Supplementary Material Online Figure S1

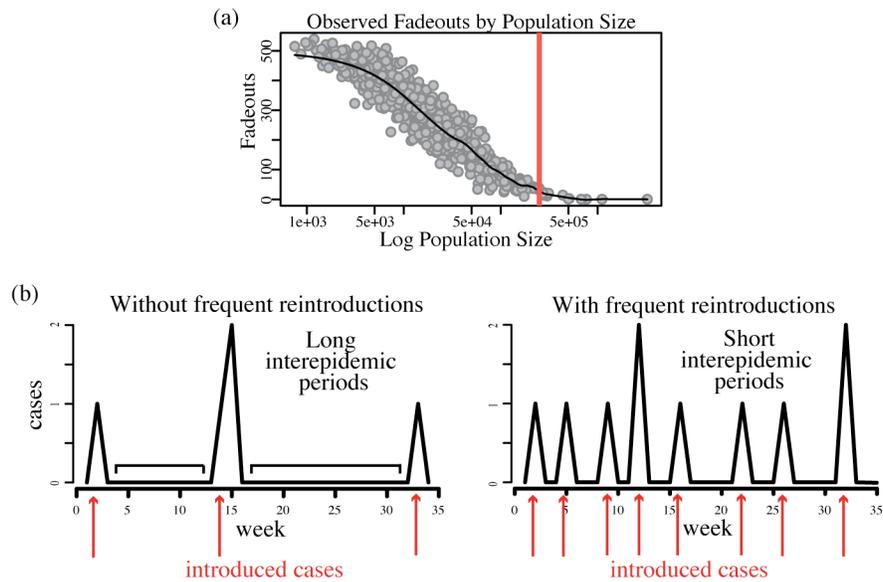Fadeouts and Interepidemic periods (adapted from [1])

Figure S1 (a) This figure illustrates the classic relationship between population size and number of measles fadeouts as seen in pre-vaccination England and Wales from 1944-1964. Red line indicates CCS [2]. (b) Schematic showing the relationship between interepidemic periods and reintroductions for measles. Introduced cases end interepidemic periods and therefore determine their length. Infrequent or few introductions (red arrows) produce long interepidemic periods (left) whereas frequent or many introduced cases produce short interepidemic periods (right) [3, 4]. See discussion for application to meningitis.

References

(1)   Bharti N, *et al*. Measles hotspots and epidemiological connectivity *Epidemiology and Infection* 2010; *138*(09): 1308-1316.
(2)   Bartlett MS. Measles periodicity and community size. *Journal of the Royal Statistical Society Series a-General* 1957; 120(1): 48-70.
(3)   Bjornstad ON, Finkenstadt BF, Grenfell BT. Dynamics of measles epidemics: Estimating scaling of transmission rates using a Time series SIR model. *Ecological Monographs* 2002; 72(2): 169-184.
(4)   Bjornstad ON, Grenfell BT. Hazards, spatial transmission and timing of outbreaks in epidemic metapopulations. *Environmental and Ecological Statistics*, 2008; 15: 265-277.

Supplementary Material Online Figure S2

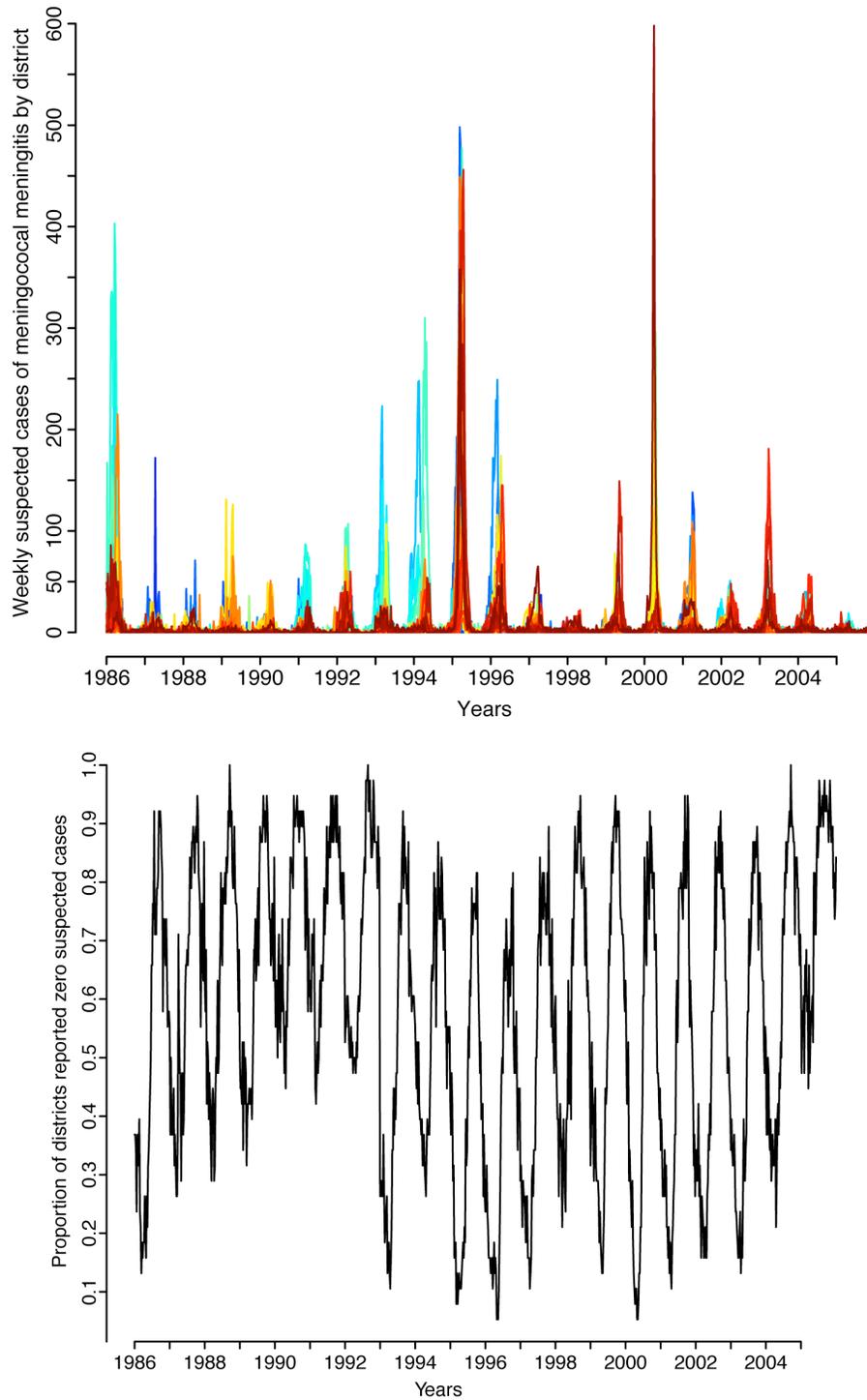Reported cases of meningococcal meningitis in Niger

Figure S2 Top: Weekly suspected cases of meningococcal meningitis by district in Niger from 1986-2005. Each color represents a different district. Bottom: Proportion of districts reporting zero suspected meningitis cases each week.

Supplementary Material Online Figure S3

Niamey: Fadeouts for meningococcal meningitis and measles
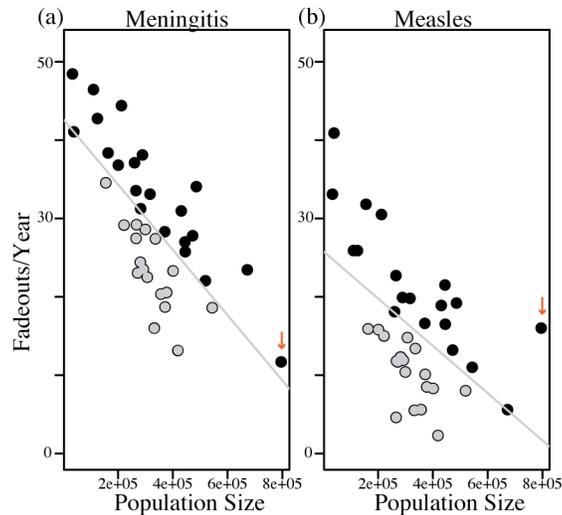
For the largest city in Niger, Niamey, meningococcal meningitis absences against population size lie along the best-fit line (Figure S3a, far right, indicated by red arrow) while this same city shows far more fadeouts than expected for measles (Figure S3b, far right, indicated by red arrow). There are two possible explanations for this. First, routine measles vaccine coverage in Niamey is high compared to other districts in Niger [1], resulting in a comparatively low density of susceptibles for measles. In contrast, due to waning meningococcal meningitis immunity and reactive meningitis vaccination, we expect the relative density of susceptibles for meningococcal meningitis in Niamey to be higher than for measles.

Second, the seasonal forcing of measles transmission is much stronger in Niamey than in most other districts in Niger [2]. While, the seasonality of meningococcal meningitis incidence appears to be similarly strong in all districts throughout the country (Figure 1a). Currently, we do not have enough data to know exactly why Niamey shows a fadeout patterns for measles different from the pattern of meningococcal meningitis absences while most other districts show similar patterns for both diseases. To tease apart these two hypotheses, future work will require additional data on vaccination and reported cases for both diseases, as well as mathematical models to address variation in transmission.

References

(1)   World Health Organization. Immunization surveillance, assessment and monitoring. In, 2007.
(2)   Ferrari MJ, *et al.* Rural-urban gradient in seasonal forcing of measles transmission in Niger. *Proceedings of the Royal Society B-Biological Sciences* 2010; 277(1695): 2775-2782.

Supplementary Material Text S1: Assessing rates of reported cases

Introduction

A bias in disease reporting across districts could skew the detection of fadeouts. If certain districts have *consistently* high or low reporting rates, this could affect their classification as a hotspot. Due to its simple epidemiology, we can estimate the reporting rate of measles for each district (though this cannot be done for meningitis).

In order to understand whether the reporting rate of measles cases across the districts of Niger affects the results presented here, we used the TSIR model [1] to determine the reporting rate of each district by reconstructing the susceptible class from reported annual district level birth rates and reported annual district level measles vaccine coverage. This is based on the assumption that, because measles is highly infectious and strongly immunizing, unvaccinated individuals acquire infection exactly once. Thus the difference between the slope of the cumulative unvaccinated portion of the population and the slope of the cumulative reported cases gives the reporting rate of measles [1].

Methods

Finkenstadt and Grenfell (2000) showed that the slope of the line that relates cumulative susceptible births to cumulative reported measles cases is proportional to the reporting rate [1]. Thus, using the monthly reported measles incidence, birth rates, and vaccine coverage for each district, we estimated the measles reporting rate for each of the districts of Niger.

The National Health Information System and the Ministry of Health of Niger reported the annual population size for each district from 2001 based on the 2001 general census of the population (RGP). These population sizes are projected forward at a growth rate specific to each district per year, with a national annual mean growth rate of 3.3% [2]. Official population sizes for the years preceding the RGP are back calculated by applying these growth rates to the RGP reported population sizes.

The National Health Information System and the Ministry of Health of Niger also reported the annual number of live births for each district from 2003 and 2004. Using the population sizes from 2003 and 2004, mean birth rates for each district was calculated by dividing the population size by the number of live births and taking the mean for each district across those two years. This rate was then used to calculate the number of live births for each district for the remaining years between 1995-2005.

The annual statistics from the National Health Information System and the Ministry of Health of Niger also reported the proportion of the population of each district that was vaccinated against measles from 2003-2008. For this analysis, when the reported coverage exceeded 100% it was reduced to a maximum value of 100%. All reported rates were then multiplied by 95% to account for the efficacy of the vaccine [3]. The mean measles vaccine coverage for each district was used because, although the years of reported vaccine coverage (2003-2008) overlapped with the years of the reported measles cases (1995-2005), the time periods during which data were available did not match

exactly. For each district, the mean proportion of vaccinated individuals was subtracted from the birth cohort to give the susceptible birth cohort.

There may be variation in the reporting rate *within* districts as a result of non-uniform population density and access to care. However, here we are concerned only with potential variation *between* the districts; the district level is the spatial scale at which these analyses were done. It is also likely that surveillance for both measles and meningitis improves during epidemics but this would occur during the absence of fadeouts and generally applies to both diseases and all districts and would therefore not likely affect the detection of hotspots.

To determine whether there was a significant difference between the reporting rates of hotspots and non-hotspots, we fit a linear mixed effects regression for cumulative cases to the cumulative reconstructed susceptible population with an interaction between district classification (binary, indicating whether a district was a hotspot or not) and the slope of cumulative reported cases against the cumulative susceptible population. The district-specific slopes of the cumulative cases and cumulative susceptible population were treated as random effects. This analysis was conducted separately for the two hotspot classifications: once for the 15 joint measles-meningitis hotspots and the remaining 23 non-hotspot districts and again for the 19 measles-only hotspots and the remaining 19 non-hotspot districts [4].

An interaction between the slopes of the cumulative reported cases against the cumulative susceptible population and the hotspot indicator would suggest a significant difference between the reporting rates for hotspots and non-hotspots, which could bias the classification of districts as hotspots.

Results

These analyses showed that the interaction between the slopes of the cumulative reported cases and the hotspot indicator were not statistically significant. The p-value of the interaction between cases and joint hotspots was $p > 0.9$. The p-value of the interaction between cases and measles hotspots was $p > 0.2$

Discussion

We found no difference between the reporting rates of measles between hotspots and non-hotspots. We conclude that the variation in the reporting rates of measles incidence between the districts of Niger did not bias the classification of districts as hotspots.

References

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(2)   Ministere de la Sante Publique, La Lutte Contre Les Endemies Secretariat General. Annuaires Statistiques du Niger, Annee 2003; 2003.

(3)   Cutts FT, Grabowsky M, Markowitz LE. The effect of dose and strain of live attenuated measles vaccines on serological responses in young infants. *Biologicals* 1995; 23(1): 95-106.

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Supplementary Material Text S2: Identifying high risk districts using alert and epidemic thresholds

Introduction

Meningococcal meningitis outbreaks in the African meningitis belt are often assessed using standard thresholds for alert (5 cases per 100,000 people per district per week, respectively) and epidemic (10 cases per 100,000 people per district per week, respectively) classification, as defined by the World Health Organization (WHO) [1]. The crossing of these thresholds, as scaled by district population size, determines whether surveillance is heightened or a reactive immunization campaign is launched. In the main paper, we avoided the use of these thresholds for two reasons. First, using a denominator for district population size by which to scale the number of cases introduces a second dimension of uncertainty, in addition to the actual number of cases. Second, and most relevant to this study, scaling cases by population size can mask the effects of host population density. Though these thresholds are certainly useful when comparing real-time disease burden and assessing immediate health care needs between locations of different sizes, this measurement can fail to detect patterns of transmission early in an epidemic and during periods with low numbers of cases. This includes importations of infection, transitions from asymptomatic carriage to clinical disease, and low levels of transmission.

Despite the lack of detailed information surrounding asymptomatic meningococcal meningitis carriage, it is known that meningococcal meningitis is transmitted directly between individuals. As with any directly transmitted infection in a population with some proportion of susceptible hosts, the number of contacts between individuals is positively related to the likelihood of transmission, and therefore strongly dependent on host population density. Due to the non-linear properties of disease transmission, particularly during the early phases of an epidemic, a high-density population poses a greater risk of infectious cases rapidly resulting in a number of secondary cases than does a low-density population. If importation events or transmission events occur more frequently in more populated districts, which would be expected of most directly transmitted infections [2, 3], the use of the alert and epidemic thresholds could diminish the strength of these signals. As this analysis was primarily interested in the effects of population density, we focused our initial analysis on the weekly reported cases for each district, which may reveal information that the threshold metrics would not detect.

To complement our spatial and statistical analyses of case counts, we completed an additional spatial analysis with the commonly used public health thresholds mentioned above. Because these thresholds account for the population size of each district, we did not focus our analyses on the relationship between the threshold indicators and population size (details below), as we did for the analysis of meningococcal meningitis case reappearances. Instead, we measured the total number of weeks spent above each threshold and the total number of threshold transitions to identify high risk districts and compare these to the 'hotspots' identified by using the suspected case counts, as detailed in the main paper.

Methods

We measured the total number of weeks spent above the alert threshold while remaining below the epidemic threshold for each district. Second, we measured the frequency of transitions from below the alert threshold to reaching or crossing the alert threshold while staying below the epidemic threshold for each district. Then, we measured the total number of weeks spent above the epidemic threshold for each district. Finally, we measured the frequency of transitions from below the epidemic threshold to reaching or crossing the epidemic threshold for each district.

We assessed the correlation between the number of weeks spent at or above either transition, for both the alert and epidemic thresholds, and population size for each district, as well as the correlation between the frequency of threshold transitions and population size. We also measured the spatial clustering by calculating Moran's I with neighbors defined as districts with contiguous boundaries for the districts where the total weeks at or above either threshold exceeded the national median [4]. Finally, we completed the same spatial analysis for the districts with more threshold transitions than exceeded the national median. We compared these results to the results of similar analyses, as completed for reappearances of weekly district case counts, discussed in the main paper.

We measured the spatial correlation of the total number of weeks spent at or above the alert threshold while remaining below the epidemic threshold for each district with values that exceeded the national median. We also measured the spatial clustering in frequency of transitions from below the alert threshold to reaching or crossing the alert threshold while staying below the epidemic threshold for districts with values that exceeded the national median. We did the same spatial analysis for 1) for the total number of weeks spent above the epidemic threshold for each district when district values exceeded the national median and 2) the number transitions from below the epidemic threshold to equal or above the epidemic threshold for districts with values that exceeded the national median.

Description and sources for reported cases, population sizes, and district boundaries are detailed in the main paper.

Results

We found low positive correlation values between population size and the total number of weeks spent above the alert threshold (correlation = 0.23, p > 0.1). We also found low correlation values between population size and the total number of weeks spent above the epidemic threshold (correlation = 0.24, p > 0.1). We found no correlation between population size and the total number transitions to either threshold (alert threshold correlation = 0.16, epidemic threshold correlation = 0.06) (Fig. S2.1).
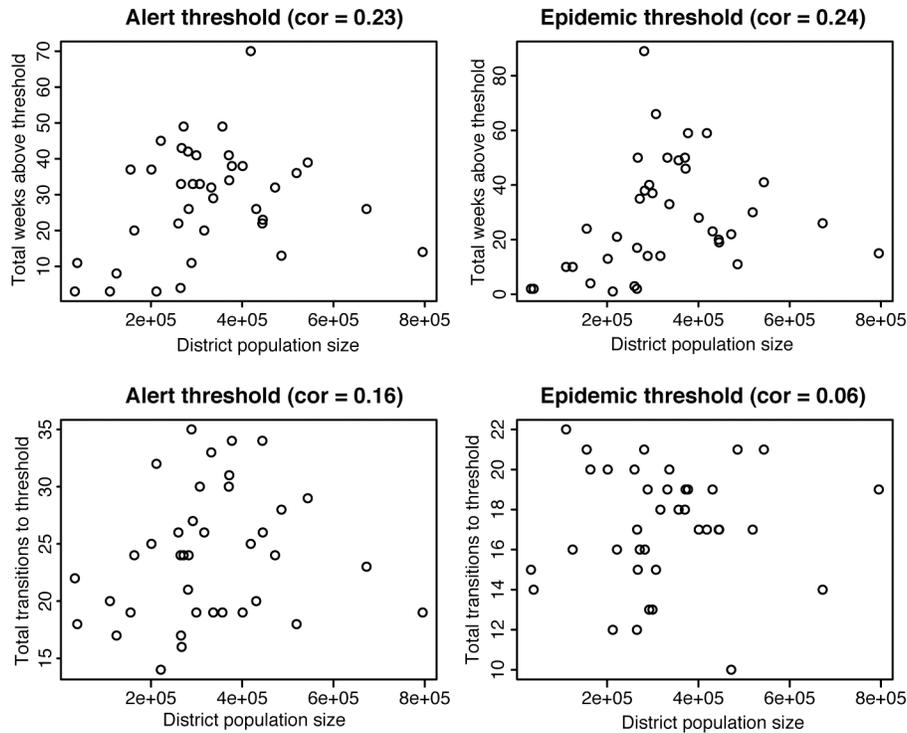
Fig. S2.1 Based on weekly, district level reports of suspected meningococcal meningitis cases from 1986-2005 from each district in Niger. Top row: total number of weeks spent at or above the alert threshold by district (left) and epidemic threshold (right). Bottom row: total number transitions to or above the alert threshold (left) and the epidemic threshold (right) by district.

We found a clustered spatial pattern in the total number of weeks spent at or above both the alert and epidemic thresholds. A positive Moran's I statistic indicates spatial autocorrelation (clustering) and a significant p-value indicates a significant departure from randomness. For the districts with a total number of weeks above the alert threshold that was greater than the national median value, we calculated Moran's $I = 0.35$, $p < 0.01$. For the districts where the total number of weeks spent at or above the epidemic threshold was greater than the national median value, we calculated Moran's $I = 0.48$, $p < 0.01$. The total number of transitions to either threshold did not show any spatial clustering. For the districts with a total number of alert threshold transitions above the national median, Moran's $I = 0.14$, $p = 0.36$. For the districts with a total number of epidemic threshold transitions above the national median, Moran's $= 0.11$, $p = 0.11$ (Fig. S2.2). For the 17 meningococcal meningitis hotspots identified in the main paper, Moran's $I = 0.34$, $p < 0.01$.

The 20 districts for which the total number of weeks spent at or above the alert threshold exceeded the national median included 16 of the 17 meningococcal meningitis hotspots, which were identified by the reappearance of suspected cases against district population size, based on weekly suspected case counts. The 19 districts for which the total number of weeks spent at or above the epidemic threshold exceeded the national median included 15 of the 17 meningococcal meningitis hotspots, as calculated by the reappearance of suspected cases against population size based on weekly suspected case counts. The 16 districts for which the total number transitions to the alert threshold exceeded the national

median included only 7 of the 17 meningococcal meningitis hotspots. The 18 districts that exceeded the national median for transitions to the epidemic threshold also included only 7 of the 17 previously identified meningococcal meningitis hotspots.
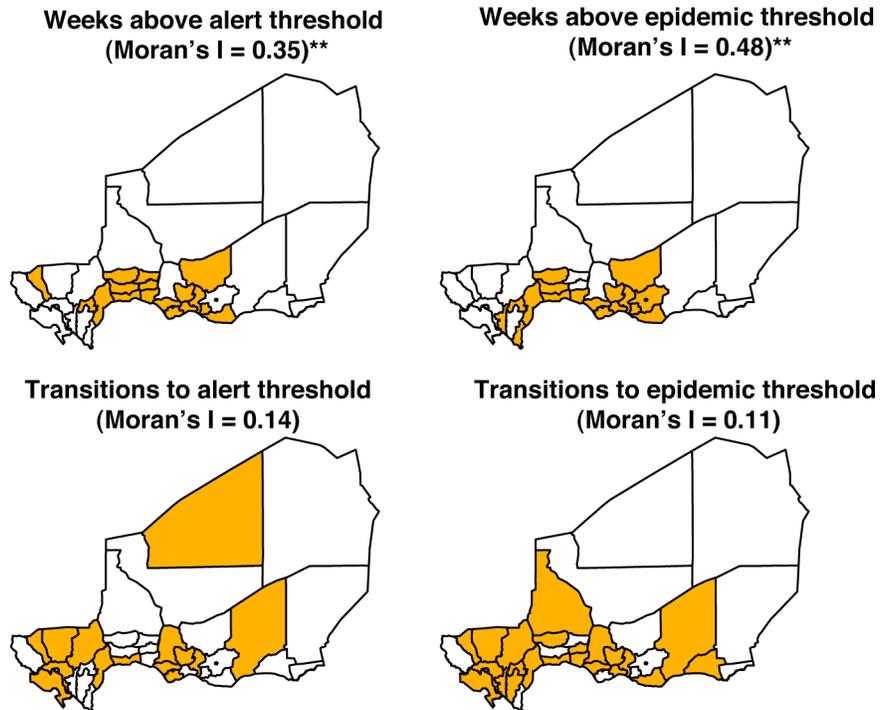

Fig. S2.2 Spatial analyses. Top row: districts are shown in orange for which total number of weeks spent above alert threshold (left) and epidemic threshold (right) exceeded the national median. Bottom row: districts are shown in orange if total number of transitions from below alert threshold to equal or above alert threshold (left) and for epidemic threshold (right) exceeded national median.

Discussion

The analyses of spatial patterns of weeks spent at or above both the district-level alert and epidemic thresholds indicate that, when correcting for population size, large numbers of suspected cases of meningococcal meningitis seem to follow a clustered spatial pattern. These results are very similar to the pattern we detected using reappearances of weekly suspected case counts. This shows that the spatial patterns that exist early in epidemics with low numbers of cases, as detected by the hotspots, are the same spatial patterns detected by the thresholds that govern intervention strategies and that case counts may allow for earlier detection than threshold triggers. We have found that case importation and reappearances may seed chains of continued local transmission, which can result in a sufficient number of cases to cross the alert and epidemic thresholds. If direct transmission is important in the spread of meningococcal meningitis, high numbers of contacts and high population density in these districts would encourage comparatively high rates of local transmission and increase the likelihood that these districts would remain above the alert or epidemic thresholds. As coverage of the conjugate vaccine increases, the patterns detected here highlight districts that spend the most weeks above

the alert and epidemic thresholds. Our analysis on absences and reappearances indicates that outbreaks in these districts may be caused by case importations or increased transitions from asymptomatic carriage to clinical cases. The set of districts that spend the most weeks above the attack and epidemic thresholds is very similar to the set of districts with high levels of reappearances of invasive meningococcal meningitis.

The total number of transitions to either threshold reveals no spatial pattern. This may indicate that the number of threshold transitions is not representative of the overall proportional caseload in any district. Some districts may be more likely to cross the thresholds, despite a low number of cases, if the population size is small. These districts may simply transition back and forth the across thresholds every year when the total number of cases rises and falls slightly throughout the meningitis belt. The total number of threshold transitions does not ultimately seem to indicate that a district will have a greater proportion of cases overall.

Conclusions

As progress continues towards eliminating the devastating meningococcal meningitis outbreaks in the African belt, there is hope that high levels of coverage with the conjugate vaccine will increase herd immunity in these vulnerable populations, breaking chains of transmission, and reducing the size and frequency of outbreaks [5]. Unfortunately, as we have seen with many other infections with long-term vaccine-derived immunity, complete vaccine coverage is nearly impossible to achieve, such that cases and outbreaks will likely continue to occur. Ideally, these will become rare events but they will continue to require reactive attention. The early detection of meningococcal meningitis continues to be very important and, using these two complementary analyses, we show that identifying districts where reappearances of meningococcal meningitis are common can help detect districts that should be of concern for surveillance due to high attack rates.

References

(1)   World Health Organization. Managing meningitis epidemics in Africa: A quick reference guide for health authorities and health-care workers. In: Response GAa, ed. Geneva: WHO Press, 2010: 30.
(2)   Bartlett MS. Measles periodicity and community size. *Journal of the Royal Statistical Society Series a-General* 1957; 120(1): 48-70.
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(4)   Moran PAP. Notes on continuous stochastic phenomena. *Biometrika* 1950; 37: 17:33.
(5)   Kieny M, LaForce F. The promise of conjugate vaccines for Africa. *Vaccine* 2007; 25(S1): A108-A110.