Surveillance for pneumococcal disease, Bangladesh – Implications for prevention

Streptococcus pneumoniae (pneumococcus) is a leading cause of childhood pneumonia worldwide. New, safe effective vaccines have been developed, but the burden of pneumococcus in Bangladesh is unclear. We conducted surveillance for pneumococcus at seven hospitals and two community sites in Bangladesh. Between April 2004 and February 2006 we identified 117 isolates of pneumococcus from blood or cerebrospinal fluid (CSF) culture. All seven hospitals and both community sites identified patients with invasive pneumococcal disease. Most strains (72%) were resistant to co-trimoxazole. Fifty-eight percent of strains identified in community surveillance would be covered by the 9-valent pneumococcal conjugate vaccine. Pneumococcal conjugate vaccine would be expected to meaningfully improve child survival in Bangladesh.

Pneumonia is the leading cause of death among children under 5 years of age in Bangladesh (1). While it is difficult to know which pathogen is responsible for a specific child's death from pneumonia, infections caused by ***Streptococcus pneumoniae*** (pneumococcus) are believed to be a major cause of fatal childhood pneumonia and meningitis worldwide (2).

Different strains of pneumococcus have molecular differences in their external capsule. Currently available pneumococcal vaccines are directed against this capsule. Each pneumococcal vaccine is active against only a handful of the more than 100 different pneumococcal serotypes. Because a minority of serotypes cause the majority of the pneumococcal disease, vaccines developed against 7-11 serotypes have been remarkably effective in reducing pneumococcal disease. A vaccine against 7 serotypes of pneumococcus has been used in children in the U.S. since 2000 and has reduced the incidence of invasive pneumococcal disease among children under 5 years of age by 75% (3). A vaccine against 9 serotypes of pneumococcus was tested in The Gambia, and reduced radiologically-confirmed pneumonia by 37%, laboratory-confirmed invasive pneumococcal disease by 77%, and overall child mortality by 16% (4).

A previous hospital-based study concluded that the most common serotypes of pneumococcus isolated among hospitalized patients in Bangladesh are different from the serotypes that are included in the available vaccines (5). Moreover, there is a lack of data on the burden of pneumococcus in Bangladesh. This hampers reaching an evidence-based decision on introduction of pneumococcal conjugate vaccine to Bangladesh.

We established surveillance at seven hospitals and two community sites to better understand the burden of pneumococcal disease in Bangladesh, and the coverage that would be expected by introducing a new vaccine.

Beginning May 2004, specimens were collected from children under 5 years

of age admitted to the seven participating hospitals with pneumonia, meningitis or very severe disease according to WHO clinical case definitions[1]. Blood and cerebrospinal fluid specimens were sent to local laboratories for culture and antimicrobial susceptibility tests. A reference laboratory, located in Dhaka Shishu Hospital, received isolates from local laboratories for confirmation and serotyping.

In Kamalapur, a densely populated low-income community in Dhaka city, households were randomly selected and beginning in April 2004, approximately 5000, children under 5 years of age were actively followed. Each week, 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 one major sign of illness - fever (either measured or reported), rapid, laboured, or noisy breathing, lethargy, cyanosis, inability to drink or convulsions were referred to ICDDR,B's clinic in Kamalapur for medical evaluation. Similarly, children with at least two minor symptoms or signs of illness including cough, runny nose, sore throat, muscle or joint pain, chills, headache, irritability, decreased activity or vomiting, were also referred to the clinic. All clinical evaluations were conducted at no cost to the patient. Participating families were also encouraged to self refer – to bring their children to the clinic if they developed signs or symptoms of illness on days that the field worker did not come to visit them in the home. In the clinic, physicians performed a standardized examination and ordered additional tests based on specific findings. Children with axillary temperature ≥38°C had blood drawn for culture.

Beginning August 2004 in Mirzapur, a rural setting, health workers visited households with approximately 13,000 children under 5 years of age each week. If a child had possible severe pneumonia (rapid respirations plus a danger sign), high fever (≥102˚F or ≥101˚F if <2 months old) or suspected meningitis or very severe disease, the child was referred to Kumudini Hospital. At Kumudini Hospital patients who met the WHO clinical case definitions for pneumonia, severe pneumonia, meningitis or very severe disease had blood or cerebrospinal fluid (CSF) collected and were enrolled in the surveillance.

From April 2004 through February 2006, 15,228 patients were enrolled, and 117 strains of pneumococcus were isolated (Table 1). Each of the seven participating hospitals were successful in isolating pneumococci from blood or CSF cultures. ***Haemophilus influenzae*** Type B (Hib), another bacterial pathogen for which an effective vaccine is available, was also commonly isolated (Table 1). Meningitis was much more common among patients with pneumococcus enrolled from the 7 hospitals (63/74, 85%) than from the community surveillance sites (4/43, 9%).

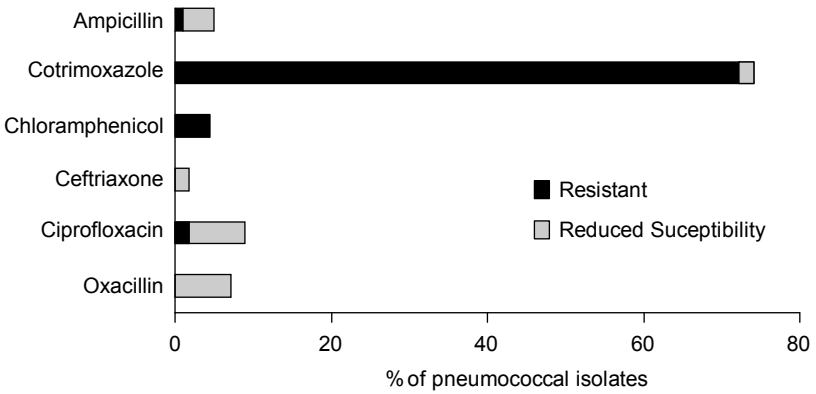
[1]A child is classified with 'very severe disease' if she/he presents with inability to drink, prostration or lethargy, severe malnutrition, stridor in a calm child, hypothermia, central cyanosis and fast breathing or severe chest indrawing in children less than two months

Table 1: Patients enrolled and culture results

	7 Hospitals	Rural	Urban
Number of patients who met case definitions (eligible)	19322	1669	5931
Number of patients who had a blood/CSF collected	8622	1027	5579
Proportion of eligible patients enrolled (%)	44.6	61.5	94.1
Number of patients who yielded a bacterial pathogen	661	32	302
Bacterial isolation rate	7.7	3.1	5.4
Number of pneumococci isolated	74	10	33
Isolation rate for pneumococci (%)	0.9	1.0	0.6
Proportion of bacterial isolates that were pneumococcus	11.2	31.3	10.9
Number of *Haemophilus influenzae* Type B isolations	60	6	1
Isolation rate of *Haemophilus Influenza* Type B	0.70	0.58	0.02
Proportion of bacterial isolates that were *Haemophilus influenzae* Type B	9.1	18.8	0.3

The antimicrobial resistance patterns were similar for strains isolated from patients identified through community surveillance and those identified during hospital surveillance (data not shown). Most strains (72%) were resistant to co-trimoxazole, the first line agent recommended for treatment of acute respiratory tract infection in children under 5 years of age by the World Health Organization (6) (Figure 1).

Figure 1: Antimicrobial resistance for all pneumococcal strains



The distribution of pneumococcal serotypes differed among cases enrolled in the community compared with cases enrolled in the hospital. Among hospitalized patients, 30% had strains of pneumococci that would be covered by the currently marketed seven-valent vaccine (4, 6B, 6A, 9V, 14, 18C, 18F, 19F, 23F) and 45% would be covered by the nine-valent vaccine (4, 6B, 6A, 9V, 14, 18C, 18F, 19F, 23F, 1, 5) tested in The Gambia. For illness identified

in the community, 40% of the strains would be covered by the seven-valent vaccine and 58% would be covered by the nine-valent vaccine.

Reported by: Dhaka Medical College and Hospital; Sir Salimullah Medical College and Hospital; Chittagong Medical College and Hospital; Shishu Sashthya Foundation; Chittagong Maa Shishu O General Hospital; Kumudini Hospital; Dhaka Children's (Shishu) Hospital and the Programme on Infectious Diseases and Vaccine Science, ICDDR,B

Supported by: Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP) at Johns Hopkins Bloomberg School of Public Health with funding through the Global Alliance for Vaccines and Immunisation

Comment

Even in ideal situations pneumococci are difficult to isolate, and so the vast majority of pneumococcal infections are unrecognized. However, this surveillance activity demonstrates that in all sites in Bangladesh where it was systematically looked for, pneumococcus was an important pathogen. In hospital settings, most pneumococcal isolates came from patients who had meningitis. Cultures are much more likely to be positive in patients with meningitis in contrast to patients with pneumonia (5). However, pneumococcal pneumonia, which is more difficult to diagnose, represents a substantially larger burden of disease. Vaccine efficacy studies suggest that pneumococci account for at least 20% of severe pneumonia (4,7).

The distribution of serotypes suggests that the majority of cases of invasive pneumococcal infections in Bangladesh could be prevented using current vaccines. Indeed, 58% of the pneumococcal strains isolated from the community, which are likely more representative of the total burden of infection, would be prevented with current vaccines. With rates of pneumonia that are 20 times the rates in the U.S., a vaccine that would be effective against 58% of strains would be expected to have an important effect on child survival in Bangladesh.

The high rate of in vitro resistance to co-trimoxazole suggests that it is not an appropriate first line agent for the treatment of presumed pneumococcal infection, especially severe illnesses associated with danger signs. Many pneumococcal strains which are associated with resistance are of serotypes included within vaccine formulations. One of the consequences of an effective pneumococcal vaccine programme in the United States was a marked reduction in the incidence of disease from antimicrobial resistant pneumococcal strains (8).

It is also notable that while searching for pneumococcus, this surveillance activity identified a large number of Hib infections. A vaccine against Hib is also available. In a study in Bangladesh, children who received Hib vaccine had a 50% protection against purulent meningitis and 34% protection against pneumonia (9). As pneumonia is the leading cause of childhood death in

Bangladesh and as purulent meningitis has a high case-fatality ratio, introduction of the conjugate Hib vaccine into Bangladesh would be expected to notably improve child survival.

Several new lifesaving childhood vaccines are now in regular use in higher income countries, including vaccines effective against pneumococcus, Hib and rotavirus. Introduction of these new, safe, and effective vaccines within Bangladesh could produce the next substantial improvement in child survival, and keep the country on the path to achieve the millennium development goals for child survival. However, each vaccine carries with it a significant cost burden. For pneumococcus, investigations to measure local effectiveness and cost effectiveness would help government officials and donors reach timely informed decisions on vaccine introduction.

References

1. Arifeen SE, Akhter T, Chowdhury HR, Rahman KM, Chowdhury EK, Alam N ***et al***. Causes of death in children under five years of age. ***In:*** National Institute of Population Research and Training. Bangladesh Demographic and Health Survey 2004. Dhaka: National Institute of Population Research and Training, 2005:125-33.
2. Greenwood B. The epidemiology of pneumococcal infection in children in the developing world. ***Philos Trans R Soc Lond B Biol Sci*** 1999;354(1384):777-85.
3. Centers for Disease Control and Prevention (CDC). Direct and indirect effects ofroutine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease-United States, 1998-2003. ***Morb Mortal Wkly Rep*** 2005;54(36):893-7.
4. Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB ***et al***. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in the Gambia: randomised, double-blind, placebo-controlled trial. ***Lancet*** 2005;365(9465):1139-46.
5. Saha SK, Baqui AH, Darmstadt GL, Ruhulamin M, Hanif M, El Arifeen S ***et al***. Comparison of antibiotic resistance and serotype composition of carriage and invasive pneumococci among Bangladeshi children: implications for treatment policy and vaccine formulation. ***J Clin Microbiol*** 2003;41(12):5582-7.
6. World Health Organization. IMCI Model chapter for textbooks. Geneva: World Health Organization, 2001. 45 p. (available at: http://www.who.int/child-adolescent-health/publications/IMCI/WHO_FCH_CAH_00.40.htm)
7. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N ***et al***. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. ***N Engl J Med*** 2003;349(14):1341-8.
8. Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold A ***et al***. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant streptococcus pneumoniae. ***N Engl J Med*** 2006;354(14):1455-63.
9. ICDDR,B: Centre for Health and Population Research. ***Health Sci Bull*** 2004;2(3):11-13.