ARTICLES

The dynamics of measles in sub-Saharan Africa

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Although vaccination has almost eliminated measles in parts of the world, the disease remains a major killer in some high birth rate countries of the Sahel. On the basis of measles dynamics for industrialized countries, high birth rate regions should experience regular annual epidemics. Here, however, we show that measles epidemics in Niger are highly episodic, particularly in the capital Niamey. Models demonstrate that this variability arises from powerful seasonality in transmission—generating high amplitude epidemics—within the chaotic domain of deterministic dynamics. In practice, this leads to frequent stochastic fadeouts, interspersed with irregular, large epidemics. A metapopulation model illustrates how increased vaccine coverage, but still below the local elimination threshold, could lead to increasingly variable major outbreaks in highly seasonally forced contexts. Such erratic dynamics emphasize the importance both of control strategies that address build-up of susceptible individuals and efforts to mitigate the impact of large outbreaks when they occur.

The interruption of measles transmission in some parts of the industrialized world is a triumph of public health[1]. Global measles immunization programmes have focused on increasing routine vaccine coverage in young children through the World Health Organization (WHO) Expanded Programme on Immunization (EPI)[2]. EPI is reinforced by wide age range Supplementary Immunization Activities (SIAs) aimed at eliminating susceptible individuals who persist in the population beyond the age recommended for vaccination through routine health services[2,3]. Recent increases in vaccine distribution through the Measles Initiative, a partnership of WHO, UNICEF, the American Red Cross, the United Nations Foundation, and the US Centers for Disease Control, have led to an estimated 60% reduction in measles mortality worldwide relative to the global burden of mortality in 1999 (ref. 2). However, measles remains a leading cause of vaccine-preventable death in children under 5 yr in much of the world (particularly parts of sub-Saharan Africa and southeast Asia)[4]. The continued persistence of measles in these low income, high birth rate countries reflects the challenges of achieving high vaccine coverage in areas with limited public health infrastructure. Major epidemics still occur and Outbreak Response Vaccination (ORV) is one of the strategies that may be deployed to mitigate the immediate morbidity and mortality impact of these occasional outbreaks[5–12].

The epidemic dynamics of measles are the best understood among acute infections[2,13–21]. Powerful herd immunity leads to a tendency for multi-annual outbreaks, forced mainly by seasonal variations in infection rate (owing to schooling patterns in industrialized countries), and generating large, characteristically biennial, epidemics in the pre-vaccination era[13,16,22]. The resulting deep inter-epidemic troughs can cause local stochastic extinction of infection in towns below a critical community size (CCS) of 300–500 thousand in Europe and North America[23]. This emphasizes the epidemiological impact of spatial heterogeneity in host distribution, which can also drive complex spatiotemporal epidemic patterns[1,16]. Demographic heterogeneities in the recruitment of susceptible individuals (owing to birth rate variations, vaccination and the age structure of transmission) also strongly impact epidemic dynamics[21,24–26]. Finally, in theory, strong seasonal forcing can drive chaotic dynamics in the measles attractor[27]. However, in practice, measles dynamics and persistence in industrialized countries are more consistent with weaker seasonality, driving epidemic limit cycles, moulded by demographic heterogeneities in space and time[15,28,29].

Previous analyses of measles dynamics have shown how seasonality in transmission and birth rates can interact to generate complex multi-annual outbreak dynamics[15,28]. The impact of demographic variations is perhaps best shown in the dynamic transition from annual to biennial cycles of measles outbreaks in England and Wales[30], driven by the decrease in birth rates following the post-World War II baby boom. In countries where birth rates are much higher, the standard SIR model parameterized on observations from industrialized countries predicts highly persistent, annual dynamics in large towns[21,31]. However, the following analysis of measles time series in Niger and its capital city, Niamey, reveals starkly contrasting patterns to such extrapolations.

Niger presents an important opportunity to understand the dynamics and control of vaccine-preventable childhood infections in a high birth rate country—a critical issue, given that this is the typical host demography in countries where these infections remain major public health problems. Niger is in the western Sahel and ranges from several densely populated cities in the south to desert climates in the north, sparsely populated by nomadic pastoralists. The country's population is approximately 13 million and its birth rate is among the highest reported in the world, at 50.73 births per year per 1,000 population[32]. Routine single-dose measles vaccine distribution through EPI was initiated in 1987. Niger's first measles-only SIA, targeting all children aged 9 months to 14 yr, was conducted in 2004 and achieved an estimated coverage of 99% of the target population[3]. Before the SIA, measles outbreaks exhibited

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annual cycles at the national scale (Fig. 1a inset), as expected, with regular timing and somewhat variable amplitude (Fig. 1a). This large-scale pattern is consistent with dynamics in the region (for example, Burkina Faso[33] or Cameroon[34]). However, our analysis of the temporal dynamics and spatial synchrony of measles outbreaks at the local scale reveals that the appearance of regular, annual outbreaks is an artefact of averaging erratic and asynchronous local epidemics (Supplementary Information C). There is one regularity, however: the timing of measles outbreaks invariably coincides with the end of the annual rainy season (Fig. 1a), which is the dominant seasonal driver in the region.

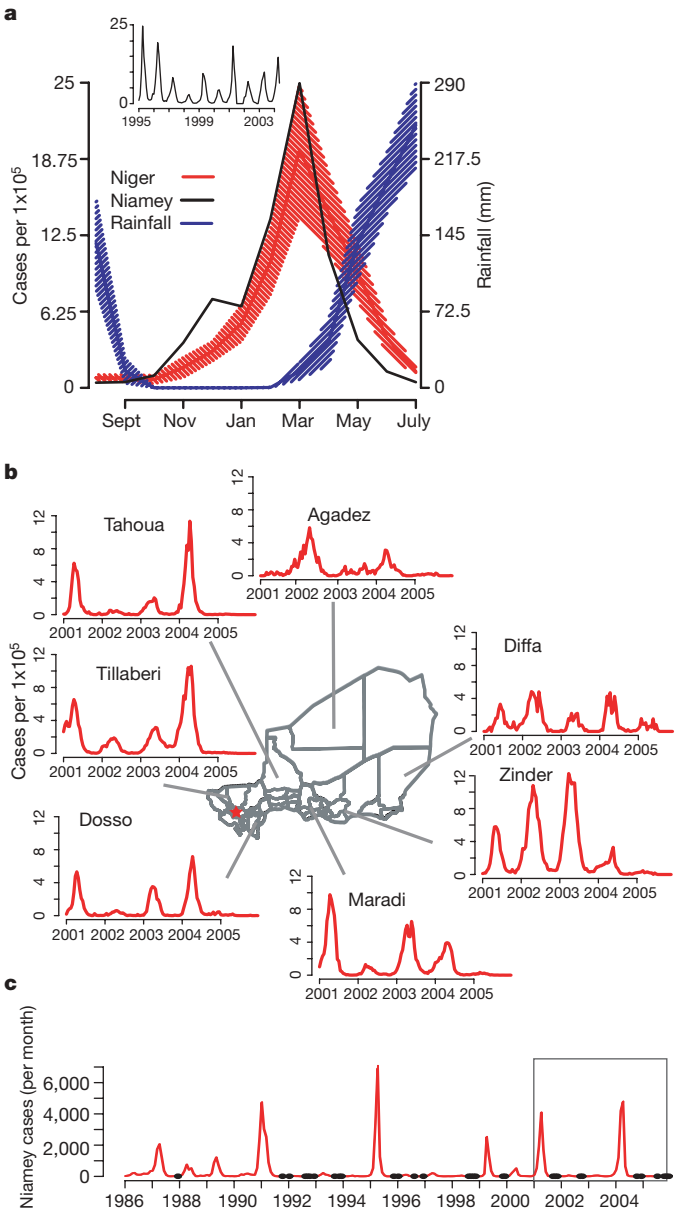

Figure 1 | Time series dynamics of measles outbreaks in Niger. a, Mean number of reported measles cases per 10,000 nationwide in Niger from 1995 to 2004, and the mean monthly rainfall over the same time period (blue). Shaded regions give ±2 standard deviations. Black curve, mean monthly cases of measles in Niamey from 1986 to 2005. Inset, monthly measles time series from 1995 to 2004. **b**, Weekly measles case reports from seven departements of Niger, 2001–2005. Red asterisk, Niamey. Each departement is an aggregate of 3–8 arrondissements. **c**, Case reports per month for the city of Niamey from 1986 to 2005. The box indicates the time frame shown in **b**. Black dots, months with 0 reported cases.

Seasonality and dynamics in Niamey

For model parameterization, we focus on the relatively well-documented time series of incidence from 1986 to 2002 (before the national SIA) from Niger's capital city, Niamey (Fig. 1c)—a city of approximately 750,000 persons (according to the 2001 National Census), which is twice the historical CCS for measles in Europe and North America[23,35]. On the basis of lessons from Europe and North America and given Niger's high birth rate, we would expect persistent annual measles cycles[21,31]. In contrast, empirical patterns over the last 30 yr testify to highly erratic outbreaks; monthly case reports from 1986 to 2004 reveal occasional large outbreaks followed by years of very few cases (Fig. 1c). Similarly, annual measles incidence rates in Niamey between 1975 and 1985 ranged from 1–5%[36], consistent with this irregular pattern.

Measles epidemics in Niamey decline at the onset of the rainy season, regardless of the magnitude of the outbreak (Fig. 1a, c). This indicates that powerful seasonal forcing of transmission may be driving irregular, fragile dynamics even in such a large, high birth rate population. We explore this issue using a stochastic time series Susceptible–Infected–Removed (TSIR) epidemiological modelling framework, which has been applied successfully to measles dynamics elsewhere[22,25,30]. The TSIR model allows us to estimate the form of seasonality in transmission (below). First, however, we use sinusoidal forcing[15] to illustrate the general dynamical consequences of varying seasonal amplitude. Figure 2a shows a bifurcation diagram for a simple deterministic TSIR model with a fixed, 14-day infectious period and sinusoidal forcing in transmission rate[15], as a function of seasonal amplitude and birth rate. At low seasonal amplitude (Fig. 2a, seasonality = 0.2), the dynamics resemble historical patterns in the industrialized world (for example, in London): a dynamic transition from annual to biennial cycles as birth rate declines from high levels[15]. In contrast, at high seasonal amplitude (Fig. 2a, seasonality = 0.6), corresponding to that which we estimate for Niamey (Fig. 2b; see below), the range of birth rates at which the system exhibits stable 1–4 yr cycles decreases and the dynamics become chaotic over a broad range of birth rates. Further, as birth rate and strength of seasonality increase, the depth of the inter-epidemic trough becomes very shallow (to the right of the dashed contour in Fig. 2a), greatly increasing the likelihood of local stochastic extinction.

We estimate seasonal variation in the transmission rate in Niamey explicitly by applying the TSIR model to 17 yr of monthly data from the city (Fig. 1c). To account for uncertainty in the reporting rate, we use a bayesian state space approach (Methods). The estimated seasonality in the transmission rate shows a single peak, roughly in antiphase to the seasonal rainfall profile (Fig. 2b). A possible mechanistic explanation for this pattern is the increase in urban density in the dry season owing to seasonal migration from outlying agricultural areas[37]. Niamey's pattern of measles seasonality is conspicuously different from the school-term forcing observed before mass-vaccination in England and Wales that is due to mixing of children in schools (Fig. 2b)[30]. This difference is also associated with contrasting age–incidence profiles: the median age of measles infection in Niamey is less than 2 yr[36,38], compared to 4–5 yr for the England and Wales epidemics[39].

The magnitude of transmission seasonality in Niamey is fourfold that of historical London (Fig. 2b). This puts the Niamey dynamics in a large amplitude biennial regime (Fig. 2c), well within the predominantly chaotic region of parameter space for a broad range of birth rates (Fig. 2a). The strong seasonality leads to deep inter-epidemic troughs (Fig. 1c), making long-term local persistence of measles in Niamey very unlikely. The model predicts that, even for very large populations (>5 million), long-term persistence is unlikely without external reintroduction (Supplementary Information A). Thus, the CCS for measles persistence in Niamey is over an order of magnitude higher than predicted from classical studies[23,35]. There is also significant regional heterogeneity in this stochastic fragility; relative to their size, Niamey and the communities in the neighbouring regions of

Dosso and Tillaberi exhibit many more fadeouts (weeks with zero cases reported) than departements such as Maradi and Zinder (Fig. 3a).

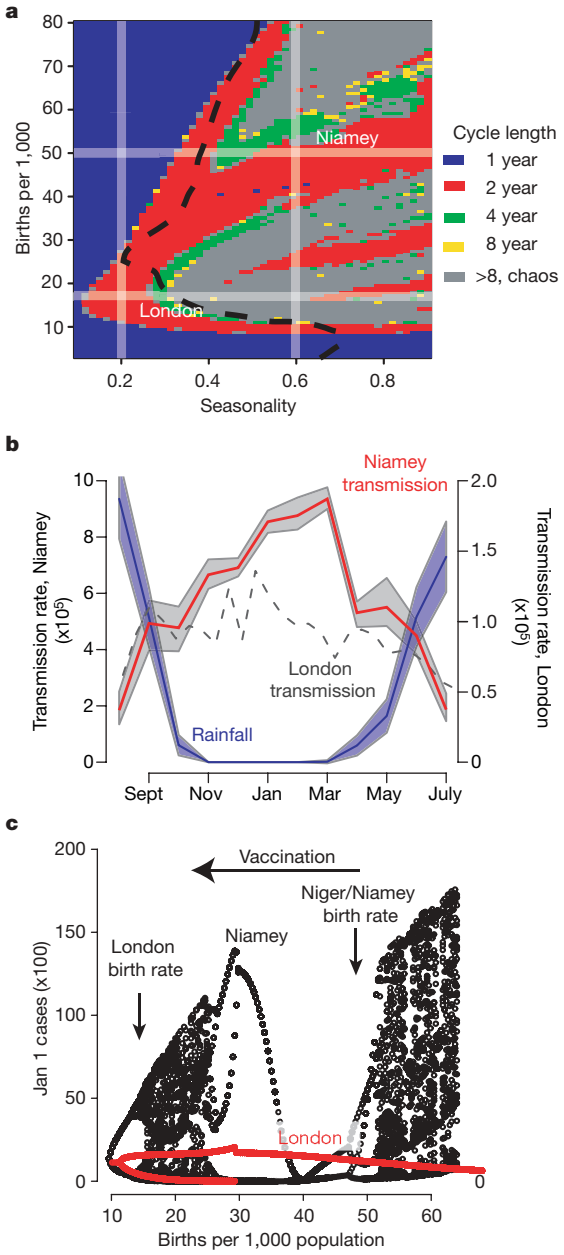

Figure 2 | Dynamic consequences of seasonal variation in measles transmission rate in Niger. **a**, Bifurcation diagram for a deterministic seasonally forced TSIR epidemic model. Seasonal transmission is modelled as a cosine wave; $\beta(t) = (\text{mean } \beta)(1+\alpha\cos(2\pi t))$. x axis, the amplitude of the seasonal forcing, α; y axis, annual birth rate per 1,000 people in the population. Colours indicate the periodicity of the epidemic dynamics. Black dashed contour, the range of parameter space above which the minimum number of cases is <1; that is, persistence is unlikely in a stochastic setting. Vertical lines, approximate seasonal amplitude of pre-vaccine London and Niamey (assuming sinusoidal forcing); horizontal lines, the approximate birth rates for both countries. **b**, Estimated seasonal transmission rate for Niamey (solid red line). Shaded grey regions, the 95% bayesian credible intervals; blue line, the mean annual rainfall per month, with ± 2 standard deviations indicated with blue shading; dashed line, the seasonality (scaled for population size) for pre-vaccine London for comparison. **c**, Bifurcation diagram for the estimated seasonal transmission rate for Niamey (black) as a function of birth rate per 1,000. The bifurcation pattern for pre-vaccination London (red) is given for comparison[15]. Increased vaccination coverage has the consequence of decreasing the effective birth rate and may lead to increasingly erratic dynamics (horizontal arrow).

Measles metapopulation dynamics

These patterns suggest the following picture of national (metapopulation) measles dynamics in Niger. Strong seasonality leads to frequent local extinction of measles at the onset of the rainy season. The relatively low connectivity in the regional metapopulation (Supplementary Information C) results in infrequent local reintroductions; this episodic coupling leads to inter-epidemic periods of unpredictable length and frequency, during which the population of susceptible individuals can grow sufficiently to fuel large magnitude outbreaks. We explore this picture using a stochastic multi-patch version of the TSIR model. The 39 arrondissements and Niamey are represented as patches, connected by stochastic dispersal with a kernel that is a power function of distance among patches parameterized to the observed correlation from 2001 to 2005 (Methods). We assume the same seasonal pattern of transmission in all patches, scaled to maintain a constant R_0. The model supports our dynamical hypothesis, capturing the qualitative pattern of episodic outbreaks at the local scale (Fig. 1b, c), and seemingly annual dynamics at the aggregate regional scale (Fig. 1a, inset). Furthermore, although it was parameterized on the basis of observations from 1986 to 2002 in Niamey, the metapopulation model predicts the qualitative pattern of regional persistence at the national scale from 2001 to 2005 (Fig. 3). In particular, the model accurately predicts relatively low persistence in the remote north and relatively higher persistence in the central regions of Maradi and Zinder (see Supplementary Information C for further discussion of the model and parameter fitting). Overall, the combination of strong seasonal forcing and weakly connected metapopulation patches generates a setting in which outbreaks of variable frequency and magnitude are the rule rather than the exception.

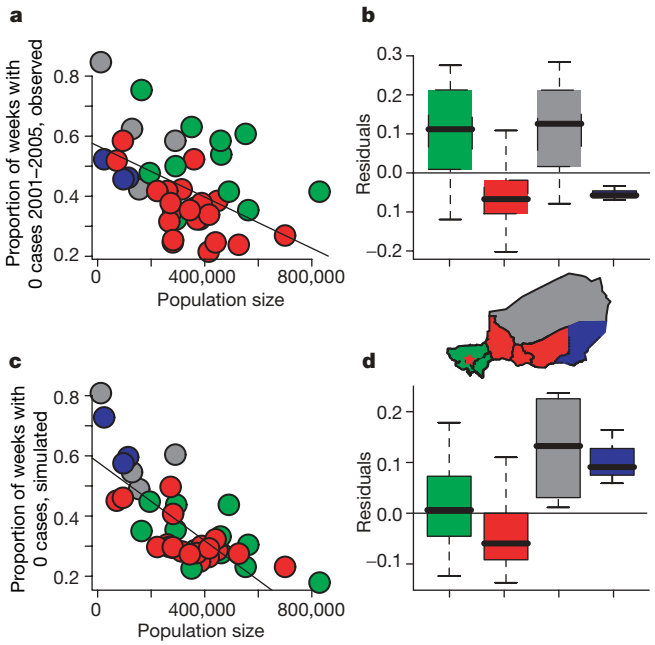

Figure 3 | Observed and predicted patterns of measles persistence in Niger. **a**, Proportion of weeks with 0 cases reported in 39 arrondissements plus Niamey plotted as a function of population size. Solid line, the mean relationship (excluding Niamey as an outlier). Arrondisements are colour coded by region. Green dots, the departements of Tillaberi and Dosso surrounding Niamey; red dots, the departements of Tahoua, Maradi and Zinder; grey and blue dots, the sparsely populated departements of Agadez and Diffa respectively (map inset). **b**, Boxplots of residuals from **a**, grouped by region (colours match map inset). Box, the interquartile range; whiskers, the range. Heavy line, the median. **c**, Proportion of weeks with 0 cases reported in 39 arrondissements plus Niamey plotted as a function of population size, as simulated from the metapopulation model. **d**, Boxplots of residuals from **c** (colours match map inset, boxes as in panel **b**).

Implications for measles control

The erratic outbreak dynamics in highly seasonal, high birth rate settings present a challenge for measles control. In particular, the strong seasonality suggests that deterministic epidemic dynamics will remain in the large amplitude (possibly chaotic) regime even as overall vaccine coverage increases (Fig. 2c). Major outbreaks can quickly overwhelm local public health resources and result in high rates of childhood mortality[3]. Thus, to mitigate the potentially devastating effects of these outbreaks, both surveillance to detect epidemics, and the right balance between routine, supplementary and reactive control strategies are key to long-term measles control strategies in the region. We now use our metapopulation model to explore these issues.

Outbreak detection in Niamey

Even for very erratic epidemics, the strong transmission seasonality in Niamey can help in predicting the annual start of outbreaks. Active monitoring of cases early in the high transmission season (September–November) strongly predicts historic outbreak size (Supplementary Information B). In an interesting parallel study[40], it was recently shown that the timing of the prior year's epidemic peak may be diagnostic of the level of susceptibility and help to predict future outbreak size in certain seasonal and chaotic systems. This relationship is only weakly predictive in our system, because high birth rates and exceedingly strong and sharply focused seasonality lead to highly synchronized epidemic peaks over a range of outbreak magnitudes (Supplementary Information B). As such, there is little power in the timing of peaks to predict the magnitude of subsequent outbreaks in this region.

Since 2004, the vaccination strategy in Niger has changed to incorporate periodic (3–4 yr interval) SIAs. Although this programme is too recent for us to evaluate the effect on seasonality and predictability on the basis of incidence data, simulation results suggest timing of the onset of outbreaks will not change, even under an established SIA programme (Supplementary Information E).

Optimal vaccination

We focus initially on the balance between routine immunization and ORV (reflecting the situation in Niger up to 2004).We initially assume that routine immunization was applied to the entire metapopulation at the relevant rate; in contrast, ORV, targeting all children regardless of immune status (that is, 6 months to14 yr, following the recommendations of ref. 8), was applied on 15 November only to the large Niamey-like patch in response to an outbreak, defined as 10 total cases in October (Supplementary Information B). Given the costs (human, logistic and financial) of mounting such a campaign we assume conservatively that ORV campaigns would not be conducted in consecutive years. We restrict our discussion to the outbreak dynamics in the large, Niamey-like patch.

Simulations stress the intuitive result that increased routine vaccination coverage reduces the mean number of cases per year (Fig. 4a). Importantly, simulations also predict that increased routine vaccination and ORV will alter the dynamics of major outbreaks (>2,500 cases), by reducing the rate at which measles will be reintroduced to Niamey following local extinction. Specifically, this reduction in the regional flux of infection results in longer intervals between major epidemics (Fig. 4c) and therefore larger epidemics, when they occur (Fig. 4d). On the face of it, Fig. 4 also implies that high levels of ORV can interact with lower levels of background vaccination (40–70%) to generate a plateau (Fig. 4a, *) or increase (Fig. 4b, *) in average cases and in large, rare epidemics (Fig. 4d,

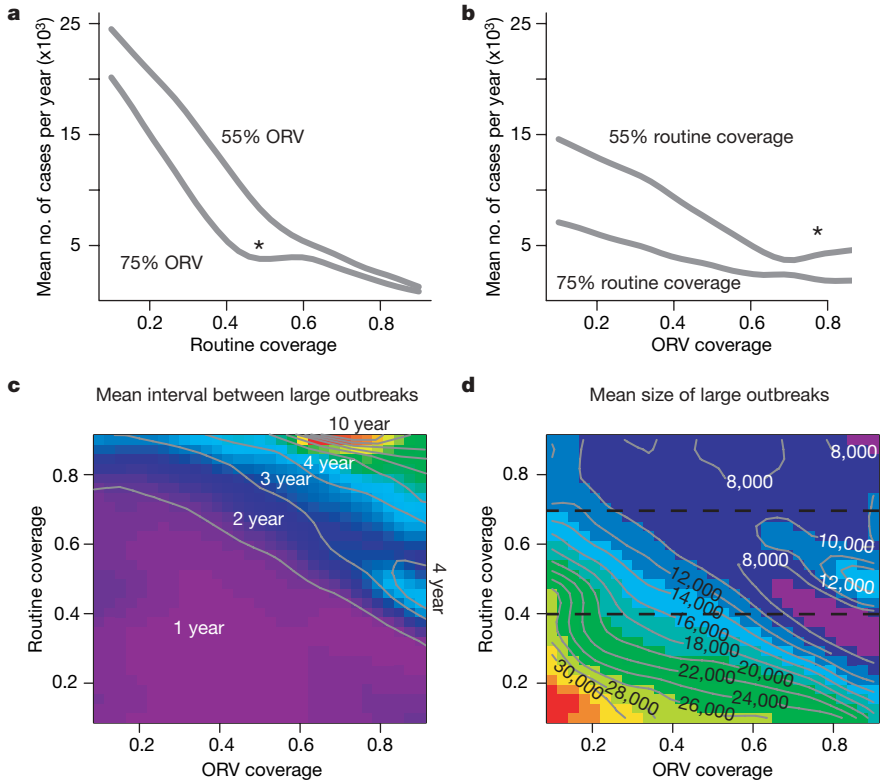

Figure 4 | Impact of vaccination programmes on outbreak magnitude and frequency in the large patch for the metapopulation model. a, Mean annual measles cases as a function of routine vaccine coverage for low (55%) and high (75%) levels of ORV coverage. The mean is taken over 50 yr of a stochastic simulation. **b**, Mean annual measles cases as a function of ORV coverage for low (55%) and high (75%) levels of routine vaccine coverage. The mean is taken over 50 yr of a stochastic simulation. **c**, Mean interval between large outbreaks (frequency) as a function of routine and ORV coverage in a Niamey-like patch. The mean is taken over 50 yr of a stochastic simulation using the estimated seasonal transmission rate for Niamey. **d**, Mean size of large (>2,500 cases) outbreaks as a function of routine and ORV coverage in a Niamey-like patch. The mean is taken over 50 yr of a stochastic simulation using the estimated seasonal transmission rate for Niamey.

between the dashed lines). However, this simply reflects the fact that, although ORV can partially compensate for low herd immunity at low routine immunization, occasional large epidemics would 'escape' this control. Overall, increasing levels of routine vaccination and ORV reduce average incidence. We predict lower incidence to interact with strong seasonal forcing in this weakly coupled metapopulation to generate large, unpredictable epidemics even at vaccination levels just below the regional eradication threshold (Supplementary Information C, D).

Given the recent introduction of SIAs in Niger, it is important to establish how periodic vaccine pulses affect the above picture. Because there has only been one SIA in Niger (in 2004), it is difficult to calibrate a detailed model of future supplementary immunization in the country. Preliminary simulations of pulsed supplementary immunization for Niger (Supplementary Information E) indicate that they can be effective, in reducing both the average number of cases and also the probability of very large, unpredictable epidemics. The major effect here is achieved by increasing average coverage and imposing a multi-annual forcing that generates more predictably spaced outbreaks (Supplementary Information E).

Discussion

The high seasonality of transmission in Niamey leads to more irregular measles dynamics than predictions that are based on historical data for industrialized countries in the northern hemisphere. This emphasizes the potential dangers of extrapolating dynamics for these sorts of highly non-linear systems without a detailed understanding of local parameters. Interestingly, although poliovirus in India exhibits similarly strong seasonality, its longer infectious period leads to more regular annual dynamics than measles[41].

The quality of the Niger data allows us a rare opportunity to generate data-driven models for measles metapopulation dynamics in the region. This analysis reveals highly non-linear behaviour, in the chaotic region of epidemic periodicity, revisiting a previous debate in population dynamics[29, 42]. The resulting high amplitude outbreaks interact with demographic stochasticity and low metapopulation coupling to generate fragile dynamics; this is reflected in a CCS for measles persistence in Niamey over an order of magnitude higher than the standard figure for less seasonally forced settings.

The key to measles eradication is to bring vaccine coverage up to the level of herd immunity[2,24,43]. This goal may be achieved through a routine two-dose vaccine schedule, as is the case in much of the industrialized world[2]; our results also stress the importance of ORVs for responding to large outbreaks in this highly seasonal setting. However, the complex, high-amplitude dynamics that result from a combination of strong seasonality and high birth rates lead to erratic boom and bust outbreaks that are likely to continue even as routine vaccination coverage improves. Increasing routine vaccination is dynamically equivalent to a reduction in birth rate[15] and may thus be expected to move the Niamey dynamics, at least initially, more firmly into the chaotic regime (Fig. 2a, c).

The optimal strategy for administering a second dose as a function of the local epidemiological environment is an important area for future research. Preliminary results indicate that regular, pulsed vaccine programmes, like SIAs, may lead to more regular dynamics (Supplementary Information E, see also refs 44 and 45), but are unlikely to eliminate major outbreaks until baseline vaccine levels reach high levels. Thus, surveillance and reactive campaigns may also be of increasing importance to mitigate the morbidity and mortality impact of large irregular outbreaks as routine vaccine coverage approaches the WHO goals for 2010 (ref. 2). The use of regional coordination of SIAs to minimize buildup of susceptibility, and the potential for re-introduction of the measles virus following local eradication, is an important consideration as regional immunization strategies are developed. Simple rules, such as thresholds for outbreak detection (Supplementary Information B) and strategies for susceptible minimization are key to optimizing intervention strategies. To this end, dynamic models rooted in local data are important tools for providing clear recommendations for control strategies.

METHODS SUMMARY

Estimating seasonality. We estimated the seasonal variation in transmission rate by fitting a TSIR model with imperfect binomial reporting to the 17-yr-long time series of monthly incidence in Niamey (1986–2002) using bayesian Markov chain Monte Carlo methods[46]. These data are before regional SIAs (the first in December 2004) or local ORVs in Niamey (2004; ref. 8). The unobserved time series of measles cases was specified as a TSIR model: $I_{t+1} \sim \mathrm{NB}(\beta_m S_t I_t^{\alpha}, \mathrm{I_t})$ where $\mathrm{NB}(a,b)$ signifies a negative binomial process[13]. S and I indicate the number of susceptible and infected hosts, respectively, β_m indicates the month-specific transmission rate and α is a tuning parameter to account for non-linearities in transmission. The time step was taken as 0.5 months, so that the TSIR model can be coupled to a binomial observation model in which the observed number of cases each month is distributed as $\mathrm{binomial}(I_{t-1}+I_t, P_{obs})$, where P_{obs} is the reporting probability for cases. Additional information is given in Supplementary Information F.

Metapopulation model. We evaluated the effect of vaccination on outbreak dynamics using a metapopulation model consisting of 40 local communities representing the 39 arrondissements plus Niamey. We modelled coupling among patches as a power function of distance, parameterized on the basis of the 2001–2005 spatially resolved data[47] (Supplementary Information C). The strength and shape of seasonal forcing for all communities matched that estimated for Niamey, and scaled such that R_0 was constant. The birth rates were taken as that reported for Niger: 50.73 births per 1,000 individuals per year. Routine vaccination was assumed to target young children across the entire metapopulation. ORV vaccination campaigns targeting Niamey only were initiated if the number of observed cases in October exceeded 10 (assuming 50% reporting; Supplementary Information F) and the time since the last ORV campaign was at least 1 yr. ORV campaigns targeted all children of 6 months to 14 yr[8], and the vaccination target was assumed to be reached within two weeks[8].

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