Incidence of *Haemophilus influenzae* type b meningitis in India


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**Background & objectives:** Vaccine policy depends on locally relevant disease burden estimates. The incidence of *Haemophilus influenzae* type b (Hib) disease is not well characterized in the South Asian region, home to 30 per cent of the world’s children. There are limited data from prospective population incidence studies of Hib in Asia, and no data available from India. We therefore carried out this study to assess the burden of Hib meningitis in India.

**Methods:** A prospective surveillance study was carried out during 1997 and 1999 in hospitals for cases of Hib meningitis from 5 administrative areas of an Indian district (Vellore, Tamil Nadu) with 56,153 children under 5 yr of age, over a 24 month period.

Results: Ninety seven cases of possible meningitis (> 10 WBC/µl in CSF) were reported, an annual incidence of 86 per 100,000 (95% CI 69 to 109) in 0-4 yr old children, and 357 per 100,000 in 0-11 month infants. Eighteen had proven bacterial meningitis, an annual incidence of 15.9 per 100,000. Eight CSF had Hib by culture or antigen testing, an annual incidence of 7.1 per 100,000 (95% CI 3.1 to 14.0) in children 0-59 months. In infants 0-11 months of age, the incidence of Hib meningitis was 32 per 100,000 (95% CI 16 to 67) and in the 0-23 month group it was 19 (95% CI 8 to 37).

**Interpretation & conclusions:** Our data are the first minimal estimate of the incidence of Hib meningitis for Indian children. The observed incidence data are similar to European reports before Hib vaccine use, suggest substantial disease before 24 months of age, and provide data useful for policy regarding Hib immunization.

**Key words** Asia - haemophilus meningitis - incidence - India - prospective study

*Haemophilus influenzae* type b (Hib) meningitis was recognized as a common cause of childhood meningitis in many regions before use of Hib vaccine in routine infant immunization. In the pre-Hib vaccine era in developed countries, the reported incidence of Hib meningitis was 11 to 50/100,000 in the 0 - 4 yr age group. While in some developing countries including The Gambia, Chile, and the Philippines, a comparable incidence has been reported, there is substantial variation in reported magnitude of Hib disease in Asian countries. Most Asian data are from retrospective hospital studies, which may not sample all cases and...
therefore may underestimate incidence; there are limited data from prospective population-based incidence studies in Asia\textsuperscript{7-9,12}, and data from India are not available.

This prospective study was therefore carried out to assess the burden of Hib meningitis in India, by estimating the incidence of Hib meningitis through prospective hospital-based case detection from a population resident in a defined geographic area, combined with an assessment of cases not detected by hospital surveillance.

**Material & Methods**

**Study region:** Hospital surveillance was carried out prospectively in the northern part of Vellore district in the Tamil Nadu State, in a population of 652,562 which was 38 per cent urban and 62 per cent rural. Vellore district has a population of 3.5 million, and is located between the cities of Chennai (formerly Madras) and Bangalore, approximately 140 km west of Chennai. The region is tropical (Vellore town: near 12 degrees N, 79 degrees E) with a monsoon climate: the mean maximal daily temperature during May is about 40°C, and the mean minimal daily temperature in January is about 18°C, with an average annual rainfall of 75-120 cm, most of which occurs in July through November. The main occupation in this area is agriculture, followed by beedi (local cigarette) and leather goods industry. Infant mortality rate in this region is 30-35 per 1000 live births and couple contraceptive protection rate is 40-60 per cent [Community Health and Development Unit (CHAD), CMC Hospital, unpublished data]. Immunization coverage for government-supplied vaccines (BCG, DPT, OPV x 3, and measles) ranges from 80 - 99 per cent in the study area. [Community Health and Development Unit (CHAD), CMC Hospital, unpublished survey data]. Hib and hepatitis B vaccines are available for private purchase.

The cases were enrolled from 4 study hospitals if they were resident in five civil administrative units in the district. These units were Vellore municipality, a town with commercial, administrative and health care services, plus the contiguous parts of surrounding rural development blocks: Vellore, Katpadi, Anaicut and Kaniyambadi blocks. This district has had substantial health programme activities and health data gathering for 40 years through the CHAD unit of the Christian Medical College and Hospital (CMCH). There were an estimated 56,153 children in the age group 0-4 yr in this population (local government health services data and demographic surveillance data from CHAD).

**Survey of practitioners, and hospitals:** A directory of all practitioners of allopathic medicine was obtained from the co-ordinator of the local disease surveillance network (NADHI)\textsuperscript{13}, which showed 32 small and large hospitals, and 88 private practitioners who provided health care to children. Doctors working in these hospitals and those in private practice were contacted individually and in groups and the surveillance project for Hib meningitis was described. They were mailed study questionnaires to determine their referral pattern for meningitis, facilities for lab investigations, and lumbar puncture (LP) and asked if they treated children with meningitis. Physicians were also contacted through local medical associations. The study encouraged referral of cases with suspected meningitis to the two tertiary care hospitals in the district.

Our survey showed that only four hospitals and one private clinic stated they routinely carried out lumbar puncture (LP) in children and collected cerebrospinal fluid (CSF) specimens. All other health care providers referred patients with clinically suspected meningitis to one of the four hospitals for diagnosis and management of meningitis. Two of the four hospitals were tertiary referral hospitals: tertiary hospital 1 (T1) with 1400 beds, a private academic institution providing service for a fee, though free or subsidized care is offered to the indigent; and tertiary hospital 2 (T2), located 2 km south of hospital T1, within urban Vellore, with 500 beds providing free care. Two hospitals were non-profit hospitals outside of urban Vellore: Secondary hospital 1 (S1) with 80 beds, located 7 km south of hospital T1, in a rural area and secondary hospital 2 (S2) outside the study area, in a small town 45 km west of hospital T1 on a major highway. Surveillance was discontinued in secondary hospital 2, after the audit at the end of the first year showed no cases from the defined study area were reported from this centre. There were no cases reported during the study period from the private clinic which reported LPs in the survey. The furthest distance from any of the study areas to the 3 referral hospitals was 25 km. Experience derived from local surveillance projects\textsuperscript{13} had shown that parents brought sick children to the tertiary hospitals in urban Vellore, or to the S1 hospital just 7 km away and seldom travelled out of this region for health care, since there were no other referral hospitals nearby.

**Case definitions:** A suspected case of meningitis was defined as a <5 yr old child resident in the study area, with clinical symptoms of meningitis (one or more of the following: fever with headache, stiff neck, bulging
A laboratory-confirmed case of bacterial meningitis was a possible case with a positive bacterial isolate in culture or antigen test positive for Hib. A laboratory-confirmed Hib case was a child with CSF leukocytosis of more than 100 WBC/µl was not routinely cultured in local practice, if there was no clinical suspicion of bacterial meningitis.

Surveillance methods: Surveillance was carried out for two years from December 1997 through December 1999. For those clinicians who saw meningitis patients, we provided a Hib study contact telephone number, as well as a study pager number and offered free culture and antigen testing of CSF specimens obtained by LP for any child less than five yrs of age with a provisional diagnosis of meningitis. On request, CSF samples were transported by study personnel from the requesting hospital to the single reference laboratory. Because of occasional lack of LP equipment in hospital T2, the Hib study provided sterile paediatric LP procedure kits, and replenished them as needed. The study did not provide microbiology facility for blood cultures, which is infrequently done in local practice. CSF with <10 WBC/µl was not routinely cultured in local practice, if there was no clinical suspicion of bacterial meningitis.

In the tertiary care hospitals, paediatric ward and casualty (emergency ward) patient registers were checked six days a week by study staff to identify children with clinical meningitis. In each hospital, clinical laboratory logs were reviewed for CSF specimens from children. After confirming the child met study criteria of age and place of residence, patients were contacted in the hospitals or their homes, and parents’ written consent for the child’s participation in the study was obtained. Data were collected by study staff on socio-economic status, symptoms, duration of illness, treatment prior to admission, laboratory investigations, antibiotics and other treatment, course in hospital, complications and outcome using a study case report form. Laboratory data for cases included CSF cell counts, protein and glucose concentration. Some children had other laboratory data obtained including blood leukocyte counts, and serum glucose. At the end of each year of the study, an audit of all lumbar punctures with submission of CSF to the laboratory was carried out at the clinical laboratories of the participating hospitals to identify possible cases missed by the ward surveillance.

Laboratory methods: All specimens were evaluated in the Microbiology Department of hospital T1; this lab was the reference laboratory for a national network of hospitals studying Hib. Microbiological culture of CSF was done using sheep blood chocolate agar for the first year, and by chocolate agar supplemented with Isovitalex (Becton Dickinson, Cockeysville, USA) in the second year, as previously described. All batches of chocolate agar were tested for growth of Hib, using reference strains. Antigen detection for Hib was done in CSF using a previously described local latex agglutination test, some specimens were also tested in the second year with a commercial latex agglutination test (BD “Directigen”, BD Bioscience, Sparks, MD, USA). Antibiotic susceptibility testing was done as described.

Child mortality survey: In order to identify severely ill children who may never have reached a hospital or had an LP, we identified all deaths during 1998 and 1999 in a subpopulation of 19,181 children 0-4 yr of age in the two rural blocks with the least access to health care, through the CHAD health information system of death reports. Families of these children were interviewed by field staff trained to assign a probable cause of death using a verbal autopsy method similar to previous reports.

Vaccine coverage in region: To determine the extent of Hib and other new vaccine use in local children, two 30-cluster sample household surveys using WHO standard methods were carried out in urban and rural communities. These surveys in the urban (n = 301) and rural children (n = 298) in the study area in 1999 showed 4 and 2 per cent coverage for three doses of Hib vaccine and 18 and 12 per cent for hepatitis B vaccine in urban and rural areas, respectively.

The project proposal and consent form were reviewed and approved by the ethics committees or Institutional Review Boards in the following institutions: CMCH, Indian Council of Medical Research, the Government of India, World Health Organization in Geneva, and Johns Hopkins University.
in USA. Each child’s parents or guardians provided informed consent for the child’s participation.

Data analysis: All data were entered in Epi-Info 6 and were analyzed using Epi-info 6 (www.cdc.gov/epiinfo) and SPSS for Windows version 9 (SPSS Inc, Chicago, IL). Annual incidence of meningitis was calculated with 95 per cent confidence intervals, assuming a Poisson distribution.

Results

Overall, 1000 cases, 441 in the first year, and 559 in the second, were identified in the three hospitals (Table). 1,000 children were enrolled and 998 lumbar punctures were done, of which 901 CSF specimens had less than 10 white blood cells/ml, 52 had 10-100 WBC/ml and 42 had greater than 100 WBC/ml. Three low-volume CSF specimens did not have microscopy done but were tested by culture and latex. Ward admission logs in hospital T2 did not contain sufficient clinical details to ascertain whether LP was performed in all cases meeting study clinical definitions of suspected meningitis. The lab audit of hospital T2 showed 4 LP were performed in subjects from study area, with one Hib identified.

Among patients with LP during the 2 years of study, there were 97 cases with possible meningitis (annual incidence 86/100 000; 95% CI, 69 to 103); 77 (80%) of these 97 possible meningitis cases were under 12 months, with 53 (55%) 0-5 months of age, an annual meningitis incidence of 527 per 100,000 in 0-5 month olds and 357 in the first 12 months of life. Eighty five of the 97 (88%) families provided information on prior medication, and 37 (44%) reported receiving some medicine, of which 27 (32%) reported the name of an antibiotic.

Of the 97 possible meningitis cases, 94 had evaluable CSF specimens, of which 45 per cent (42/94) had WBC >100/µl. Culture was done on all 97 CSF specimens and the in-house latex test for antigen detection was done on 76 CSF; 16 of 97 (16%) had bacterial isolates and of these, six were Hib. The other 10 isolates were 2 Streptococcus pneumoniae, 2 group A streptococcus, 1 group B streptococcus, 3 group D salmonella and 2 Escherichia coli. Bacterial contaminants were isolated from 6 specimens, and 75 (77%) CSF specimens had no bacterial growth. Four of 6 children with positive Hib culture had received prior antibiotics, compared to 17 of 75 (23%) children with culture negative CSF, (P = 0.059, Chi square test). Two of the five tested Hib isolates were resistant to

| Table. Population, suspected cases, and annual incidence per 100,000 of possible, probable, bacterial and Hib meningitis |
| Region | Type | Estimated No. | Incidence | No. | Incidence | No. | Incidence | Culture | Antigen | Culture | Antigen |
| Town of block | Type | < 5 yr | | | | | | | |
| Vellore | Urban | 16,407 | 385 | 1173 | 30 | 91 | 18 | 55 | 7 | 1 | 24 | 3 | 91 | 19.267 | 1.9-26.7 |
| Vellore | Rural | 13,041 | 199 | 763 | 20 | 77 | 7 | 27 | 0 | 1 | 26 | 2 | 113 | 1.138 | 0.1-24.4 |
| Kaniyambadi | Rural | 8,677 | 176 | 576 | 9 | 57 | 9 | 27 | 3 | 1 | 11 | 1 | 11 | 1.111 | 0.1-41.6 |
| Katpadi | Rural | 7,524 | 124 | 824 | 8 | 53 | 3 | 24 | 1 | 26 | 0 | 0 | 0 | 0 | 12.3-4 |
| Anaicut | Rural | 10,504 | 115 | 543 | 13 | 54 | 2 | 24 | 1 | 26 | 0 | 0 | 0 | 0 | 7.1 |
| Total no. or incidence | | 56,153 | 1000 | 890 | 199 | 866 | 64 | 37 | 16 | 2 | 9 | 8 | 15.9 | (8.3-23.7) |

ampicillin. All the CSF specimens with Hib isolated were also positive by the in-house latex test.

Of the 97 CSF specimens, 47 frozen stored specimens, including three of the six samples that were positive for Hib by culture and in-house latex, were available for later testing when a commercial Hib antigen detection kit was obtained. The commercial Hib antigen test was positive in the three Hib culture-positive CSFs that were tested, and also in two additional CSF samples, making a total of 8 laboratory-confirmed Hib cases (Table).

The crude incidence of possible meningitis in the study population was 86/100,000 (95% CI 69 to 103) 0-4 yr old children and 357/100,000 in 0-11 month olds. The incidence of study-defined probable bacterial meningitis was 37.4/100,000 children per year; 26% (11/42) of all CSFs with >100 WBC/µl had a bacterial isolate and 9 per cent (8/42) had Hib by culture or LA. Our laboratory confirmed Hib in 8.2 per cent (8/97) of all “possible” meningitis cases, 19 per cent (8/42) of “probable” bacterial meningitis cases and 44 per cent (8/18) of laboratory-confirmed bacterial meningitis cases.

Among the five administrative units included in our study, the incidence of hospital admitted possible meningitis varied 3 fold, from 53 to 150/100,000 and the incidence of confirmed Hib meningitis ranged from 0 to 11.5/100,000 (Table).

Seven of the eight laboratory confirmed Hib cases were in children under 12 months, with one child in the 12-23 month age group, equivalent to age-specific Hib meningitis annual incidence rates of 32/100,000 (95% CI 16 to 67) in 0-11 month infants, and 18.7 in 0-23 (95% CI 8 to 37) month children.

There was a substantial variation between hospitals in diagnostic LP frequency in admitted patients. Laboratory audit data showed that hospital T1 and S1 performed 553 LPs in 3,085 admissions (17.9/100 admissions), a rate 60 fold greater than 4 LPs/1,462 admissions (0.27/100 admissions) in hospital T2 (Fisher’s exact test, P<0.001).

The study recorded 6 hospital deaths in meningitis cases, one of the study hospitals. These 8 deaths were 2.5 per cent of all reported childhood deaths, and if half were meningitis, suggest an annual mortality rate for CNS infection of 20.8/100,000 in this sub-population.

Discussion

To our knowledge, this is the first prospective surveillance study of Hib meningitis in a defined geographic area of India, and indeed in south Asia. These incidence data for laboratory-confirmed Hib meningitis in this study are somewhat higher than rates reported in retrospective hospital-based studies from other Asian countries, including Hong Kong, China and Thailand, and similar to recent prospective studies from Korea (14/10^5 in children < 3 yr of age) and many European countries before Hib vaccine use (2.9 to 10.8/10^5 in children < 5 yr).

The annual incidence of laboratory proven Hib meningitis of 32/100,000 in 0-11 months old infants in this region is comparable to rates in under 1 yr children previously reported from Scandinavia, UK, and North America, which ranged from 30-50. However, we found a few older children with Hib, an observation noted by other reports and comparisons of Asian with European data. Reporting of data by 0 to 4 years may capture the Hib patterns well in the United States or Europe, but may not represent the situation accurately in other settings. Comparison of rates of proven Hib meningitis in children under 1 or under 2 yr may better describe Hib disease in some settings.

The number and incidence of laboratory-confirmed Hib meningitis cases observed in this study may be related to several factors:

1. There could be a true biologically low rate of Hib meningitis in children in this region, related to (a) genetic factors in local children, resulting in reduced infection rates, (b) early exposure to Haemophilus and other bacteria with cross-reacting antigens, leading to early natural immunity, (c) local variation in bacterial virulence and transmission, or (d) to vaccine use. Hib vaccine has been available in India since the mid 1990s, but its use in this district was less than 4 per cent, suggesting that vaccine use is unlikely to account for the relatively low observed rate.

2. Many microbiological laboratories cannot culture or identify H. influenzae reliably. We do not believe this factor explains our data, since we used an experienced reference laboratory. The data from this survey are similar to 10 yrs of hospital T1 data showing...
20 per cent of pyogenic meningitis cases show a bacterial isolate, and Hib is grown in about 5 per cent of specimens (personal communication, Dr MK Lalitha, CMCH, Vellore).

(3) The use of antigen tests should increase detection of Hib meningitis in children, because cases with previous antibiotic therapy, and problems with transport of CSF specimens may result in negative bacterial cultures9. Though some CSFs were not available for repeat testing, our use of 2 latex tests resulted in an increase from 3 to 5 *Haemophilus* cases in the 47 CSF specimens for which both Hib antigen tests were done. It is possible some Hib cases were missed in a few specimens not tested by antigen tests, or assessed with one antigen test only.

(4) We noted a substantially lower rate of diagnostic LP in one of the three hospitals where our surveillance was carried out, suggesting that many severely ill children were treated without diagnostic tests for meningitis or Hib disease. This reflects the reality of routine practice in resource-limited settings where the high patient to physician ratio, especially outside routine working hours, may not allow for performance of an LP in all eligible patients. It is likely that the diagnostic criteria specified by this study for LP were not followed systematically by physicians in this hospital, and some Hib meningitis cases may have been missed at this hospital.

Missing meningitis cases because lumbar puncture was not performed on admission was described in London in the 1970s by Goldacre30. He showed that of the 94 fatal meningitis cases he reviewed, meningitis was not diagnosed during life in 26 (28%). Most of these 26 children died before reaching the hospital, or shortly after admission; the final diagnosis of meningitis was made by autopsy. He pointed out that this is a minimal estimate of undiagnosed meningitis cases, since not all deaths were examined by autopsy. Similarly, Fraser et al31 reviewed characteristics of childhood meningitis cases in 1967-1970 in the state of Vermont, USA. They showed that towns with lower rates of overall childhood hospitalization also had significantly lower reported rates of meningitis in children, and higher rates of childhood death from obscure causes. They suggest that failure to recognize and formally diagnose bacterial meningitis was associated with lower rates of medical care utilization. They estimated 58 cases of meningitis were not reported, equivalent to 40 per cent of the 145 reported cases 31 an underestimation of nearly 30 per cent. The wide variation in utilization of health care, in the number of diagnostic LPs and in the formal diagnosis of meningitis likely also operate in this part of India. In addition, in this region, autopsies are not culturally acceptable and rarely done, so meningitis deaths without an LP in hospitals will not be diagnosed at autopsy.

(5) It is an unfortunate finding that some ill children in the community were not seen in hospital, and at least 8 died with signs of CNS infection, but without hospital admission or an LP. Some of these children may have had Hib meningitis.

The overall rate of lumbar puncture was 890/100,000 children or nearly 0.9 per cent of all children each year. However, the rate of lumbar puncture varied nearly two-fold from 547 to 1173 across the five administrative blocks, and the rate of hospitalized possible meningitis cases varied 3 fold.

The observed Hib meningitis incidence ranged from 0 in one block to 11.5 in Kaniyambadi block (KB). It is unlikely that the true rate of Hib meningitis varied so widely in this relatively small region, and we suggest the apparent variation in incidence may be related to variations in diagnostic practice and to variable access to medical care and diagnostic testing. Substantial evidence suggested that the population in KB had the most complete surveillance of all blocks, because it is rural with relatively good transportation and long established pattern of care seeking at hospital S1, which has community programmes throughout this block.

We are not aware of other prospective surveys of bacterial meningitis in Asia that also assessed possible missed cases through careful review of all hospitalizations and deaths in a defined population. The recent Hib vaccine study in Lombok, Indonesia suggests many Hib meningitis cases were not detected through routine hospital practice and microbiology: in control children less than 2 yr of age the incidence of culture-proven Hib meningitis admitted to hospital was 19/10^4; however, Hib vaccine prevented 67/10^4 possible and probable culture-negative admitted meningitis cases, suggesting that only 28 per cent of all admitted Hib meningitis cases were detected through routine hospital practice and microbiology: in control children less than 2 yr of age the incidence of culture-proven Hib meningitis admitted to hospital was 19/10^4; however, Hib vaccine prevented 67/10^4 possible and probable culture-negative admitted meningitis cases, suggesting that only 28 per cent of all admitted Hib meningitis cases were detected through routine hospital surveillance, a substantial underestimate of Hib cases32. The recent case control assessment of Hib vaccine in Dhaka, Bangladesh similarly suggests that many vaccine-preventable pneumonia cases are not detected in some settings33.

For the reasons listed above, our observed incidence of laboratory-proven Hib meningitis is a minimal
estimate for this region. This estimated incidence is in the range of rates reported from European regions.

Other diseases prevented by Hib vaccine were not assessed in this study. Data from North America in 1984 before Hib vaccine was used, reported Hib bacteraemia of 5-7/10^5 in <5 yr olds. Recent reports from Africa describe incidence rates per 10^5 of hospitalized Hib bacteremia of 17 in Mali (excluding meningitis cases) and 60 in Kenya (including meningitis). The estimated incidence/10^5 of Hib vaccine-preventable severe pneumonia ranges from 83 in children <5 yr of age to 264 in children <2 yr in Gambia and Indonesia, respectively. These data imply the overall burden of vaccine-preventable Hib disease is several-fold greater than the burden of laboratory-proven Hib meningitis, suggesting that the overall Hib disease burden is substantial in India. These data may be useful in considering the recent WHO recommendation for use of Hib vaccine in all infant immunization programmes.

Additional studies of the incidence and burden of vaccine preventable Hib disease are needed in India. We recommend that future surveillance studies should assess the degree of underestimation of the preventable Hib disease burden, by careful evaluation of the rate of diagnostic LP performed among ill and deceased children. Assessment of overall population LP rates, hospital-specific LP rates and use of verbal autopsy to determine the cause of deaths outside hospital will provide an estimate of meningitis cases not detected by hospital surveillance. The “vaccine probe” approach (use of Hib vaccine with comparison of rates of illness in vaccine recipients and control children) is a strategy which can provide direct evidence of the number and rate of Hib vaccine-preventable meningitis and pneumonia syndromes.

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Competing Interests: None

References


37. Steinhoff MC. **Haemophilus influenzae** type b infections are preventable everywhere. **Lancet** 1997; 349 : 1186-7.


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