Surveillance of Pneumococcal Meningitis among Children in Sindh, Southern Pakistan

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Background. Information about the burden of invasive pneumococcal disease among children in Pakistan is limited.

Methods. Surveillance of bacterial meningitis among children aged <5 years was set up at 18 hospitals in southern Pakistan that fulfilled the following criteria: (1) >30 pediatric admissions weekly, (2) skilled personnel to perform lumbar punctures, and (3) close proximity to an Aga Khan University Hospital laboratory collection point.

Results. A total of 2690 children were admitted to the hospital with suspected acute bacterial meningitis, and 2646 (98%) underwent lumbar puncture. Of the 2646 cerebrospinal fluid specimens obtained, 412 (16%) were purulent, and pathogens were detected by culture or latex agglutination testing in 83 (20.1%) of the purulent specimens. Of the 83 isolates detected, 48 (57.8%) were Haemophilus influenzae type b, 32 (38.5%) were Streptococcus pneumoniae, and 3 (3.6%) were Neisseria meningitidis. Overall, 81% of the pathogens detected were from children aged <1 year. More than 50% of families reported definite prior antimicrobial use. The minimum detected incidence rates of purulent meningitis in Hyderabad were 112 cases per 100,000 children aged <1 year and 45.3 cases per 100,000 children aged <5 years. After adjustment for limitations in access to care and the low sensitivity of cerebrospinal fluid culture, the adjusted incidence rates of pneumococcal meningitis were 81 cases per 100,000 children aged <1 year (95% confidence interval, 26.2–190.5 cases per 100,000) and 20 cases per 100,000 children aged <5 years (95% confidence interval, 7.3–43.7 cases per 100,000). Of the 32 children with pneumococcal meningitis, 8 (25%) died during hospitalization.

Conclusions. Our surveillance system detected a substantial burden of purulent meningitis among infants and children in southern Pakistan. H. influenzae type b and S. pneumoniae accounted for >90% of detected pathogens. The use of vaccines against these 2 pathogens could prevent a substantial portion of disease and deaths in Pakistan.

Pneumococci are a major cause of childhood mortality worldwide, causing an estimated 1 million deaths among children aged <5 years [1]. The burden of pneumococcal disease is largely underinvestigated in developing countries. However, quantification of the burden of pneumococcal disease through surveillance remains a challenge because the organism is difficult to grow and because adequate laboratory facilities are limited. This has resulted in the problem being largely invisible to health care policy planners, although efficacious vaccines are available.

Information about the burden of invasive pneumococcal disease among children in Sindh, a province of >35 million people in southern Pakistan, is extremely limited, although acute respiratory infection is known to be a major cause of childhood deaths [2]. Earlier studies were sponsored by the US Board of Science and Technology for International Development in the 1980s and focused on urban areas of northern Punjab, an area climactically and geographically distinct from southern Pakistan, which is hot, humid, and arid [3, 4]. Those studies found pneumococci to be the most common bacterial pathogen isolated from the blood of children with severe pneumonia in Islamabad and Rawalpindi [3, 4].

The primary objectives of our study were to estimate the burden of invasive pneumococcal meningitis in
children aged <5 years in Karachi and Hyderabad, Pakistan, as well as to estimate the age distribution of cases and the antibiotic-resistance patterns of pneumococcal isolates.

METHODS

This study was conducted in the 2 largest cities in the province of Sindh: Karachi and Hyderabad, with a combined population of 15 million people (2.52 million children aged <5 years, on the basis of extrapolation from the 1998 census). The port city of Karachi has a vast labyrinth of both public and private health care facilities spread across the metropolis, which makes it impossible to cover all localities in a sentinel surveillance system. On the other hand, Hyderabad is a smaller city, 164 km north of Karachi, with a population of ∼1.4 million people and a well-defined catchment area with a limited number of health care facilities where children seek care. Thus, sentinel surveillance in Hyderabad can give a more reliable assessment of the burden of pneumococcal meningitis in Sindh. At the time of the study, the national immunization program did not include a vaccine against *Haemophilus influenzae* type b (Hib) or *Streptococcus pneumoniae*.

In May 2005, prospective surveillance for 12 months was set up at 18 sentinel sites in Karachi and Hyderabad that fulfilled the following criteria: (1) >30 pediatric admissions weekly, (2) 24-h availability of skilled personnel to perform lumbar punctures for CSF analysis for children, and (3) close proximity to an Aga Khan University Hospital (AKUH) laboratory collection point. All included facilities admitted patients 24 h per day, 7 days per week. (Participating private- and public-sector hospitals are listed in the Acknowledgments.) In Hyderabad, the included hospitals represented all the facilities where specialized inpatient pediatric care was available. However, Karachi’s vast metropolis and multitudes of private health care facilities that offer differing levels of care meant that only the largest hospitals offering pediatric care that fulfilled all the inclusion criteria were included. All pediatric consultants who were members of the Sindh chapter of the Pakistan Pediatric Association were also informed of the study and the availability of free CSF analysis at the AKUH laboratory for any patient who they suspected to have possible bacterial meningitis.

Because of the lack of adequate diagnostic capabilities at the public-sector hospitals in Karachi and Hyderabad for identification of pneumococci, we used the specimen-collection network of the AKUH laboratories to pick up CSF specimens obtained from children with suspected meningitis.

**Study eligibility.** CSF specimens from any child aged <5 years who (1) underwent lumbar puncture because of clinical suspicion of meningitis, (2) resided in Karachi or Hyderabad, (3) had not undergone a neurosurgical procedure in the previous 2 weeks, and (4) had been ill for <2 weeks were eligible for inclusion in the surveillance system and for analysis at the AKUH laboratory. The judgment of whether a child had suspected meningitis and needed a lumbar puncture was left to the treating clinician. Prestudy practices of the performance of lumbar punctures at individual health care facilities were not modified, because this would have entailed obtaining of individual written patient consent for lumbar puncture, which is not standard practice in Pakistan. It also would have entailed placement of study officers at each site, which was precluded by our study budget.

**Transport of specimens and laboratory procedures.** Participating hospitals were requested to send CSF specimens obtained from any child who was clinically suspected to have bacterial meningitis to their respective AKUH laboratory collection point (usually located on the premises or within a 10-min walking distance) with a designated form that was provided to them earlier. Specimens from the collection points were transported to the AKUH laboratory 2–3 times per day, between 9 A.M. and 12 midnight. Transport time varied from half an hour for specimens from AKUH to 12 h for specimens from Hyderabad. In Karachi, the usual transport time from collection point to AKUH was 4–5 h. Specimens from Karachi were transported in the collection tubes received, whereas those from collection points in Hyderabad were processed at the AKUH laboratory in Hyderabad, and incubating cultures were sent to the AKUH main laboratory in Karachi in transport isolation media at room temperature.

CSF specimens received at the AKUH laboratory underwent immediate analysis for cell count and chemistry and were processed for culture. Additionally, if the cell count was ≥30 cells/mm³ or if the CSF glucose level was <40 mg/dL, then latex agglutination testing for Hib, *S. pneumoniae*, and *Neisseria meningitidis* was performed using antigen detection kits (Wellcogen; Remel). For culture, a CSF specimen was inoculated onto both a 5% sheep blood plate and a chocolate agar plate, as well as in brain-heart infusion broth, in accordance with routine practice. Agar plates were incubated at 35°C in 5% carbon dioxide and were examined daily for 3 days. Broth cultures were incubated at 35°C and were examined daily for 7 days.

**Antimicrobial resistance.** Pneumococcal isolates were tested for resistance to oxolinic, chloramphenicol, tetracycline, cotrimoxazole, erythromycin, vancomycin, ampicillin, and ceftriaxone by the Kirby-Bauer disk-diffusion method. Isolates that were resistant and intermediate, on the basis of Clinical and Laboratory Standards Institute guidelines, underwent an E test (AB Biodisk) for determination of MIC values [5]. E tests were performed on Mueller-Hinton agar supplemented with 5% defibrinated sheep blood. Inocula were prepared in Mueller-Hinton broth by direct suspension of pneumococcal colonies grown overnight on sheep blood agar to a density that matched a 0.5 McFarland opacity standard tube. The interpretation of results

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Results were reported to the child’s physician in real time, which is the current practice at the AKUH laboratory. Electronic and hard-copy laboratory reports were maintained by a designated laboratory technician at the AKUH laboratory. Surveillance data were entered into a computer in a timely fashion by one of the research officers functioning as project coordinator. Patient confidentiality was maintained. Age, sex, presenting features (ie, presence of fever [temperature, ³8°C], altered mental status, neck rigidity, bulging fontanelle, vomiting, seizures, and/or rash), suspected diagnosis from the physician at discharge (including suspected bacterial meningitis), area of residence, laboratory results, and hospital outcome were recorded.

Case definitions. Suspected acute bacterial meningitis was defined by fever and at least 1 of the following signs: convulsions, bulging fontanelle (in children aged <12 months), stiff neck, poor sucking or irritability, prostration or lethargy, and petechial or purpurial rash. CSF specimens with a WBC count of 10–99 cells/mm³ and a nonturbid appearance on visual examination were considered abnormal but nonpurulent (unless the CSF glucose level was low or the protein level was high; see below). Purulent CSF was defined by (1) visual turbidity, (2) a WBC count ³100 cells/mm³, or (3) a WBC count ³10 cells/mm³ in addition to a protein level ³100 mg/dL or a glucose level <40 mg/dL.

Data analysis. Data were double entered into a computer database and were analyzed using SPSS, version 14.0 (SPSS), and Excel (Microsoft). Descriptive statistics were performed for mean scores and proportions. The Ethical Review Committee of Aga Khan University approved the surveillance study.

Results
During the 12-month surveillance period (1 May 2005–31 April 2006), the surveillance system detected a total of 2690 children aged <5 years with suspected bacterial meningitis, and 2646 (98%) underwent lumbar puncture. The mean age (±SD) of children who underwent lumbar puncture was 17.55 ± 15.80 months, and 58.5% were male (41.5% were female). Of the 2646 CSF specimens, 412 (16%) were purulent, and pathogens were detected by culture or latex agglutination in 83 (20.1%) of the purulent specimens. Of those 83 specimens, 48 (57.8%) yielded Hib, 32 (38.5%) yielded pneumococci, and 3 (3.6%) yielded meningococci. *Staphylococcus epidermidis,* which was isolated from a few culture specimens, was regarded as a contaminant.

Only 15 specimens grew pneumococci on culture. An additional 17 pneumococcal cases were confirmed using latex agglutination. Among specimens in which Hib was detected, 10 had Hib detected by culture, and an additional 38 had Hib detected by latex agglutination alone. The mean age (±SD) of children with culture-confirmed or latex agglutination–confirmed pneumococcal disease was 10.44 ± 6.38 months. There were 21 male patients (65.5%), and 11 female patients (34.4%). More than 80% of pathogens detected were in specimens from children aged <1 year (figure 1).

The most common clinical presentation (figure 2) among children who received a diagnosis of pneumococcal meningitis was fever (temperature, >38°C; in 100% of patients), followed by bulging fontanelle (in 44%) and vomiting (in 31%). Overall, the families of 1423 (53%) of the children reported definite prior antimicrobial use, 725 (27%) were uncertain (ie, there was possible prior antimicrobial use), and 542 (20%) reported no prior antimicrobial use. Among the children for whom definite prior antimicrobial use was reported, information on the type of antimicrobial agent was available for 1386 (97%): of these, 846 (61%) received a penicillin agent (penicillin, penicillin,
ampicillin, or amoxicillin), and 540 (39%) received a cephalosporin.

Figure 3 shows the seasonal variation in culture-confirmed cases of pneumococcal meningitis, with an obvious winter peak in disease. Children with pneumococcal meningitis had substantial in-hospital mortality, with an in-hospital case-fatality rate of 25% (8 of 32 children). The case-fatality rate was 10.4% (5 of 48) for Hib meningitis and 6.3% (26 of 412) for all children with cases of purulent meningitis. Additionally, there were 39 children with purulent meningitis whose families took them out of the hospital against medical advice (23 children) or whose discharge status was not recorded (16 children), for whom mortality status remained unknown. The difference in the case-fatality rates of Hib meningitis and for culture-negative cases of purulent meningitis was marginally significant (OR, 2.84; 95% CI, 0.83–9.11; P = .05). The case-fatality rate for pneumococcal meningitis was significantly different from that for culture-negative cases of purulent meningitis (OR, 8.13; 95% CI, 2.76–23.7; P < .001).

Antimicrobial-susceptibility test results for 15 pneumococcal isolates obtained by culture are shown in figure 4. Overall, 26% of isolates showed intermediate susceptibility to penicillin, and 40% showed intermediate susceptibility to ceftriaxone (MIC, 0.1–1.0 µg/mL); none were fully resistant to these antibiotics. The proportion of isolates resistant to chloramphenicol was 26%; to ofloxacin, 47%; and to cotrimoxazole, 93%. Only 3 of the 15 pneumococcal isolates could be revived after freezing and shipping for serotype determination at the reference laboratory. These were determined to be serotypes 1 (1 isolate) and 19F (2 isolates).

The minimum detected incidence rate of purulent meningitis among children aged <1 year, on the basis of sentinel-site surveillance in Hyderabad, was estimated at 112 cases per 100,000 children (95% CI, 83–148 cases per 100,000), the rate of Hib meningitis was 22 cases per 100,000 children (95% CI, 11–41 cases per 100,000), and the rate of pneumococcal meningitis was 11 cases per 100,000 children (95% CI, 3.6–26 cases per 100,000). The adjusted incidence rates of pneumococcal meningitis are estimated to be 19.7 cases per 100,000 children aged <5 years and 80.6 cases per 100,000 children aged <1 year (table 1; see Discussion for explanation of adjustment).

**DISCUSSION**

Despite the inherent limitations of the use of sentinel-site surveillance to estimate the true burden of disease in countries such as Pakistan—where child mortality rates are high, health care is inaccessible to many children, and most childhood deaths occur at home—our surveillance system detected a substantial burden of purulent meningitis among infants and children in 2 cities in southern Pakistan. In Hyderabad, where the surveillance system captured cases presenting to all the large health care facilities that offer specialized pediatric care in the city, the detected incidence rates of purulent meningitis were 112 cases per 100,000 children aged <1 year and 45 cases per 100,000 children aged <5 years. The minimum detected incidence rates of pneumococcal meningitis were 11 cases per 100,000 children aged <1 year and 2.7 cases per 100,000 children aged <5 years. These incidence rates are significantly underestimated, for several reasons. First, our experience in working in several low-income communities in Karachi shows that,

![Figure 3](image1.png)

**Figure 3.** Seasonal variation in the number of cases of pneumococcal meningitis in children in Sindh, Pakistan, 1 May 2005–30 April 2006.

![Figure 4](image2.png)

**Figure 4.** Antimicrobial-resistance patterns of *Streptococcus pneumoniae* isolates causing meningitis in children in Sindh, Pakistan.
Table 1. Incidence rates of childhood meningitis in Hyderabad, Pakistan.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age &lt;12 months</th>
<th>Age &lt;59 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Populationa</td>
<td>44,571</td>
<td>222,855</td>
</tr>
<tr>
<td>With purulent CSF</td>
<td>50</td>
<td>101</td>
</tr>
<tr>
<td>With pneumococcal meningitis</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>With Hib meningitis</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Detected incidence rate, cases per 100,000 children (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purulent meningitis</td>
<td>112 (83.3–147.9)</td>
<td>45.3 (36.9–55.1)</td>
</tr>
<tr>
<td>Pneumococcal meningitis</td>
<td>11 (3.6–26.2)</td>
<td>2.7 (0.99–5.9)</td>
</tr>
<tr>
<td>Hib meningitis</td>
<td>22 (10.8–41.3)</td>
<td>5.4 (2.8–9.4)</td>
</tr>
<tr>
<td>Adjusted incidence rate, cases per 100,000 children (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal meningitisb</td>
<td>80 (26.2–190.5)</td>
<td>20 (7.3–43.7)</td>
</tr>
<tr>
<td>Hib meningitisb</td>
<td>155 (76.2–292.1)</td>
<td>38 (19.7–66.6)</td>
</tr>
</tbody>
</table>

NOTE. Hib, Haemophilus influenzae type b.

a Extrapolated from a 1998 census report [7].

b The incidence rate was adjusted by a 50% capture rate by surveillance system and 3.67-fold increased yield from the use of more-sensitive tests—namely, an immunochromatographic test of pneumococcal antigen (NOW S. pneumoniae Antigen Test; Binax). See the Discussion for further explanation.

for a variety of sociocultural, economic, and quality-of-care reasons, population health care use is low, with 70% of families of sick infants refusing to take their babies to public hospitals, despite physician referral and the availability of emergency transport (A.K.M.Z., unpublished data). In verbal autopsies, “fever with fits” is a symptom commonly described by families of infants who die at home in urban slums (A.K.M.Z., unpublished data). The large distance separating patients from hospitals that offer pediatric care is an important barrier, even in periurban areas [6]. The recent large Pakistan Demographic and Health Survey of >50,000 representative households selected from throughout the country that used verbal autopsies for 2623 deaths found that, among all children with death due to a clinical syndrome resembling meningitis (fever with seizures), almost 40% had died at home or on the way to a hospital, 40% had died at a public-sector hospital, and 20% had died at a private-sector hospital [8].

Second, prior antimicrobial use and delays in specimen transport seriously decrease the rate of detection of pneumococci. In another study involving 309 children with suspected bacterial meningitis in Karachi, the rate of detection of pneumococci from CSF specimens increased in 2.5-fold when a sensitive immunochromatographic test of pneumococcal antigen (NOW S. pneumoniae Antigen Test; Binax) was also used on purulent CSF specimens (from 9% detection with use of culture and latex agglutination only to 23% detection with use of immunochromatographic testing in addition to culture and latex agglutination) [8]. Moreover, pneumococci were detected by immunochromatographic testing in 8 (7.8%) of 103 abnormal, nonpurulent CSF specimens with WBC counts in the range 10–99 cells/mm³. Under the assumptions that (1) families of 50% of children with meningitis in Hyderabad sought hospital-based care, were captured by the surveillance system, and underwent lumbar puncture and that (2) the actual number of children with pneumococcal meningitis is 3.67 times higher than that detected by conventional methods (15 cases [6 cases × 2.5] detected from purulent CSF, plus 7 additional cases [instead of 0] from 103 abnormal nonpurulent CSF specimens, for a total of 22 cases), the adjusted incidence rates of pneumococcal meningitis are estimated to be 19.7 cases per 100,000 children aged <5 years and 80.6 cases per 100,000 children aged <1 year (table 1). This burden is 3–4-fold higher than that observed in Europe [9–11] and the United States [12], for which the reported incidence rates of pneumococcal meningitis among children aged <5 years are 4.6 cases and 3.6 cases per 100,000, respectively.

Pneumococci are becoming increasingly resistant to commonly used antimicrobial agents, which limits the treatment options in resource-constrained environments. Although resistance to penicillin has been slow to develop in Pakistan, compared with other developing countries, 27% of isolates were found to have intermediate resistance to penicillin [13, 14]. An alarming 40% of pneumococcal isolates exhibited intermediate resistance to ceftriaxone. Because meningitis is a critical, life-threatening infection, penicillin and ceftriaxone soon may not be reliable agents for the treatment of pneumococcal meningitis in Pakistan. Alternative antibiotics, such as vancomycin, are expensive and not widely available.

The use of pneumococcal vaccines in routine childhood immunization programs has the potential to significantly affect
the burden of invasive pneumococcal disease. The use of pneumococcal vaccines has shown 25% and 37% reductions in radiologically confirmed pneumonia cases in South Africa and The Gambia, respectively [15, 16]. A trial in The Gambia also demonstrated a 16% reduction in all-cause mortality [16].

Pakistan is a GAVI Alliance–eligible country, and hepatitis B vaccine was introduced in Pakistan with GAVI support. The additional cost of introducing conjugate pneumococcal vaccines, at the GAVI and UNICEF procurement cost of US$0.30 per dose of pneumococcal vaccine for Pakistan [17], is US$3.81 million (5,500,000 birth cohort × 3 doses × 0.70 [coverage] × 1.1 [vaccine wastage] × $0.30). The estimated annual number of cases of pneumococcal meningitis among children aged <5 years in Pakistan is 5500 cases, on the basis of the adjusted incidence rate of 20 cases per 100,000 children aged <5 years. Therefore, if the currently available 7-valent vaccine is introduced in Pakistan’s national immunization program and can prevent 50% of pneumococcal meningitis cases caused by the serotypes included in the vaccine, the cost per pneumococcal meningitis case averted by use of this vaccine is US $1385. A recent survey in northern Pakistan estimated the cost of treatment of pneumococcal meningitis to be $2043 per case [18].

On the basis of this calculation, introduction of the 7-valent vaccine in Pakistan would be a cost-saving intervention in prevention of meningitis cases alone.

Meningitis is responsible for only a small proportion of the deaths and disease caused by pneumococci in children. Pneumonia is one of the leading causes of death in children in Pakistan, responsible for an estimated 135,600 deaths and 1 million cases annually [2]. Data from clinical trials of pneumococcal conjugate vaccine indicate that the percentage of cases of disease due to pneumococcus is substantial; vaccine that covered only 50% of serotypes in some instances reduced the number of radiologically confirmed pneumonia cases by 20%–37% [19–24]. Because case detection is so difficult and because most pneumonia cases are nonbacteremic, the total disease burden due to the pneumococcus must be modeled. Using such models, Sinha et al. [25] have shown that, when per-head gross domestic product per averted disability-adjusted life year due to pneumococcal meningitis and pneumonia is used as a yardstick, pneumococcal vaccines will be highly cost-effective in countries, such as Pakistan, that have a high infant mortality rate.

We faced many constraints in choosing appropriate surveillance sites in Karachi and Hyderabad, which may have resulted in an underestimate of the burden of pneumococcal meningitis documented in this study. Public-sector hospitals had inadequate facilities to perform CSF analysis, culture for pneumococcus, and latex agglutination testing at the time of this study. Therefore, specimens had to be transported to the AKUH main laboratory, which caused delays in specimen processing and may have affected the yield from culture. Isolates had to be shipped abroad on chocolate slants for serotyping, and only a few could be revived after spending several days in transport. This study underscores the need to establish and maintain a sentinel-site surveillance network with adequate laboratory facilities for the detection of bacterial meningitis in public and selected private health care facilities across Pakistan, to monitor and characterize pneumococcal disease and the effectiveness of any disease intervention.

SINDH MENINGITIS STUDY GROUP


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