

Sentinel surveillance of pediatric bacterial meningitis in three Hospitals, Ethiopia

Meseret Asefa¹, Negga Asamene¹, Surafel Fentaw¹, Rajiha Abubekure¹, Abyot Bekele¹, Amete Mehret¹, Mulushewa Gebr-Egziabehair¹, Yibraleem Teklemariam¹, Alemayehu Tadese¹, kideest Alemayehu¹, Workabeba Abebe⁴, Sintayehu Abate¹, Haron Kasahun², Aysheshem Ademe², Goitom Gebr-Egziabehair³, Mehret Kokebe⁵, Genet Getnet⁶, Zegeye Hailemariam¹, Workabeba Abebe⁴, Kassie Molla⁵, Ayelegn Derbe⁶, Genet Molla⁴, Abebe Aseffa, Adugna Woyessa¹ and Eyasu Tigabu¹

¹Ethiopian Public Health Institute, Addis Ababa, Ethiopia

²World Health Organization country office, Addis Ababa, Ethiopia

³World Health Organization African regional office

⁴Tikure Anbessa Specialized Hospital, Addis Ababa, Ethiopia

⁵Gondar University Hospital, Addis Ababa, Ethiopia

⁶Yekatit12 Hospital, Addis Ababa, Ethiopia

Abstract

Introduction: Acute Bacterial meningitis (ABM) is one of childhood diseases with high fatality rate and sequelae. Globally, 1.2 million people are affected each year. Sub-Saharan African countries share the highest burden of the disease.

Objective: To estimate the disease burden, impact of vaccination & to identify circulating serotypes.

Materials and methods: This is a cross-sectional study of the period from January, 2002 to December 2015. The sources of data presented in this study were obtained from pediatric bacterial meningitis sentinel surveillance sites. All acute bacterial meningitis cases that meet the standard criteria of WHO case definitions were included in this study (WHO IB-VPD case definition).

Result: A total of 8,274, suspected meningitis cases of acute bacterial meningitis were enrolled from sentinel hospitals. Pathogens were identified in 724 (8.8 %) of the patients. More than 90% of the disease was caused by vaccine-preventable bacterias with *S. pneumoniae* being the leading cause 46.9% (n=307) followed by *H. influenzae* 31.7% (n=207) and *N. meningitides* 21.4 % (n=140). The prevalence of acute bacterial meningitis declined from 16.4 % to 2.9% (OR; 0.153, 95% CL; 0.12-0.195) with in the years (2007-2014) following Hib and PCV conjugate vaccines intervention.

Conclusion: Although this study involves 10 years of data from three sentinel Hospital sites, we have found a statistically significant reduction in the occurrence of acute bacterial meningitis following vaccine intervention. Therefore, we recommend strengthening child vaccination programs and expansion of surveillance sites to include other geographic areas.

Keywords: Acute bacterial meningitis, pediatric, Hib, PCV, Ethiopia

Introduction

Acute bacterial meningitis (ABM) is the most prevalent and potentially life-threatening type of bacterial meningitis. ABM causes the highest case and death in younger children and the elderly. The burden of the disease differs from region to region. Especially, the impact is greater in low resource countries (Matthijset et al. 2010). Globally, it is estimated that bacterial meningitis affects about 1.2 million people each year in which sub-Saharan Africa has the greatest disease burden compared to other regions (Matthijset at 2010, Dominique et al. 2012).

In 2001, the World Health Organization (WHO) and global immunization partners launched Pediatric Bacterial Meningitis Sentinel Surveillance Network (PBMSN) in different regions; to obtain high-quality data (CDC 2009). To overcome the public health problem of ABM, conjugate vaccines against ABM were introduced in many countries. A year later, the Ethiopian Minister of health decided to join the

network of pediatric bacterial meningitis (PBM) surveillance and identify Tikur Anbessa Specialized Hospital for implementation. Later on, Yekatit 12 and Gondar teaching hospitals joined the surveillance network in 2008. After five years of PBM sentinel surveillance implementation, Ethiopia introduced Hib and Pneumococcal conjugate vaccines in 2007 and 2011, respectively. However, studies in other African countries indicate that ABM still represents a significant cause of childhood morbidity and mortality. The disease cause high fatality rate (31.3%) and neurological complication (50%) with one in five survivors left with sequelae (Dominique et al, 2012, Aquino Albino et al, 2015, Heikki Peltola et al, 2001). In Ethiopia, there are limited studies that document ABM in children. The existing reports indicate that the burden of pediatric bacterial meningitis is commonly caused by *Haemophilus influenzae* (Hib), *S. pneumoniae* (Spn) and *Neisseria meningitides* (Genet and Esscher 1984;

Hailu and Muhe 2001; Ringertz 1993; Gedlu and Rahlenbeck 1995; Muhe and Klugman 1999; Wude et al. 2016). Ethiopia experienced a series of meningitis epidemics that caused thousands of cases and deaths (Estifanos, 1981). However, data on the impact of vaccination against meningitis, circulating serotypes causing specific epidemics and the overall disease burden is limited. Therefore, this study aimed to determine the disease burden, impact of vaccination & bacterial serotypes in children in three Pediatrics Bacterial Meningitis (PBM) sentinel surveillance sites.

Materials and methods

Data was generated from the sentinel surveillance sites for pediatric bacterial meningitis that exists in three hospitals. The surveillance is coordinated by Ethiopian Public Health Institute (EPHI) Clinical Bacteriology and Mycology National Reference Laboratory in collaboration with the WHO country and African region. The selection of these sentinel sites were performed based on important standard criteria related to capacity to serve a large population, availabilities of diagnostic facilities, the capacity to perform Lumbar Puncture(LP), case confirmation, willingness to join the surveillance, skilled professional staff and sustained provision of supply required for the surveillance system. Two of these sites are located in Addis Ababa city; TikurAnbessa Specialized Hospital (TASH) and Yekatit12 Hospital (Y12H) while the third site is Gondar University Teaching and Referral Hospital (GUTRH).

This is a cross-sectional study of the period from January 2002 to December 2015. The sources of data presented in this study were obtained from PBM sentinel surveillance sites. All ABM cases that meet the standard criteria of WHO case definitions were included in this study (WHO IB-VPD case definition).

Sample collection and process

Cerebro-Spinal Fluid Collection: Two sterile tubes were used to collect on average 2ml of Cerebrospinal fluid (CSF) sample in each tube from the patient. Immediately, after the CSF appearance examination performed by a responsible pediatrician, the samples with investigation form were sent to a laboratory for microbiological and other analysis. Besides, data on clinical, demographic, vaccination status, and therapeutic history of patients were collected using standard WHO PBM case investigation form.

Laboratory procedure and analysis: CSF in the first tube was used to measure glucose and protein levels. From the second tube, aliquot was taken for PCR run and cell count. Following CSF centrifugation, the

sediment was used for gram staining, and bacterial culture, while the supernatants were stored for latex agglutination. For probable meningitis positive samples, CSF appearance, gram stain reaction, white cell count, glucose and protein level were considered. Pathogen detection and characterization of the main causes were confirmed by culture, real-time polymerase chain reaction (RT-PCR), and serological test (Binex and Latex agglutination). Ten percent of collected CSF Samples were analyzed by the PCR technique for monitoring circulating bacteria serotypes and external quality control.

Sheep blood and chocolate agar (Oxoid, BE) were used for bacterial culture as recommended in the 2nd edition of the WHO manual (WHO/IVB.11.09). Multiplex real-time PCR assay targeting genes specific to *H. influenzae*, (*hpd*), *S. pneumonia*, (*LytA*), and *N. meningitides*, (center) was done, DNA extraction method was followed as manufacturer instruction (Quagen kit). Negative and positive controls were used in duplicate with each batch of analysis. PCR-grade water was added to the reaction mix in place of DNA template as a negative control and standard strains of *H. influenza* (ATTC 49247), *S. pneumonia* (ATTC 49619), and *N. meningitides* (ATTC 13077), were used for positive controls. PCR result interpretation was according to amplification cycle threshold (Ct): a value less than or equal to 35Ct considered as positive for ABM; Ct Value range between 36-40, was repeated for ABM investigation and then if the Ct value is equal or less than to 35, it was concluded as positive, whereas value greater than 35 is reported as negative for ABM. For CSF with transport media, Ct value <40 is considered positive for the organism detected per National Institute Communicable Disease protocol (NICD).

Statistical analysis: Data were entered into Epi Info version 3.5.4, then exported and cleaned by excel sheet and analyzed using SPSS statistical software version 21.0 (IBM Armonk, NY). Categorical variables were reported as proportion and were compared using the Chi-square test. A binary logistic regression model was used to determine the risk factors associated with ABM. Risk factors were included in the final model (adjusted) if the initial p-value in bivariate analysis was less than 0.05. Stepwise model was used to select variables for the final adjusted multivariate model. Variables with a p-value less than 0.05 on multivariate analysis were considered as statistically significant association. Odds ratios (OR) and 95% confidence interval (95% CI) were used.

Ethical Consideration: This study obtained ethical approval from the Scientific Ethical and Review Committee Office of the Ethiopian Public Health

Institute. Patient information confidentiality and privacy was protected using code number and the hard copy records were only accessible to researchers.

Results

Characteristics of study participant and Setting: A total of 8,274 suspected acute bacterial meningitis

were reported from three sentinel surveillance hospitals from 2002-2015. Of these patients enrolled, 57.5% were males and the mean age was 14 months. More than half (57.3%, n=4742) of study participants were enrolled by TASH, then followed by Y12H that enrolled above a quarter (25.9%, n= 2141) and the rest was enrolled by GUTRH (16.8%, n=1391) (Figure 1).

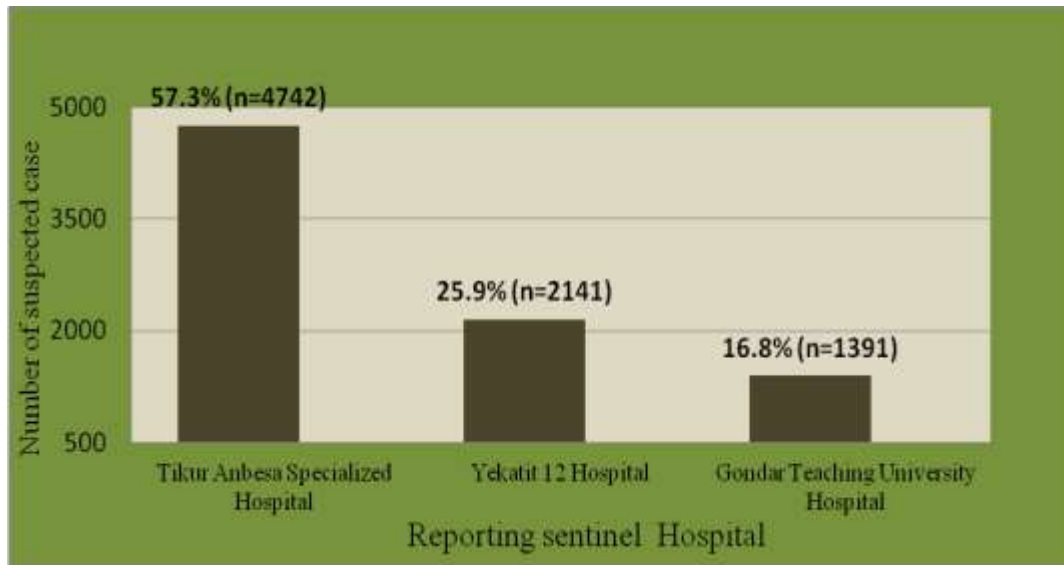


Figure 1: Suspected Meningitis Case Enrollment per sentinel surveillance sites, Ethiopia, (2002- 2015), 2016

Annual distributions of reported cases were found to be highest during 2012 and 2013 (Figure 2). Suspected meningitis increment begins in all sentinel sites in January and reaches to the peak in March and June in

both Addis Ababa and Gondar sentinel sites (data not shown). The highest confirmed meningitis cases were detected in January all over the years.

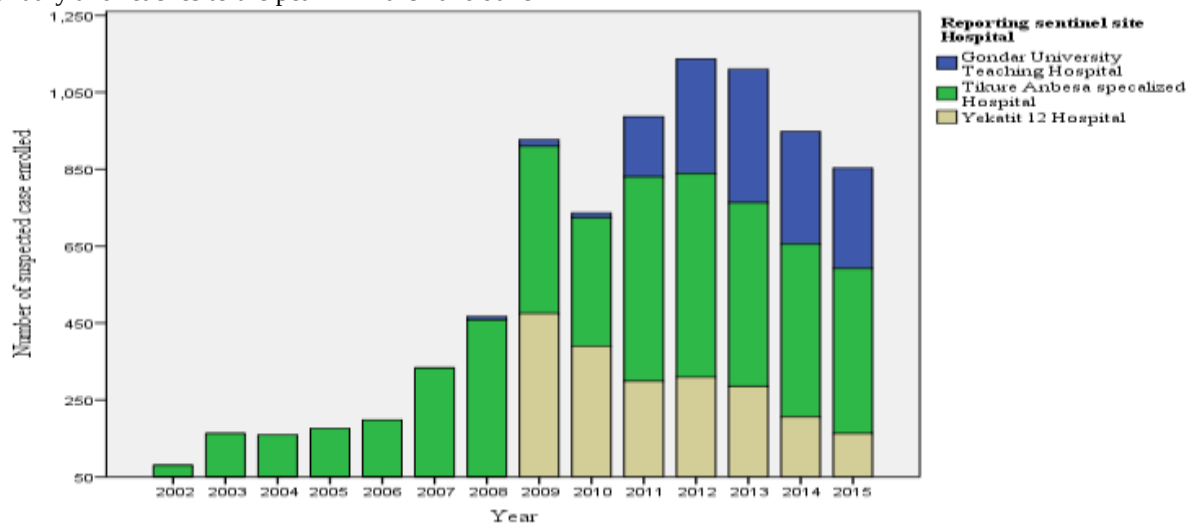


Figure 2: Suspected Meningitis Case Enrolled per year and study sites, Ethiopia, 2016

Laboratory Results: Among all CSF specimens (8,274) received at microbiology laboratory, 98.8% (n=8181) of them were analyzed. Bacterial pathogens were detected in 724 samples (8.8%). Among identified pathogens, 90.3% (n=654 of 724) of them

were vaccine preventable bacteria that are known to cause ABM; *S. pneumoniae* (Spn) 46.9% (n=307), *H.influenzae* (Hib) 31.7 % (207) and *N. meningitides* (Nm) 21.4% (n=140).

Of the 654 invasive bacteria, 61.6% (n=403) were detected by Culture, 19.4% (n=127) by PCR, 10.7% (n=70) by Latex agglutination, 6.6% (n=43) by gram stain reaction and 3.8% (n=25) by Binax. Confirmed meningitis causing ABM showed variation over the years and months using culture test as indicated in Figure 3. Before 2007, the prevalence of Hib was on the rise, however, the years onwards confirmed cases of Hib started to decline while *S.*

pneumoniae increased (Figure 3). After 2011, a decrease in confirmed pneumococcal meningitis cases was witnessed. Among the circulating serotypes of *H. influenzae*, type b was 98.1% while, type a and c account 1.9%. Serotype analysis for *S. pneumoniae* indicated nine different vaccine types and meningococcal meningitides groups A, B, C, and W135 were identified.

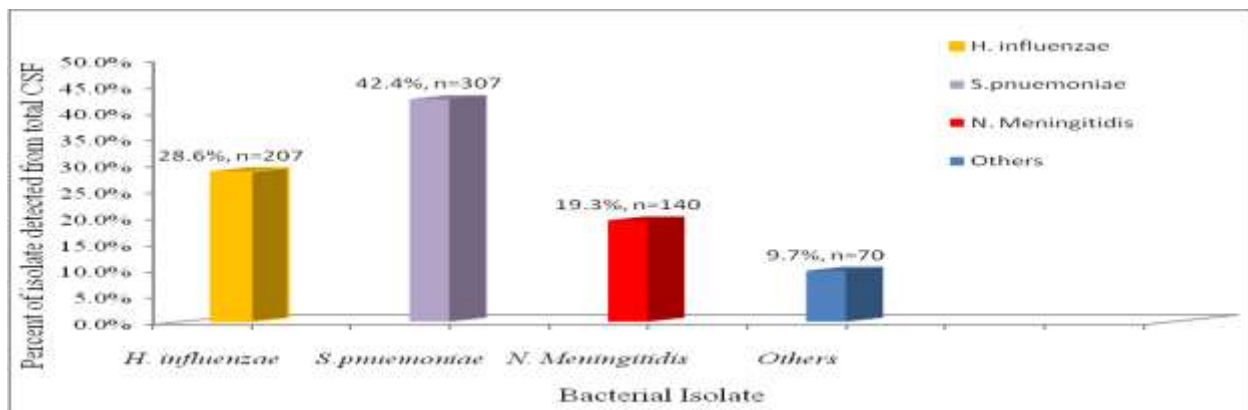


Figure 3: Number of Identified Bacterial pathogens in Children Age less than Five years old, Ethiopia 2015

Distribution of Confirmed ABM in Age and Sex:

Based on the result obtained by culture, ABM confirmation in age between 24-59 months was 7.4% (n=95 of 1278), followed by age group between 12-23 months 7.1% (n=68 of 953), and 1-11 months 5.8% (n=263 of 4055). Pneumococcal was the only organism detected in children less than one month. It was also the leading bacterial pathogen both in age group 1-11 & 12-23 months (data not shown). The prevalence of ABM in female was 4.3% (n=160 of 3685) and in male 5.3% (n= 243 of 4589).

Impact of vaccination: The prevalence of ABM before to Hib vaccine intervention was 16.4 % (n=127

of N=776) while decrease to 2.9% (n=173 of N=5964) after the intervention. It is better to say before intervention the outcomes is 80% more likely as indicated in table 1 (OR=0.195 at 95% CI (0.165, 0.23). During this study period (2002-2015), 66 patient deaths were recorded and males were highly affected group than females. The proportion of death in infant were higher (75.8 % (n=50 of N=66). Among this, 18.2% (n=12) of death was linked to the three bacterial isolates namely, Hib 16.7 % (n=2), Spn 50.0 % (n=6) and Nm 33.3% (n=4).

Table 1: Odds of Probable Meningitis Pre & Post Vaccine Exposure in Children, Ethiopia, 2015

Hib conjugate vaccine	Turbidity or WBC		Odd ratio	OR[at 95% CL]	P-value
	Positive	Negative			
Pre vaccination, [2002-2006]	281	776	.34(34%)	1	
Post vaccination, [2008-2015]	435	6551	.07(7%)	0.195[0.165,0.23]	0.000

Binary Logistic and Multivariate Analysis of Associated Variables with ABM:

In bivariate logistic regression analysis age categories, turbid CSF appearance, Leukocyte count per millimeter cube greater than 100 and 10-100, CSF protein greater than 100 and gram stain showed strong statistically significant association with presence of ABM. Whereas sex and glucose level were not significant. And also in multivariate logistic regression analysis patient sample with turbid CSF appearance OR 42.1

(CL at 95% [17.9, 98.5) and Leukocyte count per millimeter cube greater than 100 and 10-100 OR 64.6 (CL at 95% (28.4, 146.7) 4.4 (2.8, 7.1), respectively) were having strong significant association with ABM. Besides, CSF with protein greater than 100 OR 5.1(CL at 95% (2.7, 9.5) and gram stain reactive OR 3.6 (CL at 95% (2.5, 5.1)) were also statistically significant associated factors, whereas all age categories were not statistically significant associated factors (Table 2).

Table 2: Predicting Associated Risk Factors of Acute Bacterial Meningitis in children less than five years, Ethiopia, 2016

Risk factors	ABM(N=640)	CSF Negative (N=7540)	Bivariate Unadjusted; at 95%,CL; OR(Lower, Upper)	Multivariate Adjusted at 95%,CL; OR (Lower, Upper)
ge category, months				
<1	77(12.0%)	1522(20.2%)	1	
1-11	335(52.3%)	3711(49.2%)	1.8(1.4, 2.3)	1.2 (0.87,1.6)
12-23	96(15.0%)	852(11.3%)	1.2(1.6,3.0)	1.1 (0.67, 1.6)
24-59	132(20.6%)	1455(19.3%)	2.3(1.7, 3.1)	1.2 (0.76, 1.7)
CSF appearance				
Clear	253(39.5%)	5915(78.4%)	1	
Turbid	375(58.6%)	315(4.2%)	27.8(22.9, 33.9)	42.1(17.9, 98.5)
Others	8(1.3%)	454(6.0%)	.412(0.202, .838)	.54(.26, 1.1)
Missing	4(0.6%)	856(11.4%)		
Leukocyte count, cell/millimeter cube				
<10	197(30.8%)	4407(58.5%)	1	
10-100	39(6.1%)	205(3.2%)	4.3(2.9, 6.2)	4.4(2.8, 7.1)
>100	349(54.5%)	210(2.8%)	37.2(29.7, 45.5)	64.6(28.4, 146.7)
Missing	55(8.6%)	2718(36%)		
CSF protein				
Negative	57(8.9%)	1311(17.4%)	1	
Positive	327(51.1%)	107(1.4%)	70.3(49.1, 99.1)	
Gram stain reaction				
Gram-	227(35.5%)	5705(75.7%)		5.1(2.7, 9.5)
Gram+	393(61.4%)	324(4.3%)	30.5(25.0, 37.2)	3.6(2.5, 5.1)
Missing	20(3.1%)	1511(20.0%)		

Discussion

One of our major finding was the burden of vaccine-preventable bacteria that cause ABM has been decreasing from 16.4% in pre-vaccine administration (2002-2006) into 2.3% (2007-2014). Very close to reports in other studies, above ninety percent (90.0%) were vaccine-preventable bacterial diseases (Matthijs et al. 2010; Dominique et al. 2012; CDC 2009; Aquino Albino et al. 2015; HeikkiPeltola et al. 200; Gedlu and Rahlenbeck 1995). However, other bacteria like group B streptococci in neonate and gram-negative bacteria such as *Acinetobacter* and *Salmonella* species were also identified.

Based on this study, our data analysis showed a reduction in ABM burden over the years. Even though, the surveillance system improved the detection capacity of sentinel site laboratories, the prevalence of ABM showed a dramatic change in reduction from 16.4 to 4.9%. Before the introduction of Hib conjugate vaccine in 2007, the prevalence of Hib was on the rise. However, after Hib vaccine started confirmed cases were declining while *S. pneumoniae* started to increase (Figure 3). Similar PBM prevalence trends were also observed in other studies conducted in Ethiopia before vaccines introduction (Genet and Esscher1984, Hailuand Muhe, 2001, Ringertz 1993). In general, the prevalence of confirmed ABM reduced by 82.3 %. Specifically, the prevalence of Hib meningitis decreased from 4.5 % to 0.6 % in TASH. Compared with the previous report (30.4%) from Gondar (Wude et al 2016), the present study showed a reduction to 1.4%. Regarding Pneumococcal meningitis, it declined by 51.2% after two years of PCV10.

Another important finding was ABM distribution in deferent age groups and sex. In this study, during the pre-vaccination period, more than half of confirmed meningitis was detected in children's age group between 01-11 months. However, following intervention, confirmed meningitis caused by Hib and Spn was less detected in this age group, which indicates the best vaccine schedule period. The above quarter of Nm (38.9%) was detected in the age group between 24-59 months in contrast, detection was very low in the age group between 1-11months (19.4%) (Katherine et al. 2009; Gijs et al. 2009; Aguilera et al. 2002). Moreover, our study analyzed the circulating bacterial serotypes. The emergence of a non-vaccine type strain over seven years was very low in Hib (2.4% n=5), whereas *S. pneumoniae* shift by more than half (54.8%) within three years which is in line with the finding of other studies (Wude et al, 2016, WHO, 2014, Katherine et al. 2009). Compared to the previous study conducted in Ethiopia (Muhe and Klugman 1999), before vaccine intervention, the frequency of serotype strains changed from 54.3% of PCV10 coverage to 33.3%, 76.1% of PCV13 coverage to 45.2% and 23.9% non-vaccine type serotype to 54.8%.

In bivariate logistic regression analysis age categories, turbid CSF appearance, Leukocyte count per millimeter cube greater than 100 and 10-100, CSF protein greater than 100 and gram stain positive for vaccine target bacteria were strongly statistically significant associated determinant factors with presence of ABM. And also in multivariate logistic regression analysis patient sample with turbid

CSF appearance OR 42.1 (CL at 95% [17.9, 98.5), Leukocyte count per millimeter cube greater than 100 and 10-100 OR 64.6 (CL at 95% (28.4, 146.7) 4.4 (2.8, 7.1), respectively), CSF protein greater than 100 OR 5.1 (CL at 95% (2.7, 9.5) and gram stain positive for vaccines target bacteria OR 3.6 (CL at 95% (2.5, 5.1)) were also strongly statistically significant associated factors with ABM, whereas age categories of patient 1-11ms, 12-23ms & 24-59ms OR 1.2 (CL at 95% [0.87, 1.6), 1.1 (0.67, 1.6, 0.76, 1.7) were not statistically significant associated factors.

Conclusions

The finding from this study showed that most of the detected bacteria causing PBM were vaccine-preventable. The decrease in the prevalence of ABM can be attributed to the vaccine intervention. There was also a shift in serotype distribution of *S. pneumoniae* and *N. meningitidis*. Therefore, it is recommended that the vaccine coverage should be strengthened. To monitor the shift in serotype replacement the surveillance system should be expanded. Moreover, the introduction of a multivalent meningococcal meningitides vaccine is also recommended.

Acknowledgements

We acknowledge Global alliance for vaccine immunization (GAVI) for funding to health system strengthening program of vaccine-preventable disease surveillance in the country. Our honors full thanks, to our collaborators from the World Health Organization country office and African region of Inter-country Support for their assistance and critical review of this manuscript. We also appreciate the technical teams at each sentinel sites for their contribution and support for the implementation of PBM surveillance.

Conflict of interest: Authors declare that they have no competing interest.

Reference

Agrawal S & Nadel S (2011). Acute bacterial meningitis in infants and children: epidemiology and management. *Paediatric Drugs*, 13(6):385–400.

Anderson E, Begg N, Crawshaw S, Hargreaves R, Howard A & Slack M (1995). Epidemiology of invasive Hib in England & Wales in the pre-vaccination era. *Epidemiology Infection* 115(1):89–100.

Arslan A (2012). Etiology of bacterial meningitis in Ethiopia, 2007 – 2011: a retrospective study. Thesis submitted as a part of the Master of Philosophy Degree in International Community Health, pp 95.

Centers for Disease Control and Prevention (2006). Vaccine preventable deaths and the global immunization vision and strategy, 2006–2015. *MMWR Morbidity and Mortality Weekly Report* pp 511–515.

Centers for Disease Control and Prevention (2009). Progress in introduction of pneumococcal conjugate vaccine worldwide, 2000–2008. *Morbidity and Mortality Weekly Report*, 57:1148–1151.

Centers for Disease Control and Prevention (2009). Sentinel Surveillance for Pediatric Bacterial Meningitis in the World Health Organization African Region. *Morbidity and Mortality Weekly Report*, 58(18):493–497.

Garcia S, Lagos R, Munoz A, Picon T, Rosa R, Alfonso A, et al. (2012). Impact of vaccination against Hib with & without a booster dose on meningitis in four South American countries. *Vaccine*, 30(2):486–92.

Gedlu E & Rahlenbeck SI (1995). Pyogenic meningitis in children in north-western Ethiopia. *Tropical Paediatric*, 15(3):243–7.

Gijs T, Berbe F, Caroline BT, Priscilla S & John J (2009). Twenty Years of Pediatric Tuberculous Meningitis: a retrospective cohort study in the western Cap of South Africa. *Pediatrics* 123; e1 doi: 10.1542/peds.2008-1353.

Hailu M & Muhe L (1984). Childhood meningitis in a tertiary hospital in Addis Ababa: clinical and epidemiological features. *Ethiopian Medical Journal*, 39(1):29–38.

Harrison LH, Trotter CL & Ramsay ME (2009). Global epidemiology of meningococcal disease. *Vaccine*, 24(27): Suppl 2:B51–63. doi: 10.1016/j.

Jams P, Sheena C & Mathurams S (2012). Hib vaccine: Review of observational data on long term vaccine impact to inform recommendations for vaccine schedules. *Johns Hopkins Bloomberg School of Public Health*, 2:3–13.

Jean F, Anne P, Christine M & Susan H (2002). Outbreak of serogroup W135 meningococcal disease after the Hajj. *Emerging Infectious Diseases*, 8(8):761–767.

Katherine L, Lara J, James P, Emily H, Maria D, Natalie M, et al. (2009). Hib and pneumococcal global burden of disease study. *Lancet*, 374:893–902.

Martin A, Hakeem T, Awine O, Ousman S, Kawsu S, David N, et al. (2008). Seasonality and outbreak of a predominant *Streptococcus pneumoniae* serotype 1 clone from The Gambia: in West Africa. *BMC Microbiology*, 8:198.

Matthijs C, Allan R & Diederik V (2010). Clinical Microbiology and Epidemiology for ABM. *Clinical Microbiology Reviews*, 23(3):467–492.

- Mude M, Tsehaynesh L, Yared M, Afework K, Workeabeba A, Beyene M, et al. (2016). Surveillance of bacterial meningitis, Ethiopia, 2012–2013. *Emerging Infectious Disease*, 22(1):75–78.
- Muhe L & Klugman K (1999). Pneumococcal and Haemophilus influenzae meningitis in children's hospital in Ethiopia. *Tropical Medicine & International Health*, 4 (6):421–7.
- Nhantumbo A, Cantarelli V, Caireao J, Munguambe A, Come C, Pinto G, et al. (2015). Frequency of Pathogenic Paediatric Bacterial Meningitis in Mozambique: The Critical Role of Multiplex Real-Time Polymerase Chain Reaction to Estimate the Burden of Disease. *PLoS One*, 10(9):e0138249.
- Peltola H (2001). Burden of meningitis and other severe bacterial infections of children in Africa: implications for prevention. *Clinical Infectious Diseases*, 32(1):64–75.
- MRingertz S, Muhe L, Krantz I, Hathaway A, Shamebo D & Freij L (1993). Prevalence of potential respiratory disease bacteria in children in Ethiopia. *Acta Pediatrics*, 82(10):843–8.
- Wenger J, Hightower A, Facklam R, Gaventa S & Broome C (1990). Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. The Bacterial Meningitis Study Group. *Journal of Infectious Disease*, 162(6):1316–23.
- Yixing L, Zundong Y, Zhujun S, Manshi L, Xiaofeng L, Hardeep S, et al. (2014). Population-based Surveillance for Bacterial Meningitis in China, during.