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Impact of the introduction of the *Haemophilus influenzae* type b conjugate vaccine in an urban setting in southern India

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ABSTRACT

Introduction: *Haemophilus influenzae* type b was the leading cause of bacterial meningitis in infants and children below the age of two years prior to the introduction of *H. influenzae* type b conjugate vaccines. In December 2011, the Indian government introduced *H. influenzae* b vaccine in the state of Tamilnadu. A prospective surveillance for bacterial meningitis was established at the Institute of Child Health in Chennai to evaluate the etiology of meningitis and impact of the vaccine.

Material and Methods: Infants aged one to 23 months who were admitted to the hospital with symptoms of suspected bacterial meningitis were enrolled and lumbar puncture was performed. Cerebrospinal fluid samples were analyzed for white blood cells, protein, and glucose. Bacterial culture and a latex agglutination test for common bacterial pathogens were performed.

Results: Between January 2009 and March 2014, 4,770 children with suspected bacterial meningitis were enrolled. Prior to the introduction of the vaccine, an average of 11.7 cases of *H. influenzae* b meningitis and 31.1 cases of probable meningitis with no etiology were identified each year. After introduction, the number of cases were reduced by 79% and 44% respectively. The average *H. influenzae* b vaccine coverage after introduction was 69% among all children with clinically suspected meningitis. In contrast, the mean number of aseptic meningitis and pneumococcal meningitis cases remained stable throughout the pre and post vaccination period; 28.2 and 4.8 per year, respectively.

Conclusions: *H. influenzae* b conjugate vaccine reduced the number of cases of *H. influenzae* b meningitis and probable meningitis within the first two years of its introduction. The impact against meningitis was higher than the vaccination rate, indicating indirect effects of the vaccine. India has recently scaled up the use of Hib conjugate vaccine throughout the country which should substantially reduce childhood meningitis rates further in the country.

1. Introduction

Historically, *Haemophilus influenzae* type b (Hib) was a major cause of morbidity and mortality in young children globally. As recently as 2000, Hib accounted for 370,000 deaths and over eight million cases of severe disease globally, most notably pneumonia and meningitis [1]. However, with the implementation of Hib conjugate vaccines (Hib-CV), Hib disease has been virtually eliminated in countries where there has been wide-spread use of the vaccine. Hib-CV is composed of Hib capsular polysaccharide polyribosylribitol phosphate conjugated to a protein carrier. The Hib-CV vaccines that are currently available were found to be over 95% efficacious in preventing invasive disease (confirmed etiology in blood, CSF, or normally sterile body fluid), of which meningitis is the most lethal manifestation and results in serious neurological

Abbreviations: CSF, Cerebrospinal fluid; DTP, Diphtheria-tetanus-pertussis; GBS, *Group B Streptococcus*; Hib, *Haemophilus influenzae* type b; Hib-CV, *Haemophilus influenzae* type b conjugate vaccines; ICH & HC, Institute of Child Health and Hospital for Children; LAT, Latex agglutination test; LP, Lumbar puncture; WBC, White blood cell count; WHO, World Health Organization.

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sequelae in 30 to 40% of cases [2–4]. Hib-CV was licensed in the USA in 1990. Subsequently, there was rapid uptake of the vaccine in high income countries. However, in the year 2000 only five of the poorest countries eligible for vaccine funding support from Gavi were using Hib-CV. By 2009, 83% of the 72 Gavi eligible countries were using the vaccine [5]. India was one of the last Gavi eligible countries to introduce the vaccine.

Hib disease has remained largely uncontrolled in India where the Hib-CV was not included in National Immunization Schedule until Dec 2011 when the States of Tamilnadu and Kerala introduced the vaccine based on the recommendation of the National Technical Advisory Group on Immunization and the Indian Academy of Pediatrics, and as part of a stepwise national introduction [6,7]. As of 2000, 72,000 Indian children under the age of five years old were estimated to die of Hib disease, a number which was unlikely to have been reduced significantly in the absence of the Hib-CV in the national program since the majority of these deaths occur in the poorest children who have the least ability to purchase the vaccine from the private sector [6,8]. Although Hib-CV was widely used in the private sector in India and Indian manufacturers are the leading supplier of Hib-CV globally, the vaccine's cost prevented widespread use in most children. Thankfully, by the end of 2015 the Hib-CV was introduced publicly in India nationwide.

Surveillance for bacterial meningitis was previously established in four hospitals in India (Christian Medical College in Vellore, Tamilnadu; the Institute of Child Health and Hospital for Children in Chennai, Tamilnadu; Chhatrapati Shahuji Maharaj Medical University in Lucknow, Uttar Pradesh and Kalawati Saran Children's Hospital in New Delhi) beginning July 2008 in an effort to define the burden of meningitis due to Hib and other bacterial pathogens, and assess the need for prevention and treatment strategies. Details of this surveillance effort have been published previously [9,10]. In December 2011 Hib-CV was introduced in Tamilnadu as a part of a pentavalent combination vaccine which included the following antigens: Diphtheria-Tetanus-Pertussis (DTP), Hepatitis B, and Hib-CV. The surveillance was continued in Chennai, Tamilnadu, to evaluate the impact of Hib-CV introduction in the state.

2. Material and methods

This study took place at the Institute of Child Health and Hospital for Children (ICH & HC), a 537-bed public pediatric hospital located in Chennai, Tamilnadu, Southern India. ICH & HC is a referral hospital and caters to the needs of patients from all over Tamilnadu and bordering areas of the neighboring state Andhra Pradesh. Children admitted to the hospital between the ages >30 days to <24 months (the ages who are at the highest risk for Hib disease) were screened for clinically suspected meningitis through daily surveillance in the hospital wards. Enrollment could occur at any time during admission. Clinically suspected bacterial meningitis was defined as acute onset fever with one or more meningeal signs (neck stiffness, altered consciousness or other meningeal sign), following WHO surveillance criteria [11]. Acute fever was defined as fever with an onset within the five days prior to presentation which was ascertained from the child's parent or guardian or a documented temperature of $\geq$38 °C on admission. Additional inclusion criteria were added since meningeal signs seen in older children and adults are rare in this age group. The presence of one or more of the following signs prompted inclusion: seizure, altered consciousness, bulging fontanelle, or clinical suspicion of meningitis by the attending physician (regardless of other signs).

After enrollment clinical information including physical findings and antibiotic use was obtained from the documentation in the medical record of the child or, in the event of missing information, was obtained from the patient's caregiver. Demographic data was obtained by interviewing the patient's caregiver. Vaccination records were obtained from the patient's vaccination card, including DTP and Hib-CV immunization status. Severe malnutrition was defined by WHO criteria as a weight to age Z-score greater than three standard deviations below WHO average [12]. Final diagnoses and outcomes were recorded from the discharge records. Lumbar puncture (LP) was performed after obtaining consent from the guardian. LP kits were provided to the physicians, and an individual from the laboratory was present at the time when the procedure was performed to ensure the immediate transport and processing of the specimen. Patient care was provided by regular clinical staff following the hospital's standard of care.

Cerebrospinal fluid (CSF) samples were analyzed for protein, glucose, total white blood cell count (WBC), Gram stain, and cultured for bacterial pathogens using chocolate agar plates incubated in a CO_2 enriched atmosphere. Samples with abnormal CSF findings (CSF with $\geq$10 WBC per mm^3) were further examined using a latex agglutination test (LAT) kit with assays specific for Hib, *Streptococcus pneumoniae*, *Group B Streptococcus* (GBS), *Escherichia coli* K1, and *Neisseria meningitidis* groups A, B, C, Y and W135 (Directigen™ Meningitis Combo Test; Becton, Dickinson and Company). The LAT was added in addition to culture as Indian studies and prior experience demonstrated that most patients would be treated with antibiotics prior to LP, cultures yields would be low, and that LAT provided rapid determination of the etiology of bacterial meningitis [10,13–15]. The LAT kits were tested during every run with the manufacturers provided negative controls and every 15 days with the manufactures provided positive controls. The kits were tested with known positive bacterial isolates on arrival to the clinical laboratory and if any concerns were brought up on specific cases. If the CSF volume obtained was limited, the available CSF was prioritized for sequential testing with WBC, LAT, and biochemistry. CSF bacterial culture was not prioritized as prior experience showed limited sensitivity for detecting bacterial meningitis in this population [9,10]. LAT could also be performed at the attending physicians request, regardless of other CSF findings, if the clinical suspicion for bacterial meningitis was high.

Cases of clinically suspected meningitis were categorized based on the laboratory findings; confirmed bacterial meningitis (positive culture and/or LAT for a known bacterial pathogen), probable meningitis (either $\geq$100 WBC per mm^3, or 10–99 WBC per mm^3 with raised protein concentration [$\geq$100 mg/dL] or lowered glucose concentration [<40 mg/dL], or visually cloudy CSF with no confirmed pathogen), and aseptic meningitis ($\geq$10 WBC per mm^3, not fitting criteria for probable or confirmed bacterial meningitis).

January 2009 to March 2012 was considered the pre-introduction period based on Hib-CV immunization rates in clinically suspected meningitis cases. Even though the vaccine was introduced in December 2011, we chose to consider April 2012 as the start of the post-vaccine period since prior to April the proportion of children with clinically suspected meningitis who received any Hib-CV remained flat and starting in April a sharp rise in vaccination was noted. The ratio of case numbers before and after introduction were calculated using the number of cases before introduction divided by the number of years, divided by the number of cases after introduction divided by the number of years. Technical assistance and on-site evaluation were provided by staff from the Department of International Health, Johns Hopkins Bloomberg School of Public Health (JHSPH), and assistance with improving laboratory procedures by Christian Medical College, Vellore, India. Informed consent was obtained from the child's caregiver prior to obtaining pre-admission clinical history, demographic data, and for sample processing. Ethical clearance was obtained from the Institutional Review Board at the ICH&HC, Johns Hopkins University, and from the International Clinical Epidemiol-

ogy Network. Data were managed using Access 2007® (Microsoft®), and analyzed using Excel 2007® (Microsoft®) and Stata IC 10© (StataCorp). The pre and post introduction demographic indicators were compared using the chi-squared test, and the ratio of case numbers were compared using Fisher's two-sided exact test.

3. Results

Between January 2009 and March 2014, 4,770 children with clinically suspected meningitis were enrolled (Table 1). A combination of fever, seizures, and altered consciousness were the most common indicators for suspicion of meningitis; a more thorough description of the clinical characteristics of suspected meningitis in this population has been described previously [9]. LAT was performed on 608 CSF samples; 337 tests were performed on CSF with ≥10 WBCs per mm^3 and 271 were done CSF on samples with <10 WBCs per mm^3. Of the CSF 365 samples with a WBC ≥10 WBC per mm^3, 92% were tested with the LAT. Of the children with clinically suspected meningitis, 148 (3.7%) were found to have CSF findings consistent with aseptic meningitis, while 136 (3.5%) children were found to have CSF findings of probable bacterial meningitis without a confirmed bacterial pathogen. The LAT was positive in 75 (22.3%) of the 337 samples with a WBC ≥ 10 per mm^3 and in three (1.1%) of the 271 samples with a WBC < 10 per mm^3. The three positive LAT results (one each of *S. pneumoniae*, Hib, and GBS) from patients with low WBC findings were felt to be false positives by the attending physicians but have been included in this analysis as they fit study criteria for inclusion. There were 12 positive CSF cultures. All cultures that were positive for pathogens on the LAT were also positive based on LAT results for the same pathogen (two *S. pneumoniae*, one Hib, and one *N. meningitidis*). Over the course of the surveillance period, 87 cases of bacterial meningitis were confirmed, 1.8% of all clinically suspected meningitis. Hib accounted for 43 cases of confirmed bacterial meningitis. Most Hib cases (93%) occurred in a bell-shaped distribution between the ages of one and ten months (Fig. 1), with the peak occurring at six months of age. *S. pneumoniae*, the second most commonly identified pathogen, accounted for 25 cases. Across the study period 266 (5.6%) of clinically suspected meningitis cases, 13 (8.8%) children with aseptic meningitis, 23 (16.9%) with probable bacterial meningitis, and 23 (26%) confirmed bacterial meningitis died. Among confirmed bacterial meningitis cases there was clear variation in fatality rates based on pathogen: 32% of children with *S. pneumoniae* meningitis died, while 14% of children with Hib meningitis died.

Several demographic and clinical characteristics remained the same before and after introduction, including gender distribution and maternal education (Table 2). Post introduction cases were relatively younger, with mean age of 10.2 in pre and 9.2 months post introduction periods respectively, and with a higher proportion of severely malnourished children (14% and 17%, respectively, p = 0.004). A higher proportion of children had a LP performed in post introduction period compared to pre-introduction period (pre and post introduction 79% versus 92%, p < 0.001), as well as a higher proportion of children receiving antibiotics prior to LP in the post introduction period (73% versus 85%, p < 0.001). Vaccination with one or more DTP shots over all ages was similar, but full vaccination with three DTP shots was lower post introduction (78% versus 73%, p < 0.001). DTP coverage in older infants was excellent. Throughout the surveillance period, the proportion of children immunized with at least one dose of the DTP vaccine remained relatively steady at approximately 90% (Fig. 2), and 97% of children 12 months and over were fully vaccinated with three DTP doses, which is well above the Tamilnadu state average for urban children in this age range, 85% [16].

Table 1
Summary of meningitis surveillance.

Meningitis category	Total
Clinically suspected:	4,770
Aseptic	148
Probable bacterial	136
Confirmed bacterial:	87
Hib	43
S. pneumoniae	25
Group B *Streptococcus*	7
Neisseria meningitidis	3
Pseudomonas sp.	2
Acinetobacter sp.	2
Other*	5

* *Citrobacter freundii, Enterobacter* sp., *Klebsiella* sp., *Salmonella paratyphi, Salmonella* sp.

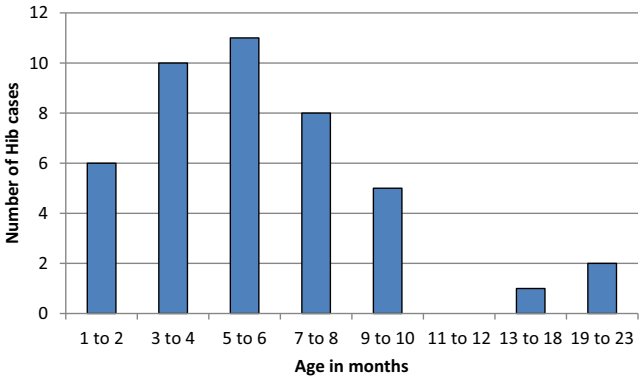

Fig. 1. Age distribution of confirmed Hib meningitis cases.

Prior to April 2012, vaccination with at least one dose of Hib-CV in children presenting with clinically suspected meningitis remained relatively uncommon but steady near 8%. The proportion of children vaccinated with at least one dose of Hib-CV increased steadily from 35% in April 2–12 to 85% in September 2013, after which it remained constant (Fig. 2). An average of 69% children were immunized with at least one Hib-CV over this time, while 53% were fully vaccinated with three doses. Introduction occurred in both older and younger infants. In the introduction period 52% of children under 12 months old and 55% of children 12 months and older were fully vaccinated with 3 doses of Hib-CV.

The average number of children with aseptic meningitis identified remained relatively stable at 28.2 per year, with no significant difference between the pre and post introduction periods (p = 0.954). However, the average number of probable bacterial meningitis cases identified was higher before the introduction of the Hib-CV compared to after; 31.1 and 17.5 per year, respectively, a reduction of 43.7% (95% CI:16.5, 62.8%, p = 0.002) (Table 3). After the introduction of Hib-CV, the number of Hib meningitis cases was dramatically reduced (Fig. 2). Between January 2009 and April 2012, the average annual number of Hib meningitis cases identified was 11.7. After introduction of Hib-CV, the yearly average number of Hib cases was 2.5; a 78.6% (95% CI: 45.6, 93.4%) reduction comparing pre and post introduction periods (p < 0.001). The proportion of confirmed bacterial meningitis cases that was due to Hib decreased from 55% to 28% in the post-Hib vaccination period. The average annual number of *S. pneumoniae* cases remained similar between pre and post introduction, with 4.8 identified yearly. Comparing pre and post introduction hospitalization rates, Hib-CV prevented 9.2 cases of Hib meningitis and 13.6 cases of probable meningitis per year at the Institute of Child Health, Chennai, India.

Table 2
Comparison of demographic and clinical characteristics of suspected bacterial meningitis patients from pre-Hib-CV introduction and post Hib-CV introduction eras.

	Pre Hib-CV	(%)*	Post Hib-CV	(%)*	P value**
Total enrolled	3,181		1,589		
Female	1,342	(42%)	676	(43%)	0.808
Age > 12 months	1,297	(41%)	537	(34%)	<0.001
Severe malnutrition	440	(14%)	270	(17%)	0.004
Maternal education, >primary	2,390	(77%)	1,186	(75%)	0.078
DTP, ≥1 dose	2,851	(90%)	1,415	(90%)	0.511
DTP, 3 doses	2,525	(78%)	1,165	(73%)	<0.001
Hib-CV, ≥1 dose	242	(8%)	1,088	(69%)	<0.001
Hib-CV, 3 doses	167	(5%)	842	(53%)	<0.001
Antibiotics prior to LP	1,819	(73%)	1,239	(85%)	<0.001
LP with CSF	2,511	(79%)	1,464	(92%)	<0.001

* Denominator excludes missing data.
** Chi squared comparing pre-versus post vaccine introduction values.

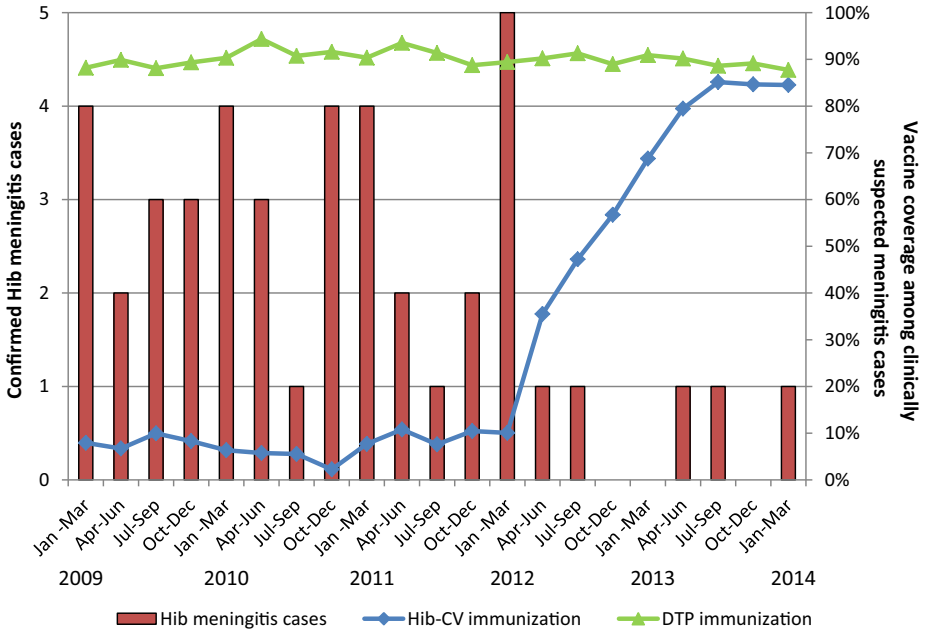

Fig. 2. Quarterly cases of Hib meningitis relative to immunization coverage with one or more doses of Hib-CV or DTP.

Table 3
Trends in meningitis in the pre and post Hib-CV introduction eras.

Meningitis Category	Cases per year		Reduction	P value*
	Pre Hib-CV	Post Hib-CV		
Aseptic	28.3	28.0	1%	0.954
Probable bacterial	31.1	17.5	44%	0.002
Confirmed bacterial	21.2	9.0	58%	<0.001
Hib	11.7	2.5	79%	<0.001
S. pneumoniae	4.9	4.5	8%	0.845

* Two-sided exact test of ratio of case numbers.

The average number of children who were identified that did not meet criteria for aseptic, probable bacterial, or confirmed bacterial meningitis decreased from 906 to 740 per year before and after introduction, a reduction 18.3% (95% CI: 13.0, 23.3%, $p < 0.001$). There was a peak in enrollment the second half of 2009 coinciding with a global influenza pandemic, at which time this category of case identification reached the equivalent 1374 cases per year. Excluding this time frame, pre-introduction yearly identification rate was 818 for patients who did not meet criteria for aseptic, probable bacterial, or confirmed bacterial meningitis, resulting in a reduction 8.8% (95% CI: 2.6, 14.7%, $p = 0.006$) comparing pre to post introduction time frames.

Four cases of Hib meningitis occurred in children who had received Hib-CV; one prior to regional vaccine introduction in Tamilnadu and three after introduction. Two received a full course of three doses of Hib-CV vaccine, one received two doses, and one received one dose. The partially vaccinated children were incompletely vaccinated for their age based on the Indian immunization schedule (3 doses given at 6, 10 and 14 weeks of age).

4. Discussion

This is the first study to demonstrate the effectiveness of the introduction of Hib-CV in the Indian National Immunization

Schedule. The rapid impact seen in this study within a two year period is a credit to the excellent immunization system in place in Tamilnadu, which has maintained basic pediatric vaccination coverage >90% for decades and has facilitated the early introduction of the pentavalent Hib-CV, DTP, hepatitis B vaccines [17]. It also demonstrates the potential impact that the Hib-CV could have throughout India, where greater than 20% of the global Hib morbidity and mortality occurs.

The impact on Hib disease seen in this study from India is comparable or superior to that what has been observed with introduction of the Hib-CV in other low-income countries. After introduction of Hib-CV in Kenya a 47% reduction in the incidence of invasive Hib disease in children under 12 months old was seen in the first year, which increased to 89% in the second year [18]. In Mali, the incidence of invasive Hib disease in children aged 24 months old was reduced by only 19% after the first year of introduction but improved to 67% and 81% reduction after the second and third years of introduction, respectively [19]. In neighboring Bangladesh a 83% drop in the incidence of Hib meningitis was seen 1 year after introduction, but the analysis was restricted children less than 1 year old [20]. After five years invasive Hib disease was reduced by greater than 99% in the United States and in The Gambia [21,22]. It is likely that Tamilnadu will see similar reductions due to the consistently high primary immunization rate.

One of the major benefits of Hib-CV is the large herd effect, which is thought to be due to reduction in transmission of the organism since the vaccine is known to have significant impact on reducing nasopharyngeal colonization with Hib [21]. A 10% higher reduction in Hib meningitis was seen when compared to the overall vaccination coverage with one Hib-CV dose during the study period or 26% higher reduction if full vaccination with 3 doses of Hib-CV is used. The magnitude of the effect is similar to what has been seen in other studies [23,24], including an earlier study in Vellore, south India which noted a 65% reduction in yearly Hib disease with a 35% private vaccination coverage of Hib-CV in children less than two years of age, without a significant change in the number of *S. pneumoniae* cases [25]. Similarly, no decrease in the yearly *S. pneumoniae* cases was seen in this study after Hib-CV introduction. Combined, these observations are suggestive of herd immunity from vaccination, but are not conclusive given that this study was not designed to evaluate herd immunity.

The reduction in probable bacterial meningitis is like what has occurred in other nations. A study from Uganda noted a 53% (95% CI: 11,68) reduction in probable bacterial meningitis without confirmation of a pathogen [26]. A hamlet randomized trial in Indonesia found that Hib-CV prevented 16 Hib meningitis cases per 100,000 child years, but prevented nearly twice as many cases of probable bacterial meningitis without confirmation of a pathogen; 31 per 100,000 child years [27]. In Bangladesh a 30% reduction in the incidence of purulent meningitis was noted in children under one year old within the first year of Hib-CV introduction, with no drop in *S pneumoniae* meningitis [20]. These studies suggest that a large proportion of Hib meningitis cases were not detected, which is thought to be due to a combination of low lumbar puncture rate in children with suspected meningitis, limited access to laboratory facilities, low quality diagnostic technique, and extensive antibiotic use prior to obtaining CSF for analysis [28]. In the present study, the reasons for the relatively high culture negative probable bacterial meningitis rate is likely due to the large proportion of children who received antibiotics prior to collection of CSF (77% of enrolled patients), leading to sterilization of CSF before the etiological agent could be detected. The reduction in probable bacterial meningitis after Hib-CV introduction strongly suggests that a significant number of these cases might have been due to Hib.

This study has several limitations. First, certain demographic changes were noted in the population before and after introduction which could hypothetically change the trend of Hib disease. However, most of the changes (higher proportion of children less than 12 months old, severe malnutrition, and increase in the number of LPs done) could reasonably be expected to increase Hib disease or Hib disease detection while the increase in antibiotics prior to LP would be expected to decrease identification. However, although the changes were statistically significant, they were proportionately small and unlikely to account for a dramatic shift. Additionally, parent reporting, which is known to be less accurate, was used to discern signs, symptoms, and pre-hospitalization antibiotics when documentation was not available. However, this is unlikely to have led to missed meningitis cases, given that the basic signs of fever, altered mental status, and seizures are readily discernable by parents. Parents are more likely to over report such symptoms, rather than under report them.

A decrease was seen in patients identified who did not fit aseptic, probable bacterial, or confirmed bacterial meningitis case definitions was seen after the introduction of Hib-CV. Some the difference seen may be accounted for by an increase in enrollment that was seen during the H1N1 influenza pandemic, which took place in the second half of 2009 [29]. Excluding this time frame, an 8.8% decrease was noted. It is not clear why this decrease occurred. Hib-CV would be expected to impact hospital admission for pneumonia to some extent, but this study was not designed to assess the impact of Hib-CV on disease beyond meningitis. More likely explanations include changes in local healthcare (although there as there were no new hospitals, changes to public insurance, or changes in referral flow that the authors are aware of) or natural yearly variation in hospital admission rates.

The culture positive rate was exceedingly low, and diagnosis of bacterial pathogens relied on LAT results, raising concerns that many positive LAT results may be false positives. However, 271 LATs were performed on patients with low CSF WBC counts (<10 per mm^3), three of which were positive by LAT and could be reasonably considered clear false positive. This suggests good overall specificity of the test. Unfortunately, it was not possible to calculate the incidence of Hib and other bacterial meningitis using a catchment area denominator because ICH & HC is a referral hospital for Tamilnadu and the bordering areas of Andhra Pradesh. The proportion of children vaccinated with Hib-CV remained lower than vaccination with DTP at the end of the study. The reason for this in not known but could potentially be caused by persistence of DTP in public vaccine stocks, private vaccination with DTP alone, incomplete catchup vaccination, or a combination of these factors.

Even though Hib meningitis disease has a very high mortality rate and sequelae among survivors, Hib causes far more cases of pneumonia than meningitis, which was not assessed in this study and has yet to be evaluated in India. Previous Indian studies have shown that Hib accounted for 13 to 19% of pneumonia [6]. A global meta-analysis found Hib-CV to be 21% (95% CI: 3, 36) effective against radiographically conformed pneumonia [1]. It is likely that Hib-CV will have a similar impact on pneumonia in India. The potential impact of Hib-CV on reducing morbidity and mortality from pneumonia is a major impetus for the sustained use of this vaccine. Finally, the success of the introduction of Hib-CV demonstrates that Indian states can effectively introduce new vaccines to the public immunization systems. Other newer vaccines that are likely to have a high impact on childhood morbidity and mortality, such as the pneumococcal conjugate vaccine and rotavirus vaccines, should be strongly considered for introduction.

5. Conclusions

This study demonstrated the rapid impact of Hib-CV in reducing Hib meningitis and probable bacterial meningitis lacking confirma-

tion of a pathogen. Since the end of 2015, Hib-CV has been introduced in all states in the country. Therefore, a substantial drop in Hib meningitis cases can be expected in India.

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Declaration of interest

M.S. has received research funding from GlaxoSmithKline, Merck, and Pfizer (previously Wyeth Lederle Vaccines), has served on the scientific advisory boards of GlaxoSmithKline, Merck, Pfizer, and received honoraria for these activities. The other authors declare no conflicts of interest, real or perceived.

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References

[1] Watt JP, Wolfson LJ, O'Brien KL, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Haemophilus influenzae type b in children younger than 5 years: global estimates. Lancet 2009;374:903–11.
[2] Black SB, Shinefield HR, Fireman B, Hiatt R, Polen M. Vittinghoff E. Efficacy in infancy of oligosaccharide conjugate Haemophilus influenzae type b (HbOC) vaccine in a United States population of 61,080 children. The Northern California Kaiser Permanente Vaccine Study Center Pediatrics Group. Pediatr Infect Dis J 1991;10:97–104.
[3] Peltola H, Eskola J, Kayhty H, Takala AK, Makela PH. Clinical comparison of the Haemophilus influenzae type B polysaccharide-diphtheria toxoid and the oligosaccharide-CRM197 protein vaccines in infancy. Arch Pediatr Adolesc Med. 1994;148:620–5.
[4] Mulholland K, Hilton S, Adegbola R, Usen S, Oparaugo A, Omosigho C, et al. Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine [corrected] for prevention of pneumonia and meningitis in Gambian infants. Lancet 1997;349:1191–7.
[5] Vaccine Information Management System. International Vaccine Access Center: Johns Hopkins Bloomberg School of Public Health. Database accessed 6/2013.
[6] NTAGI subcommittee recommendations on Haemophilus influenzae type B (Hib) vaccine introduction in India. Indian Pediatr. 2009;46:945-54.
[7] Consensus recommendations on immunization, 2008. Indian Pediatr. 2008;45:635-48.
[8] Bassani DG, Kumar R, Awasthi S, Morris SK, Paul VK, Shet A, et al. Causes of neonatal and child mortality in India: a nationally representative mortality survey. Lancet 2010;376:1853–60.
[9] Fitzwater SP, Ramachandran P, Nedunchelian K, Kahn G, Santosham M, Chandran A. Bacterial meningitis in children <2 years of age in a tertiary care hospital in South India: an assessment of clinical and laboratory features. J Pediatr 2013;163:S32–7.
[10] Ramachandran P, Fitzwater SP, Aneja S, Verghese VP, Kumar V, Nedunchelian K, et al. Prospective multi-centre sentinel surveillance for Haemophilus influenzae type b & other bacterial meningitis in Indian children. Indian J Med Res 2013;137:712–20.
[11] WHO. Recommended standards for surveillance of selected vaccine-preventable diseases. WHO/V&B/03.01: The Department of Vaccines and Biologicals; 2003.
[12] de Onis M, Blössner M. WHO global database on child growth and malnutrition. World Health Organization, Department of Nutrition for Health and Development. 1997;WHO/NUT/97.4.
[13] Chinchankar N, Mane M, Bhave S, Bapat S, Bavdekar A, Pandit A, et al. Diagnosis and outcome of acute bacterial meningitis in early childhood. Indian Pediatr 2002;39:914–21.
[14] Deivanayagam N, Ashok TP, Nedunchelian K, Ahamed SS, Mala N. Bacterial meningitis: diagnosis by latex agglutination test and clinical features. Indian Pediatr 1993;30:495–500.
[15] Mani R, Pradhan S, Nagarathna S, Wasiulla R, Chandramuki A. Bacteriological profile of community acquired acute bacterial meningitis: a ten-year retrospective study in a tertiary neurocare centre in South India. Indian J Med Microbiol 2007;25:108–14.
[16] International Institute for Population Sciences (IIPS) and ICF. 2017. National Family Health Survey (NFHS-4), India, 2015-16: Tamil Nadu. Mumbai: IIPS.
[17] International Institute for Population Sciences and Macro International. National Family Health Survey 3, 2005–06: India. Mumbai2007.
[18] Cowgill KD, Ndiritu M, Nyiro J, Slack MP, Chiphatsi S, Ismail A, et al. Effectiveness of Haemophilus influenzae type b Conjugate vaccine introduction into routine childhood immunization in Kenya. JAMA 2006;296:671–8.
[19] Sow SO, Tapia MD, Diallo S, Keita MM, Sylla M, Onwuchekwa U, et al. Haemophilus influenzae Type B conjugate vaccine introduction in Mali: impact on disease burden and serologic correlate of protection. Am J Trop Med Hyg 2009;80:1033–8.
[20] Sultana NK, Saha SK, Al-Emran HM, Modak JK, Sharker MA, El-Arifeen S, et al. Impact of introduction of the Haemophilus influenzae type b conjugate vaccine into childhood immunization on meningitis in Bangladeshi infants. J Pediatr 2013;163:S73–8.
[21] Adegbola RA, Secka O, Lahai G, Lloyd-Evans N, Njie A, Usen S, et al. Elimination of Haemophilus influenzae type b (Hib) disease from The Gambia after the introduction of routine immunisation with a Hib conjugate vaccine: a prospective study. Lancet 2005;366:144–50.
[22] Progress toward elimination of Haemophilus influenzae type b disease among infants and children–United States, 1987-1995. MMWR Morb Mortal Wkly Rep. 1996;45:901-6.
[23] Moulton LH, Chung S, Croll J, Reid R, Weatherholtz RC, Santosham M. Estimation of the indirect effect of Haemophilus influenzae type b conjugate vaccine in an American Indian population. Int J Epidemiol 2000;29:753–6.
[24] Gallo G, Ciofi degli Atti ML, Cerquetti M, Piovesan C, Tozzi AE, Salmaso S. Impact of a regional Hib vaccination programme in Italy. Vaccine. 2002;20:993-5.
[25] Verghese VP, Friberg IK, Cherian T, Raghupathy P, Balaji V, Lalitha MK, et al. Community effect of Haemophilus influenzae type b vaccination in India. Pediatr Infect Dis J 2009;28:738–40.
[26] Lewis RF, Kisakye A, Gessner BD, Duku C, Odipio JB, Iriso R, et al. Action for child survival: elimination of Haemophilus influenzae type b meningitis in Uganda. Bull World Health Organ 2008;86:292–301.
[27] Gessner BD, Sutanto A, Linehan M, Djelantik IG, Fletcher T, Gerudug IK, et al. Incidences of vaccine-preventable Haemophilus influenzae type b pneumonia and meningitis in Indonesian children: hamlet-randomised vaccine-probe trial. Lancet 2005;365:43–52.
[28] Seehusen DA, Reeves MM, Fomin DA. Cerebrospinal fluid analysis. Am Fam Physician 2003;68:1103–8.
[29] Choudhry A, Singh S, Khare S, Rai A, Rawat DS, Aggarwal RK, et al. Emergence of pandemic 2009 influenza A H1N1. India. Indian J Med Res. 2012;135:534–7.