post-introduction surveillance

If the introduction of Hib vaccines is planned, the burden of Hib can be monitored as noted above to evaluate the impact of vaccine, reduction in incidence of disease, and Hib vaccine-related adverse events (61). Adverse events following any vaccine are of critical importance to immunization programmes, and adverse events, including breakthrough disease, can be monitored following the administration of Hib vaccine. Surveillance of adverse events may be conducted with passive or active reporting of events (62). Most reporting systems monitor events passively, and such events can be tabulated periodically to estimate the burden of these events.

CONCLUSION

The introduction of Hib vaccines in developing countries is currently limited by a number of factors. Prominent among these are limited evidence that invasive Hib disease is a problem of sufficient importance to warrant investment in vaccination programmes. While the first childhood vaccines were introduced without systematic disease-burden studies, contemporary national policy-makers and international donors must often consider the need for Hib vaccine against competing priorities. In this scenario, disease-burden studies also become valuable as tools to provide data for economic studies and vaccine-evaluation projects and to build infrastructure for post-introduction evaluation of the impact of vaccine. While disease-burden studies

have increased in sophistication in recent years, practical limitations must be addressed to design studies that are feasible and that provide credible evidence. While population-based studies may be considered, alternative study designs, such as hospital-based studies or vaccine probe studies, may provide useful evidence to guide policy-makers especially when combined with studies of long-term sequelae and economic analysis.

ACKNOWLEDGEMENTS

We thank Min Kyoung Oh for her assistance in the preparation of this manuscript.

REFERENCES

1. Bland J, Clements J. Protecting the world's children: the story of WHO's immunization programme. *World Health Forum* 1998;19:162-73.
2. Amin R, Hill RB, Horton SATP, Kamara C, Chowdhury J. Immunization coverage, infant morbidity and infant mortality in Freetown, Sierra Leone. *Soc Sci Med* 1992;35:851-6.
3. Babaniyi OA. A 10-year review of morbidity from childhood preventable diseases in Nigeria: how successful is the Expanded Programme on Immunization (EPI)? An update. *J Trop Pediatr* 1990; 36:306-13.
4. Landaverde M, Di Fabio JL, Ruocco G, Leal I, de Quadros C. [Introduction of a conjugate vaccine against Hib in Chile and Uruguay]. *Rev Panam Salud Publica* 1999;5:200-6.
5. Salisbury DM. The introduction of *Haemophilus influenzae* type b immunization into the United Kingdom: practical steps to assure success. *Pediatr Infect Dis J* 1998;17(Suppl 9):S136-9.
6. Kane MA, Brooks A. New immunization initiatives and progress toward the global control of hepatitis B. *Curr Opin Infect Dis* 2002;15:465-9.
7. FitzSimons D, Van Damme P, Emiroglu N, Godal T, Kane M, Malyavin A *et al*. Strengthening immunization systems and introduction of hepatitis B vaccine in central and eastern Europe and the newly independent states. *Vaccine* 2002;20:1475-9.
8. Holdaway MD, Turk DC. Capsulated *Haemophilus influenzae* and respiratory-tract disease. *Lancet* 1967;1:358-60.
9. Hughes JR, Sinha DP, Cooper MR, Shah KV, Bose SK. Lung tap in childhood: bacteria, viruses, and mycoplasmas in acute lower respiratory tract infections. *Pediatrics* 1969;44:477-85.
10. Makela P. [*Haemophilus influenzae* type b causing acute epiglottitis and meningitis]. *Duodecim* 1968;84:981-3.
11. Schlech WF, III, Ward JI, Band JD, Hightower A, Fraser DW, Broome CV. Bacterial meningitis in the United States, 1978 through 1981. The National Bacterial Meningitis Surveillance Study. *JAMA* 1985;253:1749-54.
12. Bolan G, Barza M. Acute bacterial meningitis in children and adults: a perspective. *Med Clin North Am* 1985;69:231-41.
13. Nottidge VA. *Haemophilus influenzae* meningitis: a 5-year study in Ibadan, Nigeria. *J Infect* 1985; 11:109-17.
14. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr Infect Dis J* 1993;12:389-94.
15. Coen PG, Heath PT, Garnett GP. The Hib immunization programme in the Oxford region: an analysis of the impact of vaccine administration on the incidence of disease. *Epidemiol Infect* 1999;123:389-402.
16. Fox-Rushby JA, Hanson K. Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis. *Health Policy Plan* 2001;16:326-31.
17. DeRoeck D, Deen J, Clemens JD. Policymakers' views on dengue fever/dengue haemorrhagic fever and the need for dengue vaccines in four southeast Asian countries. *Vaccine* 2003;22:121-9.
18. Love J, Shaul JF. Immunization today. *Med Clin North Am* 1950;34:1713-37.
19. Das A, Ghosal SC. Diphtheria in Calcutta. *Lancet* 1951;1:1410-2.
20. Niessen LW, Grijseels EWM, Rutten FFH. The evidence-based approach in health policy and health care delivery. *Soc Sci Med* 2000;51:859-69.
21. Brinsmead R, Hill S, Walker D. Are economic evaluations of vaccines useful to decision-makers? Case study of *Haemophilus influenzae* type b vaccines. *Pediatr Infect Dis J* 2004;23:32-7.

22. Monto AS, Higgins MW, Ross HW. The Tecumseh study of respiratory illness. VIII. Acute infection in chronic respiratory disease and comparison groups. *Am Rev Respir Dis* 1975;111:27-36.

23. Bijlmer HA, van Alphen L, Greenwood BM, Brown J, Schneider G, Hughes A *et al*. The epidemiology of *Haemophilus influenzae* meningitis in children under five years of age in The Gambia, West Africa. *J Infect Dis* 1990;161:1210-5.

24. Ferreccio C, Ortiz E, Astroza L, Rivera C, Clemens J, Levine MM. A population-based retrospective assessment of the disease burden resulting from invasive *Haemophilus influenzae* in infants and young children in Santiago, Chile. *Pediatr Infect Dis J* 1990;9:488-94.

25. Kim JS, Jang YT, Kim JD, Park TH, Park JM, Kilgore PE *et al*. Incidence of *Haemophilus influenzae* type b and other invasive diseases in South Korean children. *Vaccine* 2004;22:3952-62.

26. Rerks-Ngarm S, Treleaven S, Chunsuttiwat S, Muangchana C, Jolley D, Brooks A *et al*. Prospective population-based incidence of *Haemophilus influenzae* type b meningitis in Thailand. *Vaccine* 2004;22:975-83.

27. World Health Organization. Global Programme for Vacccines and Immunizations, Vaccine Research and Development. Generic protocol for population-based surveillance of *Haemophilus influenzae* type b. Geneva: World Health Organization, 1997. 29 p. (WHO/VRD/GEN/95.05).

28. Levine OS, Schwartz B. The rationale for population-based surveillance for *Haemophilus influenzae* type b meningitis. *Pediatr Infect Dis J* 1998; 17(Suppl 9):S195-8.

29. Mwangi I, Berkley J, Lowe B, Peshu N, Marsh K, Newton CRJC. Acute bacterial meningitis in children admitted to a rural Kenyan hospital: increasing antibiotic resistance and outcome. *Pediatr Infect Dis J* 2002;21:1042-8.

30. Youssef FG, El-Sakka H, Azab A, Eloun S, Chapman GD, Ismail T *et al*. Etiology, antimicrobial susceptibility profiles, and mortality associated with bacterial meningitis among children in Egypt. *Ann Epidemiol* 2004;14:44-8.

31. Glismann S, Ronne T, Tozzi A. The EUVAC-NET Project: creation and operation of a surveillance community network for vaccine preventable infectious diseases. *Euro Surveill* 2001;6:94-8.

32. Invasive Bacterial Infections Surveillance (IBIS) Group of the International Clinical Epidemiology Network. Are *Haemophilus influenzae* infections a significant problem in India? A prospective study and review. *Clin Infect Dis* 2002;34:949-57.

33. Steinhoff MC. Invasive *Haemophilus influenzae* disease in India: a preliminary report of prospective multihospital surveillance. IBIS (Invasive Bacterial Infections Surveillance) Group. *Pediatr Infect Dis J* 1998;17(Suppl 9):S172-5.

34. World Health Organization. Regional Office for Africa. VPDU. Surveillance for the new *Haemophilus influenzae* type b (Hib) vaccine to start in the African region. *Vaccine Prevent Dis Bull* 2001;2-2.

35. Wilson N, Mansoor O, Wenger J, Martin R, Zanardi L, O'Leary M *et al*. Estimating the *Haemophilus influenzae* type b (Hib) disease burden and the impact of Hib vaccine in Fiji. *Vaccine* 2003;21: 1907-12.

36. Levine OS, Lagos R, Muñoz A, Villaroel J, Alvarez AM, Abrego P *et al*. Defining the burden of pneumonia in children preventable by vaccination against *Haemophilus influenzae* type b. *Pediatr Infect Dis J* 1999;18:1060-4.

37. Mulholland K, Hilton S, Adegbola R, Usen S, Oparaugo A, Omosigho C *et al*. Randomised trial of *Haemophilus influenzae* type b tetanus protein conjugate for prevention of pneumonia and meningitis in Gambian infants. *Lancet* 1997;349:1191-7.

38. World Health Organization. Estimating the local burden of *Haemophilus influenzae* type b (Hib) disease preventable by vaccination. A rapid assessment tool. Geneva: World Health Organization, 2004:1-67. (WHO/V&B/01.27).

39. Six and one-half month old infant with fever and irritability. *S D J Med* 1975;28:7-10.

40. Chad ZH, Pearson EL, Reece ER, Powell KR. *Haemophilus influenzae* type b meningitis: occurrence in three siblings over a two-year period. *Pediatrics* 1980;66:9-13.

41. Granoff DM, Sargent E, Jolivette D. *Haemophilus influenzae* type b osteomyelitis. *Am J Dis Child* 1978;132:488-90.

42. Kenny JF, Isburg CD, Michaels RH. Meningitis due to *Haemophilus influenzae* type b resistant to both ampicillin and chloramphenicol. *Pediatrics* 1980;66:14-6.

43. Lolekha S, Cooksley G, Chan V, Isahak I, Ismael S, John J *et al*. A review of Hib epidemiology in Asia. *Southeast Asian J Trop Med Public Health* 2000;31:650-657.

44. Hinman A. Eradication of vaccine-preventable diseases. *Annu Rev Public Health* 1999;20:211-29.

45. Archibald LK, McDonald LC, Addison RM, McKnight C, Byrne T, Dobbie H *et al*. Comparison of BACTEC MYCO/F LYTIC and WAMPOLE ISOLATOR 10 (Lysis-centrifugation) systems for detection of bacteremia, mycobacteremia, and fungemia in a developing country. *J Clin Microbiol* 2000;38:2994-7.

46. Herva E, Sombrero L, Lupisan S, Arcay J, Ruutu P. Establishing a laboratory for surveillance of invasive bacterial infections in a tertiary care government hospital in a rural province in the Philippines. *Am J Trop Med Hyg* 1999;60:1035-40.

47. McIntyre P, Jepson R, Leeder S, Irwig L. The outcome of childhood *Haemophilus influenzae* meningitis. A population based study. *Med J Aust* 1993;159:766-72.

48. Miller MA, McCann L. Policy analysis of the use of hepatitis B, *Haemophilus influenzae* type b-, *Streptococcus pneumoniae*-conjugate and rotavirus vaccines in national immunization schedules. *Health Econ* 2000;9:19-35.

49. Review panel on *Haemophilus influenzae* type b (Hib) disease burden in Bangladesh, Indonesia and other Asian countries, Bangkok, 28-29 January 2004. *Wkly Epidemiol Rec* 2004;18:173-80.

50. Clemens J, Brenner R, Rao M, Tafari N, Lowe C. Evaluating new vaccines for developing countries: efficacy or effectiveness? *JAMA* 1996;275: 390-7.

51. Wenger JD, Hightower AW, Facklam RR, Gaventa S, Broome CV. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. The Bacterial Meningitis Study Group. *J Infect Dis* 1990;162:1316-23.

52. McIntyre P, Amin J, Gidding H, Hull B, Torvaldsen S, Tucker A *et al*. Vaccine preventable diseases and vaccination coverage in Australia, 1993-1998. *Commun Dis Intel* 2000;(Suppl):1-83.

53. Domínguez À, Bou R, Carmona G, Latorre C, Pineda V, Sanchez F *et al*. Invasive disease caused by *Haemophilus influenzae*: the sensitivity of statutory reporting. *Ann Epidemiol* 2004;14:31-5.

54. Wenger JD. Epidemiology of *Haemophilus influenzae* type b disease and impact of *Haemophilus influenzae* type b conjugate vaccines in the United States and Canada. *Pediatr Infect Dis J* 1998; 17:S132-S6.

55. Mulholland K, Levine O, Nohynek H, Greenwood BM. Evaluation of vaccines for the prevention of pneumonia in children in developing countries. *Epidemiol Rev Vaccines* 1999;21:43-55.

56. Klar N, Donner A. Current and future challenges in the design and analysis of cluster randomization trials. *Stat Med* 2001;20:3729-40.

57. Ferreccio C, Ortiz E, Astroza L, Rivera C, Clemens J, Levine MM. A population-based retrospective assessment of the disease burden resulting from invasive *Haemophilus influenzae* in infants and young children in Santiago, Chile. *Pediatr Infect Dis J* 1990;9:488-94.

58. Mills OF, Rhoads GG. The contribution of the case-control approach to vaccine evaluation: pneumococcal and *Haemophilus influenzae* type b PRP vaccines. *J Clin Epidemiol* 1996;49:631-6.

59. Vadheim CM, Greenberg DP, Eriksen E, Hemenway L, Christenson P, Ward B *et al*. Protection provided by *Haemophilus influenzae* type b conjugate vaccines in Los Angeles county: a case-control study. *Pediatr Infect Dis J* 1994;13:274-80.

60. Shapiro ED. Case-control studies of the effectiveness of vaccines: validity and assessment of potential bias. *Pediatr Infect Dis J* 2004;23:127-31.

61. Chen RT, Glasser JW, Rhodes PH, Davis RL, Barlow WE, Thompson RS *et al*., and The Vaccine Safety Datalink Team. Vaccine Safety Datalink Project: a new tool for improving vaccine safety monitoring in the United States. *Pediatrics* 1997; 99:765-73.

62. Vadheim CM, Greenberg DP, Partridge S, Jing J, Ward JI, and Kaiser-UCLA Vaccine Study Group. Effectiveness and safety of an *Haemophilus influenzae* type b conjugate vaccine (PRP-T) in young infants. *Pediatrics* 1993;92:272-9.

63. Echeverria P, Smith EW, Ingram D, Sade RM, Gardner P. *Hemophilus influenzae* b pericarditis in children. *Pediatrics* 1975;56:808-18.

64. Mayo-Smith MF, Spinale JW, Donskey CJ, Yukawa M, Li RH, Schiffman FJ. Acute epiglottitis. An 18-year experience in Rhode Island. *Chest* 1995;108:1640-47.

65. Almuneef M, Alshaalan M, Memish Z, Alalola S. Bacterial meningitis in Saudi Arabia: the impact of *Haemophilus influenzae* type b vaccination. *J Chemother* 2001;13(Suppl 1):34-9.

66. Dickinson FO, Perez AE, Galindo MA, Quintana I. [Impact of vaccination against *Haemophilus influenzae* type b in Cuba]. *Rev Panam Salud Publica* 2001;10:169-73.

67. Standaert SM, Lefkowitz LB, Jr., Horan JM, Hutcheson RH, Schaffner W. The reporting of communicable diseases: a controlled study of *Neisseria meningitidis* and *Haemophilus influenzae* infections. *Clin Infect Dis* 1995;20:30-6.

Appendix

Options of study design for Hib disease-burden studies in developing countries

Option of study design	Reference no.	Outcomes for analysis	Advantages	Disadvantages
Case report	63	Not applicable	Ease of investigation; fast reporting	Not representative; no comparative information on different pathogens or manifestations of disease
Case series	64	Proportion and number of cases due to Hib, other pathogens Case-fatality rate	Usually involves one hospital; easier logistics; often retrospective, non-systematic data collection	Sometimes limited to manifestation of one disease or one pathogen
Single hospital study	65	Proportion and number of cases due to Hib, other pathogens Case-fatality rate	Usually involves one hospital; easier logistics; more systematic data collection, may be prospective	May not be population-based; may not be representative
Local or national surveillance or administrative databases	66,67	Number of hospitalizations or deaths due to bacterial meningitis or incidence of Hib meningitis and/or mortality rates due to Hib disease	Data may be accessible in computerized format; often captures more severe outcomes	May not be representative of entire population if under-reporting present; may not include less severe outcomes
Rapid Hib disease-burden assessment (RAT)	35	Cases (incidence) and deaths (mortality) due to Hib meningitis and pneumonia Case-fatality rate	Faster than hospital- or population-based studies Not labour-intensive Less expensive	Not direct incidence estimate Depends on assumptions from scant literature
Hospital network	32	Cases and deaths due to manifestations of severe Hib disease (meningitis, pneumonia, sepsis) Case-fatality rate	Logistically easier than population-based study	More difficult to estimate incidence
Population-based study		Cases and deaths due to manifestations of severe Hib disease (meningitis, pneumonia, sepsis) Case-fatality rate	Allows incidence calculation Allows direct calculation of incidence and mortality rates; allows estimation of % with clinical sequelae	Logistically difficult; resource-intensive May require training and capacity-strengthening for laboratory
Case-control study	59	Hib vaccine effectiveness Attributable fraction of disease manifestation (e.g. meningitis) due to Hib Indirect Hib incidence estimate	Provides estimate of Hib vaccine effectiveness Less resource-intensive compared to cluster randomized effectiveness trial	Moderately expensive Potentially subject to bias
Vaccine 'probe' study	50	Hib vaccine effectiveness Attributable fraction of manifestation of disease (e.g. meningitis) due to Hib Indirect Hib incidence estimate	Gives vaccine effectiveness Methodologically rigorous Less subject to bias	Expensive Requirement of a larger sample size Complicated Indirect incidence estimate