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Measles hotspots and epidemiological connectivity

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SUMMARY

Though largely controlled in developed countries, measles remains a major global public health issue. Regional and local transmission patterns are rooted in human mixing behaviour across spatial scales. Identifying spatial interactions that contribute to recurring epidemics helps define and predict outbreak patterns. Using spatially explicit reported cases from measles outbreaks in Niger, we explored how regional variations in movement and contact patterns relate to patterns of measles incidence. Because we expected to see lower rates of re-introductions in small, compared to large, populations, we measured the population-size corrected proportion of weeks with zero cases across districts to understand relative rates of measles re-introductions. We found that critical elements of spatial disease dynamics in Niger are agricultural seasonality, transnational contact clusters, and roads networks that facilitate host movement and connectivity. These results highlight the need to understand local patterns of seasonality, demographic characteristics, and spatial heterogeneities to inform vaccination policy.

Key words: Infectious disease control, infectious disease epidemiology, measles (rubeola), spatial modelling, vaccine-preventable diseases.

INTRODUCTION

Vaccination has interrupted the transmission of measles in most of the world [1] but areas with significant risk of measles morbidity and mortality are still found in Africa and South Asia. In general, affected areas are in low-income nations where vaccination rates are below the herd immunity threshold and malnutrition rates are high [2–5]. To understand current measles dynamics in high burden areas, we analysed reported cases in Niger, where measles is a major health issue. We begin by reviewing the relatively simple dynamics revealed in previously studied measles systems.

Measles dynamics are relatively well understood, especially for industrialized countries, and are often used as a paradigm for acute immunizing infections [6–11]. Previous studies have shown that the

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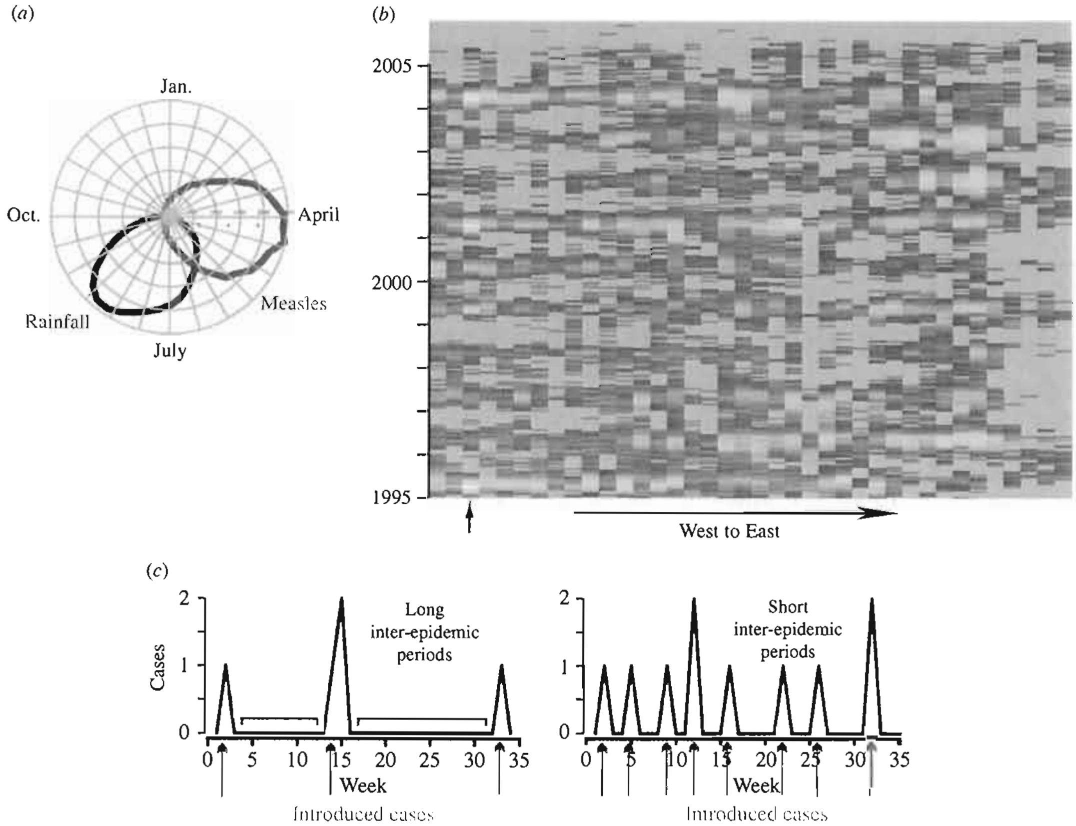

Without frequent re-introductions

With frequent re-introductions

Fig. 1. (*a*) The seasonality of measles is strongly out of phase with the rainy season (red line is mean reported cases in Niger, blue line is mean rainfall in mm in Niger, time moves clockwise). (*b*) Reported cases form 1995 to 2005 (bottom to top) arranged from west to east (left to right). Note that the large outbreaks occur in different years between the eastern and western districts, Yellow = high cases, red = low cases, grey = zero cases. Note the irregular periodicity of the outbreaks in Niamey as indicated by vertical black arrow in b, (*c*) Introduced cases end inter-epidemic periods and therefore determine their length. Infrequent or few introductions (grey arrows) produce long inter-epidemic periods (left) whereas frequent or many introduced cases produce short inter-epidemic periods (right).

multi-annual dynamics of measles epidemics are strongly influenced by birth rates, vaccination rates, and seasonality in transmission [6, 9, 11, 12]. The highly analysed pre-vaccination measles dynamics of England and Wales (1944–1964) showed strongly synchronized, regular biennial epidemics forced by the seasonal aggregation of children in schools [10, 11]. The susceptible pool was replenished through relatively low birth rates ($\sim$0·02/person per year). Local persistence of the infection through epidemic troughs occurred above a *critical community size* (CCS) of around 250 000–400 000 inhabitants [13]. Below this threshold measles routinely went stochastically extinct during troughs [see Supplementary material 1, Fig. S1 (available online)]. In England and Wales during this period, cities and towns were generally highly connected by roads and rails making it possible for individuals to travel the entire distance of the island within the 2-week infectious period of measles. Measles introductions from larger cities ignited subsequent epidemics in smaller towns [11, 13] such that epidemics began in large cities and dispersed outwards in hierarchical travelling waves [10].

In contrast to the highly connected towns in England and Wales, a common mode of transportation in Niger is walking along roads, resulting in a dominance of short distance movements. Nationally aggregated case reports from Niger show measles epidemics occurring annually during the dry season (Fig. 1*a*); however, at more refined spatial scales, weekly incidence reveals highly irregular outbreaks [14] (Fig. 1*b*). Each year, the magnitude of epidemics varies greatly between the various regions of Niger with no consistent spatial pattern. A combination of high birth rates and strong seasonal forcing generates locally erratic outbreak dynamics with frequent local extinctions.

Local persistence through epidemic troughs is rare in Niger, where the CCS has been estimated at well over a million [14] and the largest city, the capital, Niamey, has a population of about 700000 [15]. In spite of frequent local extinctions, Niger faces measles epidemics during most dry seasons. Given these pronounced colonization and extinction dynamics, human movement and spatial transmission are clearly key issues in understanding the local epidemic patterns [14].

Most of Niger's employment is agriculturally related and the annual rainy season dictates agricultural production and labour [16], resulting in dynamic patterns of land use [17]. The strong seasonality of outbreaks prompted Ferrari *et al.* [14] to speculate that agriculturally driven human movements determine the timing of outbreaks. They hypothesized that the epidemic patterns reflect how a portion of the population tends to live in lower density agricultural areas during the rainy season and higher density urban centres during the dry season [16, 18] and that the seasonal fluctuations in population density determine the highly seasonal transmission rates. This behavioural mechanism is analogous to the way aggregation of school children during term times forced the epidemic timing of measles in England and Wales. However, Ferrari *et al.* show that the result of the agricultural cycles in Niger is dramatically stronger seasonality in transmission [10, 11, 14, 19].

Unlike the UK, Niger shares borders with seven countries within a larger region in which measles is also an ongoing problem. Specifically, directly to the south of Niger along major roads are the highly populated northern Nigerian states of Kano, Katsina, and Jigawa. While the total population of Niger is around 14 million, the population of these three Nigerian states totals around 20 million [20]. In 2003, Nigeria's national measles immunization coverage was estimated at 35%, the lowest in the WHO AFRO region [21] and these northern states are often the most affected states within Nigeria as a whole during outbreaks [22, 23]. Niger and the six other nations with which it shares borders were estimated to have national measles immunization coverage between 61% and 91% in 2003 [21].

As in many countries with high disease burden and low income, data directly addressing movement and migration for Niger are scarce. In the absence of detailed data, we used geographic proxies for movement and migration. Specifically we used reported measles incidence in conjunction with statistical models, GIS road network data, and high-resolution precipitation estimates to infer patterns of transmission and relevant movement and migration.

To assess spatial coupling and connectivity in Niger, we estimated recolonization events, or the relative number of measles introductions in each district [11]. Due to underlying movement patterns, immigration events tend to increase with population size while the proportion of zeroes (or the number of weeks with zero reported cases) scales inversely with population size [11, 13] (Fig. S1). In other words, we generally expect large populations to attract more immigrants and have fewer weeks with zero reported measles cases than small populations.

The well-established overall correlation between the proportion of time with zero incidence and the population size results from the interaction of stochasticity and the inherent cyclic dynamics of measles [13, 24]; however, outliers to this overall pattern can be very informative [25]. Districts with fewer zeroes than expected have potential epidemic importance as 'hotspots' for measles introductions [26]. These hotspots can occur for one of two reasons: (1) increased transmission as a result of high population density or (2) high connectivity to other places which leads to an excess of measles introductions.

Supplementary immunization activities (SIAs) provide a 'natural experiment' to differentiate between these two mechanisms. Conducted in Niger in 2004 and 2007, SIAs are large-scale, pulsed vaccination campaigns that deplete the pool of susceptible individuals, reducing the likelihood of measles transmission. Because Niger's SIAs are national vaccination campaigns, they are held within national boundaries, within a defined period of time [27]. Individuals who are not in the country during an SIA are not vaccinated as part of the SIA. SIAs are not coordinated between Niger and its neighbouring countries. It has been previously shown that reported cases immediately following similar vaccination campaigns tend to reflect immigration from nearby non-SIA areas [28, 29]. While the number of post-SIA cases may also be influenced by overall vaccine efficacy and the number of missed individuals within the target group, our analysis shows that the post-SIA patterns in Niger were consistent with non-SIA years and therefore are likely to a be reliable signal of measles' spatial transmission across Niger's borders.

To explore whether the hotspots highlighted by the SIAs in Niger are the result of consistent, high connectivity during non-SIA years, we compared the length of the inter-epidemic periods (number of consecutive weeks with zero reported measles cases) from the ten non-SIA years of the time series from these hotspots to those of all the other districts. Cases following a local extinction result from introductions through immigration. Therefore, long inter-epidemic periods indicate very few immigration events, low connectivity, and very few introductions of measles while short inter-epidemic periods indicate frequent immigration events, high connectivity, and frequent measles introductions (Fig. 1 *c*) [11].

The spatial distribution of these hotspots suggests important regional clustering of transnational migration from Nigeria and the importance of the road network for spatial connectivity, movement of people, and re-introductions of measles.

METHODS

Reported cases

We obtained weekly reported measles cases from 1995 to 2005 (Fig. 1 *b*) [14] as well as from the first 8 weeks of 2008 from 35 districts and three urban districts (38 total districts) in Niger from the Ministry of Health of Niger [15]. Some underreporting occurs during this period [14] [see analysis in Supplementary material 2 (online)]. Reported measles incidence from 2006 to 2007 was not obtained.

Total fadeouts and population size

We refer to more than two consecutive weeks with zero reported cases as an inter-epidemic period and define each 2-week period with zero reported cases as a fadeout. Due to the infectious period of measles (about 2 weeks), we did not include single weeks with zero reported cases because they do not suggest a local broken chain of transmission. It is important to clarify that by focusing only on weeks with zero reported cases instead of weeks with low case-reporting we are emphasizing the process of re-introductions rather than an increase in the total magnitude of cases [26]. The former addresses movement while the latter addresses density. Here, we are not measuring the rate of increase in cases but rather the likelihood of the introduction of a case.

We expect a negative relationship between local population size and the proportion of zeroes, or the proportion of weeks in the time-series with no reported measles incidence. Essentially, smaller populations should fade out more than larger populations due to demographic stochasticity [11, 13] (Fig. S1). Here we focus our analysis on the residuals from the predicted relationship of the linear regression between fadeouts and population size. Districts with the fewest fadeouts relative to population size (negative residuals) have more introductions than expected and are potentially epidemically important for the regional spread of measles.

As an initial indication of the impact of movement on measles persistence, we tested for spatial autocorrelation in the residuals from the linear fit of the proportion of zeros on population size by calculating Moran's I with neighbours defined as districts with contiguous boundaries [30]. A positive Moran's I statistic indicates spatial autocorrelation (clustering) and a significant P value indicates a significant departure from randomness.

Reported cases following vaccination campaigns

At the end of 2004 and 2007, Niger's Ministry of Health carried out large-scale SIAs in Niger [31]. The 2004 SIA was a 'catch-up' campaign to immunize individuals aged from 6 months to 15 years [5] and in 2007 a 'follow-up' SIA was conducted, targeting children aged from 6 months to 5 years. The SIAs of 2004 and 2007 reported achieved coverage levels of 99% and 100%, respectively [5, 15]. SIAs reduce the overall density of susceptibles in a population and thereby halt local chains of transmission and highlight spatial connectivity by flagging likely imported cases [28, 29].

We calculated the number of cases reported in each district immediately following each SIA (all 52 weeks of 2005 and the first 8 weeks of 2008). We identified districts with more reported cases for population size than the national mean following *both* SIAs as 'hotspots' for measles re-introductions. We analysed the spatial autocorrelation of the hotspots using a Moran's test as described above with hotspots treated as a binary variable (i.e. 1 = district identified as a hotspot; 0 = district not identified as a hotspot).

Rates of re-introductions

We used local measles extinctions to gain information on spatial connectivity and human movement [11]

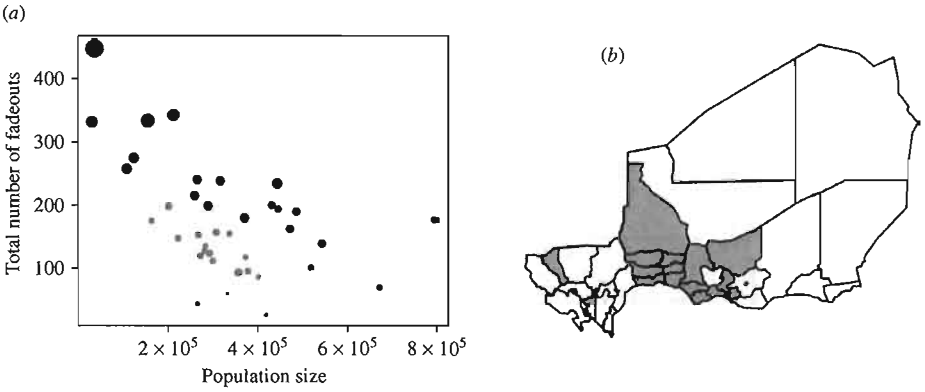

Fig. 2. (*a*) Fadeouts and population size from 1995–2005. Districts with the fewest fadeouts per population size are shown in grey. Only fadeouts of more than 1 week are included. Size of dots is related to mean length of inter-epidemic period; colours indicate positive (black) or negative (grey) residuals from fit of total number of fadeouts on population size. (*b*) Districts with negative residuals (grey) are primarily clustered along the central southern border.

and examined whether the results from the analysis on post-SIA cases for population size in 2005 and 2008 agree with the length of inter-epidemic periods by population size from 1995 to 2004 [11]. Using a Cox proportional hazard regression model, we fit the length of the inter-epidemic periods as waiting times to determine the hazard rate of re-introductions (similar to [26], see this reference for details) (Fig. 1*c*). Specifically, population size is the independent variable, inter-epidemic lengths the response variable, and hotspots are indicator functions. Accounting for population size, we compared the re-introduction rates of the hotspots identified by the post-SIA analysis to all the other districts.

Environment and settlement data

Niger's district population sizes were obtained from the official census reports from Niger. All other population sizes were obtained from the CIA *World Factbook* [20]. Daily rainfall estimates were obtained from 2003 to 2008 from NOAA's Climate Prediction Center's CPC Morphing Technique [32]. These were aggregated and smoothed to create an annual rainfall signature. ESRI shapefiles for administrative boundaries were obtained from Global Administrative Areas v.0.9 (GADM) [33]. Minor modifications were made for the three urban districts based on the Global Rural Urban Mapping Project (GRUMP) urban extents grid [34] (see below). An urban extents map was obtained from the GRUMP urban extents grid [35] and was converted to a polygon shapefile in ArcGIS. Road maps were obtained from the USGS early warning roads file [36], VMAP0 [37], and from the Visual Media Unit in the Communications and Information Services Branch of the United Nations Office for the Coordination of Humanitarian Affairs. These three maps were manually merged to obtain the highest possible resolution of roads.

RESULTS

Spatial correlation and coupling patterns

The relationship between population size and total number of fadeouts showed an overall negative relationship, as expected ($R^2 = 0{\cdot}31$) (Fig. 2*a*). We identified 19 districts that have negative residuals from the regression of fadeouts on population size, indicating that these districts have higher than expected levels of measles persistence (grey points in Fig. 2*a*). A line fit to the data excluding Niamey (Fig. 2*a*, point on far right) revealed these same 19 districts with negative residuals. Our analysis revealed that these 11 districts are significantly spatially autocorrelated (Moran's I statistic $= 0{\cdot}30$, $P < 0{\cdot}01$) and concentrated around the central southern portion of Niger (Fig. 2*b*). Having identified these locations, we explored their epidemic importance and spatial distribution.

Reported cases following vaccination campaigns

We used SIAs to differentiate between the two previously mentioned mechanisms which are most likely to lead to a lower than expected number of fadeouts (either increased disease transmission due to high population density or a disproportionate number

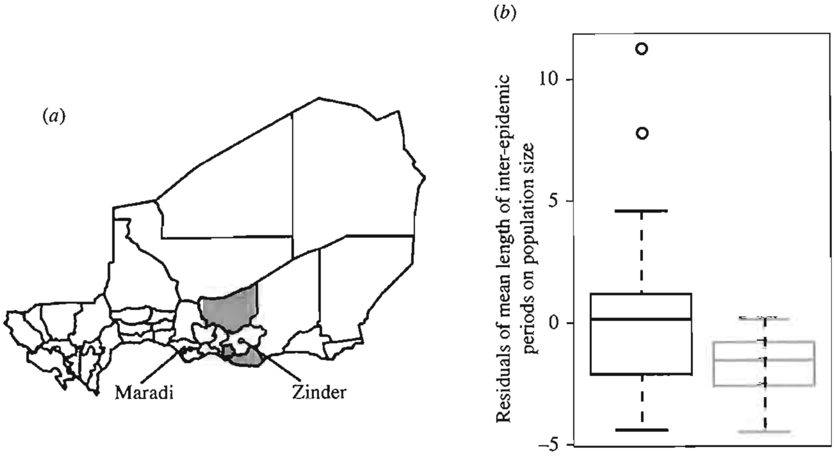

Fig. 3. (*a*) Hotspots following both SIAs. These six districts (in grey) in southern Niger near the Nigerian border were identified as having the most cases, when corrected for population size, following both SIAs studied here. (*b*) These districts also have significantly shorter waiting times to re-introductions from 1995 to 2004 (grey) than all other districts (black) ($P<0.01$) and may have the strongest connections to a measles reservoir or 'core' in Nigeria.

of measles introductions due to human movement patterns [28, 29]). We found six districts with more cases than the national mean following both SIAs when corrected for population size. These six potential hotspots vary in population size but are spatially autocorrelated: all six are found along or near the central southern border of Niger (Fig. 3*a*) (Moran's I statistic$=0.174$, $P<0.05$). Each of these districts also contains segments of primary roads (Fig. 4). We next determined whether these hotspots were epidemically important for the 10 years of reported cases when SIAs did not occur (1995–2004).

Rates of re-introductions

The length of inter-epidemic periods in non-SIA years provides an additional measure of the rate of re-introduction in the districts. Population size is strongly negatively correlated to the length of the inter-epidemic periods ($P<0.0001$, Cox proportional hazard regression model) in the districts, indicating that re-introductions are more likely in highly populated districts. We further found that the six hotspots, identified from post-SIA cases, have a significantly higher rate of re-introductions relative to population size than do the other 32 districts for 1995–2004 ($P<0.01$, Cox proportional hazard regression model) (Fig. 3*b*).

Roads and hotspots

Niger has seven primary roads that cross its national border, four of which cross the Niger–Nigeria border. Three of these transnational primary roads to Nigeria cross through one of the six hotspots identified from post-SIA cases (Fig. 4).

DISCUSSION

The estimated CCS for measles in Niger [14] is much larger than for previous studies of developed countries. Measles routinely goes locally extinct across districts of all population sizes in Niger. In fact, Niamey, the largest city, shows more fadeouts than expected from its population size (Fig. 2*a*). This lack of local persistence throughout Niger highlights the importance of migration for the regional persistence of measles.

Overall, measles is more persistent in the more populous regions of Niger. The outliers to this relationship reveal valuable information about spatial connectivity and disease introductions (Fig. 2*a*) [11]. We found that six districts clustered along the south central border of Niger tend to have more re-introductions of measles than expected from their population size in both SIA and non-SIA years. These six districts all lie along primary roads (Fig. 4) and are likely to receive disproportionate numbers of migrants.

It is worth noting that the northernmost hotspot is demographically different from the others. The southern half of this district has high population density while the northern half is sparsely inhabited. Additionally, this district is not entirely Hausa, as is the majority of southern Niger and northern

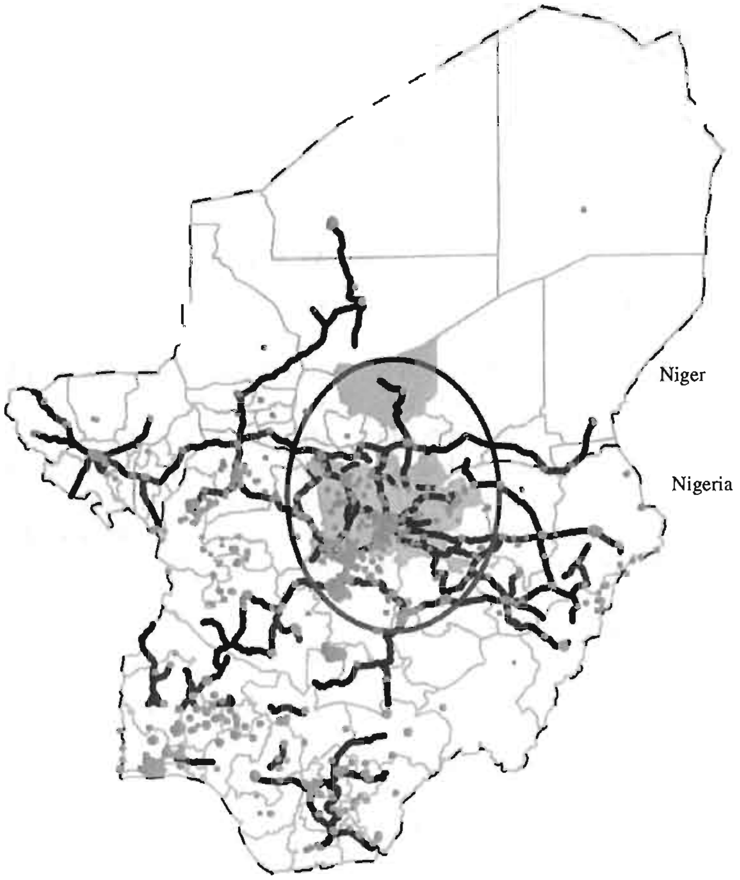

Fig. 4. Primary roads (blue) directly connect the ethnically similar areas of southern Niger and northern Nigeria's large, dense, urban centres (urban extents shown in yellow). The Niger/Nigeria boundary (dashed black line) lies between the six hotspots identified within Niger (shaded in red) and the large, dense urban areas in northern Nigeria (shaded in green). Due to the close proximity and high degree of contact between these two areas, we define this area as an epidemically important contact cluster (circled in red).

Nigeria; a formerly nomadic Taureg population also resides here. This district is probably identified as a hotspot due to the connectivity of the southern portion, with direct access via primary roads to the large and growing city of Zinder, as well as northern Nigeria.

We conclude that the six hotspots identified in this study are epidemically important as a result of high connectivity and transnational human movement patterns, which are strongly influenced by routes of primary roads. Proximity, shared road networks, and cultural similarities between northern Nigeria and southern Niger suggest that these two areas interact as part of the same effective meta-population [38]. Although we lack reported measles cases from Nigeria, these transnational social and economic connections greatly influence measles dynamics in Niger and surrounding nations [28].

Similar to the core-satellite dynamics seen in previously studied measles systems, Niger's hotspots are probably satellite populations that are highly connected via primary roads to a core where measles persists all year [10, 19, 25]. A core is essential for reintroductions of measles following synchronized widespread local extinctions. We reason that this measles reservoir is the group of northern Nigerian states immediately south of the Niger border. These states contain dense urban areas and have a high burden of measles [22, 23] (Fig. 4).

A high degree of connectivity between the cities in southern Niger and the dense urban areas in northern Nigeria is not surprising. Southern Niger and northern Nigeria are culturally very similar: the majority of the residents in each of these areas are Hausa [17, 38, 39]. These two areas are economically dependent on each other and the movement that occurs between them is a vital part of the economic and agricultural system [38]. The resulting level of contact between these areas significantly influences the epidemiology in this region and we conclude that this area constitutes an epidemically important contact cluster (Fig. 4).

Control implications

Revealing strong connectivity between southern Niger and northern Nigeria allows us to identify an epidemically important contact cluster. Measles epidemics taking place within Niger do not occur in isolation and the districts of Niger do not define an isolated meta-population. This emphasizes that infectious diseases in this area cannot be controlled by public health policy limited to political boundaries, but instead must consider the disease dynamics of the larger region.

We propose that surveillance and intervention could have a greater impact by regarding southern Niger and northern Nigeria as a single meta-population with an epidemic core that probably resides in the dense urban states of northern Nigeria. Vaccinating only parts of this contact cluster based on political boundaries is unlikely to achieve the necessary proportion of immunized individuals within the meta-population to interrupt measles transmission. This phenomenon is hardly specific to Niger; transnational movements between countries that are economically linked have previously been shown to reduce the impact of nationally planned SIAs [28]. In these situations, planning simultaneous SIAs for countries with transnational epidemically important contact clusters could improve the efficacy of these campaigns.

By identifying epidemically important contact clusters and the potential epidemiological importance of cross-border movement, we have shown that even when measles dynamics have been pushed into a highly irregular epidemic regimen [14], the spatial coupling of a core-satellite meta-population is likely to be similar to previously studied measles systems, where epidemics are more familiarly regular [25].

These results are widely applicable and in the future we suggest that when possible, public health strategies should identify epidemically important contact clusters, ideally across multiple infections, and apply surveillance and intervention measures to the identified meta-population for maximum effectiveness. Identifying these contact clusters and understanding the extent of local movements will help to achieve successful outcomes for disease intervention. This approach emphasizes public health solutions designed specifically for areas with ongoing disease to increase the efficiency and success of surveillance and vaccination campaigns.

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NOTE

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/hyg).

DECLARATION OF INTEREST

None.

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