Rural–urban gradient in seasonal forcing of measles transmission in Niger

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Seasonally driven cycles of incidence have been consistently observed for a range of directly transmitted pathogens. Though frequently observed, the mechanism of seasonality for directly transmitted human pathogens is rarely well understood. Despite significant annual variation in magnitude, measles outbreaks in Niger consistently begin in the dry season and decline at the onset of the seasonal rains. We estimate the seasonal fluctuation in measles transmission rates for the 38 districts and urban centres of Niger, from 11 years of weekly incidence reports. We show that transmission rates are consistently in anti-phase to the rainfall patterns across the country. The strength of the seasonal forcing of transmission is not correlated with the latitudinal rainfall gradient, as would be expected if transmission rates were determined purely by environmental conditions. Rather, seasonal forcing is correlated with the population size, with larger seasonal fluctuation in more populous, urban areas. This pattern is consistent with seasonal variation in human density and contact rates due to agricultural cycles. The stronger seasonality in large cities drives deep inter-epidemic troughs and results in frequent local extinction of measles, which contrasts starkly to the conventional observation that large cities, by virtue of their size, act as reservoirs of measles.

Keywords: seasonality; Niger; critical community size; TSIR model; epidemic metapopulation

1. INTRODUCTION

Measles is the exemplar for the study of the nonlinear dynamics of infectious disease (Bolker & Grenfell 1993; Grenfell *et al*. 1994; Earn *et al*. 2000; Keeling & Grenfell 2002; Conlan & Grenfell 2007; Ferrari *et al*. 2008). Seasonal variation in transmission rates, lifelong immunity following infection, the replenishment of susceptible individuals through births and demographic stochasticity leading to local extinction of measles are major determinants of its multi-annual dynamics (Bolker & Grenfell 1993; Earn *et al*. 2000; Rohani *et al*. 2002) and long-term persistence (Keeling & Grenfell 1997; Conlan & Grenfell 2007). Even very weak seasonal fluctuations in transmission rates interact with the epidemic clockwork to generate stable cycles of incidence (Aron & Schwartz 1984; Bauch & Earn 2003; Dushoff *et al*. 2004). The birth rate governs the accumulation of susceptible individuals in the troughs between outbreaks, and changes in birth rates change the dynamics from over-compensating multi-annual cycles to deterministic chaos (Earn *et al*. 2000).

While many pathogens exhibit behaviour characteristic of seasonally forced cycles, the explicit mechanism of seasonal forcing has rarely been identified (Altizer *et al*. 2006;

Grassly & Fraser 2006). Seasonality in water-borne (e.g. cholera) and vector-borne (e.g. malaria) pathogens is well understood; however, teasing out the cause of seasonality for directly transmitted pathogens has proven harder. Undoubtedly the best-documented example of an explicit mechanism for seasonal transmission of a directly transmitted pathogen is the school-term forcing of measles transmission in England and Wales in the pre-vaccination era (Fine & Clarkson 1982; Schenzle 1984; Finkenstadt & Grenfell 2000). Transmission rates increased during school terms when children were aggregated, and declined during school holidays. Other studies of immunizing childhood infections, such as pertussis and chicken pox, have shown similar trends of increased transmission during school terms (London & Yorke 1973; Gomes *et al*. 1999; Deguen *et al*. 2000). Elsewhere, there is considerable debate as to the mechanistic basis of seasonality for directly transmitted pathogens (e.g. influenza: Lipsitch & Viboud 2009; meningitis: Broutin *et al*. 2007), ranging from seasonal fluctuations in susceptibility to environmental drivers or abundance of non-human hosts (Altizer *et al*. 2006; Grassly & Fraser 2006).

Measles dynamics in Niger are strongly seasonal, with outbreaks beginning at the start of the dry season and peaking at the onset of the rainy season (Ferrari *et al*. 2008). In the capital city, Niamey, this strong seasonality, combined with high birth rates, results in outbreaks that are highly variable in magnitude from year to year, and perhaps chaotic (Ferrari *et al*. 2008). Elsewhere in the

country, while the magnitude of outbreaks is variable, the seasonal timing is highly consistent. Ferrari *et al.* (2008) proposed that the seasonal timing of measles outbreaks in Niger results from rural–urban migration within the country in response to agricultural cycles. At the onset of the rainy season, people tend to return from urban to rural areas to pursue agriculture, resulting in a drop in urban population densities and a concomitant decline in measles transmission rates. Guyer & McBean (1981) suggested that same mechanism may explain the seasonal measles outbreaks in Yaounde, Cameroon. From this hypothesis, we would predict seasonality to scale with human population density and urbanization.

An important consequence of seasonality is that incidence can fall to very low levels in the troughs between outbreaks. Endemic persistence of measles transmission has classically been seen only for conurbations above a 'critical community size (CCS)' of 300 000–500 000 inhabitants (Bartlett 1957; Keeling & Grenfell 1997; Bjørnstad *et al.* 2002; Grenfell *et al.* 2002; Conlan & Grenfell 2007). These large cities then serve as local reservoirs that can seed outbreaks in smaller municipalities following local extinction, giving rise to travelling waves of outbreaks along a population gradient (Grenfell *et al.* 2001). Ferrari *et al.* (2008) showed that the combination of high birth rates and strong seasonality in Niamey drives frequent local extinction of measles. Despite several large population centres across Niger, strong seasonality in measles transmission rates drives local instability of measles dynamics and impacts regional persistence.

Here, we present an analysis of 11 years of weekly measles case reporting across Niger and show that the magnitude of seasonal forcing is positively correlated with population size, which lends support to the hypothesis that seasonal and other transmission heterogeneities in West African measles are driven by changes in human density. Further, we show that this correlation between population size and seasonal forcing means that all departments of Niger are below the CCS required for persistence. Thus, long-term, regional persistence of measles in Niger depends on regional metapopulation dynamics that are likely to extend well beyond national boundaries.

2. MATERIAL AND METHODS

We analysed weekly case reports of measles from the Ministry of Health of Niger from 1 January 1995 to 31 December 2005. The country of Niger is divided into 38 administrative units: 34 districts and 4 urban centres (Agadez, Maradi, Niamey and Zinder). For reporting purposes, the city of Agadez was separated from the district of Tchirozerine in 2001, and in 2002 the district of Abalak was split into Abalak and Tchin-Tabaraden. As the reported data span this time frame we aggregated the reported cases after the splits into the earlier demarcations for consistency, resulting in 35 districts and 3 urban centres (Niamey, Maradi and Zinder).

The majority of the population in Niger is clustered in two major regions surrounding the capital city Niamey in the southwest, and surrounding the large cities of Maradi and Zinder in the south-centre of the country. The northern and extreme eastern portions of the country are very sparsely populated. Thus, for our analyses we divide the country into three broad regions: the arrondissements of Tillabery and Dosso (including the city of Niamey); the arrondissements of Tahoua, Maradi (including the city of Maradi) and Zinder (including the city of Zinder); and the northern and western arrondissements of Agadez and Diffa (see coloured regions in figure 2*d*). The former two regions tend to have large outbreaks that are more correlated within than between regions (figure 1*c*; Bharti *et al.* in press). The latter is characterized by much more episodic measles outbreaks (figure 1*c*). We also considered an alternative regional grouping that divides the arrondissement of Tahoua into eastern and western departments (allocated to the Niamey and Maradi regions, respectively), and the results we present are robust to this alternative grouping (see the electronic supplementary material, figure S3).

We estimate the seasonal fluctuation in transmission rate for each reporting district by fitting the time series susceptible–infected–recovered (TSIR) model of Finkenstadt & Grenfell (2000) to the reported incidence aggregated into two week intervals, because 14 days is the approximate infectious generation time for measles (see the electronic supplementary material for more detail). Following Bjørnstad *et al.* (2002), we first reconstruct the unobserved time series of susceptible individuals as the residuals from the relationship between the cumulative reported incidence and the cumulative births. As some children will be vaccinated, and thus will not be susceptible to measles, we discounted the reported birth rate (51.73 births per 1000) by an assumed 70 per cent vaccination coverage (Ferrari *et al.* 2008). Vaccination coverage is likely to have increased over the time frame 1995–2005; WHO estimates that coverage with a single dose of measles vaccine ranged from 50 to 85 per cent over that timeframe (WHO 2009). In addition Niger conducted large-scale national campaigns in 2001 and 2005. Unfortunately, we do not have accurate regional reporting of vaccine coverage to permit a finer-scale accounting of vaccine coverage. However, while the changing vaccination coverage may bias estimates of the absolute transmission rate, estimates of the seasonal fluctuation in transmission rate are not strongly biased by assuming the mean vaccination coverage over that period (see the electronic supplementary material, appendix S2).

Measles incidence is likely to be under-reported. The TSIR model (below) accounts for this by estimating the reporting rate as the slope of the relationship between the cumulative reported incidence and the cumulative (vaccine-discounted) births. To account for variation in reporting rates, we estimated the time-varying reporting rate by fitting a smoothing spline with 2.5 d.f. (Bjørnstad *et al.* 2002). The TSIR model of Finkenstadt & Grenfell (2000) fits the time varying transmission rate as an unknown constant multiplied by a seasonally varying scaling factor. We modelled the seasonally varying component as a piecewise constant function with 13 (i.e. 4-week intervals) levels from January 1 to December 31. We estimated the parameters of the TSIR model from the reconstructed susceptible time series and the reported incidence as corrected by the reporting rate using least squares (Finkenstadt & Grenfell 2000). As the absolute value of the seasonal transmission rate is likely to be biased by the unknown vaccination rate, we present the seasonality as the variance of the seasonally varying scaling factor (see the electronic supplementary material, appendix S2).

To explore the effect of climatic factors and human aggregation on seasonality we fitted the estimated amplitude of
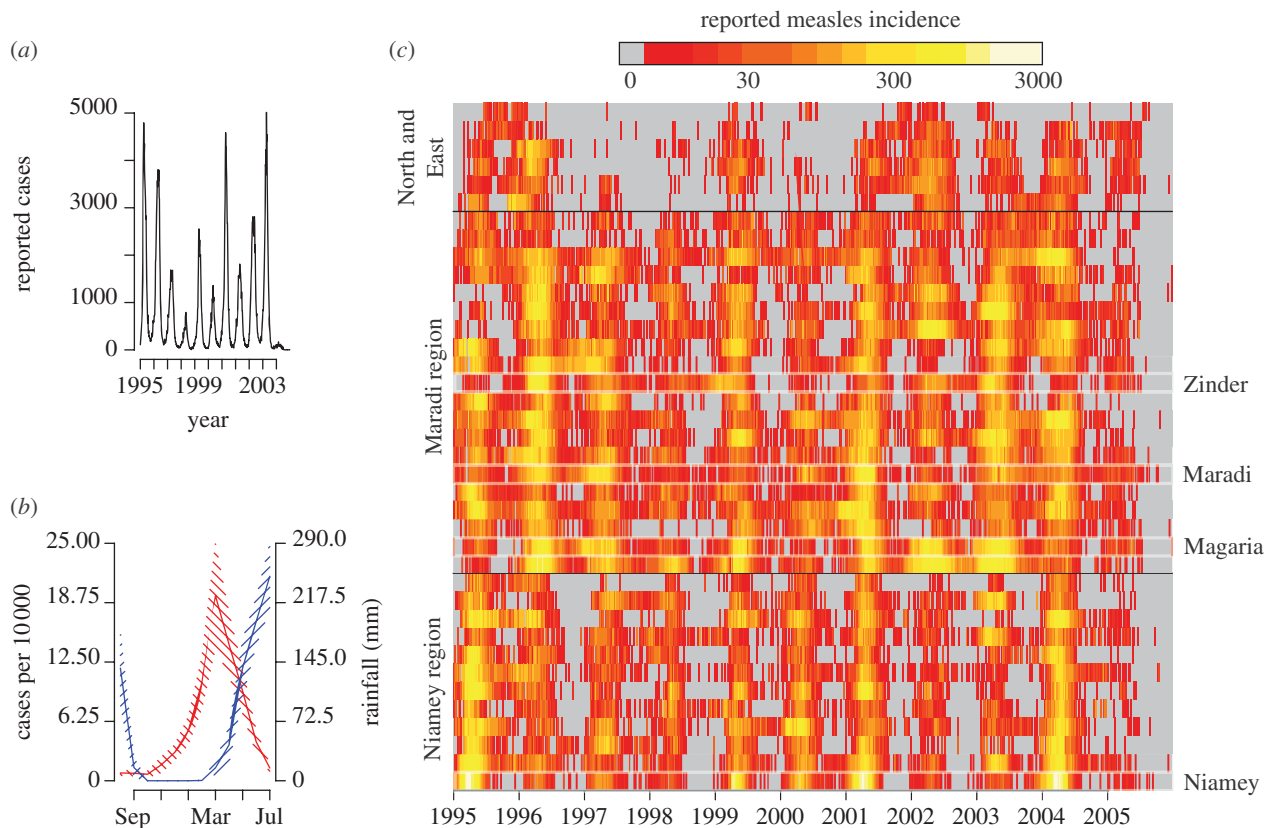
Figure 1. (*a*) Weekly reported cases for all of Niger from 1995–2005. (*b*) The mean number of monthly cases in Niger over 1995–2005 (blue) compared with the mean monthly rainfall in Niamey (red). Shaded regions give ±2 s.e. (*c*) Logarithm of weekly reported measles incidence for all 35 districts and 3 urban centres over the time period 1995–2005. Each row of the matrix indicates one location. Weeks with 0 reported cases are shown in grey. Locations are grouped into the western arrondissements surrounding the city of Niamey, the southern arrondissements surrounding the city of Maradi, and the sparsely populated northern and eastern arrondissements (see map in figure 2).

seasonal forcing as a function of district rainfall and population size. Daily rainfall estimates were obtained from 2003 to 2007 from NOAA's Climate Prediction Center's CPC Morphing Technique (NOAA National Weather Service 2009). For analysis we used the average annual rainfall in each district over 2003–2007. As rainfall is 0 throughout the country during the dry season, this provides a measure of the magnitude of the difference between the dry and rainy seasons. District population sizes were taken from the official 1995 census report from Niger.

We explored the interaction between seasonality and the CCS for measles by simulating measles dynamics using the TSIR model with a two-week time step across a range of population sizes and amplitudes of seasonal forcing. We first simulated a generic case, with sinusoidal forcing $\beta_t = \beta_1(1 + \beta_2 \cos(2\pi t/26))$, where β_1 is the mean transmission rate and β_2 controls the amplitude of seasonality (London & Yorke 1973). While the estimated seasonality for the Niger districts is not strictly a sinusoid (below), the pattern is crudely captured by a smooth wave. Thus, the sinusoid allows us to explore the general relationship of CCS and seasonal amplitude in terms of a single parameter, β_2. In all simulations we scaled β_1 relative to population size to give the same average R_E (the expected number of secondary cases due to the first infectious case in a partially immune population) as was previously estimated for the capital city, Niamey (Ferrari *et al.* 2008). We further set the birth rate equal to the reported birth rate for Niger (50.73 births per 1000). We simulated time series for populations ranging

from 100 000 to 1 000 000 and seasonal forcing β_2 ranging from 0.1 to 0.8, which spans the range of seasonal amplitudes estimated for measles (pre-vaccine London ≈ 0.2 and contemporary Niamey ≈ 0.6; Ferrari *et al.* 2008). At each parameter combination we simulated 200 years of measles incidence with a small immigration rate of approximately 10 infected individuals per year. After a burn-in period of 150 years, we measured persistence as the proportion of years with two consecutive two-week intervals of 0 incidence.

We additionally conducted simulations using the estimated seasonality for the 38 districts and urban centres of Niger. These simulations were conducted as above, but using the estimated seasonality rather than generic sinusoidal forcing. For each location, we scaled the seasonal transmission rates by the population size (as above) to maintain the same average R_E. As above, for each of the 38 seasonal patterns, we simulated 200 years of measles time series across a range of population size (10 000–700 000, the range of district population sizes) and recorded persistence in the last 50 years of the simulation.

3. RESULTS

At the national scale, measles in Niger show regular annual outbreaks (figure 1*a*) that are strongly out of phase with the annual rainy season (figure 1*b*). Across the country, measles outbreaks tend to begin at the onset of the dry season and increase until the beginning of the rainy season (figure 1*b*,*c*). At the sub-national scale,
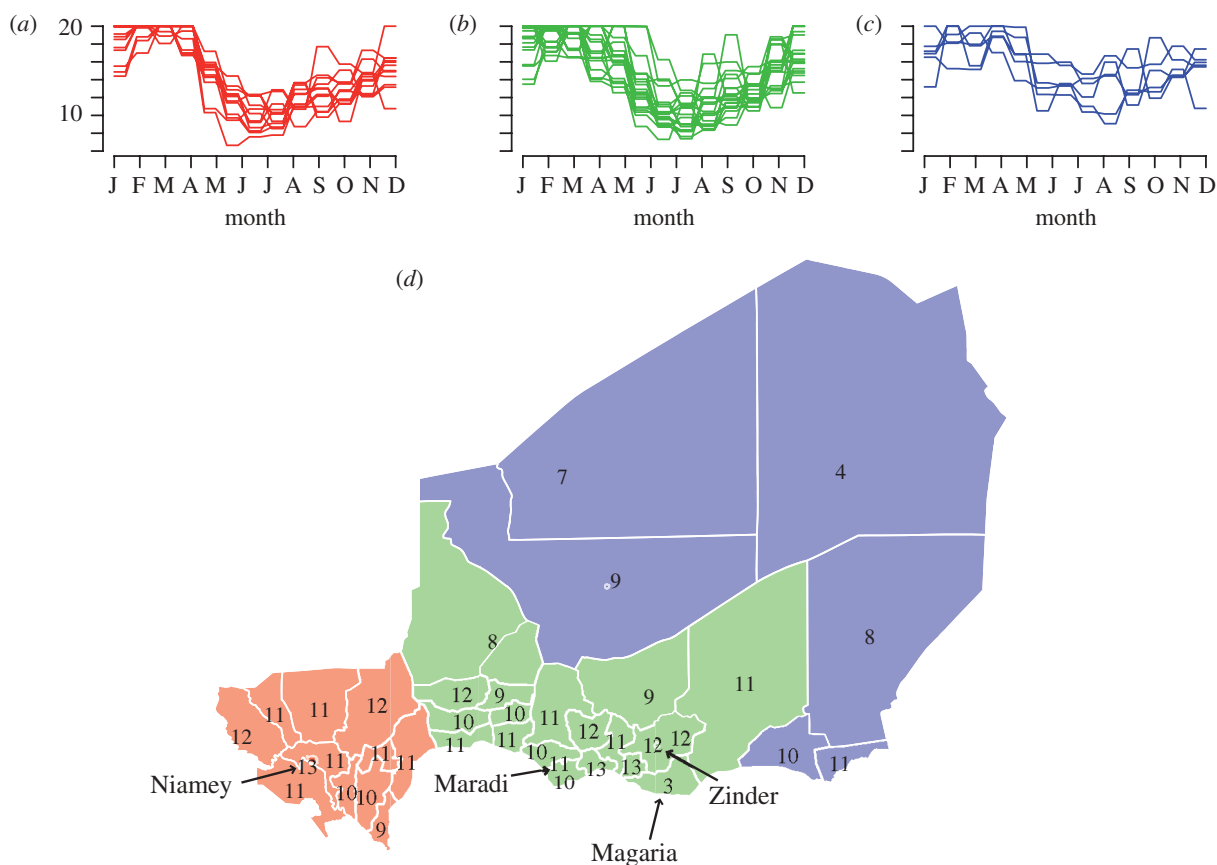
Figure 2. (*a*) Estimated seasonal forcing of measles transmission rate (10× for display) for (*a*) the 11 districts and the city of Niamey corresponding to the red shaded area in (*d*), (*b*) the 18 districts and the cities of Maradi and Zinder shown in the green area in (*d*) and (*c*) the six districts shown in blue in (*d*). (*d*) Map of the departments and urban centres of Niger with the estimated range of the seasonal forcing (10× for display) shown for each.

measles dynamics in the 38 districts and urban centres are less regular. While the timing of measles outbreaks tends to be very regular, suggesting a common seasonal forcing, the magnitude of measles outbreaks varies greatly from year to year and across the country (figure 1*c*). Despite large variation in the amount of rain across the country (ranging from 1200 mm per year in the south to 50 mm per year in the North), the timing of measles outbreaks is highly correlated across the rainfall gradient (figure 1*c*).

The shape of the seasonal forcing of measles transmission is roughly consistent across the country (figure 2*a*–*c*; electronic supplementary material, figure S1). There is strong variation, however, in the amplitude of the seasonal fluctuation. The sparsely populated northern and eastern districts show consistently lower amplitude forcing than the southern and western districts. Within the southern and western districts, the highest seasonal amplitudes were associated with the densely populated urban centres of Niamey (in the west) and Maradi (in the east; figure 2*d*). Districts with high seasonal amplitude tended to cluster around the major urban centres in Niamey, Maradi and Zinder (figure 2*d*). The overall trend in seasonal amplitude follows the dominant north–south rainfall gradient and total annual rainfall is positively correlated with seasonal amplitude ($p <$ 0.001, $R^2 = 0.37$; figure 3*a*). However, this pattern is not consistent within each of the three regions of the country. Indeed, in the western districts surrounding Niamey the amplitude of seasonal forcing is negatively

correlated with rainfall ($p = 0.03$, $R^2 = 0.3$), and in the districts surrounding Maradi the relationship is not statistically significant ($p = 0.2$, $R^2 = 0.09$; figure 3*a*). The relationship is also not statistically significant in the northern and eastern districts.

The amplitude of seasonal forcing was strongly positively correlated with the population size in each department or urban centre across the entire country ($p = 0.001$, $R^2 = 0.27$; figure 3*b*). This pattern also holds within the three regions of Niger; the linear relationship is significant in the western region containing Niamey ($p = 0.05$, $R^2 = 0.30$) and the southern region containing Maradi and Zinder (excluding the department of Magaria, which is a marked outlier; $p = 0.02$, $R^2 = 0.24$; figure 3*b*). To compare rainfall and population size, we fitted an ANCOVA with the three regions as categorical variables and population size and rainfall as covariates. Population size was a significant predictor of seasonality ($p < 0.05$) with rainfall in the model. Rainfall alone was not significant ($p = 0.17$), though there was a significant interaction of rainfall and region ($p < 0.05$), suggesting that the effect of rainfall on seasonality is not consistent across the country. These results hold for an alternative grouping of districts that assigns the departments of Tchin-Tabaraden, Illela, Tahoua and Bkonni to the Niamey region, and the department of Maine-Soroa to the Maradi region (see the electronic supplementary material, figure S3).

The Magaria outlier has an estimated range of seasonal forcing of 0.34, the lowest in the country, despite a
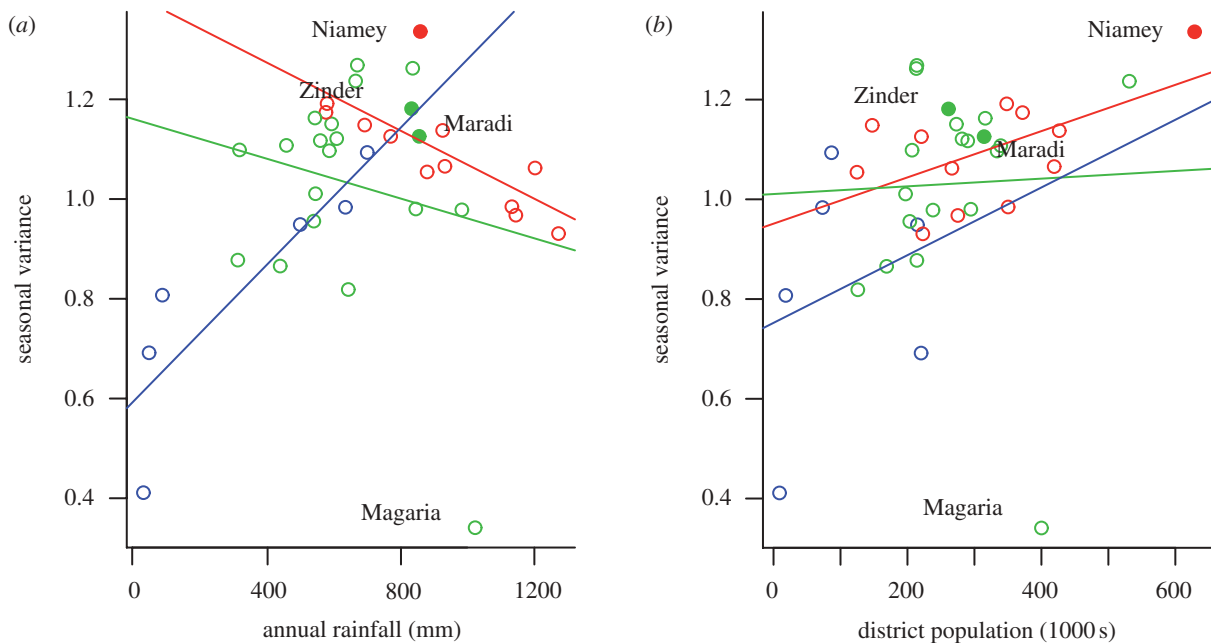
Figure 3. (*a*) Estimated variance of seasonal forcing for the 38 departments and urban centres as function of mean annual rainfall during the period 2003–2006. Colours indicate the three regions (see map in figure 2). Solid lines are the regression fit for each region. Urban centres are shown as solid points. The department of Magaria, which is a strong outlier and was excluded from the analysis, is indicated. (*b*) Estimated variance of seasonal forcing for the 38 departments and urban centres as function of district population size (colours and lines are as in *a*).

relatively large population of 400 000 (figure 3*a*). This department is distinctive as it lies on the southern border with Nigeria. The border with Nigeria is very porous and there is frequent north–south movement of people between Niger and northern Nigeria (Raynaut 2001; Miles 2005; Bharti *et al.* in press), where measles is highly endemic and vaccination rates are low. The relatively low estimated seasonality in Magaria may reflect frequent reintroduction of measles following local fadeout (see figure 1*c*), which would manifest itself as though measles transmission rates were higher throughout the year.

Bartlett (1957) first suggested that measles should be more persistent in large cities. For the simple generic model with sinusoidal forcing, an increase in the strength of seasonal forcing will increase the CCS for the long-term persistence of measles cycles (figure 4*a*). Above a critical degree of seasonal forcing, the threshold population size for persistence increases rapidly by several orders of magnitude (not shown). For the explicit seasonal patterns estimated for the Niger departments, the predicted pattern is qualitatively the same, though less smooth due to variation in the shape of the seasonal forcing (figure 4*b*). While many of the districts of Niger are large enough to support persistent measles cycles with weak seasonality, the correlation between population size and seasonal forcing means that local persistence is unlikely across the full range of district population sizes in Niger. Notably, while measles is expected to fade out locally at least once in 50 years in most of the Nigerien districts, the likelihood of local extinction is, on average, lower for districts of moderate size (figure 5). Indeed, the proportion of years with a local fade-out increases for large conurbations in the three largest districts (including Niamey, the largest). The quadratic relationship is significant both with and without Niamey in the

analysis ($p = 0.047$ and $p = 0.066$, respectively). This stands in stark contrast to the classic pattern observed in Europe and North America, where the largest cities act as reservoirs for local measles persistence.

4. DISCUSSION
Measles transmission in Niger is strongly seasonal across the entire country and the magnitude of seasonal forcing correlates with population size. The amplitude of seasonal forcing was broadly correlated rainfall. However, while the rainfall gradient is probably the ultimate determinant of human settlement and aggregation in Niger, population size is the most consistent predictor of measles seasonality across the country (figure 3*a*,*b*). Thus, the pattern of seasonality is consistent with the hypothesis that seasonal transmission is driven by anthropogenic rather than climatic factors. Previously, Guyer & McBean (1981) attributed the seasonality of measles in Cameroon to aggregation of people in cities during the dry season in response to agricultural cycles. It is probable that such seasonal aggregation is a contributing factor to the seasonal pattern in Niger; however, it is difficult to exclude the influence of seasonal variation in mobility (due to the saturation of roads in the rainy season) and reporting of measles cases. While variation in reporting rates may somewhat bias the observed seasonal amplitude, the consistent pattern of large magnitude variation in measles outbreaks across the country is consistent with strongly over-compensating cycles due to seasonal forcing (Ferrari *et al.* 2008) rather than observational errors due to reporting. Seasonal changes in density due to school terms have been classically implicated in driving transmission rates of childhood infections in Western Europe (Fine & Clarkson 1982; Gomes *et al.* 1999; Deguen *et al.* 2000; Finkenstadt & Grenfell 2000) and
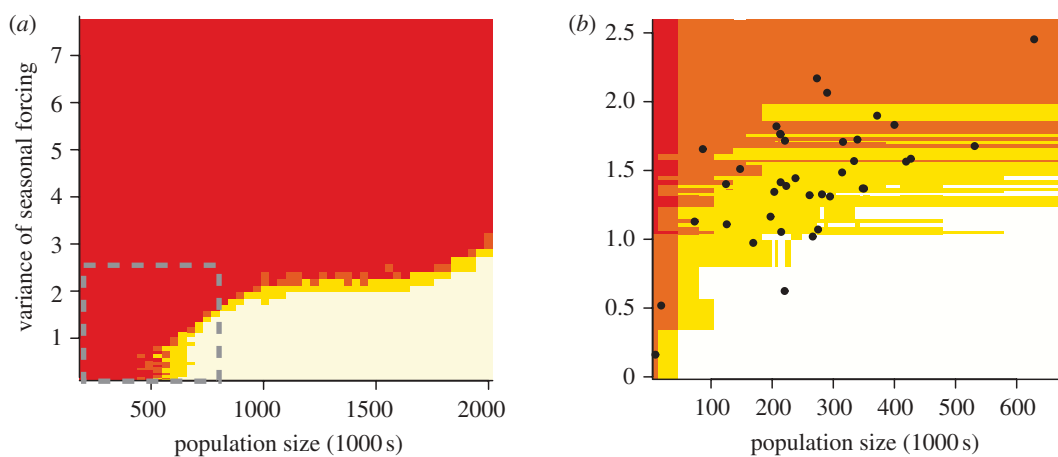
Figure 4. Probability of measles fade-out as a function of population size and the amplitude of seasonal forcing. (*a*) The percentage of years (out 50) with two consecutive two-week intervals with 0 measles incidence for a model with sinusoidal seasonal forcing. The grey dashed box indicates the approximate parameter range for (*b*). (*b*) The same as (*a*) using estimated seasonal forcing for the 38 districts of Niger. Black dots indicate the population size and amplitude of seasonal forcing for the districts of Niger. (Red, more than 50%; orange, between 10% and 50%; yellow, between 0% and 10%; white, no fade-outs).
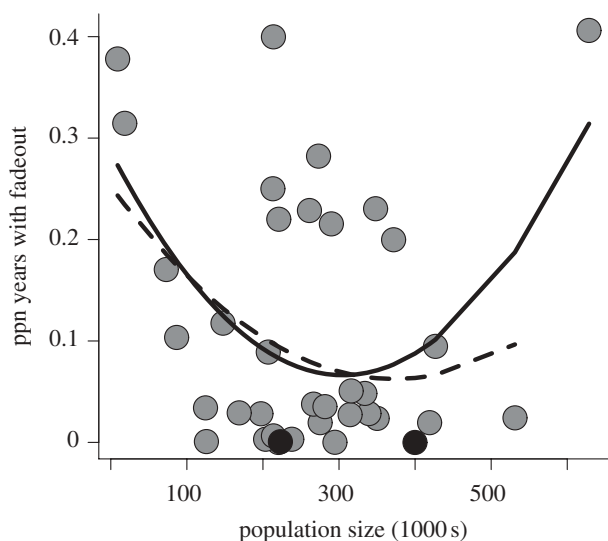

Figure 5. The proportion of years with fade-outs for the 38 districts of Niger (grey dots). The two districts that had fade-outs every year are shown in black. Curves are the best-fit quadratic function with (solid) and without (dashed) Niamey included.

North America (London & Yorke 1973). In Niger, however, school terms are unlikely to be a major driver of measles seasonality as incidence is predominantly in children younger than school age (Ferrari *et al.* 2010).

Seasonal forcing of measles transmission can have strong consequences for the predictability and stability of both local (Bolker & Grenfell 1993; Keeling & Grenfell 1997; Earn *et al.* 2000; Rohani *et al.* 2002; Conlan & Grenfell 2007) and regional dynamics (Bolker & Grenfell 1995; Grenfell *et al.* 1995). In Niamey, very large seasonal fluctuations in measles transmission rates coupled with high birth rates drive large outbreaks followed by stochastic extinction of measles, which must be followed by reintroduction of infection from elsewhere. Our analysis of the reported incidence from 1995–2005 shows that the dynamics are characterized by seasonal outbreaks followed by frequent local extinctions. Thus maintenance of endemic measles in Niger requires rescue from local extinction either by internal migration of cases within

Niger or transnational/international imports. The characteristic stability of metapopulations arises from the asynchrony in local extinction and the possibility for recolonization from elsewhere in the metapopulation (Hanski 1998). The strong synchrony of the seasonal transmission rates across Niger means that epidemic troughs tend to occur at the same time (figure 1*c*), reducing regional persistence due to synchronous extinction risk (Grenfell *et al.* 1995; Keeling *et al.* 2004).

Pre-vaccination England and Wales are perhaps the best-studied seasonally forced epidemic metapopulation (Grenfell & Bolker 1998; Grenfell *et al.* 2001; Xia *et al.* 2004). In that setting, seasonal forcing due to school terms was roughly constant across the metapopulation and endemic measles in the largest cities gave rise to hierarchical waves of measles spread outward from cities larger than approximately 300 000 people to smaller municipalities that tended to experience local fade-outs in the inter-epidemic troughs (Grenfell & Bolker 1998; Grenfell *et al.* 2001; Xia *et al.* 2004). The CCS for measles has been classically assumed to be in the order of 250 000 to 500 000, based on both theoretical and empirical investigation (Keeling & Grenfell 1997). Conlan & Grenfell (2007) showed that the CCS may be lower for high-birth-rate settings. These previous studies, however, assumed relatively low seasonality, consistent with the school term forcing of pre-vaccination England and Wales. Here we show, both for a generic sinusoidal model of seasonality and for the explicit seasonal pattern observed in Niger, that the CCS scales non-linearly with the amplitude of seasonal forcing, such that at the observed limits of measles seasonality (the urban districts of Niger) the CCS is likely to be several millions.

In Niger, seasonal forcing correlates with population size, meaning that measles is less persistent in the largest cities than it is in cities of moderate size. As such, the large cities of Niger do not play the classic role as reservoirs for measles infection during the seasonal troughs. This may, in part, explain why the dynamics in Niger do not exhibit the hierarchical wave-like spread that was seen in England and Wales (Grenfell *et al.* 2001).

The combination of highly synchronous seasonal forcing (though of varying magnitude) and dynamic

instability of measles in large cities conspires to maintain relatively weak spatial correlation of measles dynamics across Niger. Since no single region in Niger appears to be able to act as a long-term reservoir for measles, based on the empirical observation (figure 1) or the theoretical prediction (figure 5), the connectivity between regions—and perhaps beyond the national borders—(Yameogo *et al.* 2005; Bharti *et al.* in press), is likely to be important to the large-scale persistence of measles in this seasonally forced metapopulation. This phenomenon may present challenges to public health planning as the magnitude of outbreaks is locally variable and there may be many outbreaks across the country separated by large distances, which can increase the costs of response. Large-scale pulsed vaccination strategies, such as the supplemental immunization activities currently conducted in conjunction with the Measles Initiative, may be a useful strategy to coordinate regional dynamics with the effect of reducing regional variation in the magnitude of measles outbreaks (Choisy *et al.* 2006). Further, these dynamics suggest that the maintenance of measles within Niger is a function of metapopulation dynamics at a scale beyond national boundaries (Bharti *et al.* in press), as is seen, for example, in the dynamics of meningitis (Bharti *et al.* in preparation). Thus, to the extent that it is logistically possible, control strategies aimed at measles elimination should consider the coordination of vaccination activities at the regional scale.

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