Childhood very severe pneumonia and meningitis-related hospitalization and death in Yemen, before and after introduction of *H. influenzae* type b (Hib) vaccine

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معدلات الإدخال في المستشفيات والوفيات ذات الصلة بالالتهاب الرئوي والتهاب السحايا الشديدة جداً في اليمن قبل وبعد إدخال لقاح المستدمية النزلية من النمط بي

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الخلاصة: لقد أدرج لقاح المستدمية النزلية من النمط "بي" في البرنامج اليمني للتمنيع في عام 2005. وتقارن هذه الدراسة بين معدلات الإدخال في المستشفيات والوفيات ذات الصلة بالالتهاب الرئوي الشديد جداً والالتهاب السحائي الناجم عن جميع الأسباب قبل وبعد إدخال لقاح المستدمية النزلية المتقارن من النمط "بي"، وتعرض نتائج الترصُّد لالتهاب السحايا الجرثومي في عام 2010. وهي دراسة استعادية أجريت على البيانات التي جمعت في الفترة 2000-2010 وشملت جميع الأطفال الذين تراوحت أعمارهم بين شهرين و60 شهراً في المستشفى الرئيسي لطب الأطفال في صنعاء. وقد اتضح وجود انخفاضات يُعتدُّ بها إحصائياً ومثيرة للاهتمام في معدلات الإدخال إلى المستشفى والموت الناجم عن جميع أسباب التهابات السحايا في الفترة التي سبقت إدخال اللقاح مقارنةً بالفترة التي تلت إدخال اللقاح. إلا أن معدل الإدخال إلى المستشفى والوفيات بسبب الالتهاب الرئوي الشديد جداً لم يتحسن إلا قليلاً، وكانت هناك بيِّنات على تناقص، ولكن دون أن يكون له ميل يُعتدُّ به إحصائياً، مما يدل على أن الالتهاب الرئوي الشديد جداً كان بمثابة نقطة نهائية غير نوعية تترافق بأسباب متعددة للأمراض (منها جرثومي ومنها فيروسي). ولا يزال الالتهاب الرئوي الشديد جداً هو السبب الأكثر انتشاراً للأمراض الشديدة وللموت بين صغار الأطفال، ولاسيّما من يقل عمره عن 12 شهراً.

ABSTRACT *Haemophilus influenzae* type b (Hib) vaccine was included in the Yemen immunization programme in 2005. This study compared the rates of very severe pneumonia and all-cause meningitis hospitalization and death, before and after introduction of conjugate Hib vaccine, and reports the results of the 2010 bacterial meningitis surveillance. A retrospective analysis was made of data collected for 2000–2010 for all children aged 2–60 months in the main children's hospital in Sana'a. Compared with the pre-Hib vaccination period, the post-Hib period showed significant and impressive reductions in the rates of hospitalization and death for all-cause meningitis. However, hospitalization and death for very severe pneumonia improved only modestly, and there was evidence of a decreasing but non-significant trend indicting that very severe pneumonia was a non-specific endpoint with multi-etiologies (both viral and bacterial). Very severe pneumonia remains the leading cause of severe morbidity and death for young children, particularly those aged < 12 months.

Hospitalisations et décès dus à une pneumonie très sévère ou à une méningite chez l'enfantau Yémen, avant et après l'introduction du vaccin *H. influenzae* de type b (Hib)

RÉSUMÉ Le vaccin contre *Haemophilus influenzae* type b (Hib) a été inclus dans le programme de vaccination du Yémen en 2005. La présente étude a comparé les taux d'hospitalisation et de décès dus à une pneumonie très sévère et à une méningite toutes causes confondues, avant et après l'introduction du vaccin Hib conjugué ; elle a par ailleurs présenté les résultats de la surveillance de la méningite bactérienne de 2010. Une analyse rétrospective a été menée afin de recueillir des données sur la période de 2000 à 2010 pour tous les enfants âgés de 2 à 60 mois dans le grand hôpital pour enfants de Sanaa. Par rapport à la période précédant la vaccination par le Hib, la période suivant cette dernière a présenté des réductions significatives et remarquables dans les taux d'hospitalisation et de décès pour méningite toutes causes confondues. Toutefois, les taux d'hospitalisation et de décès pour pneumonie très sévère n'ont diminué que modestement. Des éléments montrent certes une tendance à la baisse, mais non significative, et indiquent que la pneumonie très sévère n'était pas un critère d'évaluation spécifique lorsque les étiologies étaient multiples (à la fois virale et bactérienne). La pneumonie très sévère reste la cause principale de morbidité sévère et de décès chez le jeune enfant, notamment chez l'enfant de moins de 12 mois.

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Introduction

Haemophilus influenzae type b (Hib) is an important cause of meningitis and pneumonia-related morbidity and mortality among children under 5 years old *(1)* The World Health Organization (WHO) recommends that all countries should include Hib vaccine in their national immunization programme and, where possible, these countries should measure the impact of the vaccine on the burden of the disease *(2,3)*. Studies from many developing countries have reported significant progress towards almost total elimination of invasive Hib diseases after the introduction of vaccination *(4–6)*. In the Eastern Mediterranean Region (EMR), a study in Morocco reported that the introduction of Hib vaccine reduced Hib meningitis by 75% *(7)*. Hib vaccine was also reported to reduce non-culture-confirmed meningitis *(6,8)*, and hospital laboratory data showed a significant reduction in suspected bacterial meningitis of unknown etiology *(9,10)*.

The effect of Hib vaccine on radiologically-confirmed pneumonia in several case–control studies found reductions in reported cases of 22%–55% *(1–13)*. However, in at least one study the majority of cases were of mild to moderate severity and only 2.5% had severe lobar pneumonia. That study suggested that the effect of Hib vaccine on pneumonia severity needs investigation *(11)*. A recent systematic review of the literature on the effect of Hib vaccine on the incidence, severity, morbidity and mortality of childhood pneumonia reported a summary effect of 4% on clinical pneumonia, 6% on clinically severe pneumonia and 18% on radiologically-confirmed pneumonia *(14)*, but no summary effect on WHO-defined very severe pneumonia was reported. Cases of very severe pneumonia tend to have low blood culture results, may have both viral and bacterial etiology and some may have concomitant meningitis *(15)*.

It is not known whether the introduction of Hib vaccine reduces the prevalence of very severe pneumonia and all-cause meningitis hospitalization and related mortality, and whether it may be used as a proxy for Hib vaccine effectiveness in resource-poor health settings, where laboratory services may be unreliable and suboptimal and where most affected children may have attended after using antibiotics for several days before hospitalization.

Yemen is a least developing country, and the only low-income country in the Arabian Peninsula. In early 2005, the GAVI Alliance supported the introduction of Hib vaccine as part of the national immunization programme, given in combination with diphtheria/polio/tetanus and hepatitis B vaccine. Three doses of the combined vaccines are given free of charge at the age of 6, 10 and 14 weeks. In early 2011, conjugate pneumococcal vaccine was included in the national immunization programme, and rotavirus vaccine was introduced in August 2012, both supported by the GAVI Alliance. The objectives of this study in Sana'a were: to compare the rates of very severe pneumonia and all-cause meningitis hospitalization and death and to compare the inpatient case fatality rate (CFR) of both, before and after introduction of conjugate Hib vaccine to the Yemen national immunization programme; and to report the results and the outcome of the 2010 bacterial meningitis surveillance in Al-Sabeen Hospital, 5 years after the introduction of Hib vaccine.

Methods

Study setting and background

The study was conducted in Al-Sabeen Hospital for Women and Children, which is the main paediatric hospital located in Sana'a, the capital of Yemen. This government-run hospital provides both primary and secondary care to the urban and rural population of Sana'a city and the surrounding areas (approximately 3 million inhabitants). The services include walk-in outpatient clinics during working days. It has a 15-bed emergency unit that provides paediatric and neonatal services 24 hours a day, supported by laboratory and radiology services. The hospital has 2 paediatric medical wards (45 beds), an infectious isolation ward (20 beds) and a paediatric surgical ward (22 beds). The coverage rate of Hib vaccine (dose 3) in the catchment areas and the national coverage rate exceeded 85% (Table 1).

Case management

Children aged 1 months to 5 years who attend the emergency unit with clinically very severe pneumonia and those attending with clinical features of meningitis are usually assessed by the on-duty paediatrician. An intravenous line is usually established and blood is usually collected for full blood count, C-reactive protein and blood smears for malaria. Chest X-ray for very severe pneumonia is also done routinely. For children with suspected meningitis, after obtaining parents' verbal consent, lumbar puncture (if not contraindicated) is usually performed to examine the CSF. CSF samples are usually sent for cell count and differential, protein and glucose. Gram stain and CSF culture is usually done in the hospital when reagents and facilities are available or samples are immediately sent to private laboratories adjacent to the hospital when facilities are not available. If parents are unable to pay for these private services, Gram stain and CSF culture are usually not done. In recent years, with WHO Regional Office for the Eastern Mediterranean (EMRO) technical and financial support, almost all CSF samples have been investigated in the hospital laboratory. However, in 2010, only 48% and 65% of samples were Gram stained or cultured respectively (see data in the Results) indicating

Table 1 Vaccine coverage rate of dose 3 of conjugate *Haemophilus influenzae* type b (Hib) vaccination among children aged < 12 months in Sana'a city and rural Sana'a and the estimated national coverage rate 2006–2010

Area/variable	2006	2007	2008	2009	2010
Sana'a city[a]					
Vaccinated population (no.)	50 088	55 178	57 343	59 892	66 107
Target population (no.)	55 869	59 529	62 833	66 231	70 001
Coverage rate (%)	90	93	91	90	94
Rural Sana'a[a]					
Vaccinated population (no.)	24 800	27 336	28 086	27 009	28 806
Target population (no.)	28 169	29 851	30 835	31 602	32 126
Coverage rate (%)	88	92	91	85	90
Estimated national coverage[b] ***(%)***	85	87	87	86	87

[a]*Source: Annual statistics reports 2006–10, Ministry of Public Health and Population, Yemen.*
[b]*Source: Yemen. Estimates of national immunization coverage: 2010 revision (30).*

that these services are still suboptimal. Cases with very severe pneumonia are usually started with intravenous ampicillin and gentamicin, with oxygen supplementation via nasal catheter at a rate of 2 L/min. Cases with suspected meningitis are usually started on intravenous ampicillin and a 3rd-generation cephalosporin.

Bacterial meningitis surveillance

Since 2006 Al-Sabeen Hospital has been a major site of the bacterial meningitis surveillance network in Yemen, with technical and financial support from EMRO. The hospital laboratory service, however, is suboptimal because cerebrospinal fluid (CSF) results only occasionally report the results of Gram stain of organisms if regents are available, and culture is sometimes not done. Latex agglutination to detect bacterial antigen is not available, and cultures, if performed, are usually reported to have no growth. Most children with very severe pneumonia or suspected meningitis have usually been on oral or parenteral antibiotics for several days before attending the emergency unit.

Study design

This was an observational, retrospective analysis of data collected over an 11-year period (2000–2010) and of the 2010 bacterial meningitis surveillance data collected in special forms designed and supplied by EMRO.

Out of a total of 21 701 children who attended the outpatient clinics in 2010, 5164 attended the paediatric emergency unit and were the basis of the main study, and 305 children aged 2–60 months with suspected bacterial meningitis were included in the active surveillance reported here.

Data collection

Data collection at the hospital

Information recorded for each hospitalized patient at Al-Sabeen Hospital include the date of admission, age and sex of the child and inpatient diagnoses recorded in the admission log book. The death log book records the name, age, sex of the child and cause and date of death, and are signed by both the attending paediatrician and nurse. At the end of every calendar year, summary data on all children hospitalized and total deaths for each inpatient paediatric ward are obtained from the records and statistics unit. Information on the causes of hospitalization and death by age group (< 12 months, 12 months–5 years and > 5 years) and the male:female proportions of each age group are obtained from the admission, discharge and death log books of each paediatric ward. Data are collected using proforma datasheets and then entered using Microsoft *Excel* spreadsheets.

Definitions

The clinical definition of very severe pneumonia used at this hospital is cough, rapid breathing and lower chest in-drawing and at least one of the following danger signs: clinical cyanosis, unable to breastfeed or drink, lethargy or not alert. The clinical definition of meningitis is fever of sudden onset with one or more one of the following relevant signs: convulsions, neck stiffness, bulging anterior fontanel in children aged < 12 months, poor sucking, altered consciousness, irritability, toxic appearance and/or purpuric rash.

Pre-/post-Hib vaccination study

For this study, data of the total children aged 2–60 months who were hospitalized and died with WHO-defined very severe pneumonia and all-cause meningitis were included. We stratified the data according to age group and subgroups (< 12 months and 12–60 months), and sex (male and female) for each year. Data for children hospitalized with severe gastroenteritis and dehydration were also included in the study analysis as a control group. Patients were divided into 2 groups related to the year of Hib vaccine introduction (2005): the pre-Hib vaccine period (2000–2004) and the post-Hib vaccine period (2006–2010). The year of Hib vaccine introduction, i.e. the transitional year, was excluded.

Bacterial meningitis surveillance

For the 2010 bacterial meningitis surveillance, the data was entered in *Excel* spreadsheets. Information for each child with suspected clinical meningitis included the child's code number (without names), age (months), sex, vaccination status (yes, no or unknown) and treatments (oral or parenteral antibiotic) given prior to hospitalization. CSF specimens that were analysed and results that included cell count, protein, glucose, Gram stain and culture were recorded. Based on the recent WHO recommended surveillance standard for case identification of bacterial meningitis *(16)*, we defined a child to have probable bacterial meningitis if the CSF was purulent (cloudy and/or cell count ≥ 100/mm^3), and to have presumptive bacterial meningitis if the CSF was Gram-stain positive. Gram-stained positive results can rapidly provide evidence of bacterial meningitis even if culture fails *(16)*. No latex agglutination tests were available. The outcome of a child in the surveillance was defined as alive and well on discharge or treatment failure (death or developed neurological complication).

Ethical considerations

Because the data were obtained retrospectively, no names were recorded, none of the parents were interviewed and none of the children were followed up, and we were therefore advised that ethical approval was not needed for this study. However, approval to conduct this study was obtained from the hospital director, and the head of the academic unit of Al-Sabeen Hospital.

Data management and statistical analysis

Summary data of each calendar year (2000–2010) were imported into *SPSS* software, version 11.5. Variables created include counts of total number of hospitalizations, number of cases and rates of very severe pneumonia, all-cause meningitis and diarrhoea-related hospitalization and death. Variables for the proportions by sex and 2–60 months age group (and < 12 and ≥ 12 months subgroups) for both hospitalization and the outcome (alive on discharge or dead) were also analysed. No etiological diagnosis was available in the hospital records. We used Mann–Whitney non-parametric test to compare proportions in the 2 periods (pre- and post-Hib). We measured and compared the median and interquartile range (IQR). We calculated the percentage of median difference with 95% confidence interval (CI) between the 2 periods. We also measured and compared inpatient CFR for each age-related subgroup hospitalized before and after Hib vaccine introduction. For this analysis we used simple binary logistic regression with logit link function. The sum of each subgroup and the proportion who died (case fatality) was the binary variable (event: death). In the model we included the pre- and post-Hib period variable which was also included as a predictor factor.

We also conducted descriptive analysis of the bacterial meningitis surveillance data for 2010. Using logistic regression controlling for age and sex we compared the unvaccinated with those vaccinated in terms of 2 main outcomes: development of purulent CSF (probable bacterial meningitis) and treatment outcome on discharge: alive and well, or treatment failure (death and or neurological complications). The statistical package calculated the odds ratio (OR), 95% CI and *P*-value.

For all the statistical analysis, the significant level was set at ≤ 0.05. Analysis was performed using *Minitab* software, version 13.2.

Results

Rate of hospitalization in the pre- and post-Hib periods

Between 2000 and 2010 inclusive, 37 323 children aged 2–60 months were hospitalized. WHO-defined very severe pneumonia, all-cause meningitis and diarrhoea-related hospitalization accounted for 10 745 (28.8%), 2526 (6.8%) and 6523 (17.5%) cases respectively. The proportion of cases for each disease who were < 12 months old were 75%, 74% and 74% respectively. Of the total 1652 deaths, the number of very severe pneumonia, meningitis and diarrhoea-related deaths were 271 (16.4%), 181 (11.0%) and 273 (16.5%) respectively.

Among those aged 2–60 months, the post-Hib period (2006–2010) saw statistically significant median reductions compared with the pre-Hib period (2000–2004) in the rate of hospitalization for very severe pneumonia [23% (95% CI: 16% to 61%] (*P* = 0.0122) and meningitis [34% (95% CI: 12% to 49%] (*P* = 0.0283), while for diarrhoea hospitalization the difference was not significant [26% (95% CI: –16% to 73%]. Among the < 12 months and ≥ 12 months subgroups the median reductions in hospitalization for very severe pneumonia were statistically non-significant [9% (95% CI: –2.2% to 69%] and significant [59% (95% CI: 18% to 68%] respectively; and for meningitis the reductions were significant [33% (95% CI: 0% to 48%] and non-significant [34% (95% CI: –68% to 53%] respectively for the same age groups. In contrast, the median reductions in diarrhoea-related death were non-significant for both age subgroups [17% (95% CI: –29% to 75%) and 48% (95% CI: –64% to 68%) respectively] (Table 2).

Rate of inpatient death in the pre- and post-Hib periods

For the 2–60 months age group the rate of very severe pneumonia death showed a median reduction of 60% (95% CI: –36% to 71%) in the post-Hib period, a modest reduction but not statistically significant. The all-cause meningitis death rate was significantly reduced with a median reduction of 69% (95%

Table 2 Cases of very severe pneumonia, all-cause meningitis and dehydrating diarrhoea hospitalization and death: estimation of median reduction in the period after introduction of *Haemophilus influenzae* type b (Hib) vaccine (2006–2010) compared with the pre-Hib period (2000–2004)

Variable	Pre-Hib period		Post-Hib period		Post-Hib versus pre-Hib periods		
	Total cases	Median (IQR)	Total cases	Median (IQR)	Median reduction (95% CI)	*P*-value	Median reduction (95% CI)
	No.	No.	No.	No.	No.		%
Very severe pneumonia hospitalizations							
All	5451	1088 (1060–1121)	3832	836 (618–880)	–252 (–657 to –196)	0.01	23 (16 to 61)
Age < 12 months	3867	741 (727–837)	3119	678 (478–743)	–63 (–452 to 63)	0.21	9 (–2 to 69)
Age ≥ 12 months	1584	347 (242–377)	713	142 (129–157)	–203 (–254 to –31)	0.01	59 (18 to 68)
Males	3684	752 (708–758)	2700	594 (423–630)	–142 (–474 to –82)	0.01	21 (8 to 63)
Females	1767	347 (337–374)	1132	236 (192–256)	–111 (–104 to –77)	0.01	32 (20 to 56)
Very severe pneumonia deaths							
All	171	47 (14–49)	76	19 (10–19)	–28 (–42 to 6)	0.35	60 (–36 to 71)
Age < 12 months	136	37 (12–38)	73	16 (10–19)	–19 (–32 to 6)	0.40	57 (–23 to 62)
Age ≥ 12 months	35	9 (2–11)	3	0 (0–1.5)	–8 (–11 to –1)	0.03	89 (–200 to 100)
Males	112	30 (9–32)	43	10 (6–11)	–20 (–28 to 2)	0.21	67 (0 to 75)
Females	59	15 (5–17)	33	7 (4–9)	–7 (–14 to 5)	0.25	53 (–125 to 73)
Meningitis hospitalizations							
All	1336	272 (232–300)	944	179 (158–224)	–77 (–135 to –15)	0.03	34 (12 to 49)
Age < 12 months	1010	209 (175–226)	686	124 (114–168)	–60 (–114 to –14)	0.03	33 (0 to 48)
Age ≥ 12 months	326	72 (42–85)	258	52 (40–63)	–14 (–42 to 21)	0.30	34 (–68 to 53)
Males	864	181 (158–183)	665	131 (115–152)	–36 (–78 to –10)	0.04	15 (7 to 38)
Females	472	97 (71–117)	275	48 (43–72)	–43 (–83 to –5)	0.04	42 (5 to 65)
Meningitis deaths							
All	128	27 (20–31)	37	8 (5–10)	–19 (–26 to –8)	0.01	69 (50 to 87)
Age < 12 months	90	18 (15–22)	35	7 (5–9)	–11 (–16 to –5)	0.01	61 (33 to 76)
Age ≥ 12 months	38	7 (5–11)	2	0 (0–1)	–7 (–13 to –4)	0.01	100 (60 to 100)
Males	72	12 (11–20)	20	3 (2.5–6)	–9 (–20 to –5)	0.01	75 (50 to 82)
Females	56	11 (8–15)	17	3 (2–5)	–8 (–15 to –3)	0.02	67 (45 to 93)
Diarrhoea hospitalizations							
All	3407	571 (521–898)	2520	597 (361–600)	–202 (–430 to 79)	1.00	26 (–15 to 73)
Age < 12 months	2474	459 (369–639)	1900	447 (257–470)	–96 (–363 to 99)	0.68	17 (–29 to 75)
Age ≥ 12 months	933	163 (127–258)	620	135 (82–160)	–46 (–168 to 25)	0.21	48 (–64 to 68)

Table 2 Cases of very severe pneumonia, all-cause meningitis and dehydrating diarrhoea hospitalization and death: estimation of median reduction in the period after introduction of *Haemophilus influenzae* type b (Hib) vaccine (2006–2010) compared with the pre-Hib period (2000–2004) (*concluded*)

Variable	Pre-Hib period		Post-Hib period		Post-Hib versus pre-Hib periods		
	Total cases	Median (IQR)	Total cases	Median (IQR)	Median reduction (95% CI)	*P*-value	Median reduction (95% CI)
	No.	No.	No.	No.	No.		%
Diarrhoea deaths							
All	146	29 (19–39)	108	22 (15–28)	–7 (–25 to 7)	0.47	23 (–11 to 50)
Age < 12 months	112	22 (15–30)	84	17 (12–21)	–6 (–18 to 5)	0.47	22 (–14 to 50)
Age ≥ 12 months	34	7 (4–9)	24	5 (3–7)	–2 (–7 to 2)	0.40	25 (0 to 50)

IQR = interquartile range; CI = confidence interval.

CI: 50% to 87%), while diarrhoea-related death showed a non-significant median reduction of 23% (95% CI: –11% to 50%). For children aged < 12 months and 12–60 months, although the median reductions for very severe pneumonia were non-significant [57% (95% CI: –23% to 68%) and 89% (95% CI: –200% to 100%) respectively], the magnitude of the reduction was clinically important. Significant reductions in meningitis-related death rates of 61% (95% CI: 33% to 76%) and 100% (95% CI: 60% to 100%) respectively was observed. For diarrhoea-related death, the median reduction was not significant for either age subgroup [22% (95% CI: –14% to 50%) and 25% (95% CI: 0% to 50%) respectively] (Table 2).

Inpatient CFR showed statistically significant reductions in the post-Hib period for very severe pneumonia and all-cause meningitis but not for diarrhoea-related hospitalization (Table 3).

Epidemiology of bacterial meningitis in 2010

The characteristics of 305 children aged 2–60 months (62% males) with suspected bacterial meningitis recorded in the 2010 bacterial meningitis surveillance in Al-Sabeen Hospital are shown in Table 4. The vaccination status showed 66% were Hib vaccinated, 28% unvaccinated and 6% vaccination status unknown. Of the 305 cases, 83% were on antibiotics and 65% had CSF cultured. The rate of purulent CSF (probable bacterial meningitis) was 17%, almost 3 times more common in the unvaccinated compared with the vaccinated group (Table 4).

Of the 53 children with purulent CSF, 39 (74%) were aged < 12 months. Among the treatment failures (n = 12), 4 (33%) had purulent CSF compared with 49 (17.0%) of the successfully treated group (n = 239). Of the 12 treatment failures 8 (66.7%) were unvaccinated. Among the 12 failures, there were 3 (25%) deaths, while 4 (33%) developed obstructive hydrocephalus, 3 (25%) spastic cerebral palsy and 2 (17%) subdural fluid collection.

Gram staining was performed in only 147 (48%) of the collected samples of CSF, of which 40 cases (46%) were unvaccinated and 95 (47%) vaccinated. Gram-positive diplococcic pairs (*Streptococcus pneumoniae*) were reported in 11 (28%) and 10 (11%) respectively. Only 1 case of Gram-negative cocobacilli (*H. influenzae*) was recorded in the vaccinated group. There were 3 deaths (3.4%) and 5 cases (5.8%) of neurological complications among the unvaccinated children, compared with no deaths and 4 (2%) cases of with neurological complications among the vaccinated children.

Binary logistic regression analysis was done controlling for age and sex with the vaccinated group as the reference. The unvaccinated group had a statistically significant higher proportion of cases with purulent CSF (27/86, 31.4%) compared with the vaccinated children (23/201, 11.4%) (adjusted OR = 3.5; 95% CI: 1.8–6.6) (P < 0.001). Treatment failure (death/neurological complications) among the unvaccinated group (8/87, 9.2%) was also significantly higher compared with the vaccinated group (4/199, 2.0%) (adjusted OR = 3.8; 95% CI: 1.1–13.9) (P = 0.045) (Table 4).

Discussion

In this study, information on WHO-defined very severe pneumonia and all-cause meningitis-related hospitalization and death, before and after Hib vaccine introduction is reported for the first time in Yemen. The statistically significant decline in the number of hospitalizations for all-cause meningitis among children aged 2–60 months in the post-Hib period (median reduction of 34%) is strongly evidence of the impact of this intervention. The decline in meningitis-related death rates among the 2–60 months group and subgroups

Table 3 **Pre- and post-Hib *Haemophilus influenzae* type b vaccination period: case fatality rate of hospitalized children by cause and age groups**

Variable	Case fatality rate		Coefficient (SE)	OR (95% CI)	*P*-value
	No.	%			
Very severe pneumonia					
All ages					
Pre-Hib	171/5451	3.14		1	0.004
Post-Hib	76/3832	1.98	−0.47 (0.14)	0.62 (0.48 to 0.82)	
Age < 12 months					
Pre-Hib	136/3867	3.52		1	0.004
Post-Hib	73/3119	2.34	−0.42 (0.18)	0.66 (0.49 to 0.88)	
Age ≥ 12 months					
Pre-Hib	35/1584	2.21		1	0.005
Post-Hib	3/713	0.42	−1.68 (0.60)	0.19 (0.06 to 0.61)	
All-cause meningitis					
All ages					
Pre-Hib	128/1336	9.58		1	< 0.001
Post-Hib	37/944	3.92	−0.96 (0.19)	0.38 (0.26 to 0.56)	
Age < 12 months					
Pre-Hib	90/1010	8.91		1	0.004
Post-Hib	35/686	5.10	−0.60 (0.21)	0.55 (0.37 to 0.82)	
Age ≥ 12 months					
Pre-Hib	38/326	11.7		1	< 0.001
Post-Hib	2/258	0.78	−2.83 (0.73)	0.06 (0.01 to 0.25)	
All-cause dehydrating diarrhoea					
All ages					
Pre-Hib	146/3407	4.29		1	1.00
Post-Hib	108/2520	4.29	0.0001 (0.13)	1.00 (0.78 to 1.29)	
Age < 12 months					
Pre-Hib	112/2474	4.53		1	0.87
Post-Hib	84/1900	4.42	−0.03 (0.19)	0.98 (0.73 to 1.30)	
Age ≥ 12 months					
Pre-Hib	34/933	3.64		1	0.82
Post-Hib	24/620	3.87	0.06 (0.27)	1.10 (0.63 to 1.81)	

SE = standard error; IRQ = interquartile range; OR = odds ratio; CI = confidence interval.

(median reductions of 69%, 61% and 100%) is also a striking and important finding, and reflects an impressive effect of the introduction of Hib vaccine.

The impact of Hib vaccine on all-cause very severe pneumonia-related hospitalization and death showed a modest decline in our study, since very severe pneumonia is a non-specific endpoint that can be caused by multiple pathogens of bacterial or viral origin. In addition, Hib pneumonia is difficult to identify and there is no sensitive and specific test to diagnose Hib-related pneumonia death.

The significant reduction in the proportion of hospitalized cases of very severe pneumonia among those aged 2–60 months (23% median reduction) was mainly due to the statistically significant median reduction of 59% among those aged ≥ 12 months. There was no concomitant statistical significant reduction in the rate of very severe pneumonia-related death among children aged 2–60 months and/or < 12 months. However, the median reduction of 60% and 57% respectively in death was clinically important even though the 95% CI included zero. The magnitude of the impact of Hib vaccine on clinically important outcomes should be considered *(17)*.

The non-significant reduction in hospitalization among the < 12 months age group may indicate that *H. influenzae* is less likely to be the etiology pathogen among this subgroup. Al-Sabeen Hospital was one of the sites of the Severe

Table 4 Al-Sabeen Hospital bacterial meningitis surveillance data: 2010

Variable	Not vaccinated		Vaccination status N/R		Vaccinated		Total	
	(*n* = 87)		(*n* = 17)		(*n* = 201)		(*n* = 305)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Males	57	66	10	59	122	61	189	62
Females	30	34	7	41	79	39	116	38
Age group (months)								
< 12	76	87	14	82	164	82	254	83
≥ 12	11	13	3	18	37	18	51	17
Previous antibiotics								
No	5	6	0		22	11	27	9
Yes	81	93	14	82	174	87	269	88
N/R	1	1	3	18	5	2	9	3
Purulent CSF[a]								
Yes	27	31	3	18	23	11	53	17
Gram stain done								
Yes	40	46	12	71	95	47	147	48
Gram stain result								
Gram negative	29	73	11	92	83	87	123	84
Gram negative coccobacilli	0	0	0	0	1	< 1	1	< 1
Gram positive cocci pairs	11	13	1	6	10	5	22	7
CSF culture done								
Yes	53	61	13	76		66	199	65
CSF culture results				t				
Haemophilus influenzae type b	0	0	0	0	1	< 1	0	0
Streptococcus pneumoniae	0	0	0	0	1	< 1	0	0
Outcome								
Alive	79	91	17	100	197	98	293	96
Treatment failure	8	9	0	0	4	2	12	4

[a] *Cloudy cerebrospinal fluid and/or cell count ≥ 100/mm³.*
N/R = not recorded.

Pneumonia Evaluation Antimicrobial Research (SPEAR) study performed in 7 countries including Yemen. In this study, the bacterial isolates obtained from blood and lung aspirates in 110 children aged 2–59 months, *Staph. aureus* (*n* = 47) was the most common organism isolated *(18)*. Blood cultures of the very severe pneumonia cohort (*n* = 151) in the Al-Sabeen site of the SPEAR study, showed that 28 (19%) were positive for bacterial growth. Of those, *Staph. aureus* isolates were 23 (82%), of which 21 (91%) were isolated from children aged < 12 months [Banajeh S, unpublished data]. It is therefore possible that in this study very severe pneumonia-related hospitalization among this age group was most likely due to other pathogens, and *Staph. aureus* may be an important etiology. A recent study from India reported that the most common bacterial pathogen isolated from blood/pleural fluid cultures in cases of childhood pneumonia was *Staph. aureus* among children aged < 5 years *(19)*. A recent review showed that Hib vaccine was associated with a 6% significant reduction in severe pneumonia, 18% non-significant reduction in radiologically-confirmed pneumonia and a 7% non-significant reduction in pneumonia mortality *(20)*. This could explain our findings of modest reductions in very severe pneumonia-related hospitalization and death in the post-Hib period, particularly among the < 12 months subgroup. Our results concerning very severe pneumonia before and after Hib vaccine introduction are further supported in a recent analysis of data to estimate severe pneumonia-related morbidity and mortality for 192 countries including Yemen *(21)*. In that review, Rudan et al. estimated that for Yemen in 2010 cases of all-cause

severe morbidity due to acute lower respiratory infections, unadjusted and adjusted for Hib vaccine, were 137 073 and 131 540 respectively for children aged under 59 months (4% reduction), and in 2011 the number of deaths were 11 173 and 11 306 (1.2% increase) *(21)*.

Pneumococcal vaccine was introduced into the Yemen national immunization programme in early 2011. Based on a recent review, pneumococcal vaccine may result in a significant 29% reduction in radiologically-confirmed pneumonia, significant 11% reduction in severe pneumonia and non-significant 18% reduction in pneumonia mortality *(20)*. Decline in pneumonia-related severity and death due to the 2 vaccines could result in an increase of pneumonia due to *Staph. aureus*, and other non-vaccine preventable pathogens. However, vaccine interventions alone may not significantly reduce the burden of severe pneumonia morbidity and mortality at both the community and health facility level. Interventions that reduce the prevalence of major risk factors such as malnutrition, non-breastfeeding, use of solid fuels in the house and crowding at the community level *(20,21)* need consideration. Other interventions that ensure adequate oxygen supply to hospitals with pulse oximeter to detect hypoxaemia, effective and adequate antibiotic supplies and early/easy access to health facilities are also crucial. All these interventions are important to achieve a dramatic reduction in severe pneumonia morbidity and mortality *(20,21)*.

Although introduction of Hib vaccine in Kenya reduced the incidence of Hib disease by 12% from baseline *(22)*, a recent study reported inpatient pneumonia CFR trends from 9 health facilities remained unchanged before and after Hib vaccine introduction mainly due to variability of CFRs across the study sites *(23)*. However, our study showed a significant reduction in pneumonia CFRs after Hib vaccine introduction in a single health facility. It is unlikely that these reductions in very severe pneumonia and meningitis-related CFR in our study are due to improvements in the quality of the hospital care, since the rates of diarrhoea-related hospitalization and in-hospital mortality and CFR remained unchanged before and after Hib vaccine introduction.

This study had several limitations. First, the data analysis was retrospective and obtained from a single health facility. However, Al-Sabeen Hospital is the major paediatric health facility and attracts more than 75% of sick children in the catchment areas, and the data collected were large with reasonably accurate information on cause-specific hospitalization and death according to age group and sex. Hospital-based studies in developing countries have shown good agreement with community findings regarding causes of childhood deaths *(24)*, and our study data may be sufficient to reflect the disease burden at the community level.

Second, risk factors for hospitalization and inpatient death such as healthcare seeking behaviour, malnutrition and other socioeconomic risk factors were not included in the study due to lack of information. We assumed that these risk factors for severe gastroenteritis are generally similar to those for very severe pneumonia and meningitis. The lack of association between Hib vaccination and severe gastroenteritis indicates an absence of major bias. Veirum et al. reported good consistency between these settings, with risk factors having the same direction of association when comparing risk factors for mortality at both hospital and community levels *(25)*.

In countries such as Yemen with inadequate vital registration, accurate inpatient data about childhood death by cause, sex and age group could be an important tool to provide robust population cause-specific mortality fractions *(26)*. The data of Al-Sabeen Hospital bacterial meningitis sentinel surveillance in 2010 showed that latex agglutination testing was not available to detect possible bacterial pathogens. CSF culture was extremely unlikely to yield bacterial growth, since 88% of the children with suspected meningitis were on antibiotics prior to hospital admission. With only 65% of the collected CSF samples cultured, 48% of CSF samples Gram stained and no available latex agglutination testing, it is clear that, despite EMRO technical and financial support, the hospital laboratory services remain suboptimal. Our findings of 1 case of *H. influenzae* identified by Gram stain compared with 22 of *Strep. pneumoniae* among 305 children aged < 5 years suggests a strong impact of the Hib vaccine in the catchment areas. Meningitis hospital data were reported to be similar in a network of hospitals and may represent that in the community *(27)*. With the extensive use of antibiotics in suspected bacterial meningitis prior to hospitalization, CSF Gram stain has been reported to be a more useful and reliable method to identify CSF pathogens with a high sensitivity and specificity (98.3% and 98.7% respectively) than CSF culture or latex agglutination testing, and should be encouraged in poor-resource settings *(28)*. Our study showed that unvaccinated children are more likely to have purulent CSF, and more likely to die or develop permanent neurological complications.

We presume that the rates of viral meningitis hospitalization would remain stable in the pre- and post-Hib periods and in the 2010 bacterial surveillance and therefore could not have affected our findings. Lewis et al. reported that the proportion of patients with purulent CSF dropped from 18% in 2001–2002 to 8% in the 4th post-Hib vaccine year, and that during the same period the number of non-purulent cases remained constant

(6). A recent 7-year period study in United States children's hospitals reported that the viral hospitalization rate declined minimally from 94% in 2005 to 91% in 2011 *(29)*.

With the introduction in Yemen of pneumococcal vaccine in 2011, our study may provide important baseline data that may help in assessing the impact of the newly introduced vaccine. However, this needs an efficient surveillance system that includes more training on Gram staining and availability of latex agglutination and real-time polymerase chain reaction testing.

Conclusion

This study showed that in comparison with the pre-Hib period, the rates of all-cause meningitis hospitalization and death were significantly reduced in the post-Hib period. However, the rates of very severe pneumonia-related hospitalization and death were only modestly reduced, indicating that pneumonia is still the leading cause of severe morbidity and death for young children, particularly those under 12 months.

We also observed a significant reduction in CFR for all-cause meningitis and very severe pneumonia but not for gastroenteritis. In 2010, active bacterial meningitis surveillance recorded 22 cases with *Strep. pneumoniae* identified by Gram stain, which were equally distributed among vaccinated and unvaccinated children. Only 1 case with *H. influenzae* was identified. Compared with the vaccinated children, unvaccinated children with suspected meningitis were 3.5 times more likely to have purulent CSF, and almost 4 times more likely to be treatment failures (death or permanent neurological complications).

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