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Meningococcal meningitis in Mali: a long-term study of persistence and spread

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Summary
Objectives: Meningococcal meningitis (MM) is still a huge threat in the African meningitis belt. To fight against epidemics, a strengthened health information system, based upon weekly collected data, was set up in Mali. We aimed to study the spatio-temporal dynamics of MM in this country between 1992 and 2003.
Methods: We were first interested in the impact of population size on the disease persistence. We then used cross-correlation analysis to study the spread of the disease on three different spatial scales, i.e., inter-region (global) and inter-district and intra-district (local) levels.
Results: We found no persistence of MM at district level in Mali during the whole of the study period. However, we found persistence on a nationwide scale after the 1997 big epidemics, as opposed to the 1992—1996 time periods. In terms of spread, two main regions seem to lead MM dynamics in Mali, even if on a local scale the 'cities—villages' diffusion pattern was not systematically observed.
Conclusions: This study improves knowledge on the spread and persistence of MM in Mali in recent years. It constitutes a first spatial study describing persistence and spread of MM in an African meningitis belt country. The next step should be the integration of vaccination and genetic variability data to clarify the route of spread of the disease in the human population.

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Introduction

Neisseria meningitidis, causing meningococcal meningitis (MM), is a strictly human bacterium, transmitted from person to person by oral and tracheobronchial secretions.[1] A large proportion (10–25%, according to the World Health Organization (WHO)) of a population can be asymptomatic carriers in endemic times, and there is no animal reservoir.[2] In West Africa this highly infectious disease is very seasonal, appearing in the dry season between December and June, fading out each year with the first rainfall of the African monsoon.[3] Typically, other infectious agents responsible for meningitis do not have the same seasonality. The physiopathologic hypothesis is a seasonal inflammation of the nasopharyngeal sphere, caused by dry and dusty Harmattan winds, which creates a seasonally reinforced possibility for *N. meningitidis* to cross the nasopharyngeal barrier and contaminate the bloodstream and the brain. A recent work has shown how much the onset of meningitis epidemics in Mali is strongly correlated with a 'winter maximum', whose average week is the 6th of the calendar year.[4] Beyond strong seasonality of annual MM cases, larger MM epidemics also occur every 8 to 12 years.[5]

Many serogroups of *N. meningitidis* are known, but the most prevalent are serogroups A and C.[6] Moreover, the spread of serogroup W135 in sub-Saharan Africa since the years 2000–2001 is a growing threat.[7–9] Serogroup A was the main cause of the great epidemics of the meningitis belt[3] in sub-Saharan Africa until the end of the 20th century. This area, from Senegal to Ethiopia, recorded

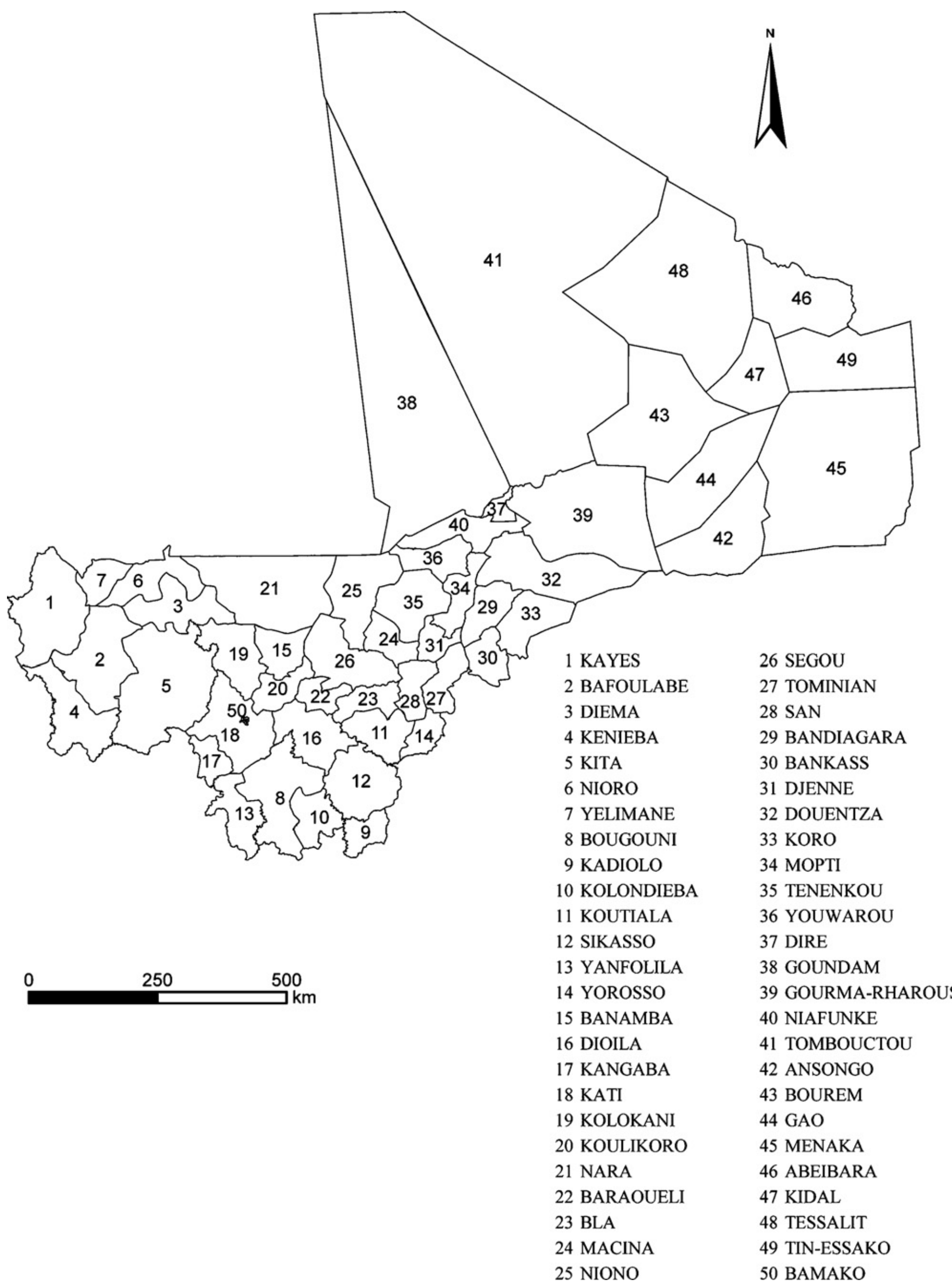

Figure 1 Administrative units (districts) in Mali.

one of the worst known epidemics in 1996–1997, with more than 200 000 cases and more than 20 000 deaths. In Mali, the maximum was reported in 1997 with more than 11 000 cases.

At a local level, it is important to understand how the disease spreads within the human population. A new field in epidemiology, combined with ecology, studies the impact of population size and flux on persistence and spread of infectious diseases. These issues have already been studied for two other vaccine-preventable diseases, pertussis and measles.[10–14] In a metropolitan analysis, these studies used the concept of 'critical community size' (CCS) initially developed by Bartlett.[15] This argues that the local persistence of a disease may be possible without any reintroduction from outside of the community if a population size threshold is achieved. If case reporting does not show any fade-out for a given population, it means that this community can behave like a reservoir for the disease. Such a fact may influence surveillance and vaccination strategies. It also contributes to a better understanding of both the global and local dynamics of the disease.

In the 'cities–villages' concept presented by Anderson and May,[16] infectious disease transmission progresses from urban places ('cities') to the countryside ('villages'). Such a result, if validated, could imply the identification of a recurrent source of infection and thus allow a targeted control by vaccination.

With these kinds of approaches, we aimed to study the spatio-temporal dynamics of MM in Mali between 1992 and 2003. We first focused on the impact of population size on persistence of the disease. We then studied the spread of the disease on three different spatial scales. We compared MM dynamics (1) across the eight administrative regions and (2) the many different districts that represent the administrative level of the district health systems. Finally, (3) we investigated MM spread within each district, testing the city–village concept. This double approach of persistence and spread of the disease provides new insights into both MM epidemic dynamics and control debates.

Methods

Epidemiological data

The WHO has defined three kinds of meningitis case in Africa. A 'suspected case' is a clinically based one. A 'probable case' is either a suspected case viewed in an epidemic context, or a suspected case with a cloudy cerebrospinal fluid. A 'case' is confirmed when the etiology is biologically established. In Mali and other Sahelo-Sahelian countries, most of the reported cases are just suspected ones, because few health centers are able to achieve a lumbar puncture, which would be the first step to diagnosis. However, the symptoms of acute meningitis like fever, photophobia, and stiff neck, are really well known and specific enough.

For our analysis, we collected the suspected cases reported weekly in each district (see Figure 1) by locality from 1992 to 2003 by the strengthened meningitis surveillance system in Mali. This warning system is based upon weekly reporting from each health center, including zero case reporting.[17] District population numbers were extracted from the 1998 national population census.[18]

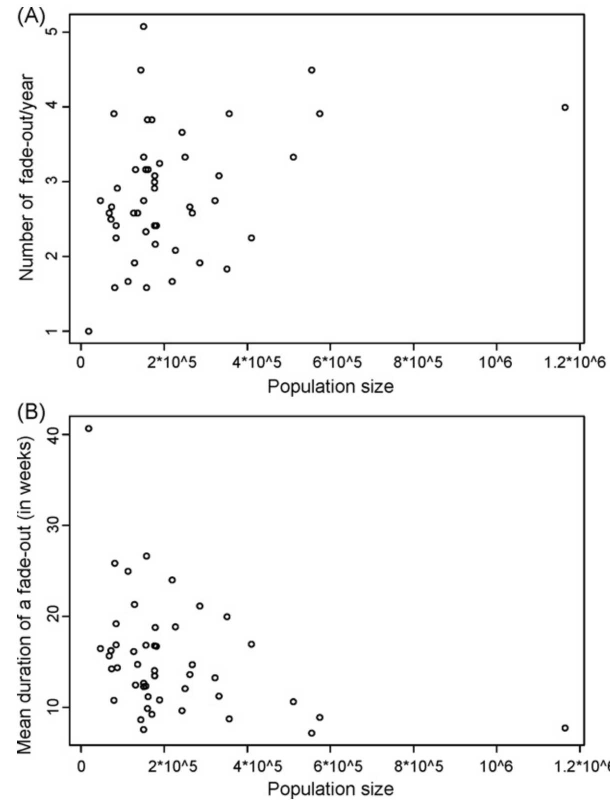

Figure 2 (A) Mean number of fade-outs by year and (B) mean duration of a fade-out in weeks, in relation to the population size, in 48 districts of Mali from 1992 to 2003. A fade-out is defined as at least 2 weeks with no new cases in the locality.

Persistence and population size

The WHO states that the average incubation time is around 4 days (range 2–10 days), and the French health authorities recommend a treatment time of 7–10 days. Hence, we defined

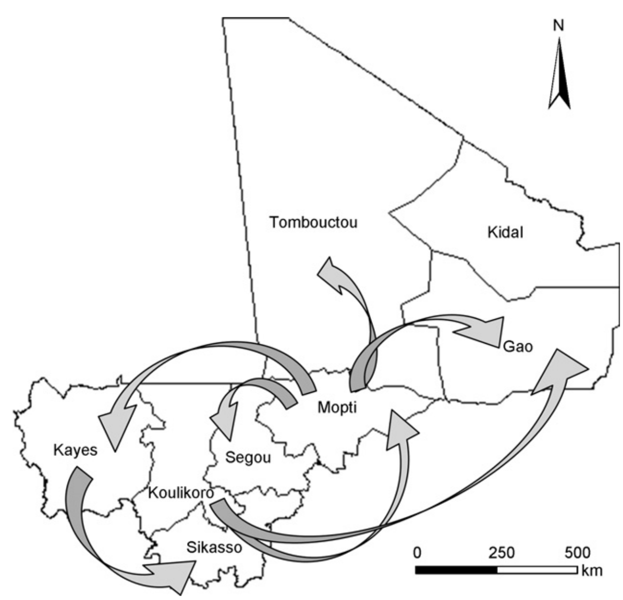

Figure 3 Meningitis spread between administrative regions in Mali from 1996 to 2003.

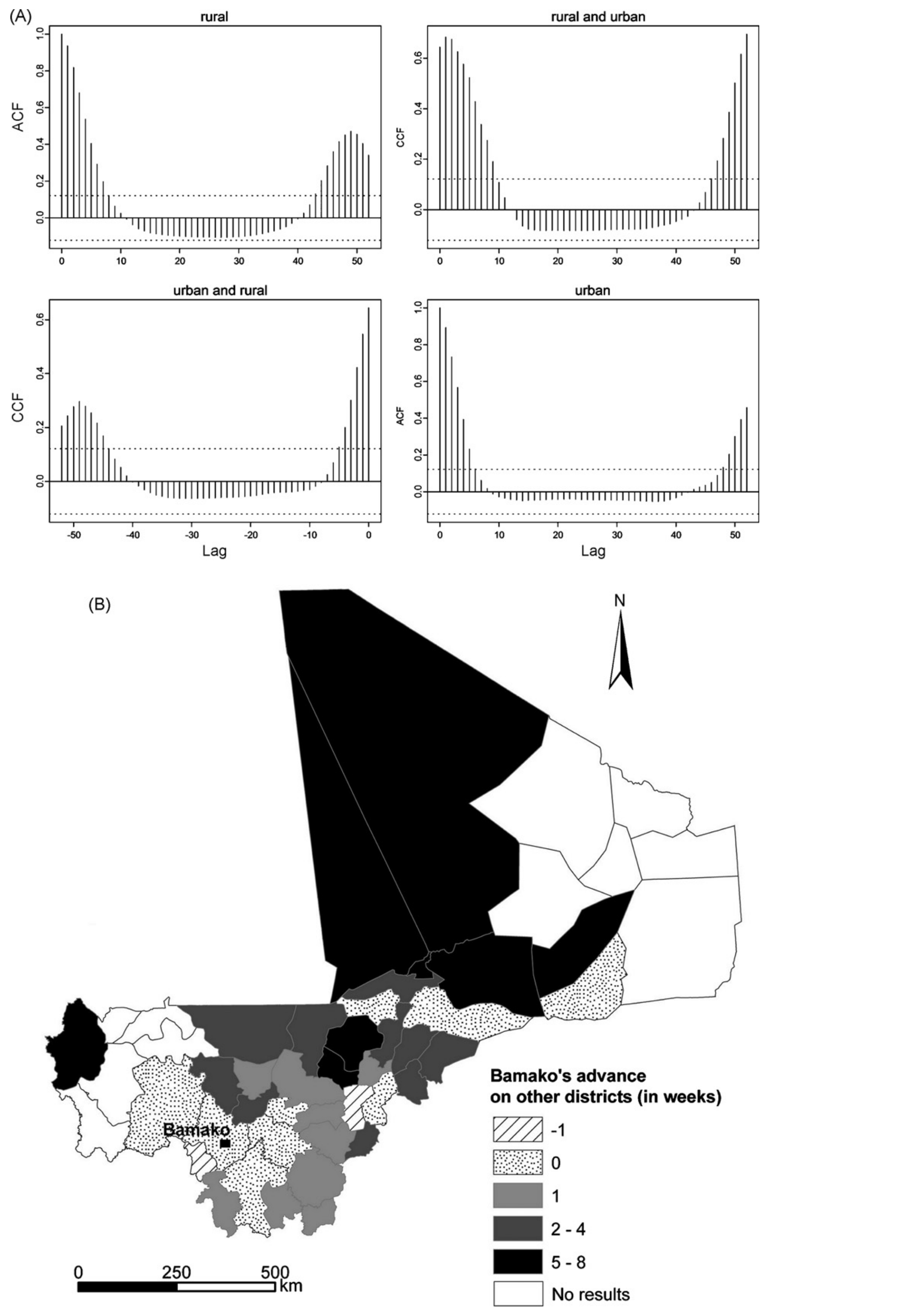

Figure 4 (A) Auto- and cross-correlation between the time series of Bamako termed 'urban' and the sum of cases in all other localities termed 'rural' from 1996 to 2000. The top left and bottom right graphs illustrate autocorrelation patterns at a weekly lag for rural and urban time series, respectively. The off diagonal graphs show cross-correlation between the two specified time series. The top right shows positive weekly lags (leads) for urban cases; the bottom left, negative weekly lags. Dashed lines indicate 95% approximate confidence intervals for no correlation. (B) Map of time-lags in weeks between Bamako time series and each other district time series computed by

a fade-out as a two-week period without any new reported case in a given locality. We also tested the three-week period threshold, which gave similar results (not shown).

After a survey of missing values in the Malian districts for the cases reported between 1992 and 2003, we were left with 48 districts. We transformed each series into binary form with '1' when one case or more was reported and '0' in the case of the zero case indication. Missing values were transformed into '1' in order not to exaggerate the fade-out effect. At the beginning of each time series, a '1' was generated as a starting point to the analysis of fade-out. We calculated the number of fade-outs and their duration and plotted the results as a function of population size.

Spread of the disease: a multi-spatial scales approach

We studied the MM spread on three different spatial scales, i.e., at regional, inter-district, and intra-district level, performing cross-correlations between time series of MM cases. Cross-correlation consists of the calculation of a standard correlation between two time series at different time-lags. We computed all our analyses with S-plus Software.

On the regional scale, we were able to compute time series running from 1996 to 2003 for seven of the eight regions of Mali.

We then focused on the inter-district scale. We sought to determine if any district was systematically in advance of the others between 1996 and 2000. After regional scale results, we were mainly interested in Bamako as a potential source of the disease, because this city, which with a population of one million people is the only large city in Mali, represents both the most densely populated area of Mali and the biggest community size in this very rural country. We made all pair-comparisons and built up a synthetic map with the software ESRI® ArcMap 8.3.

Finally, inside each district, we decided to test the 'cities—villages' framework by classifying the chief-town as 'city' (urban) and the other localities as 'villages' (rural). Indeed, the chief-town of each district, which contains the district authorities and services and is the district's eponymous locality, often has a real urban part, in contrast with villages or so-called other localities. For each district we generated two time series, one termed 'urban', corresponding to time series of MM cases of the chief-town, and the other termed 'rural', constituted of the sum of cases in all other localities of the district. However, since all chief-towns do not necessarily represent the most populated locality in the district, we performed similar analyses defining as 'urban' the most populated locality. We computed cross-correlation analyses and built up synthetic maps.

Results

Persistence of meningitis

The mean number of fade-outs by year and the mean duration of a fade-out in relation to the population size for the 48 districts investigated are shown in Figure 2A and Figure 2B, respectively. There was no persistence of MM at the district level during the period 1992—2003. Even Bamako experienced several fade-outs each year. The number of fade-outs by year and the duration of these fade-outs are dependent on population size. The district of Bamako had the least number and duration of fade-outs. The framework of critical community size in metapopulation biology is thus achieved with meningitis in Mali, but without reaching any sufficient community size for local persistence by district. The district of Bamako had the least number and duration of fade-outs, and it experienced a mean duration of a fade-out of around 8 weeks each year (Figure 2B).

Spread of meningitis

At the regional level, Koulikoro region (including the city of Bamako) and Mopti region were synchronous, but Mopti was the only one to have an advance of one week on the south and west (Kayes, Sikasso, Segou). Koulikoro region appeared at 5 and 4 weeks earlier than Gao and Timbuktu regions, respectively. On the other hand, the region of Kayes seemed to be in advance of Sikasso region (2 weeks), and Mopti region was only 2 weeks in advance of the north (Timbuktu and Gao regions). These results on a regional scale introduce the hypothesis of a global spread from the west and south to the north of Mali, with a big synchronism between the regions of Kayes, Koulikoro, and Segou and a special role played by the region of Mopti as well as the city of Bamako. Results are summarized in Figure 3.

At inter-district level, we found that the district of Bamako was in advance of all other districts for one week between 1996 and 2000 (Figure 4A). This global result was confirmed by a detailed pair-wise analysis summarized in a map (Figure 4B). This map shows several rings around Bamako, whose time-lag becomes longer from Bamako's neighboring districts towards districts at the periphery of the country. However, two districts are in advance of Bamako: Kangaba and San. This may be due to the fact there was not one but several 'sources' of MM in Mali between 1996 and 2000, in accordance with the absence of any local persistence of the disease.

Finally, inside each district, we found three kinds of spread: (1) the chief-town in advance of the remainder of the localities (rural) in 14 districts, (2) the chief-town in delay with the remainder of the localities in 17 districts, and (3) a synchronism between time series in five districts. This emphasizes the great variety of situations observed in Mali. Results obtained for each district are summarized on a map (Figure 5A). When defining the urban time series as the most populated locality (Figure 5B), we obtained the opposite pattern with, in most cases (15 districts), the 'urban' time series in advance of the 'rural' ones, making more relevant the definition of 'urban' as the most populated locality. This result needs to be put into context with the contrasting population distribution in Mali. Indeed, during the period under scrutiny, 1996—2000, districts with an internal spread from the chief-town or from the most populated locality are mainly situated in the north of the country (very low popula-

cross-correlation analyses between 1996 and 2000. A positive time-lag represents an advance of Bamako. On the contrary, a negative advance means a lead from the other district.

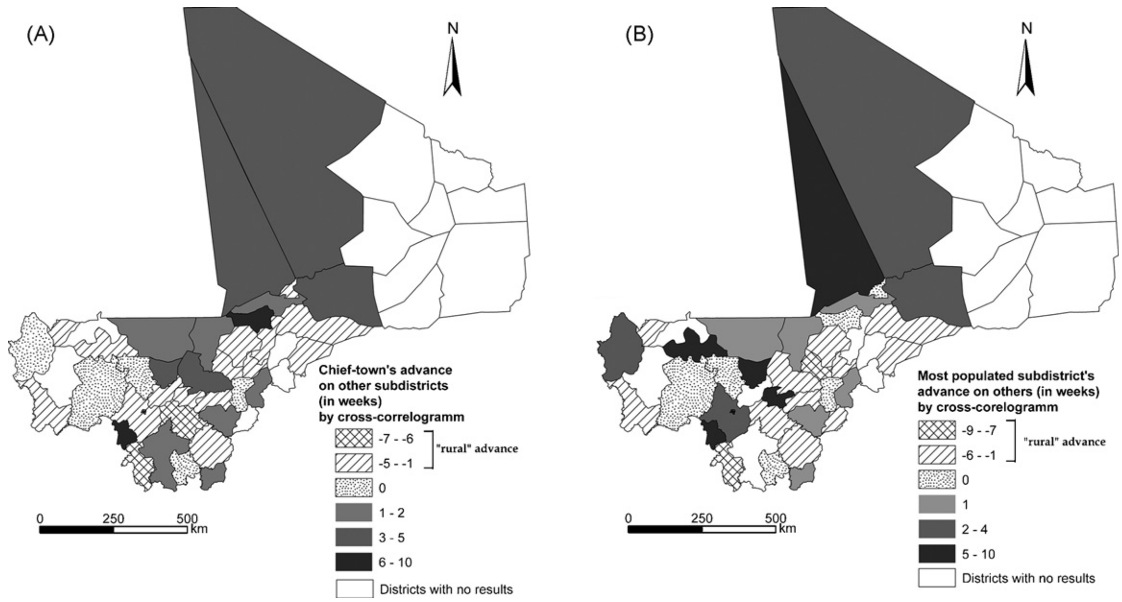

Figure 5 (A) Map describing the time-lag between the chief-town (termed 'urban') and the sum of the remaining locality cases (termed 'rural') computed by cross-correlation from 1996 to 2000. A positive time-lag means an advance of the chief-town time series. (B) Same as (A) with 'urban' defined as the most populated locality time series.

tion density), whereas epidemics damaged mainly the south part of Mali (higher population density) in terms of absolute number of cases, so that districts with an internal 'city—villages' spread have a rather scattered population.

Discussion

In this study, we did not observe persistence of MM at district level in Mali. Indeed, there are a lot of periods of disappearance of the disease on this spatial scale. This result is also confirmed on a broader scale from 1992 to 1995 by considering the whole country together. However, this lack of persistence contrasts strongly with the next period. In 1996, there was only one two-week fade-out. And after 1997, there was no fade-out, with never more than one week without any case in the entire country (results not shown). Moreover, this nationwide persistence from 1997 to 2003 was not induced by a local one; even Bamako, the most populated district, experienced several fade-outs each year from 1997 to 2003. This could be explained by a potential increase in the number of asymptomatic carriers after the big epidemics in 1997, probably representing a big reservoir of the disease, helping to maintain its global persistence even in inter-epidemic periods. Further investigations are needed to specify if this global persistence after 1997 represents a real change in the disease spatial dynamics in Mali or if it is drawn from the better epidemiological surveillance. Indeed, after the great 1996—1997 epidemics, a specific international outlay on seasonal meningitis was promoted by the WHO to improve disease surveillance and response.

Our analysis of spread at a national level showed that Bamako might not be the unique source of the disease for the whole country, since the Mopti region seems to also act as a potential source. Taking into account that Sikasso region leads only 1 week before Timbuktu, we may suppose that there is an effective spread from the south towards the north of the country. The successive steps may be, first the city of Bamako and Mopti region, then southern and western parts of the country, then the north part following the big axes of communication: the Niger River and the road from Bamako to Gao through Mopti. It is relevant because Bamako is the largest city in Mali, the most densely populated area of the country and Mali's bridgehead towards the rest of the country. It is also relevant for Mopti, which is very close to Burkina Faso in terms of neighboring and of exchange intensity, and represents one of the poorest areas in Mali. Furthermore, on a national scale, the 1-week advance of Bamako's district on all the others appears very weak, in contrast with other diseases.[19]

After the big epidemics in 1996 and 1997, we can consider that a lot of people had acquired an immunity induced by infection, carriage, or vaccination, since reactive vaccination was performed, as recommended by the WHO,[20] at different times following the wave of the epidemic. The short advance of Bamako during the years 1996—2000 may correspond, in these conditions, to a spatio-temporal heterogeneity in disease dynamics due to the contrasting immune statuses of the population. The next step should be studies into the other dynamics and spatial spread of MM, including serogroup and clonal complex information when available. How do epidemics due to one serogroup interfere with the dynamics of another serogroup? This question is of great interest with regard to vaccination strategies in the long-term, which are permanently under debate.[20—26]

Conclusions

The spatio-temporal dynamics of MM show heterogeneous patterns in Mali during the timer period 1992—2003. There was no MM persistence of the disease at a district level during the whole period. Inside each district, we showed the spread of the disease from city to villages as well as from villages to city. This heterogeneity can be explained by many factors, including immunity status of the population as well as both socio-demographic and climatic conditions, which are very different in the north and south of Mali. The next step in this study should be the integration of vaccination and serogroup data[27,28] in order to clarify the main spatial pattern of MM spread on different scales. The challenge is now (1) to understand the disease spread in order to clearly identify the potential source and (2) to understand the interference between serogroups circulating in the same population.

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