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Meningitis and climate: from science to practice

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Abstract

Meningococcal meningitis is a climate sensitive infectious disease. The regional extent of the Meningitis Belt in Africa, where the majority of epidemics occur, was originally defined by Lapeysonnie in the 1960s. A combination of climatic and environmental conditions and biological and social factors have been associated to the spatial and temporal patterns of epidemics observed since the disease first emerged in West Africa over a century ago. However, there is still a lack of knowledge and data that would allow disentangling the relative effects of the diverse risk factors upon epidemics. The Meningitis Environmental Risk Information Technologies Initiative (MERIT), a collaborative research-to-practice consortium, seeks to inform national and regional prevention and control strategies across the African Meningitis Belt through the provision of new data and tools that better determine risk factors. In particular MERIT seeks to consolidate a body of knowledge that provides evidence of the contribution of climatic and environmental factors to seasonal and year-to-year variations in meningococcal meningitis incidence at both district and national scales. Here we review recent research and practice seeking to provide useful information for the epidemic response strategy of National Ministries of Health in the Meningitis Belt of Africa. In particular the research and derived tools described in this paper have focused at "getting science into policy and practice" by engaging with practitioner communities under the umbrella of MERIT to ensure the relevance of their work to operational decision-making. We limit our focus to that of reactive vaccination for meningococcal meningitis. Important but external to our discussion is the development and implementation of the new conjugate vaccine, which specifically targets meningococcus A.

Keywords: Meningococcal meningitis; Meningitis belt; Climate; Mineral dust; Relative humidity; Epidemics; Reactive vaccination; Forecasting; Risk factors; Africa; Statistical models

Introduction

Meningococcal meningitis is an infection of the thin lining that surrounds the brain and spinal cord. While there are many causes of meningitis, the epidemic form of the disease is caused by bacteria *Neisseria Meningitidis*. Meningitis is one of the most feared diseases in Africa because of its rapid onset and high rates of long-term disability and fatality. Epidemics pose a serious threat to populations and place a severe burden on public health systems and on socio-economic development.

Getting science into policy and practice is a challenge, particularly in public health where evidence-based policies are expected. For diseases such as meningitis that are climate sensitive, there is the perception that climate information may be relevant to improving control measures. However, delivering apparently simple changes into an epidemic response strategy requires applied cross-disciplinary science focusing on practical solutions to problems that evolve with time.

The MERIT (Meningitis Environmental Research Information Technologies) initiative was launched in 2007 as a multi-sectoral partnership led by the World Health Organization (WHO) to provide a platform for public health specialists, epidemiologists, immunologists, microbiologists, demographers and climate and environment specialists to work together to provide innovative solutions for the control of meningococcal meningitis epidemics in the African Sahel. The history of MERIT, its membership and its processes are described in detail elsewhere (Thomson et al. 2013). The International Research Institute for Climate and Society (IRI) has played a key role in MERIT since its inception, helping to frame the initiative and Steering Committee, while IRI staff, students, adjuncts and partners followed key lines of inquiry. In

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2012 the MERIT initiative was endorsed by an external panel of experts (Thomson et al. 2013).

For over a century, epidemics of meningococcal meningitis have occurred in Africa. Until recently, the main control approach has been reactive vaccination after an outbreak has reached a defined threshold. Delays in vaccine procurement and delivery limit the success of this approach, which is also unable to prevent the occurrence of new epidemics (Roberts 2008). Meningococcal conjugate vaccines, which can prevent meningococcal carriage and thus interrupt transmission, may be effective at preventing epidemics and are currently being 'rolled out' across the region (LaForce et al. 2007). Despite the rapid implementation of a new conjugate vaccine (which targets serogroup A only), a recent review indicated that there is still a need for further work to identify the host, organism and environmental factors that contribute to the geographic location, seasonality and inter-annual variability of meningococcal disease and to predict and control epidemics in Africa (Greenwood 2013).

Over the 6 years that MERIT has been active three operational areas have been identified as a priority for research - with the focus shifting over time from reactive to preventive vaccination strategies (MERIT 2012). These areas are:

1. improve the impact of reactive mass vaccination campaigns, prepare for the following epidemic season, and refine the response strategy for epidemics. After the introduction of the new conjugate vaccine, this refers to epidemics due to serogroups other than A;
2. preventive vaccination campaigns; guide the introduction of the conjugate A vaccine and estimate its impact, and
3. forecasting the location of future epidemics on 5 to 10-year time horizons in order to assess possible vaccine needs.

Broad spatial and seasonal patterns of meningitis in Africa have been related to climate and other risk factors since the eco-epidemiology of the disease was first described (Lapeyssonnie 1963). Yet, the introduction of climate information and other risk factors as part of a control strategy is relatively new (World Health Organization 2004).

This paper reviews the advances and challenges in science and practice to develop Early Warning Systems (EWSs) for meningococcal meningitis in Africa. Specifically, the paper overviews the main characteristics of epidemic meningitis in Africa, reviews the current understanding of the role of climate upon the spatial and temporal variability of the disease, discusses the conceptual and mathematical models that combine risk factors to explain the spatiotemporal epidemic patterns, and presents tools and statistical models recently developed with potential operational application in the context of epidemic response. Important but external to our discussion is the development and introduction of the new conjugate vaccine that specifically targets meningococcus A.

Meningitis epidemics in sub-Saharan Africa

The Meningitis Belt

The Meningitis Belt (Figure 1), comprising much of semi-arid sub-Saharan Africa, features high levels of seasonal endemicity and epidemics during the dry season. The belt was first associated to an area between latitudes 4° and 16° N receiving between 300 and 1100 mm of annual rainfall in a single rainy season (Lapeyssonnie 1963) and included parts of Burkina Faso, Niger, Nigeria, Chad and Sudan. The belt was subsequently extended to parts of Benin, Cameroon, Central Africa Republic, Uganda, Kenya, Rwanda, Ethiopia, The Gambia, Ghana, Mali and Senegal (Cheesbrough et al. 1995; Moore 1992; World Health Organization 1998). Epidemics in the Meningitis Belt are due to serogroups A, C, X, Y and W135, with serogroup A historically accounting for 80–85% of all cases. Important epidemics with serogroup W135 have emerged in the recent past, including 2002 in Burkina Faso, with 13,125 suspected cases and 1,510 deaths (World Health Organization 2003).

Spatial and temporal dynamics of meningitis

Epidemic waves following crescendo-decrescendo patterns in the Meningitis Belt have occurred every 8 to 14 years (Moore 1992; Broutin et al. 2007) (Figure 2). Periodicity of meningitis and synchrony among countries has changed through time (Broutin et al. 2007). While Burkina Faso has shown a constant cycle of around 12 years since 1939, periodicity in Sudan has increased from around 9 to 12–13 years since the 70s and in Nigeria has decreased from around 12 to 8–9 years since the mid 70s. Only after the mid 60's have Niger and Mali featured periodicities of 8–10 and 12–14 years, respectively, and Ghana, Togo and Benin showed 12-year cycles up to the 60s, with no periodicity detected thereafter. There is a significant correlation in meningitis epidemics among countries, although it alternates between perfect or out-of phase synchrony in the majority of comparisons (Broutin et al. 2007).

From the 1980s, epidemics occurred throughout the Meningitis Belt in Benin, Burkina Faso, Chad, The Gambia, Ghana, Mali, Niger, Nigeria, Senegal and Togo. Severe epidemics occurred in Ethiopia, Sudan and Chad in 1987–1990, with more than 30,000 cases reported in Sudan in 1988 (World Health Organization 1998). In 1995–1997 a strong epidemic wave (Figure 2) affected Niger (more than 25,000 cases in 1995 and more than 16,000 cases in 1996), Northern Nigeria (more than 100,000 cases in 1996), Burkina Faso (more than 40,000

Figure 1 The Meningitis Belt. Extracted from (World Health Organization 2003).

cases in 1996 and more than 20,000 in 1997) and Mali (more than 7,000 cases in 1996, more than 10,000 in 1997).

Until recently, Niger has been one of the countries in the belt with the largest disease burden and for which the longest district-level weekly records are available. Figure 3 displays the weekly number of cases at national level and the seasonal cycle box plot of incidence by week for 38 districts in Niger from 1986 through 2008. From 1986 to 2005 Niger had an average annual incidence rate of 95.9 cases per 100,000 population and case fatality rates of 8.2% (Djingarey et al. 2008). The largest epidemic occurred in 1995. In addition, 1986, 1993, 1994, 1996 and 2000 were epidemic years with incidence greater than 100 per 100,000 at the national level.

Meningitis incidence is seasonally dependent, with cases increasing at the beginning of the dry season from November/December, typically peaking in February-March-April and declining rapidly with the onset of rains in May (Figure 3). In Niger, incidence peaked at week 14 of the year on average and epidemics lasted on average 10 weeks (Djingarey et al. 2008). Incidence displays strong spatial and interannual variability at regional (Figure 2), national (Figure 3) and district levels (Paireau et al. 2012; Tall et al. 2012).

Risk factors

Risk factors for epidemics are not fully understood. The heterogeneous spatial and temporal distribution of epidemics (Figures 2 and 3) suggests that a complex interaction involving host, organism and environment is necessary for an epidemic to occur (Greenwood 1987; Moore 1992). A significant proportion of the global population carries the bacteria asymptomatically in the nose and throat, and never develops the invasive disease. The bacteria are transmitted from one person to another through respiratory droplets or throat secretions. Under certain circumstances, the bacteria become pathogenic, invading the naso-pharageal epithelial cells (colonization) and entering the blood stream (invasion). The case fatality rate generally ranges between 10% and 15% in the belt (Trotter & Greenwood 2007). The risk of acquiring meningococcal disease decreases with age. Disease or carriage

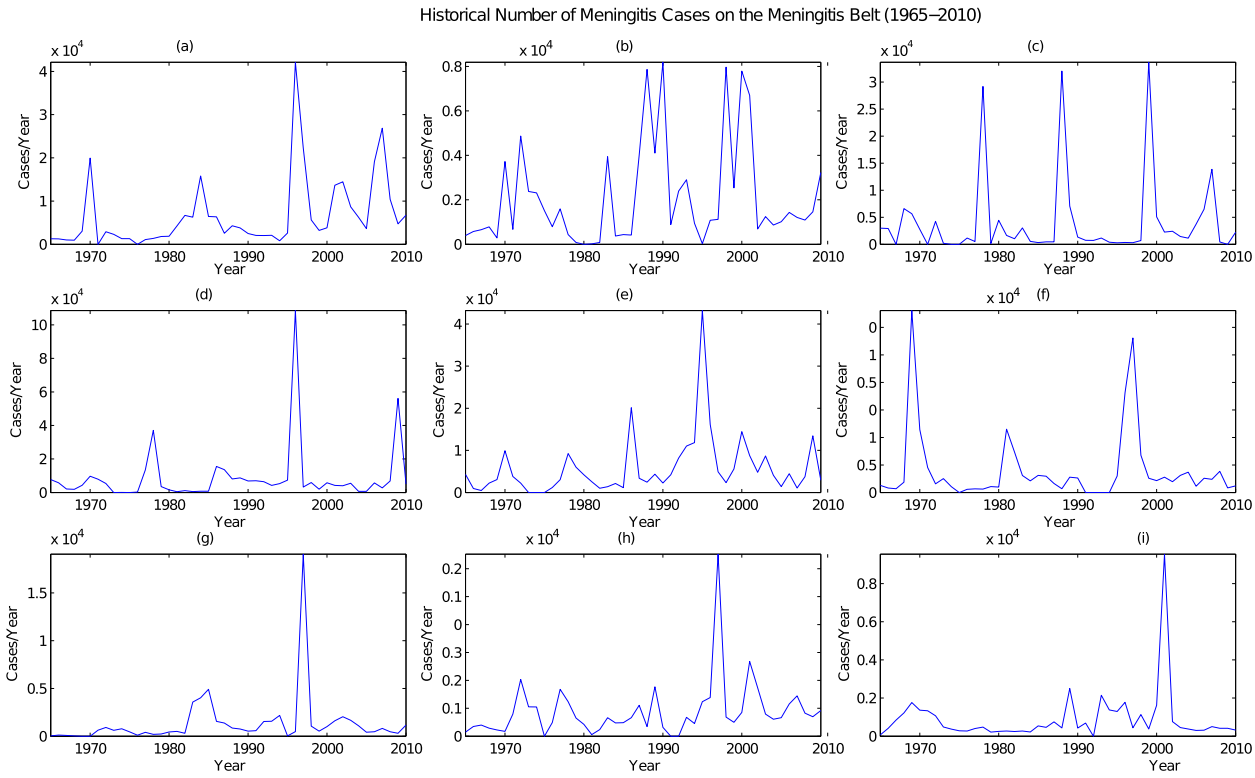

Figure 2 Times series of number of meningitis cases between 1965 to 2010 in (a) Burkina Faso, (b) Chad, (c) Sudan, (d) Nigeria, (e) Niger, (f) Mali, (g) Ghana, (h) Togo, and (i) Benin. Source of data: WHO.

protects against disease caused by the same serogroup (Trotter & Greenwood 2007). As carriage does not necessarily induce invasive disease (Wenzel et al. 1973), humoral immunity (Griffiss et al. 1987) and herd (i.e. population) immunity to a prevalent strain (Greenwood 1987) may be among the most important factors in the prevention of epidemics. Clone virulence or introduction of novel clones of a serogroup in a susceptible population, though population movements, contributes to trigger epidemics (Moore et al. 1989). Over the past 40 years ST-1 complex/subgroup I/II, ST-4 complex/subgroup IV, and ST-5 complex/subgroup III (shifting to ST-7 since the mid 90's) have successively caused the majority of serogroup A epidemics in the Meningitis Belt (Harrison et al. 2009). However, the introduction of novel clones during periods of susceptibility is insufficient to trigger epidemics. A clear evidence of this insufficiency is that even during major epidemic waves, meningitis is suppressed during the rainy season. During the dry season, coincident respiratory infections and climate conditions including high levels of mineral dust are thought to increase invasive disease and transmission (Moore 1992; Mueller & Gessner 2010). Other risk factors may be genetic susceptibility (Davila et al. 2010), poverty and household crowding (Moore 1992), and exposure to smoke from cooking fires (Hodgson et al. 2001).

The role of climate and dust

Environmental and climate conditions have long been highlighted as driving factors of epidemics (Waddy 1952; Lapeyssonnie 1963; Greenwood et al. 1984; Cheesbrough et al. 1995). Epidemics and seasonal upsurges in endemic disease occur during the dry season and subside at the onset of the rains (Lapeyssonnie 1963; Molesworth et al. 2002; Sultan et al. 2005). The broad spatial pattern and seasonality of meningitis suggests that certain environmental factors, such as low absolute humidity (Cheesbrough et al. 1995; Molesworth et al. 2003) and relative humidity (Dukić et al. 2012), temperature (Dukić et al. 2012) and dusty atmospheric conditions (Thomson et al. 2006; Agier et al. 2013a; Pérez García-Pando et al. 2014) play an important role. Identifying the specific climate factor that drives epidemics is challenging because many environmental variables have a prominent seasonal cycle that covaries with disease incidence. In addition, although the interactions between mucosal epithelial cells and *Neisseria Meningitidis* are well known (van Deuren et al. 2000), the effects of climate and dust on the pathogenesis and transmission of the bacteria have not been studied in vivo (Palmgren 2009).

Figure 4 displays seasonal cycle box plots of climate and dust variables by week simulated with an

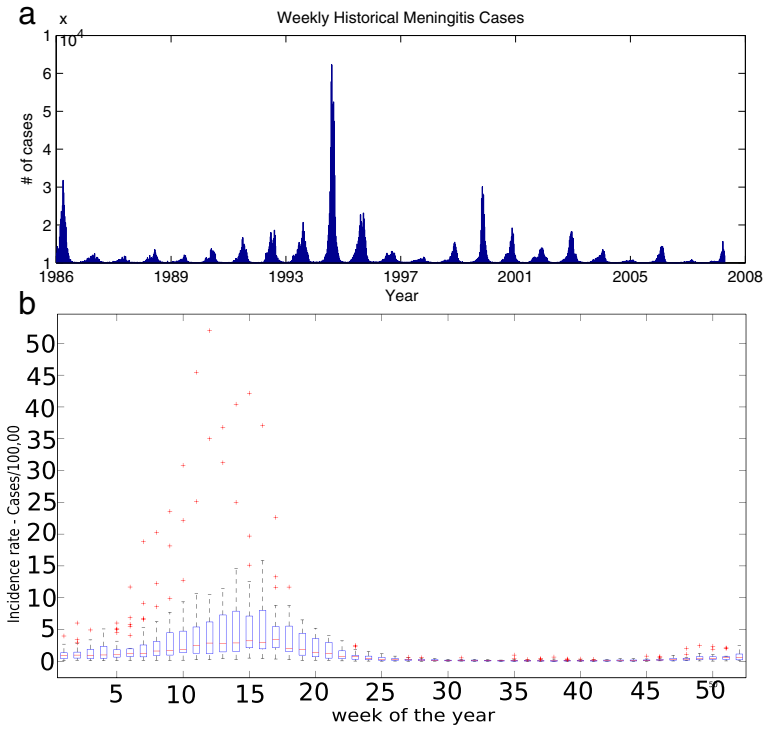

Figure 3 Number of cases per week between 1986 and 2008 in Niger (a) and seasonal cycle box plot of incidence (cases/100,000) by week for 38 districts in Niger from 1986 through 2008 (b). (b) each box shows the range in which the central 50% of the data fall. The box borders show the first and third quartiles and the crossbar shows the median. Values (outliers) exceeding the quartile values by more than factor of 1.5, the interquartile distance, are marked as crosses.

atmospheric dust model (Pérez et al. 2011) for 38 districts in Niger between 1986 and 2008. The seasonal cycle is controlled by the migration of the Intertropical Convergence Zone (ITCZ) that leads to the alternation during the year of two main climate regimes. In boreal winter, the Harmattan, a surface stream of dry and dusty air that is part of the African continental trade winds, sweeps from the northeast towards the Gulf of Guinea. In summer, flow from the southwest brings moisture from the oceans and coastal vegetated regions. Dry season weekly median concentrations of mineral dust range from 200 to 400 μg/m^3 with values reaching up to 500–1000 μg/m^3. The seasonal cycles of surface concentrations and column–integrated dust optical depths differ (Figure 4) because dust originating from the Sahara is transported at different altitudes during the year. From December to March, absolute humidity is at its minimum, on the order of 5 g/m^3. Temperature reaches its lowest values in December/January and steadily increases until April, while relative humidity stays below 40% during the dry season with values decreasing as temperature increases, reaching a minimum of around 20% at the end of March. Humidity exhibits strong year-to-year variability during the transition from the dry to the wet season and year-to-year changes have been shown to be gradual (Seefeldt et al. 2012).

Absolute humidity and land-cover type were found to be the best predictors in a spatial multivariate model of the broad spatial distribution of epidemics (Molesworth et al. 2003) (Figure 5). Areas with contrasting seasons in the Sahel are more likely to have epidemics with risk decreasing towards the southern peripheral regions where the dry season is shorter and less extreme. Areas without contrasting seasons, both in the humid parts of coastal and Central Africa and in the dry Saharan region show low risk of epidemics, the latter due to low population density in desert areas.

The abrupt shift in the seasonal cycle of the total number of cases in Mali at the sixth week of the year has been related to the dry season wind maximum (Sultan et al. 2005). In Niger, the average seasonal peak in meningitis is preceded by a week or two by a peak in dust optical depth (Martiny & Chiapello 2013). One important difficulty in uncovering drivers of infectious diseases is to identify the appropriate scale of analysis (Pascual & Dobson 2004) since local determinants of epidemics may obscure the impact of larger-scale environmental conditions. The relationship between disease and

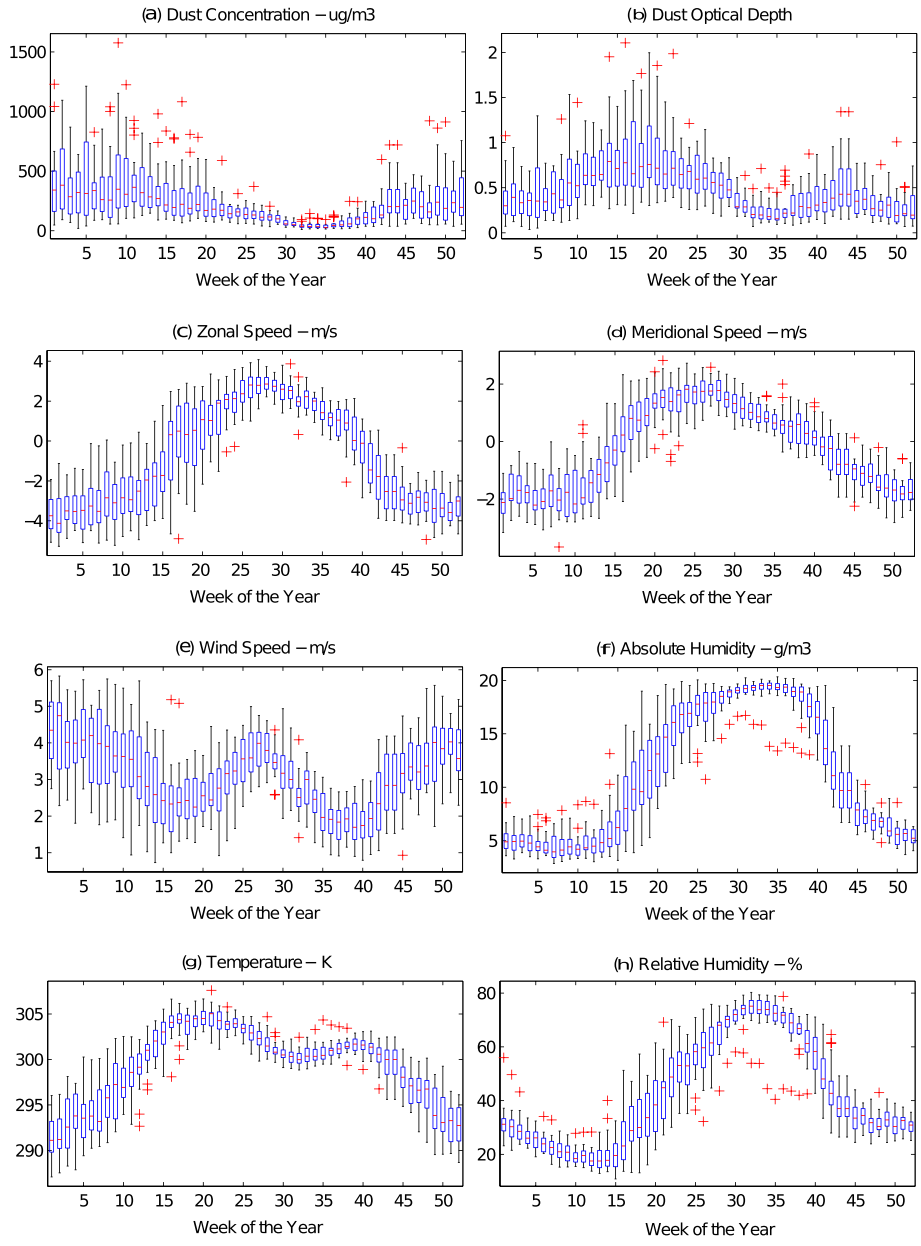

Figure 4 Seasonal cycle box plots by week for 38 districts in Niger between 1986 and 2008 for a) dust concentration, b) dust optical depth at 550 nm, c) zonal wind speed, d) meridional wind speed, e) wind speed, f) absolute humidity, g) temperature, h) relative humidity. Each box shows the range in which the central 50% of the data fall. The box borders show the first and third quartiles and the crossbar shows the median. Values (outliers) exceeding the quartile values by more than factor of 1.5, the interquartile distance, are marked as crosses. Data were derived from a long-term simulation from 1986 to 2006 with the NMMB/BSC-Dust model (Pérez et al. 2011).

climate apparent at large spatial scales may not be appropriate to resolve local variability, which is crucial for public health interventions in the Meningitis Belt. Within multiple districts in Niger, Agier et al. (2013a) found similar time-lags between the occurrence of dust outbreaks and meningitis, which suggests that dust information may be useful in epidemiological and forecasting models. Dukić et al. (2012) applied Generalized Additive Models treating time-varying confounding processes (e.g. seasonal population migration, new strains) as a background function that varies in magnitude by year, and asked how much of the intraseasonal variability each year could be related to specific variables that vary more quickly in time. The analysis of 11 years of laboratory-confirmed meningitis cases from Navrongo, Ghana, showed that accounting for local weather improved estimates of monthly cases by up to 40%. In particular, the current maximum monthly temperature and the

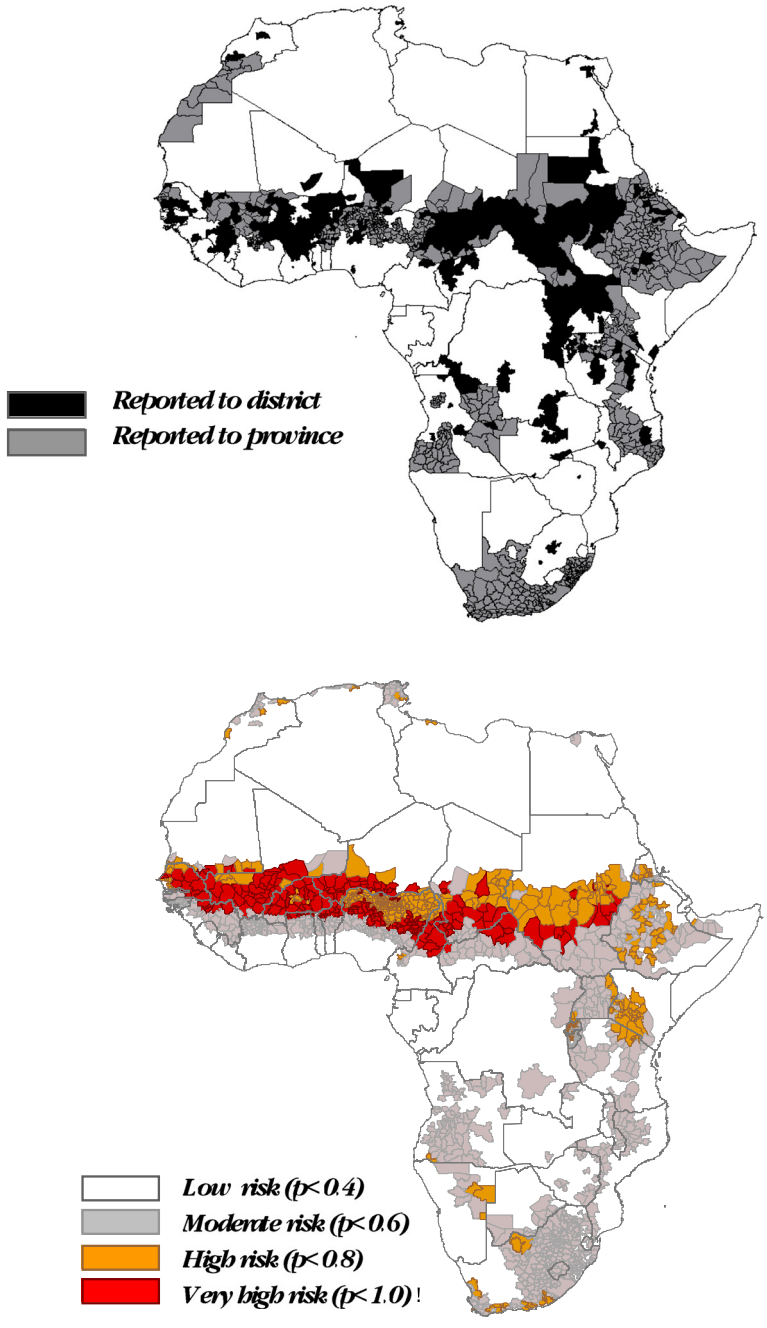

Figure 5 Distribution of districts where epidemics of meningococcal meningitis are likely to occur. Observed distribution of meningitis epidemics (1841–1999) (top panel). Predicted probability of epidemic experience based on environmental variables (absolute humidity and land-cover type) (bottom panel). Reproduced from Molesworth et al. (2003).

previous month's relative humidity and CO emissions due to fires showed the most value in anticipating meningitis cases. We note that the southern Sahel is strongly affected by biomass burning aerosols in addition to dust outbreaks during the dry season. This is consistent with the results of a survey of Navrongo-area residents, which indicted that meningitis is associated with hot and high aerosol conditions (Hayden et al. 2013).

The seasonal cycle box plot of weekly incidence for 38 districts in Niger (Figure 4) features median values below 5 weekly cases per 100,000 population and strong outliers reaching up to 50 weekly cases per 100,000 population. An ongoing debate is whether variations in climatic variables can at least in part explain year-to-year variations in seasonal incidence (amplitude) or if this influence is just related to the timing of onset,

peak and end of meningitis. However, at least in some regions, the timing of onset and peak has been associated with the amplitude of epidemics (de Chabalier et al. 2000). Several studies have related anomalies in amplitude to anomalies in climate. In semi-arid, northern Benin, 14 to 34.5% of the temporal variability of the disease over 28 years was related to low absolute humidity associated with variations of the Harmattan. Rainfall anomalies in January and dust anomalies in October appeared to be the most consistent predictors of anomalies in seasonal incidence at district level in West Africa (Thomson et al. 2006), and about 25% of the year-to-year disease variance at national scale in Niger could be explained by variations in the December-averaged meridional wind (Yaka et al. 2008). Early cases, population density, wind and dust information in the early season could explain a 41% of the year-to-year spatiotemporal variability of the disease at district level in Niger (Pérez García-Pando et al. 2014).

Conceptual, mathematical and statistical models

Meningitis dynamics may be better understood and predicted with mathematical modeling. Conceptual models combining relevant factors have been proposed to guide the development of mathematical models, understand the disease and improve practical interventions (Moore 1992; Mueller & Gessner 2010). Loss of herd immunity to specific strains may have contributed to the initiation of large-scale epidemic cycles observed in the Meningitis Belt (Figure 2). The subsequent development of herd immunity due to widespread carriage of the epidemic strain during the cycle may have limited transmission ending the epidemic wave (Moore 1992). In this conceptual model, transmission is considered seasonally independent since studies haven't found a systematic variation in the carriage prevalence of meningococcal serogroups by season (Trotter & Greenwood 2007; Harrison et al. 2009). Epidemics during the dry season were then explained by a combination of climatic conditions and widespread respiratory infections decreasing mucosal protection and thus promoting invasion rather than carriage in a low herd immunity setting.

The three main hypotheses to explain the effects of climate and environment upon seasonal incidence are an increased risk of invasive disease after infection, an increased risk of transmission (including adhesion and colonization) and a combination thereof. A more recent and refined conceptual model (Mueller & Gessner 2010) describes the heterogeneous spatiotemporal dynamics of meningitis (Figure 3) distinguishing among endemic incidence during the rainy season, ubiquitous hyperendemicity during the dry season, occasional localized epidemics, and large-scale epidemic waves spanning communities or years. In this framework, the transition from endemic to ubiquitous hyperendemic conditions would be caused by an increased risk of invasion of a virulent strain due to damage of the pharyngeal mucosa by dry and dusty climate. The transition from hyperendemicity to localized epidemics would involve increased pharyngeal colonization and/or transmission through coughing and sneezing possibly caused by viral respiratory infection epidemics or other local-scale co-factors, a hypothesis that is compatible with significant increases in carriage prevalence of the specific virulent strain during epidemics (Mueller et al. 2008) and the heterogeneous and sporadic occurrence of meningococcal epidemics (Tall et al. 2012). A regional epidemic wave would result from a wider geographic spread of epidemic co-factors such as a viral epidemic or the introduction of a new virulent strain.

In both models dry and dusty conditions are considered to affect invasion rather than carriage and transmission. Yet, the contribution of climate to carriage and transmission by, for example, enhancing seasonal viral epidemics (Fuhrmann 2010) cannot be ruled out. Besides damaging the pharyngeal mucosa, some other controversial hypotheses about the role of dust include the activation of the meningococcus through the high iron content of dust particles and the impact of high dust levels on human behavior, including crowding and reduced ventilation (Thomson et al. 2009). Results from a deterministic compartmental model showed that the irregular timing of meningitis epidemics could be caused by the interaction of temporary immunity conferred by carriage together with seasonal changes in transmission rather than seasonal changes in invasion (Irving et al. 2011). Results from a parsimonious statistical model fitted to data in Nigeria supported the hypothesis of a generalized regional increase in the rate of invasive disease and suggested that the end of an epidemic was driven more by the reduction in susceptible individuals and a decrease in transmission rather than by a decline in the rate of invasive disease (Jandarov et al. 2012).

Potential tools and models to improve epidemic response

Response to meningitis epidemics is based on weekly incidence thresholds at the district level (World Health Organization 2000): the alert threshold, defined as 5 cases per 100,000 inhabitants per week for populations greater than 30,000 inhabitants and 2 cases in one week for populations of less than 30,000 inhabitants, is used to launch an investigation at the start of an epidemic, check epidemic preparedness, start a vaccination campaign if there is an epidemic in a neighbouring district and prioritize areas for vaccination campaigns in the course of an epidemic. The epidemic threshold, which is used to step up mass vaccination, is defined as 10 cases (or 15 cases depending on context) per 100,000 inhabitants for

populations greater than 30,000 inhabitants and 5 cases in one week for populations of less than 30,000 inhabitants. This strategy depends on timely surveillance, and rapid response, which are difficult to achieve in less-developed countries. The strategy can therefore benefit from improved surveillance and forecasting tools.

Sub-district level surveillance

Data on confirmed cases at a sub-district spatial scale in Niger and Burkina Faso have highlighted significant intra-district heterogeneity and interannual variability (Paireau et al. 2012; Tall et al. 2012). Besides improving future mathematical modeling, surveillance and redefinition of weekly epidemic thresholds at the sub-district Health Centre level could improve reactive vaccination response. In Burkina Faso, if an epidemic threshold of 5 cases per 100,000 in one week was used, epidemics could have been spotted more precisely and in one quarter of instances at least one week earlier than with the current district level strategy (Tall et al. 2012).

Forecasting meningitis

Despite progress in surveillance and research, the incomplete understanding of meningitis epidemic patterns and the lack of quality data at the required temporal and spatial scales limit the use of mathematical modeling to forecast epidemics. EWSs for infectious diseases aim to identify whether an epidemic will occur and to predict the magnitude of incidence (World Health Organization 2004). The latter may be unattainable at precision, regardless of the quality of information, due to small-scale stochastic effects (Drake 2005). However, from a policy perspective, the exact magnitude of incidence is of less interest in comparison to whether or not the incidence crosses an action-triggering threshold.

Statistical models based on incidence

Given the complex nature of meningitis epidemics that seem to elude description by deterministic models, statistical models have been developed to forecast the probability of exceeding WHO's incidence-based decision thresholds. The motivation was to provide an estimate of the likelihood that the thresholds would be exceeded in the near future. Due to uncertainties in the factors that drive epidemics at the weekly time scale, these models were developed using an empirical approach i.e. no assumptions as to what drives changes in incidence were made, with the original forecasts based primarily on previously observed incidence but without considering climate information or other factors.

Beresniak et al. (2012) evaluated the risk that an epidemic would occur in a particular district after epidemics had been reported in other districts. Through a Bayesian network, the probabilities of districts on alert or epidemic situation influencing other districts were estimated for Niger. When considering districts reaching epidemic alert or epidemic thresholds potentially influencing other districts in 2004, 2005 and 2006, the proportion of the outbreaks observed that were successfully predicted for the period 2006–2008 was 63% when the epidemic threshold was used and 91% when the alert threshold was used.

Other statistical models for continuous data (observed incidence), and discrete data (below the WHO alert threshold, between the alert and epidemic threshold and above the epidemic threshold), have been considered (Agier et al. 2013b; Stanton et al. 2013). Using dynamic (generalised) linear modelling (Durbin & Koopman 2012; West & Harrison 1997), Stanton et al. (2013), assumed that meningitis incidence followed a general seasonal trend, with flexible timing and magnitude of peaks in incidence introduced by allowing the regression coefficients to evolve over time according to previously observed incidence (temporal dependence) in both the district itself, and in neighbouring districts (spatial dependence). To estimate the weekly incidence for each district, estimates of the probability of exceeding an arbitrary threshold could also be extracted for these models. In the discrete setting, a multinomial logistic Markov chain model was used to describe the transition between the three states (below alert, between alert and epidemic, and above epidemic) as defined by WHO thresholds (Agier et al. 2013b). Transition probabilities were dependent both on a general seasonal trend an on the states of neighbouring districts in the previous week. The probability of exceeding the alert/epidemic threshold in any given week was therefore a direct output of this model. Models were evaluated and compared using different policy-linked evaluation criteria. Firstly it was assumed that the primary goal of the exercise was to predict the exact weeks over which the epidemic threshold was exceeded (Criterion 1). Secondly (and alternatively), it was assumed that the primary goal was to predict whether or not the epidemic threshold would be exceeded within a given meningitis-year prior to its onset, regardless of the true time lag between the week in which incidence was first predicted to exceed the threshold and the week in which the observed incidence first exceeded the threshold (Criterion 2). Using the Niger weekly incidence data, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each of the models' predictions were calculated using both evaluation criteria. Sensitivity, also known as the true positive rate is defined as the proportion of 'positive' events that are correctly predicted. Specificity is the proportion of 'negative' events that are correctly predicted. PPV is the proportion of positive event predictions that are correct, and NPV is the proportion of

negative event predictions that are correct. A key point to note when considering these measures is that both PPV and NPV are affected by the overall prevalence of the event in question, such that by fixing sensitivity and specificity, a rare event will have a lower PPV and higher NPV than a more common event. As such, a model with low PPV is more a reflection on the rarity of crossing the threshold than on the performance of the model. Therefore, to determine whether or not the models are of use to policy makers, it is of more use to consider the values of sensitivity and specificity achieved (Table 1). In comparing the models, in general the Markov chain model outperforms the dynamic models when considering evaluation Criterion 1, whereas the opposite is true when considering evaluation Criterion 2. Using a dynamic linear model and evaluation Criterion 2, 71% of epidemics are correctly predicted prior to their onset (sensitivity) whereas 58% of years during which an epidemic is predicted to occur are correct (PPV). Using a Markov chain model and evaluation Criterion 1, 71% of instances where the epidemic threshold is exceeded are correctly predicted, whereas 78% of instances where the epidemic threshold is predicted to be exceeded are correct.

Climate/weather-based models

There is a lack of spatially and temporally resolved data on carriage, herd immunity, previous vaccination type and coverage, serogroup type, clonal virulence and coincident respiratory infections that are thought to explain the epidemic pattern. Although gridded climate and dust data generated by models and/or observations contain uncertainties, their availability at the required spatial and temporal scales is an advantage for potential meningitis forecasting to the extent that they influence the evolution of epidemics.

An exploratory analysis was undertaken on extending empirical statistical models at weekly and district scales (Stanton et al. 2013) in Niger using weather variables including temperature, specific and relative humidity, wind and dust (Stanton et al. 2011) derived from long-term integrations with a regional dust model (Pérez et al. 2011) constrained by the National Centers for Environmental Prediction/National Center for Atmospheric Research (NCEP/NCAR) reanalysis (Kalnay et al. 1996). Lagged weekly and four-weekly averaged weather variables were considered for inclusion both in a linear model with a fixed seasonal trend, and a dynamic linear model with a flexible seasonal trend. More specifically, in order to disentangle the relationship between climate variables and meningitis incidence induced through a common seasonal and/or linear trend from a potential causal relationship, the climate variables included in the models were in the form of residuals obtained by subtracting both a linear trend plus a harmonic trend of order 3 from each of the climate variables under consideration. Although there was evidence of a weak relationship between residuals of weather and meningitis, particularly when taking average conditions over the preceding 4-week period, the strength of the relationship was insignificant in comparison to the strong seasonal trend already introduced by the incidence data. In addition, the inclusion of weather in these specific statistical models decreased the models' performance in terms of being able to predict when the epidemic threshold would be exceeded.

Table 1 Model evaluation summaries for weekly-scale statistical models (Agier et al. 2013b; Stanton et al. 2013) with respect to how well they predict whether or not the incidence the following week will exceed the epidemic threshold (Criterion 1), and how well they forecast an epidemic prior to its onset during a 12 month period (Criterion 2)

Model	Evaluation criterion	SENS	SPEC	PPV	NPV
Dynamic	1	0.649	0.981	0.705	0.979
Markov chain	1	0.710	0.994	0.780	0.991
Dynamic	2	0.706	0.793	0.579	0.870
Markov chain	2	0.549	0.792	0.510	0.816

An analysis of meningitis suspected cases across the Meningitis Belt using two years of data (2007–2009) was performed Hopson et al. (2014). Meteorological variables came from the National Centers for Environmental Prediction/National Center for Atmospheric Research (NCEP/NCAR) reanalysis (Kalnay et al. 1996). The transmission of meningitis was modeled using a differential equation-based epidemiological model that has been successfully used to model Methicillin-resistant Staphylococcus aureus (Macal et al. 2012). The model distinguished among infected and susceptible population, and asymptomatic carriers, assuming a homogenous mixing of people across these groups and disease homogeneity across the belt. The number of people infected was assumed to be small compared to the overall population, with changes in district population being negligible. Both the susceptible and carriage populations were considered proportional to the overall district population, and the disease cycle was assumed to be less than two weeks. Using a linearized model and treating each district's weekly epidemiology as an independent event, cross-validated logistic regression was used to solve for the probability of crossing the alert and epidemic thresholds based only on the two years of epidemiological data. By further assuming that the proximity to neighboring districts with cases of meningitis influences the chances of having a case, it was tested if the accuracy of the predictions could be improved when the model coefficients were assumed to relate to meteorological variables. After testing over 90 meteorological

variables with varying time lags, the most consistent improvement in the model's predictions came from including relative humidity first and northeasterly winds second. A relative humidity of 40 % marked an inflection point for the probability of a district exceeding the epidemic threshold (Figure 6). Given the verified correlation between meningitis cases and the average weekly relative humidity, researchers at UCAR were able to provide public health decision makers with information about the relative humidity. In addition to producing Meningitis Belt-wide humidity forecasts, the tuned differential equation-based model described earlier can be used to predict the probability of exceeding alert and epidemic thresholds one to four weeks ahead. End-of-season meningitis forecasts are produced by forecasting the date beyond which the risks of an outbreak are lower than the climatological risk for the next six weeks.

At the seasonal scale, a study fitted a range of negative binomial generalized linear models to seasonal meningitis data (number of cases between January and May) in Niger at national and district scales based on monthly climate and dust averages, population density, and early cases prior to the onset of meningitis season in January (Pérez García-Pando et al. 2014). Early cases in December were considered as a proxy for susceptibility and/or carriage prevalence. Climate and dust data were derived from long-term integrations with a regional dust model (Pérez et al. 2011). These models were evaluated using goodness-of-fit statistics and analyzing their ability to detect whether or not a particular incidence-based threshold had been exceeded. At the national scale, the use of both early cases and November-December averaged zonal wind together provided the best fit, explaining about 57% of the year-to-year variability of the seasonal incidence (Figure 7). A national model with early cases and October-December dust concentration performed similarly. To analyze the ability of the model to detect whether or not a particular incidence-based threshold had been exceeded, if the fitted probability of the cross – validated predicted values y_t exceeding a threshold K was greater than some value c, $0 < c < 1$, then it was predicted that $y_t > K$. At the seasonal scale, it was assumed that K = 100 cases per 100,000 population (de Chabalier et al. 2000). Sensitivity and specificity of this model to predict epidemics were 0.8 and 0.87, respectively, with four out of five years correctly predicted to have exceeded the threshold over a 20-year period, whereas two of the remaining fifteen years were incorrectly predicted to exceed it. Figure 7 demonstrates that during the 1994–1996 epidemic wave, years 1994 and 1996 presented anomalously high early cases while year 1995 presented an anomalously intense Harmattan during the early season. The combination of both early cases and early season climate provided a better prediction than any of the predictors alone. Whilst the model underestimated the magnitude of incidence in 1995, the general scale of incidence appeared to be well represented. At the district scale, early-season zonal wind and dust, along with the number of early cases and population density represented about 41% of the spatiotemporal variability with a cross-validated correlation of 0.55. An example of prediction for year 1995 is displayed in Figure 8, including maps of observed incidence and predicted probabilities of exceeding the threshold at district level. If equal importance is given to sensitivity and specificity, the district model achieved values of 0.68 and 0.72 respectively. Should health decision makers be concerned about wasting resources through unnecessary vaccinations, then the model could be adjusted to prioritize maximizing specificity and negative predictive value (NPV) at the expense of sensitivity, resulting in values of 0.27, 0.98, 0.77 and 0.85 for sensitivity, specificity, PPV and NPV respectively. Considering the simplicity of the model, and more importantly, the availability of the data required to fit these models, this type of predictions early in the season could have an operational value.

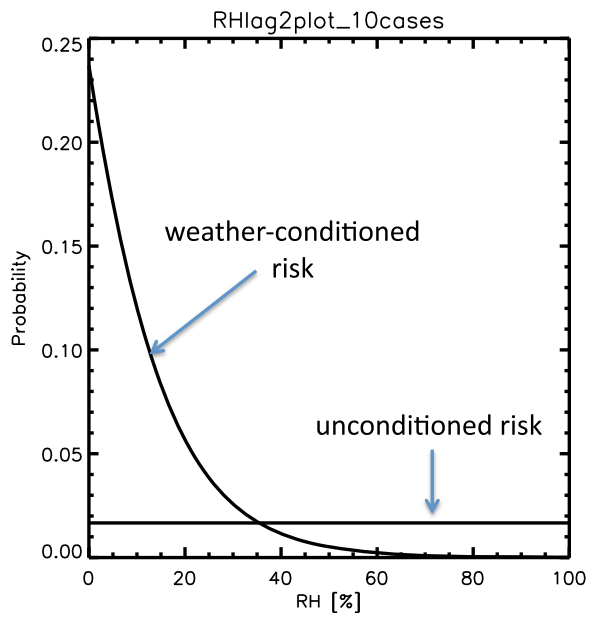

Figure 6 A log-plot of the probability of a district crossing epidemic threshold generated by a differential equation-based model of disease propagation whose coefficients depended on relative humidity and other weather variables (weather-conditioned risk) and ignored all weather variables (unconditioned risk). The line for weather-conditioned risk shows an inflection point at about 40% relative humidity, with the probability of epidemic increasing significantly in districts when the relative humidity is less than 40%. For comparison, the unconditioned risk is about 0.018, which can be understood as the probability of epidemic predicted without knowing the relative humidity. Extracted from Hopson et al. (2014).

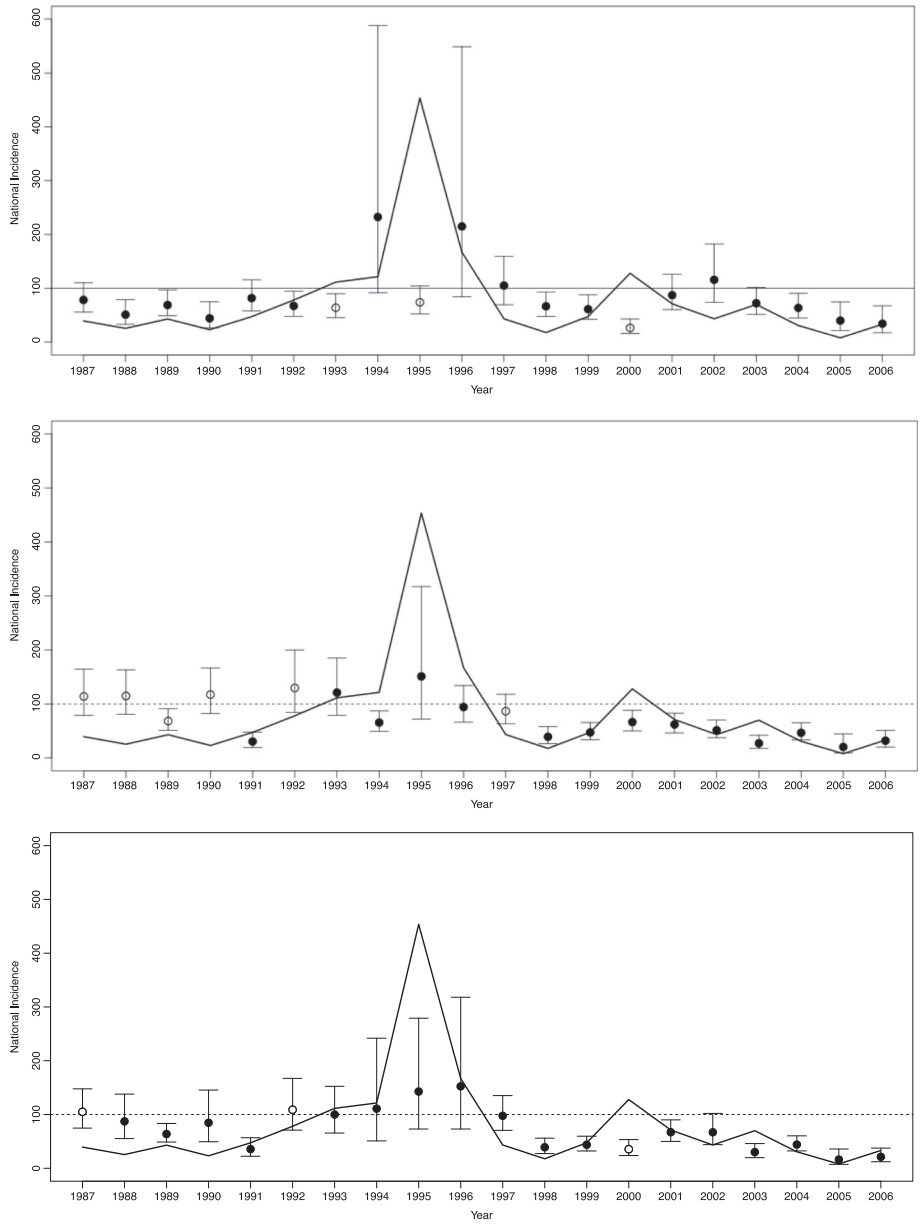

Figure 7 Observed incidence (solid black line) and cross-validated national incidence predictions (circles), with 95% confidence limits obtained by fitting a negative binomial model to the Niger national count data, using and December incidence as predictor (top panel), November-December zonal wind as predictor (middle panel), and December incidence and November-December zonal wind as predictors (bottom panel). Closed circles denote those predictions that were correctly assigned to be either above or below 100 cases per 100,000, whereas open circles are incorrect predictions. The bottom panel was extracted from Pérez García-Pando et al. (2014).

Practice and future

Model predictions contain uncertainty, which translates into complexity for decision-makers. Another challenge is the introduction of new tools to a diverse operational community in an environment that evolves rapidly as new interventions, technologies and policy options become available. As indicated above, the reactive vaccination strategy is currently being superseded by a preventive vaccination strategy focused on the delivery of the meningitis A conjugate vaccine. Statistical prediction models need to be amended to account for the introduction of the conjugate vaccine and their value needs to be tested and validated in close collaboration with decision-makers.

In order to initiate the process whereby environmental information and predictive models might be used operationally in meningitis epidemic response the MERIT community undertook a pilot outbreak prediction exercise conducted during the 2011–2012 meningitis season

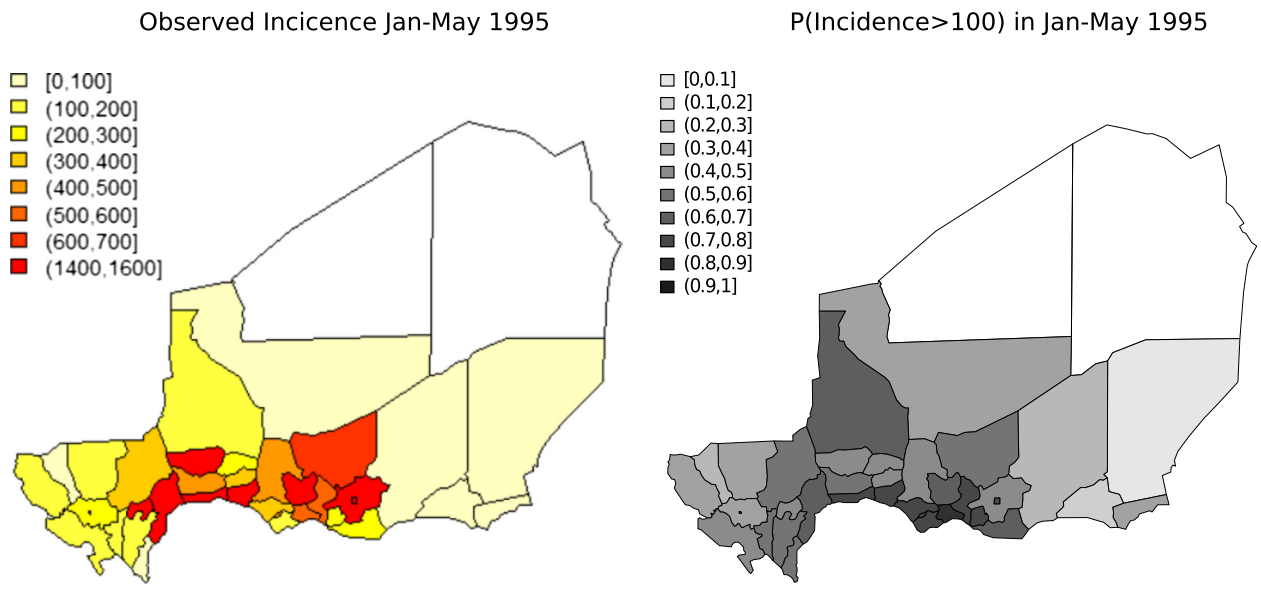

Figure 8 Maps of observed incidence for year 1995 at district level in Niger between January and May (right panel) and predicted probabilities of exceeding the seasonal epidemic threshold from a model including December incidence (national, district-level, and average of neighbors) and climate (national and district-level deviations from the national-level zonal wind and dust concentration) and population density (left panel). The modeling approach and detailed results are available in Pérez García-Pando et al. (2014).

in Africa. During this exercise public health professionals from several WHO and Ministry of Health (MoH) offices engaged with modelers, statisticians and climate/weather and environmental scientists to explore outputs from predictive models alongside the 'real time' evolving meningitis situation in four countries: Benin, Chad, Nigeria and Togo. The flow of information was continuous and led to the regular collection and quality control of both epidemiological and climate-related information. The observed and forecasted relative humidity and dust events in the region were also considered in order to analyze the environmental conditions favorable for epidemics. This exercise, which was facilitated by weekly teleconference calls and the sharing of data was also an opportunity to assess the effect of exchange of information between partners at the international and country levels. Learning from the 2011–2012 exercise, the 6th MERIT Technical Meeting, held in Accra, Ghana in November 2012 agreed to a similar exercise to be conducted in 2013 meningitis season (MERIT 2012), the results and conclusions of which will be published in the near future by the relevant participants.

Conclusions

Establishing EWSs for climate related disasters is a particular focus of the 'Global Framework for Climate Services' (Hewitt et al. 2012) and communities concerned with disaster risk reduction and climate change adaptation (Thomson 2013). Developing such EWSs for epidemic diseases (a specific type of disaster) requires the full participation of the health community and an understanding of their norms and practices. *A priori* a strong relationship between climate and environmental drivers must be shown to exist for such information to be considered useful to decision-makers. Research to date suggests that the geographic location, seasonality and year-to-year variability of meningococcal meningitis are associated in part with climatic and environmental factors. Although the determination of specific seasonal climate drivers including dust are difficult to identify, current models that incorporate environmental data, previous incidence, and/or other risk factors have shown sufficient skills to be further amended and tested for operational use. Also models are expected to improve as fine-scale surveillance and other sources of data on risk factors become available in the Meningitis Belt. The cooperation among diverse research and practice communities within MERIT provides a model for facilitating a better management of climate-sensitive diseases and provides guidance on how climate services for health might develop over time.

Competing interests

The authors declare that they have no actual or potential competing financial interests.

Authors' contributions

CPGP and MT conceived the paper and drafted large parts of the manuscript. MS and PD contributed to Section Potential tools and models to improve epidemic response and critically revised the manuscript. TH and RP contributed to Sections The role of climate and dust and Potential tools and models to improve epidemic response. RM contributed to Section The role of climate and dust and critically revised the manuscript. SH contributed to

Section Potential tools and models to improve epidemic response and critically revised the manuscript.

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