Use of Multiple Surveillance Modalities to Assess the Epidemiology of *Streptococcus pneumoniae* Infection in Bangladesh

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Measuring the broad impact of pneumococcal disease requires multiple surveillance modalities. Four major data sources elucidate the burden of pneumococcal disease in Bangladesh. The Bangladesh Demographic and Health Survey has identified pneumonia as the leading cause of childhood death. By extrapolation of mortality rates in the survey to the Bangladesh population, it has been estimated that ∼90,000 children 1 month and <5 years of age die of pneumonia every year in Bangladesh. Through hospital-based surveillance, a wide range of pneumococcal serotypes leading to hospitalization and pneumonia have been identified as a leading cause of pediatric hospitalization. Urban community-based surveillance has demonstrated that invasive pneumococcal disease (IPD) is common in the community. Rural community-based surveillance has demonstrated that serious IPD is common in rural areas. Together, these data provide a strong scientific case for the importance of pneumococcal disease prevention to child health in Bangladesh and, therefore, the potential benefit of an effective vaccine.

Pneumococcal disease causes ∼1 million deaths among children each year [1]. Pneumococcal conjugate vaccines (PCVs) reduce the incidence of invasive pneumococcal disease (IPD) [2–4] and, as found in one study in The Gambia, childhood mortality [4]. However, the decision to adopt new vaccines usually is made at the country level and is based on a variety of factors, including perceived local burden of disease and the cost and cost-effectiveness of the vaccine. Country-level data are important because pneumococcal disease burden varies by geography [5]; also, the serotypes responsible for the majority of cases of pneumococcal disease can differ [5, 6] and may be influenced by factors such as overcrowding, air quality, malnutrition, and the prevalence of HIV infection.

An optimal assessment of disease incidence prevented by a new vaccine might be achieved through a probe study, whereby the vaccine is introduced in a randomly selected population and the disease burden among vaccinated children is compared with that among nonvaccinated children. However, probe studies require years to conduct and are prohibitively expensive to conduct in each country. This article summarizes results of various surveillance activities in Bangladesh, which, taken together, provide a broad understanding of the burden of pneumococcal disease.

**BANGLADESH DEMOGRAPHIC AND HEALTH SURVEY**

The Bangladesh Demographic and Health Survey is a recurring series of nationally representative surveys designed to obtain basic indicators of social progress, including that of child health, within Bangladesh. The Bangladesh census divides the country into 262,000 separately mapped enumeration areas that are categorized as either urban or rural [7]. The 2004 Bangladesh Demographic and Health Survey randomly selected 122...
urban and 239 rural enumeration areas from the entire country in which to conduct interviews. All households in the selected enumeration areas were listed, and a systematic sample of 10,811 households were selected for interviews [8].

Trained interviewers visited each of the selected households and administered a series of questionnaires. If a child <5 years of age had died during the 5 years preceding the interview, interviewers administered a verbal autopsy—that is, a series of questions regarding symptoms experienced by the child before death. Acute respiratory illness was assigned as a cause of death if the child had a cough that started at least 3 days before death and lasted at least until the day before death and if at least 2 of the following 6 symptoms were reported: noisy breathing, stridor, grunting, wheezing, nostril flaring, or chest in-drawing. In addition, acute respiratory illness was assigned if the child had difficulty breathing or rapid breathing starting at least 1 day before death and lasting until death and at least 2 of the 6 specific symptoms listed above [9]. Neonatal deaths (i.e., during the first month of life) are not usually caused by pneumococcal disease and have different diagnostic criteria and prevention strategies.

The 2004 Bangladesh Demographic and Health Survey estimated that 4.7% of children born in Bangladesh die between their second month of life and their fifth birthday [8]. Of these postneonatal deaths, 35% are solely attributed to acute respiratory tract infection [9]. An additional 3.4% of the deaths are attributed to a combination of acute respiratory illness and diarrhea, and 28% are attributed to “possible serious infection” [9]. If half of the deaths due to acute respiratory illness and diarrhea would not have occurred if the respiratory illness had been prevented and if one-third of the possible serious infections had been due to a respiratory pathogen, then 46% of postneonatal deaths among children <5 years of age in Bangladesh could have been due to acute respiratory illness. Given these assumptions, it can be estimated that 22 of every 1000 children born in Bangladesh who survive the neonatal period die of pneumonia before their fifth birthday.

In 2005, Bangladesh’s population was estimated to be 144.2 million [10], with a crude birth rate of 28.7 births per 1000 population [8]. Thus, an estimated 4.1 million children were born in Bangladesh in 2005. A postneonatal pneumonia-specific mortality rate of 22 deaths per 1000 live births means that ~90,000 children died of postneonatal acute respiratory illness in Bangladesh in 2005.

The Bangladesh Demographic and Health Survey is important because it is a representative sample of the whole country and, thus, can be used to model national rates and transcend single-institution or single-area perspectives. The survey persuasively illustrates the contribution of respiratory disease to childhood mortality in Bangladesh. *Streptococcus pneumoniae* is also a major cause of acute bacterial meningitis during childhood [11, 12]. However, the contribution of meningitis to childhood mortality is more difficult to assess by use of the verbal autopsy method. Moreover, since children’s symptoms and deaths do not occur under medical supervision and no surgical autopsy is performed, there is residual uncertainty about the cause of death. In addition, the reporting of symptom history by survivors does not provide information on the pathogenic infections associated with the child’s death. Nonetheless, the potential burden of pneumococcal disease preventable by means of an effective immunization strategy is even greater when meningitis is also considered.

**HOSPITAL-BASED SURVEILLANCE**

Hospital-based surveillance for pneumococcal disease was initiated in 7 hospitals in Bangladesh in May 2004. These hospitals included both government and private institutions and included the largest pediatric hospitals in Dhaka, the capital, and Chittagong, Bangladesh’s second largest city. Children admitted to any of these 7 hospitals who were <5 years of age, who met a clinical case definition for pneumonia, meningitis, or very severe disease, and from whom blood or CSF samples were collected for culture were enrolled and followed up until hospital discharge. Cultures were performed at no cost to the patient. Staff members in the microbiology laboratories at each of the hospitals were trained to perform blood and CSF cultures and were overseen by an experienced microbiologist. From May 2004 through March 2007, a total of 37,333 children met the clinical criteria for enrollment, 16,505 children were enrolled, and 135 children had pneumococcus isolated from blood or CSF samples [13].

Hospital-based surveillance activity contributes multiple elements to pneumococcal disease surveillance. First, the 1107 hospitalized, enrolled children who met the case definition for pneumonia, the 2403 enrolled children who met the case definition for severe pneumonia, and the 1982 enrolled children who met the case definition for very severe pneumonia demonstrate that pneumonia is a common and serious problem in pediatric wards throughout the country. The case-fatality rates among hospitalized children were 0.06% for pneumonia, 2.7% for severe pneumonia, and 11% for very severe pneumonia [14], thus reinforcing the Bangladesh Demographic and Health Survey finding that pneumonia is a common cause of childhood death among young children, even among those who reach the hospital. Although meningitis may be a less-common syndrome than pneumonia, hospital-based surveillance has demonstrated that pneumococcal meningitis is associated with a particularly high case-fatality rate (11%; A.N., unpublished data).

Hospital-based surveillance engages respected senior physicians of major institutions in the country who are influential opinion leaders for the introduction of vaccines into the country and are those to whom government decision makers often
turn for advice. Hospital-based surveillance has demonstrated that, in pediatric hospitals throughout Bangladesh, pneumococcal infection can be identified when it is looked for appropriately. Hospital-based surveillance is also an important source of pneumococcal isolates for the characterization of local serotype distribution and antimicrobial-resistance patterns associated with severe pneumococcal disease in Bangladesh.

In Bangladesh, the major limitation of hospital-based surveillance for pneumococcal disease is that many young children with serious disease do not have access to hospitals or do not seek hospital care [15]. According to the 2004 Bangladesh Demographic and Health Survey, children living in the richest 20% of households in Bangladesh were 3 times more likely to receive care for symptoms of an acute respiratory illness at a health care facility or by a medically trained provider, compared with children living in the poorest 20% of households [8]. Thus, the cases of pneumococcal disease in hospitals in Bangladesh are likely to systematically underrepresent cases of pneumococcal disease among the segments of the population expected to bear the largest disease burden. A second limitation is that blood culture is an insensitive method for the diagnosis of pneumococcal pneumonia [3, 16] and that it markedly underestimates the proportion of cases of severe respiratory disease among children that is attributable to pneumococcus. This underestimation is compounded by the large number of patients from whom a blood culture sample is not collected. Furthermore, the serotypes of isolates from blood culture samples may not be representative of the isolates causing pneumonia, since only a fraction of the pneumococci causing pneumonia enter the bloodstream [17].

Nevertheless, hospital-based surveillance has illustrated that pneumococcus is commonly associated with cases of pneumonia in hospitals in Bangladesh. In addition, it has been used to identify serotypes of *S. pneumoniae* that are associated with severe disease and trends in antimicrobial resistance [13], thereby contributing to a better understanding of pneumococcal disease burden and characteristics.

**URBAN COMMUNITY-BASED SURVEILLANCE**

Urban community-based surveillance for pneumococcus in the Kamalapur neighborhood of Dhaka, Bangladesh, has been described recently [18]. Kamalapur is a densely populated, low-income community. The community was divided into 377 household clusters; 168 of these household clusters were randomly selected to participate in surveillance. Within each selected household cluster, field workers identified households with children ≤5 years of age and invited them to participate in the surveillance.

Beginning in April 2004, ~5000 children ≤5 years of age were placed under regular weekly surveillance. Each week, 40 field workers visited every participating household and, using a standardized questionnaire for each child, asked about signs of illness for each day of the week since the last visit. Children with 1 major sign of illness—fever (either measured or reported); rapid, labored, or noisy breathing; lethargy; cyanosis; inability to drink; or convulsions—were referred to a field clinic of the International Centre for Diarrheal Diseases Research, Bangladesh, in Kamalapur for medical evaluation. Similarly, children were referred to the field clinic if they had 2 minor symptoms or signs of illness, including cough, runny nose, sore throat, muscle or joint pain, chills, headache, irritability, decreased activity, or vomiting. Ninety-nine percent of the referred children attended the clinic. Caregivers also were encouraged to bring children to the clinic if a child developed illness on days that a field worker did not visit.

All clinical evaluations were conducted systematically, at no cost to the patient, by doctors trained in the study protocol for case management of pneumonia. Physicians performed a standardized examination, and blood samples were collected for culture from children who met clinical criteria for pneumonia, sepsis, meningitis, otitis media, fever without localizing signs, or upper respiratory tract infection.

From 1 April 2004 through 31 March 2006, a total of 6167 children met the criteria for suspected IPD. Blood culture samples of sufficient volume were obtained from 5946 (96%) of these children, and 34 (0.06%) samples grew pneumococcus. These results translate into 450 episodes of IPD per 100,000 child-years of observation [18].

Of the 34 samples with pneumococcal isolates, 14 (41%) had serotypes included in the currently marketed 7-valent PCV, 18 (53%) had serotypes included in the 9-valent PCV tested in The Gambia, 18 (53%) had serotypes included in the investigational GlaxoSmithKline 10-valent PCV, and 19 (56%) had serotypes included in the Wyeth 13-valent PCV. The incidence of IPD due to vaccine serotypes ranged from 185 to 252 episodes per 100,000 child-years of observation, depending on the vaccine (table 1). When strict case definitions were used with physician diagnoses, the most common final diagnosis for children who had positive blood-culture results was upper respiratory tract infection (62%), followed by pneumonia (24%). The more-common but less-specific case definition for pneumonia that is used with the integrated management of childhood illness algorithm classifies any child with tachypnea and either cough or difficulty breathing as having pneumonia [19]. When this more-common but less-specific case definition for pneumonia was used, 79% of the children in Kamalapur with IPD had pneumonia.

This urban community-based surveillance contributes several important elements to the understanding of pneumococcal disease in Bangladesh. First, in Kamalapur, the incidence of IPD due to 9-valent PCV serotypes was similar to the incidence...
defined through use of similar clinical criteria and microbiological methods in The Gambia (237 and 250 episodes per 100,000 child-years, respectively), where introduction of the 9-valent PCV resulted in a 16% reduction in mortality among children who had received the vaccine [4]. Second, urban surveillance demonstrated that the range of clinical syndromes caused by pneumococcus is broader than the pneumonia, sepsis, and meningitis seen in the hospitals. Third, urban surveillance demonstrated that the serotypes identified in the community were different from the serotypes isolated in the hospitals.

However, there are important limitations that restrict the representativeness of the urban community-based surveillance. First, with active surveillance, children with syndromes consistent with IPD are identified and receive treatment early. Thus, the normal course of the disease, as it would be experienced by most affected children in Bangladesh, may be altered, and the incidence of more-severe manifestations of infection may be underrepresented. Second, because blood culture is an insensitive methodology for the identification of bacterial respiratory pathogens, measures of the incidence of IPD underestimate total pneumococcal disease burden, as is the case with hospital-based surveillance. Third, the site of the urban surveillance was a single, geographically restricted area that may not be broadly representative of pneumococcal disease in Bangladesh. Indeed, although the proportion has been increasing annually, a minority of children in Bangladesh currently live in urban areas [20].

**RURAL COMMUNITY-BASED SURVEILLANCE**

Mirzapur is a mostly rural subdistrict located 60 km north of Dhaka. Pneumococcal disease surveillance was added to a neonatal intervention project operating in 6 of the 13 unions in Mirzapur, beginning in July 2004 [21]. Seventy-two health care workers conducted weekly visits to households with children \(<5\) years of age who participated in the surveillance. Children who demonstrated elevated respiratory rates and difficulty breathing, chest in-drawing, or altered consciousness or who had high fever and stiff neck or altered level of consciousness were referred, by field workers, to Kumudini Hospital (in Mirzapur) for evaluation. The travel time to Kumudini Hospital varied from 20 min to 2 h, depending on the location of a specific village. Hospital physicians evaluated referred children who came to the hospital and ordered the collection of blood and/or CSF samples for culture, if the physician believed that a culture was clinically indicated. Study physicians classified admitted patients and, beginning in March 2006, recommended blood culture for outpatients who met 1 of the PneumoADIP case definitions for pneumonia, severe pneumonia, meningitis, or very severe disease [21].

From July 2004 through June 2007, village health care workers identified cases of possible severe pneumonia or possible meningitis in children under surveillance and referred children to Kumudini Hospital 13,895 times; 10,978 children (79%) were assessed at Kumudini Hospital. Rates of hospitalization per 1000 child-years were 27 for pneumonia, 3 for severe pneumonia, 3 for very severe pneumonia, 6 for meningitis, and 0.4 for very severe disease. *S. pneumoniae* was isolated from blood or CSF samples from 13 hospitalized patients and 13 outpatients. The incidence of hospitalization due to IPD was 43 episodes per 100,000 child-years; the overall incidence of IPD among both hospitalized patients and outpatients was 86 episodes per 100,000 child-years. The incidence of IPD due to vaccine serotypes ranged from 30 to 63 episodes per 100,000 child-years of observation, depending on the vaccine (table 1).

This rural community-based surveillance contributes important elements to the understanding of pneumococcal disease burden in Bangladesh. Seventy-five percent of the population of Bangladesh lives in rural areas [20], and the community-based surveillance demonstrates that severe IPD occurs in rural areas. The rural surveillance also demonstrates that a less-intensive surveillance approach, in which patients have to travel a considerable distance to a health care facility for evaluation, produces a lower measured incidence of IPD but that the case patients identified are more likely to require hospitalization and to have meningitis.

Limitations of rural community-based surveillance include the fact that, to date, only a few serotypes have been identified.

### Table 1. Incidence of invasive pneumococcal disease in urban Kamalapur, Dhaka (April 2004–March 2006), and rural Mirzapur (July 2004–June 2007), Bangladesh.

<table>
<thead>
<tr>
<th>Pneumococcal serotypes (PCV)</th>
<th>Urban Kamalapur</th>
<th>Rural Mirzapur</th>
</tr>
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<tbody>
<tr>
<td>All</td>
<td>450</td>
<td>86</td>
</tr>
<tr>
<td>4, 6B, 9V, 14, 18C, 19F, and 23F (7-valent)</td>
<td>185</td>
<td>30</td>
</tr>
<tr>
<td>1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F (9-valent)</td>
<td>239</td>
<td>63</td>
</tr>
<tr>
<td>1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F (10-valent)</td>
<td>239</td>
<td>63</td>
</tr>
<tr>
<td>1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (13-valent)</td>
<td>252</td>
<td>63</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. of episodes per 100,000 child-years. PCV, pneumococcal conjugate vaccine.
Furthermore, the low sensitivity of blood culture for pneumococcal respiratory disease and the decision by a substantial proportion of the surveillance population to decline referral to Kumudini Hospital when recommended by the field worker may have resulted in an underestimation of the burden of pneumococcal disease.

**OVERALL PICTURE**

Taken together, periodic national health surveys with verbal autopsy, hospital-based surveillance, and active community-based surveillance in urban and rural communities lead to several important conclusions. The Bangladesh Demographic and Health Survey has identified pneumonia as the leading cause of death among children <5 years of age in Bangladesh. Hospital-based surveillance has demonstrated that pneumococcus is commonly identified as a cause of pneumonia in hospitalized children in Bangladesh. In urban community-based surveillance, the incidence of IPD has been as common as that detected in vaccine trials in Africa, where the use of PCV was associated with decreased mortality. Pneumococcus causes serious disease in rural populations. There are more serotypes responsible for disease in Bangladesh, compared with other sites globally, but current vaccines would protect a large number of children.

When these activities are ongoing simultaneously, the limitations of any single activity are substantially offset by the other activities. The Bangladesh Demographic and Health Survey does not provide pathogen-specific information, but the other activities do. Many persons with pneumococcal disease are not hospitalized, but community-based studies provide insight into the incidence of disease that does not result in hospitalization. The urban community-based surveillance was restricted to a single site, the Kamalapur neighborhood in Dhaka, but the incidence of pneumococcal-associated disease identified in multiple other sites reinforces that the high incidence of disease in Kamalapur is not an anomaly. The higher incidence of IPD that was identified in the Kamalapur surveillance was not found in the Mirzapur surveillance, whereas pneumococcal meningitis was not observed in Kamalapur, perhaps because of rapid referral and early treatment, but was seen frequently in Mirzapur and in hospitals.

Important questions about pneumococcal disease burden in Bangladesh remain unanswered. Most importantly, the extent of childhood pneumonia caused by pneumococcus, especially those strains of pneumococcus included in available PCVs, has yet to be determined in Bangladesh. In a PCV trial in The Gambia, children who received the 9-valent PCV had a 37% reduction in radiographically confirmed pneumonia [4]. However, the distribution of pneumococcal serotypes identified in Bangladesh is somewhat different from the distribution reported in The Gambia [4, 13]. Moreover, the serotypes isolated from children during urban community-based surveillance differ from the serotypes isolated during hospital-based surveillance, and the serotypes isolated from children with pneumonia differ from those isolated from children who had meningitis [13]. Pneumococcus causes pneumonia more frequently than it causes meningitis, but the case-fatality ratio associated with meningitis is much higher than that associated with pneumonia [22]. Among hospitalized children with pneumonia, the proportion of isolates covered by the 10- and 13-valent PCVs is quite similar to that found during the urban community-based surveillance (50% and 53%, respectively, for the 10-valent PCV; 59% and 56%, respectively, for the 13-valent PCV) [13, 18]. Combined with the experience of other countries, these data from Bangladesh suggest that a vaccine effective against pneumococcus serotypes commonly associated with IPD in Bangladesh would have a substantial impact on decreasing childhood mortality.

A second question frequently posed by policy makers is what impact the introduction of a PCV would have on childhood mortality. The most direct approach to answering this question would be a randomized, controlled trial of sufficient size to demonstrate the impact. This approach, however, requires years of planning, implementation, and data analysis and thus risks delaying introduction of an effective intervention that could substantially reduce childhood morbidity and mortality now. An alternative approach would be to introduce a PCV as soon as possible on the basis of its remarkable success in other populations [2–4] and the extensive evidence of widespread pneumococcal disease in Bangladesh, as indicated by the pneumococcal disease surveillance data reviewed here. The effectiveness of the vaccine could be assessed by continuing the current surveillance and by monitoring changes in the incidence and serotype distribution of IPD. In addition, case-control studies could be used to estimate vaccine efficacy with regard to the prevention of pneumonia and meningitis, and these results could be combined with cause-of-death information collected through verbal autopsies in the Bangladesh Demographic and Health Survey, to estimate the reduction in mortality.

A third unanswered question is the degree that pneumococcal serotypes vary over time in Bangladesh. The hospital-based surveillance demonstrated a difference in the serotypes of strains isolated during current surveillance activity, compared with those isolated 10 years ago, including the emergence of a nonvaccine strain (serotype 2) as the most commonly isolated serotype [13]. Moreover, there is evidence that, after the introduction of an effective PCV, the incidence of pneumococcal disease due to nonvaccine serotypes increases, although the net benefit of vaccination remains substantial [23, 24]. Thus, ongoing surveillance to monitor these trends is essential.

Ongoing multiple surveillance activities highlight the im-
importance of pneumococcal infection as a public health problem among children in Bangladesh. The results of any single surveillance activity would have provided an incomplete and, possibly, nonrepresentative picture of pneumococcal disease in Bangladesh. Taken together, the results of multiple surveillance activities provide compelling scientific evidence that pneumococcal disease causes substantial childhood morbidity and mortality, and they indicate the potential benefit of an effective vaccine. The current production cost of PCV requires subsidies for vaccination, in order to reach impoverished areas like Bangladesh and other low-income areas. It is important that PCVs are introduced in areas with ongoing multifaceted surveillance activities, like those in Bangladesh, so that the uptake and effectiveness of a PCV can be systematically measured and defined. Such data should have a dramatic impact on regional policy decisions to purchase PCV and to incorporate it into routine infant immunization programs.

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