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Abstract

OBJECTIVE To inform public health recommendations, we evaluated the effectiveness and efficiency of current and hypothetical surveillance and vaccine response strategies against *Neisseria meningitidis* C meningitis epidemics in 2015 in Niger.

METHODS We analysed reports of suspected and confirmed cases of meningitis from the region of Dosso during 2014 and 2015. Based on a definition of epidemic signals, the effectiveness and efficiency of surveillance and vaccine response strategies were evaluated by calculating the number of potentially vaccine-preventable cases and number of vaccine doses needed per epidemic signal.

RESULTS A total of 4763 weekly health area reports, collected in 90 health areas with 1282 suspected meningitis cases, were included. At a threshold of 10 per 100 000, the total number of estimated vaccine-preventable cases was 29 with district-level surveillance and vaccine response, 141 with health area-level surveillance and vaccination and 339 with health area-level surveillance and district-level vaccination. While being most effective, the latter strategy required the largest number of vaccine doses (1.8 million), similar to the strategy of surveillance and vaccination at district level (1.3 million), whereas the strategy of surveillance and vaccination at health area level would have required only 0.8 million doses. Thus, efficiency was lowest for district-level surveillance and highest for health area-level surveillance with district-level vaccination.

CONCLUSION In this analysis, we found that effectiveness and efficiency were higher at health area-level surveillance and district-level vaccination than for other strategies. Use of *N. meningitidis* C vaccines in a preventive strategy thus should be considered, in particular as most reactive vaccine response strategies in our analysis had little impact on disease burden.

keywords response strategies, meningitis, epidemics, Niger, surveillance

Introduction

Since the introduction of a serogroup A conjugate meningococcal vaccine (PsA-TT, MenAfriVac®) in the African meningitis belt in 2010, the frequency and intensity of bacterial meningitis epidemics have decreased and reached an exceptionally low level in 2013–2014 [1]. The remaining few epidemics have been due to meningococcal serogroups W and X, which are not targeted by preventive vaccination and had caused several sporadic epidemic events since 2000 [2–5]. *Neisseria meningitidis* (Nm) C has rarely been detected in carriage or meningitis in the African meningitis belt for about 30 years, with the last NmC outbreak in the region dating back to 1979 [6]. However, NmC re-emerged in an epidemic in Northern Nigeria during 2013–2014 [7], with the largest NmC epidemic ever reported during 2015, causing 8502 cases in Niger and 2845 suspected cases in Nigeria [8]. This epidemic emergence of NmC meningitis emphasises the need for continued serogroup-specific surveillance for rapid detection of epidemics. For over one decade, the control of meningitis epidemics in Niger has been based on a reactive vaccination strategy using serogroup AC or ACW polysaccharide vaccines combined with adapted treatment protocols [9]. Field experience showed that reactive vaccination often is implemented too late to influence the epidemic curve [10].

To inform public health recommendations, we evaluated the effectiveness and efficiency of current and hypothetical surveillance and vaccine response strategies against NmC meningitis epidemics during 2015 in Niger, similar to a recently published analysis suggesting a higher efficiency of health centre-level surveillance for serogroup W and epidemics after elimination of meningococcal serogroup A [11]. Our approach builds on evidence for the localised character of meningitis epidemics [12, 13] and thus is based on surveillance data at the health centre level.

Methods

Databases

First, to provide a description of NmC epidemiology in Niger during 2015, we used data from laboratory-confirmed meningococcal meningitis from routine countrywide surveillance in Niger, spanning from 1 July 2014 to 30 June 2015. Laboratory confirmation was based on polymerase chain reaction (PCR) [14], which was performed on 65% (841/1282) of suspected cases reported for this period. For the present analysis, weekly case counts were analysed at the health centre level.

Second, to evaluate surveillance and response strategies based on suspected case reporting, we compiled data on weekly suspected bacterial meningitis case counts reported by health centres from 1 July 2014 to 30 June 2015. In the context of routine countrywide epidemiologic surveillance, suspected case reports are available only aggregated at the district level. Due to limited resources for this compilation of original data at the health centre level, we compiled these data only for Dosso region. This region was selected because it had shown the highest NmC meningitis incidence during 2015, along with the capital region Niamey, where, however, the patient referral structure is less appropriate for a health centre-level analysis.

Dosso region is located in the southern part of Niger, bordered by the region of Tahoua in the east, Tillabery in the north and the west, Benin and Nigeria in the south. It had 2 372 411 inhabitants in 2015 (14% of the Niger population) and was organised in five health districts and 94 health areas (HA).

Statistical analysis

We used standard epidemiological methods to describe the NmC epidemic. We calculated weekly incidence rates (WIR) as a weekly number of suspected cases per 100 000 inhabitants and cumulative annual incidence (AI) as number of suspected or confirmed cases per 100 000 inhabitants during an epidemiological year. The Institut National de la Statistique provided the number of inhabitants per village according to the 2001 national census. We applied a mean annual growth rate of 3.3% [15]. We identified epidemic thresholds (ET) as WIR of suspected meningitis in Dosso region, based on receiver–operator curves for the detection of high AI [11, 12]. First, we chose as the primary reference standard an AI above the 95th percentile of AI in all HA in the database (172 per 100 000) and as the secondary reference an AI above the percentile of 97.5 (263 per 100 000). The optimal epidemic threshold was chosen with regard to their sensitivity and specificity in detecting HA according to the reference standards. An epidemic was defined as WIR in a HA that exceeded the corresponding threshold for at least 1 week. We tested 22 thresholds of WIR at the HA level for their performance in detecting high AI, ranging from 1 to 200 cases per 100 000 during one week, named ET1, ET2, etc. Based on this definition of epidemic signals, we evaluated the effectiveness and efficiency of surveillance (i.e. data analysis) and vaccine response strategies by calculating the number of potentially vaccine-preventable cases and number of vaccine doses needed per epidemic signal.

Three strategies were evaluated as previously described [11]. Briefly, we approximated the number of potentially vaccine-preventable cases (Nvp) as follows:

$$\mathrm{Nvp} = \mathrm{N3}w * \mathrm{PN}m * \mathrm{VC} * \mathrm{VE};$$

where N3w is the number of suspected cases observed in the surveyed HA or district from 3 weeks after exceeding the threshold; PNm is the percentage of suspected cases confirmed as Nm, estimated as 50% in both epidemic and endemic periods; VC is the expected vaccine coverage during a mass campaign in response to an outbreak, estimated at 80%; and VE is the expected vaccine effectiveness, estimated at 80%. We calculated the number of vaccine doses needed per epidemic event as the target age group 1–29 years of the total population, which was 74% for the study region, and the total number of preventable cases in the target population for 100 000 vaccine doses. To evaluate the sensitivity of our estimates to a longer delay from signal detection to effective vaccine protection, we varied this delay from three to 6 weeks.

All analyses were performed in R Studio software version 2.15.3 [16]. Maps were created with QGIS software version 1.5.0 [17].

Ethical aspects

All data were collected via the national surveillance system after authorisation by the Ministry of Public Health. Therefore, National Ethics Committee agreement was not required. Patients were, however, informed of the reason why their CSF sample was being taken and they received free care during the meningococcal season. Each health structure received the individual results of submitted samples. The retrospective disclosure of information to other partners occurred without any mention of the patient's identity.

Results

In the eight regions of Niger, a total 1144 NmC, 206 NmW, one NmX, 127 *Streptococcus pneumonia* (Sp), eight *Haemophilus influenzae* (Hi) cases were confirmed among 4318 cerebrospinal fluid (CSF) samples sent to CERMES from July 2014 to June 2015. Five regions and 25 districts reported at least one NmC case, with median WIR at district level of 0.62 per 100 000 (ranging from 0.09 to 8.84 per 100 000) and median AI at 3 per 100 000 (ranging from 0.1 to 43.4 per 100 000). During the same period, 93 HA reported at least one NmC case with median WIR at 4.31 (ranging from 0.09 to 47.2) and median AI rate at 10.8 ranging from 0.09 to 135 per 100 000 (Figure 1). The two regions with highest annual NmC incidence were Dosso with 15.7 (372 cases/2 372 411 inhabitants) and Niamey with 43.4 (496 cases/1 142 248 inhabitants) per 100 000.

In the five districts of Dosso region, we included 4763 weekly HA reports, collected in 90 HA with 1282 suspected meningitis cases. Among the 841 meningitis suspected cases sent from the region of Dosso and analysed by PCR at CERMES, 372 were due to NmC, 72 to NmW, 25 to Sp, one to Hi, six indetermined Nm, 364 negative and one not available result. At least one case of NmC was found in 33.0% (N = 31) of HA of Dosso region (Figure 2); 39 NmC cases found in two HA of Dosso district; 202 NmC cases found in 13 HA of Doutchi district; 12 NmC cases found in four HA of Boboye district; 78 NmC cases found in eight HA of Gaya district and six NmC cases found in three HA of Loga district. In total, 32% (N = 115) and 30% (N = 109) of confirmed cases, respectively, occurred among 5- to 9-year-old and 10- to 14-year-old children (Figure 3). The highest annual incidence rate was observed among 10- to 14-year-old and 15- to 19-year-old persons with 76 and 73 cases per 100 000 inhabitants, respectively.

The median AI rate in the districts of Dosso region was 43 suspected cases per 100 000 (range 11–86 cases per 100 000), with the highest rates found in the districts of Gaya, Doutchi and Dosso with 86, 73 and 43 cases, respectively, per 100 000 inhabitants. The median AI at the HA level was eight cases per 100 000 inhabitants, with substantial heterogeneity between HA of the same district (Figure 4). The highest AI rates were 624 cases per 100 000 inhabitants in the HA of Karakara in the district of Gaya and 475 cases per 100 000 inhabitants in the HA of Tombokoirey in the district of Dosso.

The median WIR at the HA level during the meningitis season from January through May was 0 (range 1–220) cases per 100 000 inhabitants, with the highest WIR being 220 cases per 100 000 in the HA of Tombokoirey (district of Dosso) during calendar week 19 (Figure 5).

The thresholds that had the best performance to detect AI beyond the 95th and the 97th percentiles were at HA level WIR of 20 and 30 cases per 100 000, respectively, and WIR of 9 and 10, respectively, at the district level.

Based on the current strategy of district-level surveillance, the total number of epidemic events in Dosso region from July 2014 to June 2015 varied from 2 to 5, depending on the chosen incidence threshold (ranging from 15 to 2 per 100 000). There would have been 22 to 45 events based on HA-level surveillance (threshold ranging from 7 to 30), leading to four or five vaccine campaigns at district level. At a threshold of 10 per 100 000, the total number of estimated vaccine-preventable cases in Dosso region was 29 with district-level surveillance and vaccine response, 141 with HA-level surveillance and vaccination and 339 with HA-level surveillance and district-level vaccination (Table 1). While being most effective, the latter strategy required the largest number of vaccine doses (1.8 million), similar to the strategy of surveillance and vaccination at the district level (1.3 million), while the strategy of surveillance and vaccination at HA level would have required only 0.8 million doses. Thus, efficiency was lowest for district-level surveillance (2.29 vaccine-preventable cases per 100 000 doses) and highest for HA-level surveillance with district-level vaccination (19.28 cases per 100 000 doses). The gain in effectiveness from moving to a finer geographical level of intervention was greater than for any change of threshold. When the assumed delay between epidemic signal and effective protection from vaccine antibody increased from 3 to 6 weeks, efficiency fell in all strategies, in particular for the HA-level surveillance and vaccination strategy, which became clearly less efficient than the strategy based on HA-level surveillance and district-level vaccination, but remained more than twice as efficient than the district-level surveillance and vaccination

Figure 1 Cumulative annual incidences of confirmed *Neisseria meningitidis* (Nm) C per 100 000 in Niger during 2015 epidemiological year. Five of the eight regions presented at least one NmC case found in 90 health areas. Most of the health areas with high incidences were located in Dosso region.

strategy. District-level surveillance and vaccination at a threshold of >10 cases per 100.000 did not prevent any cases with a delay of 5 weeks or longer (Figure 6).

Discussion

In this analysis, we found that effectiveness and efficiency were higher for HA-level surveillance and district-level vaccination compared to other strategies. Although the efficiency decreased in all strategies with the variation of the delay between epidemic signal and the effective protection from vaccine antibody, the strategy of HA-level surveillance and district-level vaccination remained more efficient than the other strategies. The gain in effectiveness from moving to a finer geographical level of intervention was greater than for any change of threshold. Serogroup C of *Neisseria meningitis* has been the most common serogroup in 2015 epidemic in Dosso region and affected more children who were fortunately part of the vaccination campaign target. However, a global shortage of meningococcal vaccines limited this campaign. Considering that vaccine shortage could lead to a large spread of the outbreak, the international health community helped Niger government to combat this outbreak by providing vaccine against serogroups A, C, Y and W [18]. In this situation of vaccine shortage, the definition of the more efficient and effective strategy for vaccine response is essential. Giving the magnitude of the 2015 outbreak, and time to acquire vaccines, the strategy of surveillance at the HA level and vaccination of the whole district seemed to be the most appropriate strategy for NmC outbreaks. This strategy can allow rapid detection of cases and more effective vaccine coverage maintained at a good level over time. It had also a good level of efficiency maintained over time, although requiring more quantity of vaccine doses. Nevertheless, for our

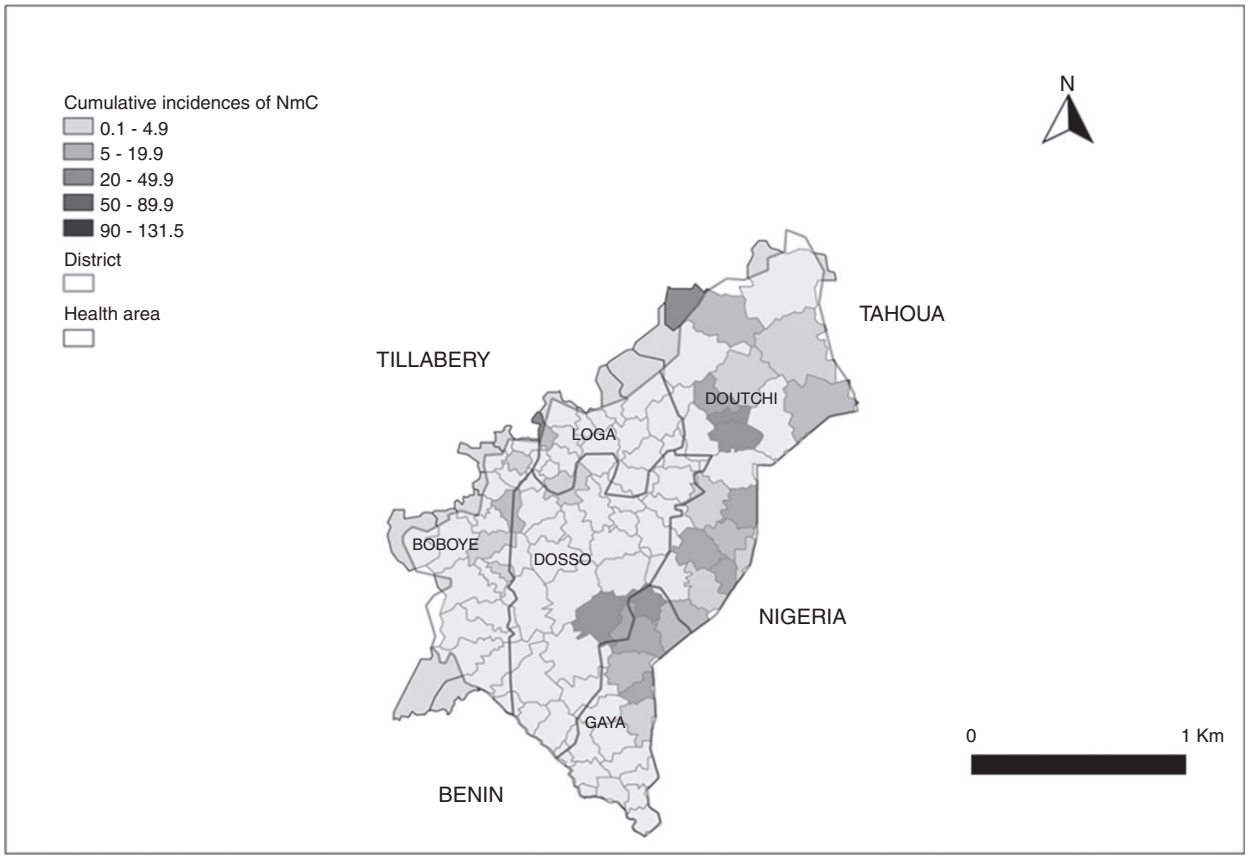

Figure 2 Cumulative annual incidences of confirmed *Neisseria meningitidis* (*Nm*) C per 100 000 in health areas of Dosso region (Niger) during the 2015 epidemiological year. The serogroups were identified by systematic polymerase chain reaction testing on cerebrospinal fluid. A total of 31 health areas reported at least one confirmed NmC case. White areas represent health areas without NmC cases. Grey areas represent health areas with at least one NmC case.

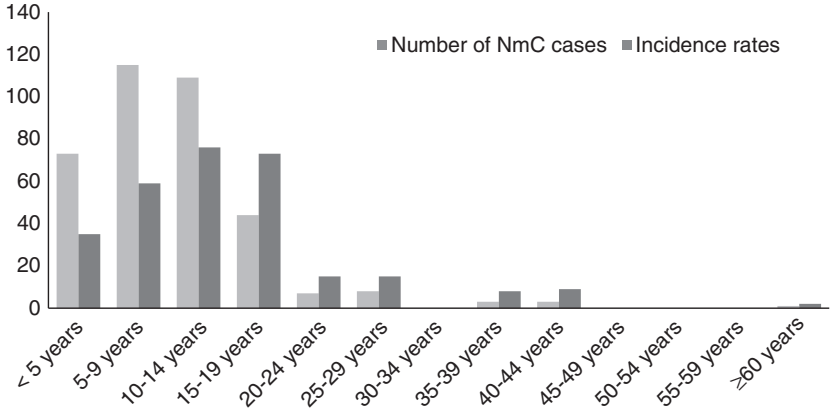

Figure 3 Distribution of PCR-confirmed *Neisseria meningitidis* C cases and annual incidence rate of NmC per 100 000 inhabitants according to the age group, Dosso region (Niger), 1 July 2014 to 30 June 2015.

simulated situation of NmA elimination, effectiveness was highest for HA-level surveillance and district vaccination [11], whereas efficiency was optimised for HA vaccination. So, the district-level response should be maintained for NmC, but the surveillance for outbreak detection should be brought to the HA level.

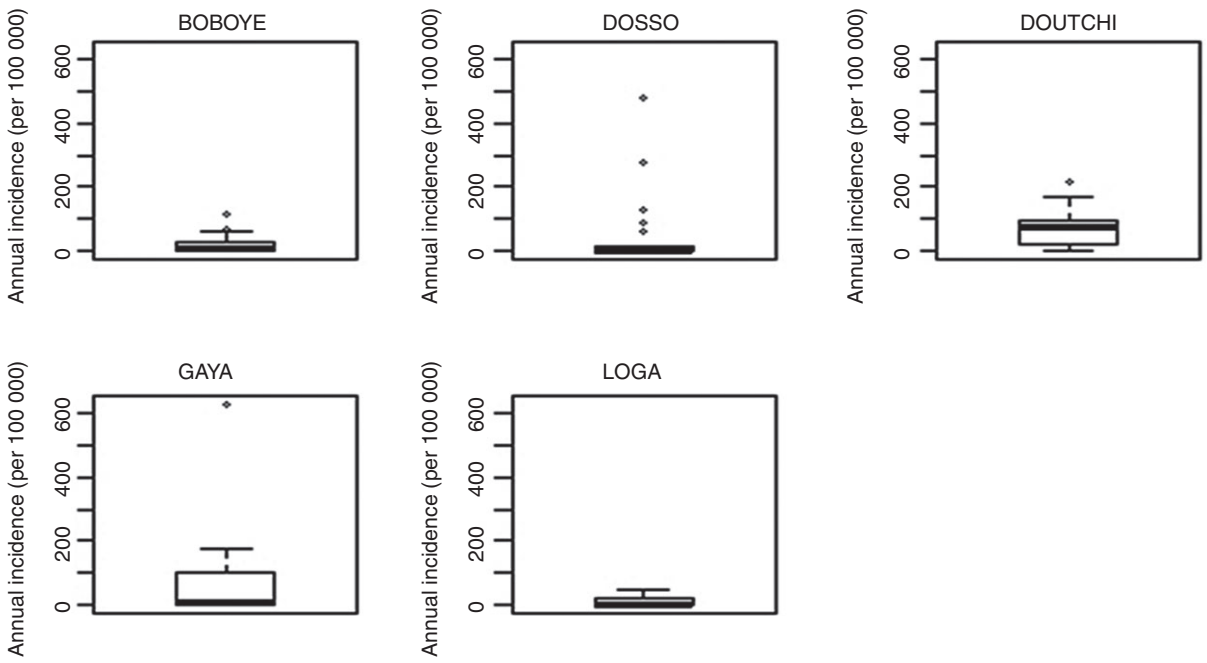

Figure 4 Annual incidences of suspected meningitis in the 91 health areas and five districts of Dosso region (Niger), 2015. Annual incidences of health areas are presented by district. The health areas that are outliers are Birni urbain (NmW) and Kiota (NmC) in the district of Boboye; Tombokoirey (no sample received), Tessa_Dosso (NmC), Goroubankassan (no sample received), Barokoira (NmW) and Saboudey (no sample received) in the district of Dosso; Dankassari (NmC) in the district of Doutchi; Kakakara (NmC) in the district of Gaya.

We also found that only half of HA in which NmC circulated experienced an epidemic, and there was great heterogeneity between NmC incidences of HA in the same district. At least one NmC case was found in 33% of the 90 HA of Dosso region, most of them without epidemic situation, suggesting that the presence of NmC does not necessarily lead to an epidemic, but that coincidence with some epidemiogenic cofactors is required. These epidemiogenic factors are likely more present at the border of Nigeria and along the Niger River which Nigerian (Niger) part is used to join Nigeria and Mali. As previously hypothesized by Mueller and Gessner [19], such a factor could be responsible for the surge in carriage prevalence observed during localised epidemics [20], and micro-epidemics of viral respiratory infections could be involved. Epidemics were more frequent on the border with Nigeria, and the region of Dosso was the first affected by the outbreak in Niger. This could be the result of the presence of the NmC as localised epidemics in the north of Nigeria in 2013 [7] associated with a low immunity of population to NmC. Indeed, vaccinations were less frequent in the population since 2010 with the introduction of serogroup A meningococcal meningitis vaccine (PsA-TT). Behavioural and cultural factors, such as high travel activity, at the Niger–Nigeria border may have interacted with the precedent factors and favoured the 2015 burden of NmC in Niger. For a better understanding of NmC emergence and expansion, carriage studies should be performed regularly in the meningitis belt particularly for the re-emerging serogroup C of Nm.

The high heterogeneity of incidences even within epidemic or non-epidemic districts concords with the results of NmA epidemics in Burkina Faso [12] and Niger for the period of 2002–2012 [21]. Although the fact that the epidemic largely affected Dosso region, this heterogeneity was visible, suggesting the necessity of surveillance at a finer spatial level than the district for a rapid detection of localised epidemics.

Children aged 5–14 years were most affected, and those aged 10–19 years were most at risk for NmC in our study. The most affected group of age found in this study for NmC was similar to that of NmX and NmA in Burkina and Togo [5].

Other authors observed that the recent NmC outbreak in Nigeria was not unusual in regard to its seasonal variation, with maximum number of cases being

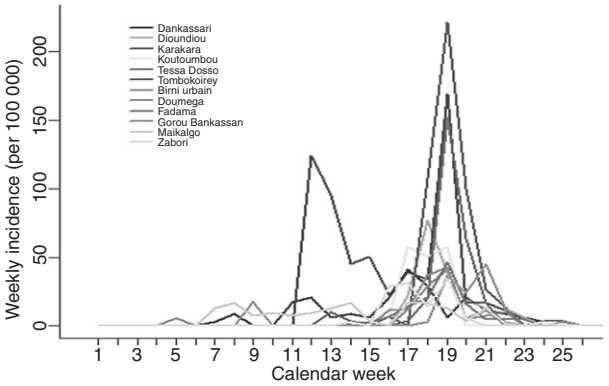

Figure 5 Epidemic curves (suspected meningitis) of selected health areas of Dosso region, Niger, 2015. Health areas with cumulative annual incidences higher than 100 cases per 100 000 inhabitants were included in this graph. Tombokoirey, Tessa Dosso and Gorou Bankassan belonged to Dosso district; Koutoumbou, Dioundiou, Karakara and Zabori belonged to Gaya district; Dankassari, Doumega, Fadama and Maikalgo belonged to Doutchi district, Birni urbain belonged to Boboye district.

reported in the dry season [7]. We also found that the period of its occurrence, the peak of the season and the magnitudes of its incidence were not unusual. The peak incidence rates of NmC were comparable to reported NmA rates [22].

This surveillance study has a number of limitations. Our analysis is based on routine surveillance data with little patient information, such as individual- or village-level vaccination status, or clinical presentation of cases. We chose only one region for our analysis of surveillance strategies, and giving the fact that this region was one of the most affected by the outbreak, we could have overestimated the incidence of NmC and the number of epidemic events. The demographic data used for incidences calculation were those of 2001 to which we applied a constant grow rate, which may not take into account the exact spatiotemporal, cultural and ethnical variations of the population.

Data linkage of suspected and confirmed meningitis cases highlighted opportunities and improvements in meningococcal surveillance in Niger. Matching of the two data sets has been possible due to enhanced surveillance activities conducted since 2002. The availability of PCR since 2002 [23] may have also improved our ability to microbiologically confirm meningococcal disease diagnosis during 2015 outbreak. This may also explain the larger proportion matched and better serogroup information for 2015 meningitis epidemic in Niger.

The changing epidemiology of meningococcal meningitis in the meningitis belt with emergence of non-A serogroup was considered a potential risk following the introduction of a monovalent serogroup A vaccine [24], while the epidemic emergence of NmC was rather unexpected. Given the quick geographical expansion of the

Table 1 Comparison of different strategies of surveillance and meningococcal vaccine response in terms of effectiveness and efficiency for preventing meningitis cases in Dosso region, Niger, 2015. This region had 2.37 million inhabitants

Strategy							
Surveillance	Vaccination	Threshold (WIR per 100 000)	*N* epidemic signals/*N* interventions	Total population concerned by the signal	Total doses (1–29 years)	Total preventable cases by vaccination	Total preventable cases per 100 000 doses
Health area	Health area	7	45/45	1 257 206	930 332	184	19.7
		10	38/38	1 116 644	826 317	141	17.1
		15	32/32	1 020 622	755 260	95	12.6
		20	24/24	702 031	519 503	62	12.0
		30	22/22	634 973	469 880	40	8.5
Health area	District	7	45/5	2 372 411	1 755 584	342	19.5
		10	38/5	2 372 411	1 755 584	339	19.3
		15	32/5	2 372 411	1 755 584	271	15.4
		20	24/4	2 161 414	1 599 446	204	12.8
		30	22/4	2 161 414	1 599 446	130	8.1
District	District	2	5/5	2 372 411	1 755 584	286	16.3
		4	4/4	2 161 414	1 599 446	173	10.8
		7	4/4	2 161 414	1 599 446	89	5.6
		10	3/3	1 735 748	1 284 454	29	2.3
		15	2/2	956 919	708 120	17	2.3

Cases <2 years of age were not excluded. Total: for entire study area Dosso region (population 2 372 411); WIR, weekly incidence rate per 100 000; HA, health area.

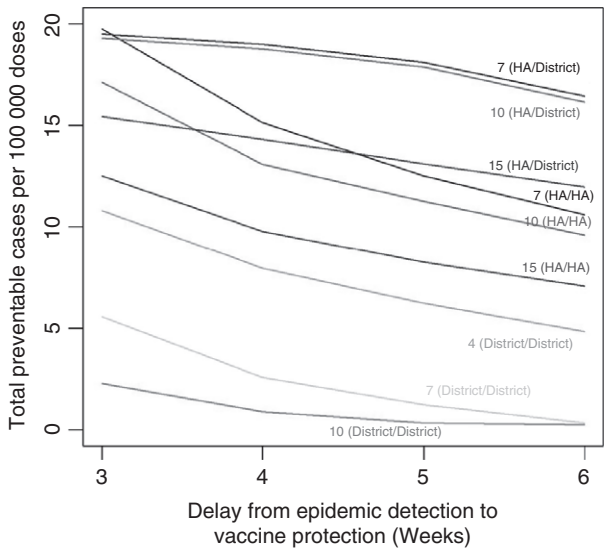

Figure 6 Comparison of different strategies of surveillance and meningococcal vaccine response in terms of efficiency for preventing meningitis cases, in Dosso region (Niger), 2015. We considered three, four, five and six weeks delay between epidemic detection and effective vaccine protection. The strategies were surveillance and vaccination at health area (HA/HA) level, surveillance at health area level combined with vaccination of the district (HA/District) and surveillance and vaccination at district level (District/District). Incidence thresholds for epidemic response were 7, 10 and 15 weekly cases per 100 000 inhabitants for surveillance at the health area level, and 4, 7 and 10 for surveillance at the district level.

serogroup from 2013, it is possible that NmC outbreaks will occur regularly in the region. Use of NmC vaccines in a preventive strategy thus should be considered, in particular as most reactive vaccine response strategies in our analysis showed limited impact on disease burden.

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