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Four years of case-based surveillance of meningitis following the introduction of MenAfriVac in Moissala, Chad: lessons learned

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Abstract

OBJECTIVE Case-based surveillance of bacterial meningitis in sentinel districts has been recommended after the introduction of the conjugated vaccine against *Neisseria meningitidis* serogroup A (NmA), MenAfriVac, in the African meningitis belt. Here we report data and lessons learnt from four years of surveillance in the district of Moissala, Chad.

METHODS All suspected cases of meningitis were referred free of charge to the district hospital for lumbar puncture and treatment. Cerebrospinal fluid samples were tested with Pastorex latex agglutination in Moissala, and inoculated trans-isolate media were used for culture and PCR at the national reference laboratory and/or at the Norwegian Institute of Public Health.

RESULTS From July 2012 to December 2016, 237 suspected cases of meningitis were notified, and a specimen was collected from 224. Eighty-three samples were positive for a bacterial pathogen by culture, PCR or Pastorex, including 58 cases due to *Streptococcus pneumoniae* with only 28 of 49 pneumococcal meningitis confirmed by culture or PCR correctly identified by Pastorex. Four cases of NmA were detected by Pastorex, but none were confirmed by PCR.

CONCLUSION Implementation of case-based surveillance for meningitis is feasible in Chad, but has required political and technical engagement. Given the high proportion of *S. pneumoniae* and its poor detection by Pastorex, continued use of PCR is warranted for surveillance outside of outbreaks, and efforts to accelerate the introduction of pneumococcal conjugate vaccines are needed. Introduction of MenAfriVac in routine immunisation and future availability of a pentavalent meningococcal conjugate vaccine will be key elements for the sustained reduction in meningitis outbreaks in the area.

keywords bacterial meningitis, meningococcal meningitis, pneumococcal meningitis, latex agglutination tests, Chad, surveillance

Introduction

The meningitis belt of the Sahel has seen multiple large epidemics of meningitis during the dry season for many decades [1]. Descriptions of the earliest epidemics were often incomplete and limited to numbers of suspected cases and deaths [2]. Historically, the largest outbreaks of meningitis have been caused by *Neisseria meningitidis* serogroup A (NmA), but serogroups C [3], X [4, 5] and W [6] have also caused outbreaks. Nonetheless, even in epidemic settings where one *N. meningitidis* serogroup predominates, cases of meningitis due to other meningococcal serogroups and other bacteria (particularly *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib)) continue to be reported [7].

An effective and long-lasting conjugate vaccine against NmA has been introduced progressively in the countries of the African meningitis belt since 2010 [8]. This

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conjugate vaccine has greatly reduced the numbers of cases due to NmA [9–12] and has also reduced NmA nasopharyngeal carriage to near-zero levels [13]. This conjugate vaccine may be having an important impact on the changing epidemiology of meningitis in the meningitis belt [14].

In the wake of the success of the conjugate NmA vaccine, non-A serogroups of *N. meningitidis* have become more prominent causes of epidemic meningitis, and other bacterial causes of meningitis, such as *S. pneumoniae*, have become proportionally more important in both epidemic and also non-epidemic periods [15]. The 2015 epidemic meningitis season was marked by a large outbreak of a novel strain of *N. meningitidis* serogroup C (NmC) in Nigeria and Niger with nearly 10 000 reported cases [16, 17].

In this changing era, efforts have been made to improve surveillance of meningitis across the meningitis belt [18]. The key objectives of this surveillance system include the accurate detection of epidemics, rapid laboratory confirmation and a reliable flow of information [19]. In Chad, after the introduction of the conjugate NmA vaccine in 2011, several districts were designated as pilot locations for a case-based surveillance system for meningitis. Designed to operate year-round, this case-based system is collecting clinical and demographic information on patients with meningitis, ensuring that cerebrospinal fluid (CSF) samples are sent to regional, national and international references laboratories for culture and PCR [20]. Such a system should provide further insight into the changes in bacterial meningitis epidemiology after the introduction of the conjugate NmA vaccine. The system was implemented in the Moissala district in southern Chad with the support of Médecins Sans Frontières (MSF) during the 2012 epidemic and following the introduction of MenAfriVac in this area. Here we report the results from the first four full years of case-based surveillance in the Moissala district.

Methods

Study setting

Moissala is a district of the Mandoul region in southern Chad. The climate in this region is typical of the Sahel region, with a short rainy season from June to September and a long dry season when meningitis outbreaks occur. Malaria season closely follows the rainy season, and transmission is high from July to November.

In 2012, the Moissala district had an estimated population of 251 000 and comprised 20 health zones, each containing a primary health centre and a district hospital in Moissala town. In 2014, the district was reorganised, the new sanitary district of Bouna was created and the population of Moissala district was estimated at around 220 000. The maximal distance between health centres and the district hospital is 83 km. The Mandoul region has one of the best coverages of the expanded programme of immunisation (EPI) in Chad, with an estimated coverage for the three doses of pentavalent vaccine (including *H. influenzae* type b) of 63% [21]. Pneumococcal conjugate vaccine had not been introduced in the EPI at the time of the study.

The last NmA outbreaks were declared in Moissala district in 2009, 2011 and 2012. In 2012, 334 probable cases were reported in the district, leading to an attack rate of 148 per 100 000, with a case fatality rate (CFR) of 3.4%. Of 72 cases for whom a serogroup could be identified, 51 were NmA and 21 were NmW. The district was not part of the three regions of Chad that received early mass vaccination with the NmA conjugate vaccine in 2011 [10], so the vaccine was first administered to persons aged 1–29 years in 2012 as an epidemic response. Vaccine coverage was high in the target population with an estimated 102% based on administrative data and 92% based on a survey in the district of Moissala after the mass vaccination campaign (S. Masson, unpublished report).

MSF has supported malaria case management in the paediatric unit of Moissala District Hospital (MDH) since 2010, and at the onset of the 2012 epidemic began instituting case-based surveillance of all meningitis cases in Moissala district.

Surveillance procedures

Reinforced surveillance with biological confirmation of hospitalised cases was established in response to the meningitis outbreak in 2012. The following data were collected prospectively for all suspect cases of meningitis at MDH: age, sex, residence, date of consultation or admission, history of vaccination against meningitis and outcome. In addition, the following information was collected from the individual clinical files: date of onset of symptoms, signs and clinical symptoms, treatment received and results of laboratory analyses. Data were collected by a medical doctor and entered anonymously in an Excel file.

From 1 January 2013, case-based surveillance was harmonised with national guidelines [20]. All suspected meningitis cases seen at peripheral health centres were referred to MDH. Lumbar puncture was performed systematically at the hospital, although referred patients received antibiotics in peripheral health centres prior to

transfer and lumbar puncture. Socio-demographic and clinical information, outcome and results of laboratory analyses were collected in the national individual notification form. An additional standard specimen collection and shipment form was used to collect data on clinical signs and symptoms. Both forms were then entered in an Excel file designed for the surveillance. Since 2015, the results of malaria diagnosis by smear or rapid test (SD Bioline Ag P.f. HRP2, Standard Diagnostics Inc., Korea) were also collected. A unique identifier was used to link clinical and laboratory data.

Laboratory analysis

All CSF samples were tested with the Pastorex Meningitis assay (Bio-Rad Laboratories Inc., Marne-la-Coquette, France) following the manufacturer's recommendations in the MDH laboratory. Also, from January 2013 to December 2015, two trans-isolate (TI) media were inoculated with 0.5–1 ml CSF each [22]. One TI medium was sent to the WHO Collaborating Centre for Reference and Research on Meningococci in Oslo for culture and PCR, and the other TI medium was sent to the General National Reference Hospital (GNRH) laboratory in N'Djamena for culture. In 2016, after PCR was established at GNRH by the MenAfriNet network (http://www.menafrinet.org), only one TI was prepared and sent to GNRH for both culture and PCR. From 2013, cell counts were also routinely performed on CSF samples at MDH.

Culture from TI medium was performed on blood agar and chocolate agar plates. Bacteria growing on these plates were identified using standard bacteriological procedures [23]. For *N. meningitidis* isolates, serogroups were determined by slide agglutination using A, B, C, X, Y, W antisera (Remel Inc, GA, USA).

In addition, for PCR in Oslo (2013–2015) or N'djamena (2016), DNA was purified from the supernatant of TI using QIAamp DNA mini kit (Qiagen) and analysed by real-time PCR for *N. meningitidis*, *S. pneumoniae* and Hib following standard procedures [23]. For all specimens positive by PCR for *N. meningitidis*, further characterisation was performed using *porA* and capsule gene-specific PCR [24, 25]. Proficiency testing of the PCR at GNRH was performed by the Center for Disease Control, Atlanta, in 2016.

Definitions and data analysis

In 2012, suspected cases were defined as fever with bulging fontanelle or petechiae in children <1 year and sudden onset of fever with neck stiffness or petechiae in patients >1 year. From 2013, following national guidelines, suspected cases were defined as sudden onset of fever with bulging fontanelle, neck stiffness or flaccid neck, altered consciousness, convulsion or other sign of meningeal involvement in children <1 year, and sudden onset of fever with neck stiffness, neurologic symptoms or other sign of meningeal involvement in patients >1 year. From January 2015, after discussion with WHO, the case definition for patients >1 year was restricted to those with sudden onset of fever and neck stiffness or other sign of meningeal involvement, in line with the revised guidelines [26].

Probable cases were defined as any suspected case with turbid, cloudy or purulent CSF; or with microscopic test showing Gram-negative or Gram-positive diplococci, or Gram-positive bacilli; or with leucocyte count more than 10 cells/mm^3. Confirmed cases were defined as any suspected case with the identification of a bacterial pathogen from the CSF by latex test, culture or PCR.

If different results were obtained by Pastorex and culture or PCR, the result of culture or PCR was considered the final identification. If an organism was identified by Pastorex, and culture and PCR were not performed, then the organism identified by Pastorex was considered the final identification.

Ethical considerations

All data and samples were collected as part of routine recommended clinical care and surveillance procedures in Chad. Data were anonymised prior to analysis. Authorisation for implementation of the surveillance system was obtained from the Chadian Ministry of Public Health.

Results

From 1 July 2012, to 31 December 2016, 237 suspected cases of bacterial meningitis were hospitalised at MDH, of whom 130 (54.9%) were males, with a median age of 2 years (Table 1). The median delay between symptom onset and presentation to MDH was 2 days (IQR 1–3, range 0–15), with 79% of suspected cases presenting within 72 h of symptom onset. Of the 203 cases with detailed clinical data available, 181 (89.2%) had fever on admission, 116 (57.1%) had neck stiffness, 80 (39.4%) reported headaches, 90 (44.5%) had vomiting and 109 (53.7%) had convulsions. Of the 68 infants <1 year of age with detailed clinical information available, 25 (36.8%) had bulging fontanelle.

Annual incidence rates varied from 16 to 29 suspected cases per 100 000 persons in 2013–2016. Confirmed bacterial meningitis cases were notified throughout the year,

Table 1 Characteristics of notified cases and confirmed cases of pneumococcal and meningococcal meningitis, Moissala, Chad, July 2012–December 2016

	Total notified $n = 237$	*S. pneumoniae* $n = 58$	*N. meningitidis* $n = 13$	Hib $n = 7$
Sex M, *n* (%)	130 (54.9)	27 (46.6)	9 (69.2)	5 (71.4)
Age, median (IQR)	2 (0–10)	6 (0–10)	6 (4–9)	0 (0–4)
<1 year	79 (33.3)	20 (34.5)	2 (15.4)	4 (57.1)
1–4 years	59 (24.9)	7 (12.1)	2 (15.4)	2 (28.6)
5–14 years	64 (27.0)	22 (37.9)	9 (69.2)	0 (0)
15–29 years	19 (8.0)	4 (6.9)	0 (0)	1 (14.3)
30–44 years	10 (4.2)	4 (6.9)	0 (0)	0 (0)
≥45 years	6 (2.5)	1 (1.7)	0 (0)	0 (0)
CFR	28 (11.8)	13 (22.4)	1 (7.7)	1 (14.3)

CFR, case fatality ratio; Hib, *Haemophilus influenzae* type b.

with a modest increase at the beginning of each year (Figure 1). The increase in number of suspected cases at the end of 2014 coincided with the malaria season, when strict application of the case definition led to the inclusion of possible cerebral malaria cases. This was the only year when the number of cases reported from July to December ($n = 52$) was higher than that reported in the first 6 months ($n = 22$), and higher than the 11–15 reported in that same period in the other years. Of the 48 patients with malaria diagnostic result reported in the database since 2015, 29 (60.4%) were positive for malaria by either rapid test or smear.

CSF was obtained from 224 of 237 (94.5%) patients, with seven insufficient samples to perform any microbiological test (latex, culture or PCR). Of the remaining 217, 83 (38.2%) were positive for a bacterial pathogen by culture and/or PCR, or Pastorex when culture and PCR were not performed, and therefore considered confirmed cases. The main pathogens identified were *S. pneumoniae* ($n = 58$), NmW ($n = 11$), Hib ($n = 7$),

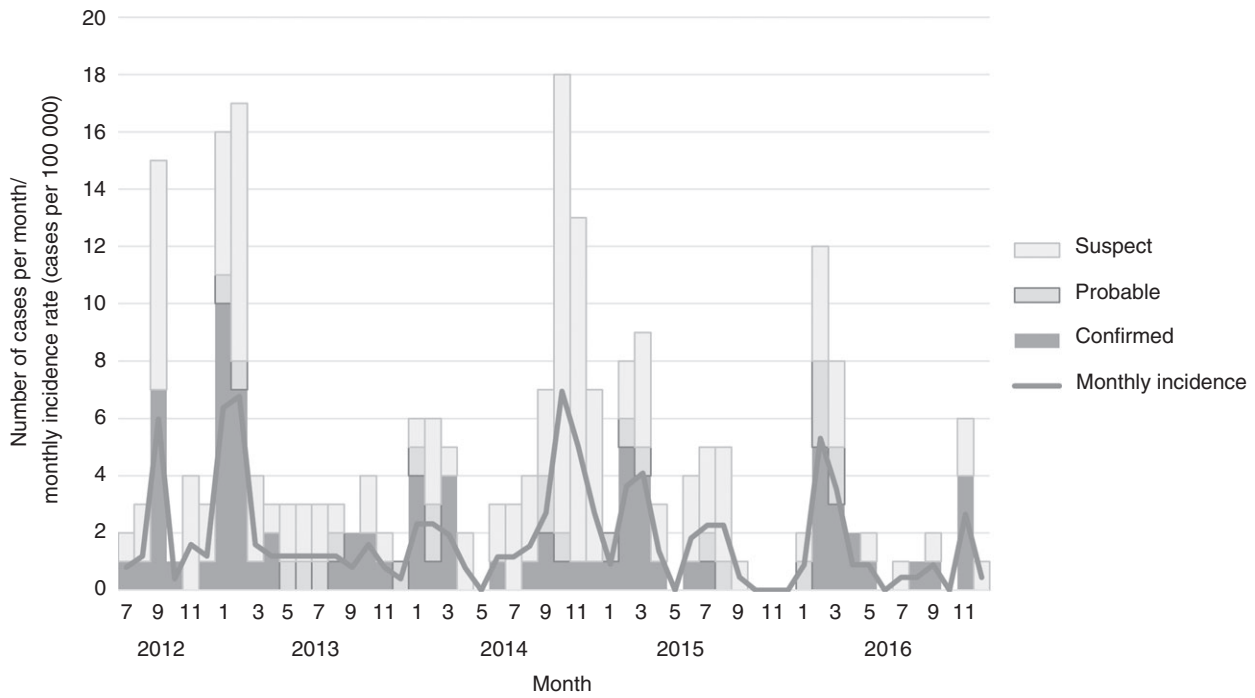

Figure 1 Weekly cases of meningitis and incidence, Moissala, Chad, July 2012–December 2016.

NmX (n = 1), NmA (n = 1), other Nm (n = 2), group B streptococcus (n = 2) and *Salmonella* spp (n = 1). In addition, 24 CSF samples were suggestive of bacterial meningitis, based on CSF aspect, cytology or Gram staining, but either negative by culture and/or PCR, or not sent for confirmatory testing, and therefore classified as probable cases (10.1% of all suspected cases). Patients with pneumococcal meningitis had a significantly higher CFR (P = 0.004). The age distribution showed that children aged <1 year and those aged 5–14 years represented the majority of cases of pneumococcal meningitis, while most of the meningococcal meningitis cases were aged 5–14 years (Table 1).

From 2012 to 2015, only 28.5% of all patients reported being vaccinated with the conjugate NmA vaccine, whereas in 2016, vaccination status was mostly reported as unknown. When considering only those in the MenAfriVac target group (i.e. aged 1–29 years in 2012) and excluding data from 2016, the proportion of vaccinated patients increased to 43.6%.

Among the 125 specimens that were tested in parallel with Pastorex on site and culture and PCR in N'Djamena and Oslo (2013–2015) or N'Djamena only (2016), Pastorex showed a relatively good correlation with culture and PCR for NmW, while the proportion of *S. pneumoniae* detected was small: only 28 of 49 (57.1%) cases of *S. pneumoniae* confirmed by culture or PCR and tested by Pastorex were correctly identified by Pastorex (Table 2). Of four NmA cases identified by Pastorex, three were tested by culture and/or PCR, of which one was identified as *S. pneumoniae* and the other two were negative. Of the 17 *S. pneumoniae* that were cultured in N'Djamena and sent to Oslo, none could be cultured in Oslo, although 15 were confirmed by PCR.

Discussion

We describe the results of a detailed case-based surveillance system for meningitis in a rural district of the African meningitis belt over four years after the introduction of the conjugate vaccine against NmA. Globally, these surveillance results were similar to those reported in other countries of the meningitis belt after the introduction of the conjugate NmA vaccine, in terms of both annual incidence of suspected meningitis cases and the distribution of pathogens outside of the 2015 NmC outbreaks [15, 27]. During the four-year surveillance period, only one possible case of NmA was detected in an unvaccinated 2-month old baby. In this case, NmA was detected only by Pastorex, which showed low positive predictive value in this context, and could be a false-positive result. This is further evidence of the impact of MenAfriVac in Chad and more generally in the meningitis belt until now [28]. However, considering the increasing number of unvaccinated children born after the mass vaccination campaign in 2012, it is crucial that the conjugated vaccine be introduced as soon as possible in the routine immunisation schedule. Among the other serogroups of *N. meningitidis*, there were only sporadic cases of NmW, and no cases of NmC, which has recently emerged in the meningitis belt as a strain with epidemic potential [17]. Although this type of sentinel surveillance is insufficient to detect all possible events following the introduction of the NmA conjugate vaccine, such as the emergence of new epidemic serogroups that are better detected by mobile investigation teams, maintaining case-by-case surveillance in some districts is important to build historical data that can be used to monitor the impact of new interventions [29]. In addition, these stable

Table 2 Identification of causative organism of bacterial meningitis by Pastorex *vs*. culture and/or PCR, Moissala, Chad, July 2012–December 2016

		Culture and/or PCR							
		NmW	Other Nm†	*S. pneumoniae*	Hib	*Salmonella* spp.	Negative	Not performed	Total
Pastorex	NmA	0	0	1	0	0	2	1	4
	NmW135/Y	6	2	0	0	0	0	5	13
	S. pneumoniae	0	0	28	2	0	3	8	41
	Hib	0	0	0	3	0	0	0	3
	Group B streptococcus	0	0	0	0	0	1	2	3
	Negative	0	1	19	2	1	86	35	144
	Indeterminate	0	0	1	0	0	0	1	2
	Not performed	0	0	1	0	0	6	20	27
	Total	6	3	50	7	1	98	72	237

Nm, *Neisseria meningitidis*; Hib, *Haemophilus influenzae* type b.
†1 NmX and 2 non-groupable Nm.

surveillance systems are beneficial for countries to build and maintain capacity in terms of surveillance and laboratory capacity and to be reactive in case some unexpected event occurs anywhere in the country.

Our results show that *S. pneumoniae* has become the leading cause of bacterial meningitis in Moissala district after introduction of MenAfriVac. Although a majority of cases were seen in the dry season typically associated with meningitis, it should be noted that sporadic cases were confirmed throughout the year. The CFR due to confirmed pneumococcal meningitis was 22.4% over the four years. This was considerably lower than CFRs that have been reported for pneumococcal meningitis in Africa, which can reach 50% [30]. One explanation for this result could be that the free referral system put in place to bring suspected cases from the periphery to the district hospital and free case management provided improved access to care, decreasing the time between symptom onset and appropriate medical care. Pneumococcal disease in high-income countries is usually described as having a bimodal age distribution, disproportionally affecting younger children and older adults. In contrast, in Moissala, 38% of cases were aged between 5 and 14 years. This is in line with other descriptions of pneumococcal disease in the African meningitis belt [27, 31, 32].

Another important lesson of this study is that case-based surveillance is feasible over a long period in a remote rural area. However, political engagement, technical and financial means, and constant technical support were required to establish and maintain the system over time. An external evaluation estimated the cost of meningitis surveillance at US$ 7449 per 100 000 inhabitants for the year 2012 in the Moissala district [33]. All these conditions and means are sometimes difficult to gather on a larger scale in resource-limited countries. In Chad for example, of the 17 districts initially planned to introduce case-based surveillance of meningitis at the beginning of 2012, only Moissala District did so, thanks to the engagement and funding of MSF. Real-time PCR was also established with the support of MenAfriNet at an estimated cost of US$ 4 per sample.

Other challenges faced in Moissala included the lack of capacity to perform lumbar puncture in peripheral health centres, which was overcome by a referral system for cases in which MSF directly paid motorcycle taxi drivers who brought patients from the periphery with a referral. The relatively broad case definition, including patients with neurological signs, led to some confusion and differences in interpretation among clinicians, particularly during the 2014 malaria season, when the strict application of the case definition led to an important increase in cases reported. Finally, the definition was refined in 2015 to include only patients with signs of meningeal involvement, which also prompted a change in the WHO case definition [26]. Despite this change, the proportion of patients with confirmed malaria remained high, which might have some implications for the comparison of surveillance data from regions with different malaria incidence.

These data also allowed us to gain understanding about the field performance of Pastorex, a tool widely recommended for confirmation of causative strains during outbreaks. Although Pastorex is currently included in the WHO recommendations for case-based surveillance of meningitis, there is less experience with this use and little data on the performance of the test outside outbreaks are available in the literature [34]. Evaluations have mostly focused on *N. meningitidis*, showing sensitivities and specificity of 88% and 93% for NmA and 85% and 97% for NmW, respectively [35–37]. Here, all NmW/Y identified by Pastorex were confirmed by culture or PCR. However, none of the NmA cases identified by Pastorex and tested by culture and/or PCR could be confirmed as such, suggesting a low positive predictive value of Pastorex for NmA in this context with low prevalence of NmA meningitis. Our results show that the sensitivity of Pastorex to detect *S. pneumoniae* is not optimal, with only 28 (57.1%) cases correctly identified by Pastorex of 49 confirmed by culture or PCR. This contrasts with another study in Burkina Faso showing that all bacterial cases (including *S. pneumoniae*) detected by culture or PCR were also positive by Pastorex [38]. Overall, our results suggest that Pastorex is not sufficiently accurate to solely rely on this test for case-based surveillance. The TI medium used for *N. meningitidis* was also inadequate for culture of *S. pneumoniae*, particularly after the delay that occurred in sending of the specimens to Oslo. In contrast, PCR does not need to be performed on viable organisms and is less sensitive to delays and transportation issues. Altogether, PCR performed at the national level seems to be the best option for a good, timely and accurate meningitis surveillance system outside of outbreaks. The development of heat-stable rapid tests with good performance for the detection of the most common causes of bacterial meningitis would also be highly useful for surveillance, as well as for diagnostic purposes, in addition to tests focusing on *N. meningitidis* serogroups for outbreak detection, as recommended by WHO [39].

Conclusion

We have presented data from a sentinel district in Chad showing that case-based surveillance of meningitis is

feasible provided sufficient engagement and means are present and very important after the introduction of MenAfriVac. Our data question the use of Pastorex as a standard tool for case-based surveillance outside of outbreaks and suggest that PCR should be used as a standard tool for laboratory confirmation at national level. In areas of the meningitis belt with high malaria incidence, collecting malaria diagnosis in suspected meningitis cases could facilitate the interpretation and comparison of meningitis surveillance data. Following the virtual elimination of NmA as a public health problem in the African meningitis belt, the pneumococcus remains the main cause of bacterial meningitis. Given its increasing importance, and also its higher CFR, it will be important to accelerate the introduction of pneumococcal conjugate vaccines and to consider broadening the target age groups to include older children and young adults upon introduction. Finally, introduction of MenAfriVac in the routine immunisation programme and future availability of a pentavalent meningococcal conjugate vaccine will be key elements for the sustained reduction in meningitis cases and outbreaks in the area.

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