

Child Health Research Project

Synopsis: The India Invasive Bacterial Infections Surveillance (IBIS) Project

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Effective infectious disease surveillance systems provide basic information on incidence and geographic distribution of known infectious agents. This information, needed at local, national, and international levels, is necessary for detecting new or re-emerging threats, documenting antimicrobial resistance, and developing new treatments and vaccines. Surveillance data can also be used to change clinical management of disease, update treatment guidelines and lists of essential drugs, educate prescribers, and guide infection control policies.

Surveillance of pathogen prevalence and drug-resistance patterns requires laboratory facilities arranged within a network designed to share, analyze, and interpret these data. The Child Health Research Project (CHR), through its Invasive Bacterial Infections Surveillance (IBIS) project, has strengthened India's surveillance capacity through support for training and laboratory methods. Specifically, project members have:

- Established a network of six hospital laboratories across India which produced the first multicenter data on the magnitude and patterns of acute invasive infections caused by *Haemophilus influenzae* and *Streptococcus pneumoniae*, and
- Prospectively monitored the distribution of invasive serotypes and antimicrobial susceptibility of these bacteria for four years.

Supported by CHR partner, the International Clinical Epidemiology Network (INCLIN) with assistance from Johns Hopkins Family Health and Child Survival, the IBIS study implemented a common protocol for clinical and laboratory surveillance in six INCLIN member institutions; the All India Institute of Medical Science in New Delhi, King George's Medical College in Lucknow, Government Medical College in Nagpur, Madras Medical College in Chennai, Christian Medical College in Vellore, and Trivandrum Medical College in Thiruvananthapuram (Figure 1).

First enrolled in the study were children under the age of 12 who were presented with radiographic evidence or WHO clinical criteria of pneumonia, clinically suspected meningitis, or cerebrospinal fluid suggestive of bacterial



Figure 1: Hospitals using the Invasive Bacterial Infections Surveillance protocol, 1993–1997

meningitis, or fever greater than 39 degrees celsius for two days or less with suspected bacterial infection. Older children and adults were also eligible for participation if they presented with similar symptoms. Consent for participation was obtained from patients or from parents or guardians of children. Exclusion criteria included hospitalization within 10 days of presentation, or conditions causing immunosuppression, such as lymphoma, leukemia, splenectomy, or patients known to be HIV-positive. Patients with a history of antibiotic therapy were not excluded from the study. In addition, hospital logs were monitored during the study period, and patients with isolates of *S. pneumoniae* and *H. influenzae* were also included if they fulfilled the inclusion and exclusion criteria.

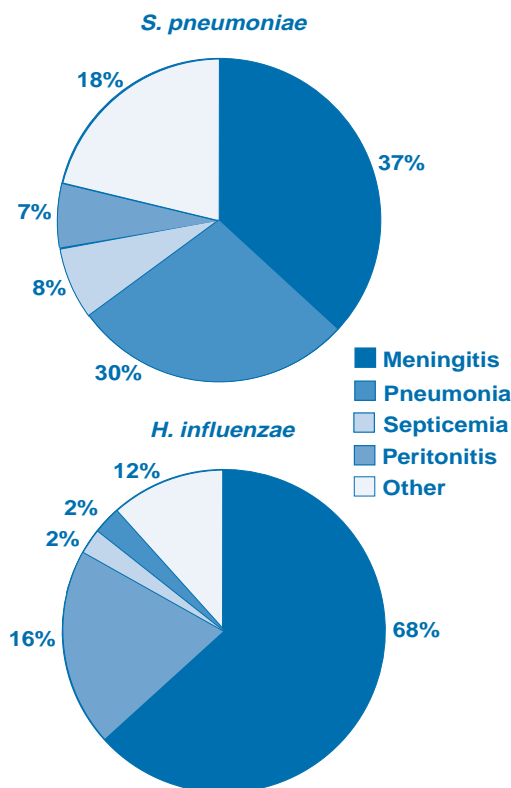
The laboratory protocol for microbiology was modified from the 1991 draft WHO manual for antimicrobial

resistance.⁽¹⁾ Antimicrobial susceptibility testing was done for penicillin, ampicillin, trimethoprim-sulfamethoxazole, and cefotaxime for *S. pneumoniae* and ampicillin, cotrimoxazole, cefotaxime, chloramphenicol, erythromycin, and trimethoprim-sulfamethoxazole in *H. influenzae* samples. Minimum inhibitory concentration (MIC) was determined by agar dilution on selected isolates for penicillin, ampicillin, chloramphenicol, cotrimoxazole, erythromycin, and cefotaxime. Standard criteria were used to classify disk diameters and MIC values as sensitive, intermediate, or resistant. Standard reference strains of *S. pneumoniae* and *S. aureus* were used to test all batches of media for adequate growth of *S. pneumoniae* and for MIC standards. Coded cultures of bacteria were periodically sent from the IBIS reference laboratory to each study center to verify laboratory procedures. Serotyping and MIC data were reconfirmed on a sample of isolates with assistance of the Johns Hopkins School of Public Health and the WHO reference center for *S. pneumoniae* at Statens Seruminstitut in Copenhagen.

The IBIS Results: Patterns of Disease and Antimicrobial Susceptibility

From October 1993 to September 1997, 5612 patients were recruited according to the clinical criteria and 186 through laboratory-based enrollment.⁽²⁻⁴⁾ *S. pneumoniae* was identified in 314 subjects and *H. influenzae* was found in 125 patients. The distribution of disease syndromes caused by the two organisms is shown in Figure 2. Of

Figure 2: Distribution of Illness Caused by *H. Influenzae* and *S. pneumoniae*



particular importance is the predominance of meningitis cases (68% of all isolates) among the *H. influenzae* cases. In contrast, there are approximately equal proportions of meningitis and pneumonia (37% and 30%, respectively) in pneumococcal cases.

Twenty-one percent (64/304) of the patients with proven pneumococcal disease died during the course of the study. Case fatality was similar in different age groups, with 22% (15/69) of children under 2 years of age dying. Fatality in children 2 to 12 years was 10% (8/79). In adolescents and adults ages 12 to 50 years, fatality was 26% (28/109), and in patients over 50 years of age, fatality was 28% (13/47). Case fatality for culture-positive *H. influenzae* meningitis cases was 20% for infants less than 1 year of age. The fatality rate was substantially lower in 1- to 4-year-old children at 5% (1 of 18).

Of the 307 pneumococcal samples that were examined, the isolates were distributed among 36 serotypes/groups, with the most commonly found being (listed in descending order) 1, 6, 19, 7, 5, 15, 14, 4, 16, and 18. Type 1 was the most common (25%, 78/307), and this frequency was consistent across all the regions. Of the 121 cultured *H. influenzae* isolates, 118 were serotyped as type b and one each was identified as type a, type d, and type e.

There were significant differences in the relative distribution of some *S. pneumoniae* serotypes/groups in different ages. In neonates, type 5 was the most common, followed by type 19. In children between the ages of 2 months and 5 years, type 6 was the most common followed by types 1 and 19. In all ages above 5, type 1 was the most often isolated, followed by type 6. On the other hand, nearly all cases of invasive *H. influenzae* disease were type b in infants and children under 5 years of age, with 76% of the cases occurring in infants less than 1 year of age. The peak of invasive *H. influenzae* disease was at 6 to 9 months of age.

The antimicrobial susceptibility profile of 307 *S. pneumoniae* isolates were tested by disk diffusion, and minimum inhibitory concentration testing was performed in 269 of these 307 samples (Figure 3). Forty percent (122) were resistant to one antimicrobial, 14% (42) were resistant to two drugs, and no samples were resistant to more than two agents. There was a significant geographical variance in the resistance of *S. pneumoniae* to cotrimoxazole and chloramphenicol. Cotrimoxazole resistance was noted in 78%, 85%, 73%, and 39% of samples and chloramphenicol resistance in 38%, 8%, 51%, and 8% of isolates from New Delhi, Chennai, Nagpur, and Vellore, respectively. After testing the *H. influenzae* samples, it was found that more than 60% were intermediately or fully resistant to chloramphenicol (Figure 4), and 38 to 41% were resistant to trimethoprim-sulfamethoxazole, ampicillin, or erythromycin. No isolates of either *S. pneumoniae* or *H. influenzae* were resistant to the third generation cephalosporin, cefotaxime. It was concluded that treatment of suspected

Figure 3: Antibiotic Resistance of *Streptococcus pneumoniae* 1993–1997

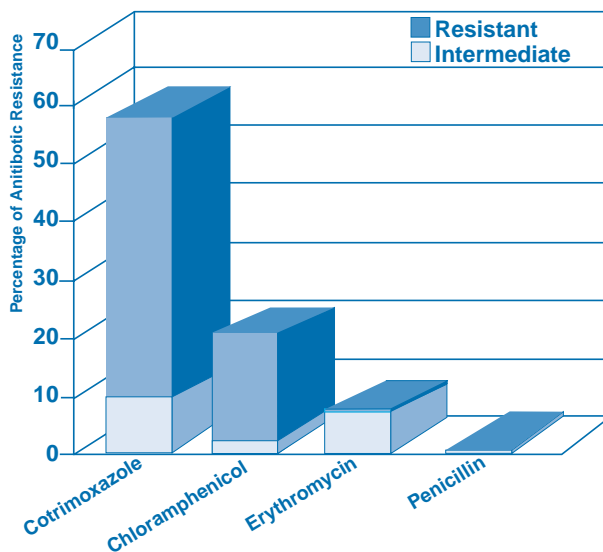
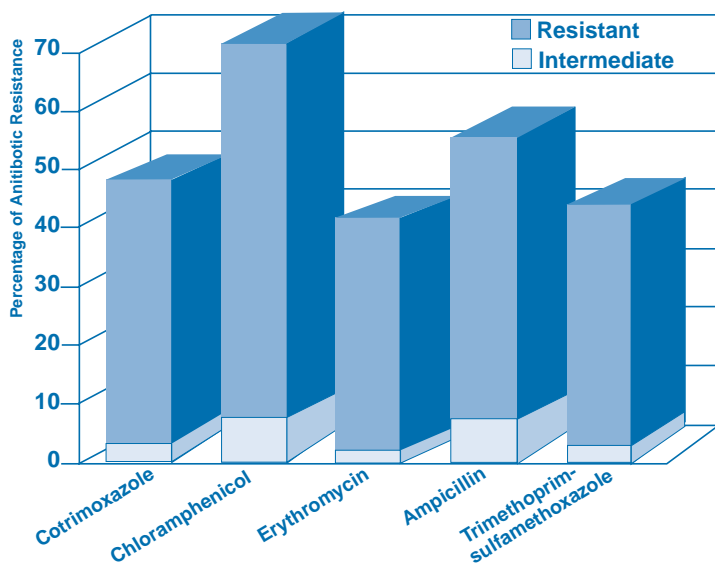


Figure 4: Antibiotic Resistance of *Haemophilus influenzae*, 1993–1997



life-threatening, invasive infections (like meningitis in children) should begin with third generation cephalosporins, and potentially be switched to more common drugs when culture results are received.

The prevalence of *S. pneumoniae*'s resistance to cotrimoxazole, penicillin or erythromycin did not significantly vary during the four years of the study. However, four strains (three of type 14 and one of type 7) with intermediate resistance to penicillin were isolated from cerebrospinal fluid samples in the last two years of the study. These findings suggest the emergence of penicillin resistance in India. Further, the prevalence of chloramphenicol resistance decreased after the second year of the study, with resistance measured at 18.5%, 24.4%, 16.4%, and 2.7% in the 1st, 2nd, 3rd, and 4th years of the study, respectively. This is possibly due to decrease in the consumption of chloramphenicol as a consequence of widely recognized

multidrug resistance in *Salmonella typhi*. Of particular significance was a variation in the pattern of antimicrobial susceptibility across the six study centers ($p=0.00001$), with patients from small towns and rural areas having much lower resistance levels to cotrimoxazole and chloramphenicol (30% and 10%) than in the large cities of New Delhi and Madras (50% to 80%). This is thought to be due to the wider availability and greater usage of antibiotics in the urban areas.

Antibiotic Resistance and Drug Use

The threat to human health posed by antibiotic resistance is of growing global concern, with multiply resistant organisms being a cause of particular distress. The major selection pressures driving changes in antibiotic resistance are patterns and volume of drug use. The IBIS study has demonstrated high levels of resistance to drugs commonly prescribed to treat invasive infections, and how those patterns of resistance changed (or did not change) over the study period. Two studies now exist that document decreases in antibiotic resistance as a result of decreased antimicrobial use.^(5,6) In 1991, in response to growing erythromycin resistance in group A *Streptococcus*, the Finnish government recommended reductions in the use of macrolide antibiotics. From 1992 to 1996, the frequency of resistance decreased from 16.5% to 8.6%.⁽⁵⁾ In a recent model relating antimicrobial consumption and the frequency of resistance, authors Austin, Kristinsson, and Anderson show that: (1) the time for the emergence of resistance under the constant selective pressure of increased drug use is typically much shorter than the decay time after the decline in drug use, and (2) significant reductions in resistance require equally significant reductions in drug consumption.⁽⁷⁾ They also emphasize the need for early intervention once drug resistance is detected.

Disease Burden of Vaccine-Preventable Illness

Murray and Lopez estimated that there were 52,000 cases of meningitis due to *S. pneumoniae* (case fatality 57%) and 51,000 due to *H. influenzae* (case fatality 21%) in India in 1990.⁽⁸⁾ Although hospital-based surveillance, as performed in the IBIS study, cannot estimate the population incidence of vaccine-preventable disease, it does accurately portray the patterns of severe disease that present for medical care. The IBIS study has, therefore, confirmed that vaccine-preventable morbidity and mortality due to these organisms remains a major problem in India. This is especially tragic given the availability of safe and effective vaccines against *H. influenzae*.

The most common serotypes/groups of *S. pneumoniae* in children under the age of 5 (those who bear the largest burden of disease) in the India IBIS study were 6, 1, 19,

14, 4, 5, and 45, and comprise 82% of the total sample of isolates. This incidence differs widely from data reported from single centers in Bangladesh and Pakistan.

The most common serotype/groups in young children reported from the Dhaka Shishu Hospital were 7F, 12F, 14, 15B, 18, 5, and 22A⁽⁹⁾, and in 1991, in Pakistan, the most common serotypes were 1, 5, 6, 9, 15, 16, 18, 19, and 31, but these showed extreme seasonal and annual variability.⁽¹⁰⁾ Two conjugate, global pneumococcal vaccines are currently in development (a 9-valent and an 11-valent) by the Wyeth-Lederle Vaccines Division of American Home Products. The 9-valent formulation includes types 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F and has been successfully tested for safety and immunogenicity in The Gambia, South Africa, and Israel.⁽¹¹⁻¹³⁾ Assuming cross protection within serotypes, the 9-valent vaccine would afford protection against 71% of isolates from IBIS study subjects in India, 61% of the most common isolates from Pakistan, and 30% from Bangladesh. Other vaccine formulations against *S. pneumoniae* are currently in development at Merck and Pasteur-Mérieux Connaught.

More than 90% of the *H. influenzae* isolates from the IBIS study were type b. These data are similar to those from Bangladesh where 98% of *H. influenzae* isolates from cerebrospinal fluid cultures were found to be type b⁽¹⁴⁾, and higher than those from Pakistan where only 64% of isolates from blood culture were identified as serotype b.⁽¹⁵⁾ Since the introduction of routine use of conjugate vaccines against *H. influenzae* type b (Hib) in the United States in 1988, cases of invasive disease have decreased by more than 95%, with incidence as low as 1.6 per 100,000 in children under 4 years of age in 1995.⁽¹⁶⁾ It is widely felt that with adequate vaccine coverage, morbidity and mortality from Hib can also be substantially reduced in the developing world.⁽¹⁷⁻¹⁹⁾ Several conjugate vaccines against Hib have been the subject of successful, prospective trials in areas with high rates of disease: the PRP-T (conjugated to tetanus toxoid)⁽²⁰⁻²¹⁾, the PRP-OMPC (conjugated to *Neisseria meningitidis* group b outer membrane protein)⁽²²⁾, and the CRM197 (HbOC) (conjugated to mutant diphtheria toxin).⁽²³⁾ In a randomized trial, also supported by the Child Health Research Project, in The Gambia⁽¹⁹⁾, the PRP-T vaccine (Pasteur Mérieux) proved safe and prevented 95% of all invasive Hib disease after three doses, and 21% of severe, radiologically confirmed Hib pneumonia after two or three doses. The same vaccine was recently tested in Taiwan in combination with an acellular diphtheria, tetanus, and pertussis (DTaP) vaccine, with 96% of children demonstrating serum antibody PRP levels indicative of protection after only two doses.⁽²¹⁾

One of the major obstacles to the introduction of an Hib vaccine in developing countries is the cost of program implementation, which is estimated to be approximately \$5.22 per child under the age of 5 in low-income Asian countries.⁽²⁴⁾ For India, the cost per life saved would be

\$1945, with an estimated 65,300 lives saved by the vaccine. Costs of treatment for Hib invasive infections are estimated at \$21 per day per child for inpatient treatment and \$5 per day per child for outpatient treatment. With the cost per DALY (disability-adjusted life year) of \$59, most of the savings to India would be in reduced mortality, not savings on the costs of morbidity. However, if incorporated into the Expanded Programme on Immunizations (EPI), the Hib vaccine would cost an estimated additional \$1.50 per dose for vaccine and \$0.18 for administration in India and other low-income Asian nations.⁽²⁴⁾

Summary

The burden of preventable invasive infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* disease has often been underestimated in the developing world because of technical difficulties in culturing the organisms. The India IBIS project has:

- Provided the first multicenter, hospital-based epidemiological data on the characteristics of invasive infections in India;
- Demonstrated significant levels of resistance to antimicrobial drugs commonly prescribed to treat these infections;
- Shown higher levels of drug resistance in urban areas, where antimicrobial use is more prevalent than in rural areas;
- Documented high levels of morbidity and mortality due to vaccine-preventable bacterial infections;
- Recommended treatment of suspected life-threatening, invasive infections (such as meningitis in children) begin with third-generation cephalosporins; and
- Determined pneumococcal serotypes that must be included in vaccine formulation for India.

The IBIS experience in India is a model for hospital-based surveillance in other regions. Carefully planned hospital surveillance could provide data useful for understanding the levels and trends of antimicrobial resistance in other parts of Asia and perhaps in Africa. Quality control issues are important to allow conclusions to be drawn with confidence.

This information can now be used by administrators, major public and private donors, and non-governmental organizations to guide changes in programs and policy to prevent illness and improve health outcomes after serious invasive infections. Action and assistance are urgently needed to reduce the consumption of antimicrobial drugs and speed the introduction of vaccines. Most of the world's children reside in the developing world, and they too should have protection against these deadly diseases.

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