SPATIAL HETEROGENEITIES IN EPIDEMIC CONNECTIVITY

IN REAL LANDSCAPES

A Dissertation in
Biology

by

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Abstract

Though largely controlled in developed countries, many vaccine-preventable human infections are major public health issues in many areas of the world. Specifically, parts of Africa have extremely high incidence of the directly transmitted diseases measles and meningitis. For directly transmitted pathogens, transmission patterns are rooted in human mixing behavior across spatial scales. Identifying spatial interactions that contribute to recurring epidemics will help define and predict outbreak patterns. This work examines the underlying mechanisms for spatial heterogeneities in host disease burden and risk across spatial scales, from regional dynamics to seasonal outbreaks in individual cities.

Using spatially explicit reported cases from recent measles and meningitis outbreaks in Niger, as well as highly detailed measles incidence from pre-vaccination England and Wales, I assess regional variations in movement and contact patterns relating to outbreaks as well as mechanisms for seasonal forcing in cities. Previously studied human disease systems emphasize the importance of real landscapes and host movements in understanding disease transmission across space. To identify critical elements of spatiotemporal disease dynamics in Niger, this work explores dynamic disease models, transnational contact clusters, road networks that facilitate connectivity, and agricultural seasonality. This work highlights the need to understand locally specific patterns of spatial connectivity and host movement to inform disease management and vaccine policy.
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Preface

Author contributions

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The work in Appendix A was done primarily by Dr. Ferrari. Although Nita Bharti was involved, this work is included so the reader can see the full methods and analyses that preceded chapter 5.

Additional collaborators are noted at the end of each chapter in the section entitled “Author Contributions”.

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Chapter 1

Introduction

The study of the spatiotemporal spread of infectious diseases has long been a key field in applied population biology. From the early 1850’s when Snow investigated a cholera epidemic in London [1], the use of statistical and mathematical approaches in epidemiology has a distinguished history. Problems in spatiotemporal disease dynamics have spawned developments in spatial geography [2], ecological dynamics [3, 4] and epidemiological modeling [5-8].

Clearly, from a public health perspective, the study of infectious disease dynamics is of critical applied importance; however, the field is also significant for the development of theory in other disciplines. Predator-prey systems [9], metapopulation dynamics [10], models of microevolution [11], ecological community dynamics [12], and a handful of other disciplines all share concepts with epidemiology.

The spatial and temporal distributions of infection are strongly influenced by the specific mode of transmission. These can range from direct transmission, which requires little more than contact among hosts, to transmission mediated by environmental conditions, to complex multi-species interactions for vector-borne pathogens. Even in the simpler case of directly transmitted infections, spatiotemporal dynamics of infection are driven by complex interactions of many factors of both host and pathogen. In the present work, I focus on one important element of this picture: the epidemiological impact of spatial heterogeneities in epidemic connectivity for directly transmitted human pathogens. Specifically, this refers to the variation in rates of human movement between and within
population subunits over space due to social, seasonal, or economic reasons as well as the availability of travel routes (such as airlines [13] or roads [14]). I use epidemiological models and analyses of epidemic and population data to address this issue in the context of the dynamics and control of directly transmitted infections of humans.

Public health background

High levels of vaccine preventable mortality in low-income regions are a serious public health issue [15, 16]. The global burden of infectious diseases is spatially aggregated such that populations in Africa and South Asia face the highest risk of morbidity and mortality from many vaccine preventable diseases [17, 18].

As an exemplar, the West African, Sahelian nation of Niger has a high burden of both measles and meningitis. Important contributing factors are extremely high birth rates, low vaccine coverage, and strong seasonal swings in transmission (discussed in detail in chapters three and four) [19, 20]. While measles has been studied extensively in pre-vaccine industrialized nations [21-28], comparatively little is known about measles dynamics in currently affected areas and even less is known about meningitis.

This gap in epidemiological knowledge highlights ongoing public health issues in low-income nations: effective control measures must be designed for the dynamics of the system in which they will be used. Landscape heterogeneities in epidemic connectivity and seasonally varying host mixing are central to areas with ongoing epidemics of measles and meningitis. I assess the impact of these factors on the disease dynamics of Niger.
For the remainder of this introduction, I present background information on the pathogens and key data sources and methods, as well as relevant concepts in disease dynamics. The chapter concludes with a brief prospectus of the remaining chapters in the thesis.

*Measles: the virus and the vaccine*

The measles virus belongs to the genus *Morbillivirus*, along with canine distemper virus, phocine distemper virus, rinderpest virus, peste des petites ruminants and other less known pathogens [29]. These are negative sense, single stranded RNA viruses, which do not survive well outside of the host organism [30]. Measles infects only humans and the virus is transmitted from an infected host to a susceptible one, either by direct contact via respiratory droplets or aerosolization from coughing or sneezing [30]. Following infection, recovered individuals gain strong, lifelong immunity to future infections [5].

The measles vaccine is an attenuated virus, which effectively mimics the strong, long-term immunity that follows natural measles infection [30]. Following a single dose of the vaccine about 85% of recipients gain long-term measles immunity [30]. Following the recommended second dose of the measles vaccine, approximately 99% of recipients gain long-term immunity [30].

The vaccine requires a cold chain throughout storage and transport, which means it must be maintained between -25° C and + 8° C [31]. This temperature sensitivity has contributed to the logistical difficulties of vaccine delivery in low-income nations.
Meningococcal meningitis

Caused by the bacterium *Neisseria meningitis*, meningitis is transmitted via a primarily respiratory route like the measles virus, though it does not spread as easily or rapidly. A complicating factor in transmission is the prevalence of asymptomatic carriers. While these individuals are generally not diagnosed, they are infected and thought to be important in transmission [32]. Also unlike measles, immunity wanes within three years from both infection and the currently used vaccine [33, 34]. For this reason, vaccination in many parts of Africa is done reactively [35].

The highest incidence of meningitis worldwide is spatially aggregated within a region of Africa known as the meningitis belt [36-38] (fig. 1.1). Although it is a directly transmitted disease, environmental factors, not population density, are cited as the

Figure 1.1. WHO map showing global meningitis risk
primary cause of timing, intensity, and spatial patterns of meningitis incidence [39-41]. Outbreaks are strongly seasonal and highly unpredictable [42-44] and consequently, vaccine supplies are consistently limited during outbreaks [17, 35]. Allocating the vaccine supply reactively throughout affected areas is a serious challenge in meningitis prevention.

**Data Sources**

Data are key to parameterize and validate epidemic models and the extremely rich disease and demographic data sets described below are vital components to understanding the disease dynamics of each system.

*Epidemiological data for measles*

From England and Wales, I obtained biweekly reported measles cases, annual population size, and birth rate from each of 952 towns in England and Wales from 1944 to 1964 [22]. Cases were reported from children who sought medical attention and diagnoses were made based on physical symptoms and reported to a government agency.

Niger provides an excellent and unique opportunity to understand the dynamics of infectious diseases in a current setting. In these analyses, I use weekly reported cases at the district level from 1995 to 2005 [20]. Measles diagnoses are made based on symptoms; patients present with a very distinct rash [30]. Because the rash is unique, there is a low probability of misdiagnosis from false positives but a real probability of unreported cases. I address underreporting in chapter four. Demographic data consist of national birth rate and district population size. The Ministry of Health of Niger collected these incidence and demographic data [45].
Epidemiological data for meningitis

In Niger, diagnoses of meningococcal meningitis are either lab confirmed, confirmed by cloudy cerebrospinal fluid, or confirmed when symptoms meet the definition for a suspected case during an outbreak [35]. False positives have a low probability of occurring because clinical symptoms are distinct and apparent. The devastating effects of the disease tend to strongly discourage and diminish underreporting of symptomatic cases. In these analyses, I use weekly reported cases at the district level from 1985 to 2005 from a national surveillance system [35]. The district population sizes and national birth rates are the same as above for measles.

Environmental and geographical data for Niger

Road maps of Niger were obtained from the USGS early warning roads file [46], VMAP0 [47], and from the Visual Media Unit in the Communications and Information Services Branch of the United Nations Office for the Coordination of Humanitarian Affairs (chapters 3 and 4). I also use high-resolution satellite imagery of Niger from the Defense Meteorological Satellite Program (DMSP) (chapter 5) and daily rainfall estimates from 2003 to 2008 from the National Oceanographic and Atmospheric Administration’s (NOAA) Climate Prediction Center’s (CPC) Morphing Technique [48] (chapters 3-5).

Epidemiological dynamics and models

Mathematical models have been used extensively in epidemiology during the last century [19, 49], with a rapid increase in use stimulated by the work of Anderson and May [5]. Like all models, models of infectious diseases exist across a range of transparency, from simple to extremely complex with varying amounts of flexibility and accuracy [6].
Because of its simple, consistent natural history and excellent historical database, measles is often considered the ideal pathogen for modeling the dynamics of immunizing infections [22, 24, 27, 28, 50].

\( R_0 \) and herd immunity: Thresholds for control

Central to the theory of epidemiology is the basic reproductive number, \( R_0 \), defined as the number of secondary infections caused by a single infection in a completely susceptible population [5]. If a pathogen has an \( R_0 \) value below one, it will be unable to invade a host population; if \( R_0 \) is above one, the pathogen will likely invade [5]. Once infection is established, the dynamics of local epidemics are captured in the effective reproductive ratio, \( R \), which discounts \( R_0 \) by the proportion of susceptible individuals in the population. Thus, a great many analyses of local disease dynamics, particularly emerging diseases, focus on estimating \( R_0 \) and \( R \) [5, 6, 49, 51, 52].

Local dynamics and models of measles

The simplest dynamic model for epidemics (which embodies the role of the basic reproduction number) is the Susceptible-Infected-Recovered (SIR) model [49]. In its most basic form (the Simple Epidemic), this nonlinear model is deterministic and assumes continuous time, homogenous hosts, ‘mean field’ mass action mixing, long-term immunity from infection, and no influential demographic processes. This model can be altered and augmented in many ways to include any of the following: demographic processes (births, deaths), waning immunity or no immunity (SIRS, SIS), incubation periods (SEIR), infection-induced mortality (SI), stochasticity, and countless other possibilities. From this basic model, more complex models have been able to modify or
link the SIR structure to other models, increasing its range of uses. Specifically, I discuss the inclusion of discrete time steps to bring the model closer to notification data [52], host (or pathogen) population heterogeneity in space [53], and temporal forcing (seasonal changes in transmission) [6].

*Relating measles models to the time series data*

The SIR family of models with the addition of specific biological characteristics works extremely well as a general descriptor of measles dynamics [5]. However, a key step in quantitatively characterizing spatiotemporal dynamics has been the development of methods to estimate measles transmission parameters from the rich notification time series (see above for details on time series) (for example [21]) that exist for the virus. To this end, a significant adjustment to the SIR framework was the addition of a discrete time, stochastic enhancement [52]. While previously developed discrete time models could not make predictions as accurately as continuous time models, this model allowed for the estimation of parameters directly from the disease time-series. The time-series SIR (TSIR) model successfully linked disease data (which is reported in discrete time) to mechanistic models (which performed better in continuous time). Using the TSIR model, one could estimate parameters such as seasonality (in particular, seasonal swings in transmission), spatial coupling, and in some cases age structure [52] directly from incidence data. This was successfully done for measles in pre-vaccination England and Wales [21]. Currently, more sophisticated methods to fit continuous-time models are being developed [54-57].
Demographic stochasticity and spatial coupling

As mentioned earlier, measles infection initiates lifetime immunity in individuals. The strength of this acquired measles immunity results in violent epidemics, which extinguish themselves by ‘using up’ susceptible individuals [20, 58]. These nonlinear dynamics are inherently unstable in the troughs between epidemics [5]. During these troughs, if the chain of transmission is not broken and low levels of cases are sustained, then a subsequent outbreak occurs when susceptible density has increased via births, leading to repeated epidemics interspersed with deep troughs. However, if the chain of transmission is broken between epidemics and the disease fades out, then a subsequent epidemic starts only when cases are introduced from elsewhere. In locations where the infection fades out, the population is below a Critical Community Size (CCS)[59].

The size of the CCS is influenced by birth rates, vaccination rates, and seasonality in transmission [59]. For measles, this threshold has been consistently observed between 250,000-400,000 in pre-vaccine developed countries [59] while in Niger, the combination of very high birth rates, patchy routine vaccine coverage, and very strong seasonal transmission appears to increase the CCS by an order of magnitude from that of pre-vaccine developed countries [20].

Spatial interactions among population subunits become important when populations are below the CCS and experience regular fadeouts, as new outbreaks require reintroductions from elsewhere. The signature of the interactions between the subunits of the population is seen in the spatial patterns of fadeouts and subsequent reintroductions (we return to this in chapters 2-4). Regions that are well connected via human movement (for directly
transmitted diseases) will tend to experience rapid re-introduction of infection following fadeout [60]. Variation in the rates of movement between population subunits can lead to highly structured spatial progression of outbreaks across regions (e.g., traveling waves of measles [22] and influenza [61], the long range movement of SARS [62], and the spread of HIV along roads [14]).

**Spatial heterogeneities in epidemic connectivity: Regional dynamics**

Spatial heterogeneities in epidemic connectivity are significant in assessing regional dynamics and reintroductions of cases following fadeouts in populations below the CCS. Variation in connectivity of population subunits can significantly impact regional epidemic dynamics. Accurate spatial representation of host movement has been previously highlighted by the development of a wide variety of data-informed dynamic models [2, 6, 20, 24, 53, 63].

Mapping spatial patterns of disease incidence (or vector abundance) and host density to assess host movement and risk of infection can be a useful tool for gaining a biological understanding of host and pathogen spatial distributions in realistic landscapes [1, 3, 13, 64-67]. For some diseases, this has enabled methods in prospective public health, rather than reactive control [68-70].

**Linking local dynamics with regional models**

As previously mentioned, to account for multiple coupled host populations in space, the SIR or TSIR models can be linked to a variety of spatial models. In particular, this has been done for measles in pre-vaccination England and Wales [53]. The dynamics of ‘patches’ were predicted individually using the TSIR model, and were then coupled to
each other at each time step with a metapopulation model such that population connectivity was positively related to spatial proximity and population size (known as a gravity model in the sociological and spatial geography literature [2] and detailed in chapter 2). This model worked very well for developed countries with continuous work and school related movement [53] but failed to capture the erratic dynamics of a strongly seasonal system with pronounced spatial and temporal variation in host movement, as seen in West Africa [20] (chapters 3-4).

Today, high levels of seasonal host migration across regions prioritized for measles vaccination, such as West Africa, emphasize the continuing need to model dynamic populations in realistic landscapes with real patterns of host mixing. This work takes another step towards modeling spatial and social structure by using dynamic and statistical models to evaluate the impact of spatial heterogeneities in dynamic social contacts in the disease-burdened populations of West Africa [71].

Transmission rates: Mechanisms of seasonal forcing

While \( R_0 \) is a central quantity in epidemiology, its average value is slightly less informative when investigating strongly seasonal local dynamics. Seasonal fluctuations in host density and other factors can lead to seasonal changes in transmission rates; as transmission rates change, the value of \( R_0 \) changes as well [72-74].

Fluctuating patterns in transmission force the dynamics of outbreaks, resulting in violent epidemics [20, 58]. Seasonal patterns of incidence are seen frequently in directly transmitted diseases and, though the mathematics of complex patterns of seasonal dynamics have been studied thoroughly [73, 74], the mechanism underlying seasonal
forcing is frequently unclear. Mechanisms of seasonality are not always investigated due to the difficulty in acquiring this level of detail in host or pathogen population data.

Seasonal forcing determines the rate, magnitude, and timing of epidemics. A common explanation for the underlying cause of seasonality is host behavior, i.e., local host mixing changes through time. Calibrating transmission rate and population density is a fundamental challenge in infectious diseases. A rare example where this mechanism of seasonality was explicitly shown is in the seasonal mixing of susceptible children as school terms drove measles epidemics in England and Wales [24]. Similarly, Ferrari et al. [20] put forth the hypothesis that agriculturally influenced seasonal host aggregation may drive the timing of measles outbreaks in Niger [75]. Seasonal contact rates are an important component of host mixing. This work addresses a continuing need in the field by indirectly estimating fluctuating population density in regions with sparse demographic data and ongoing measles outbreaks.

Statistical methods

Throughout this work, I use a wide variety of statistical methods, which are detailed in individual chapters. Methods include linear models, hazard regressions, and measures of spatial autocorrelation to assess various aspects of host spatial connectivity (chapters 2-4). I also use GIS-based data extraction and spatial analyses to explore spatial and landscape heterogeneities (chapter 3-5).

Prospectus

I investigate measles dynamics in pre-vaccination populations of England and Wales to understand host movement patterns and spatial heterogeneities within a highly detailed,
data rich system. I then compare and contrast these findings to the current situation in Niger, where the dynamics of measles and meningitis are poorly understood major public health concerns, which require a more detailed mechanistic understanding for successful management.

In chapter two, I investigate ‘edge effects’ from spatially detailed reported measles cases from pre-vaccination England and Wales. This study system is one of the best understood in the field so I investigate the predictions of a spatial metapopulation model shown to produce highly accurate results. As the edges, or boundaries, of a spatial system are the most robust test of a spatial model [76], I look closely into a gravity model, fit to the measles dynamics of England and Wales [53], to analyze the dynamics of measles along the coast. I explore heterogeneities in epidemic connectivity between cities and towns stemming from spatial position.

In chapter three, I look further into the effects of realistic landscapes and human movements on disease dynamics. Here, I shift the focus to the ongoing measles epidemics in Niger. The chaotic dynamics produce unpredictable outbreaks and illustrate the importance of understanding local human movement (epidemic connectivity) in the ecology of the system [20]. Strong seasonal transmission and large urban populations in neighboring countries make Niger a satellite population for measles, as seen by the many fadeouts and reintroductions of disease. I analyze spatial heterogeneities in persistence and reintroductions, to assess the role of host epidemic connectivity between the districts of Niger.
I take this analysis a step further in chapter four, when I investigate the role of human movement in another directly transmitted human infection in Niger. I present a comparative analysis between measles and meningitis in Niger to evaluate similar spatial heterogeneities, in spite of major epidemiological differences. Here, I compare spatial patterns of epidemic connectivity between the two diseases. I also investigate a possible effect of density dependence in the transmission of meningitis, which has long been attributed mainly to environmental causes [39, 41, 44]. Consistent patterns of epidemic connectivity between districts could serve as a potential indicator for human movement and risk of infection in this region.

In chapter five, I critically analyze seasonal movement patterns in Niger by exploring methods for calibrating transmission rates and population density in three cities. While preceding chapters emphasize connectivity and heterogeneity between districts, here I focus on fluctuating density within districts. Although it is not possible to directly measure fluctuations in population density in this region, I develop a method to measure relative density between seasons within cities by using digitally defined urban extents and serial, high-resolution nighttime lights imagery. Since nighttime lights correlate to population density [77, 78], here I explore the relationship between seasonally fluctuating brightness and seasonally varying transmission rates as estimated from the reported cases from each city.

Summary

This research investigates the spatiotemporal dynamics of measles in historical England and Wales and the spatiotemporal dynamics of measles and meningitis in present-day

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Chapter 2

Measles on the Edge: Coastal Heterogeneities and Infection Dynamics
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Keywords: measles, epidemiology, gravity model, edge, metapopulation, infectious disease
Abstract

Mathematical models can help elucidate the spatio-temporal dynamics of epidemics as well as the impact of control measures. The gravity model for directly transmitted diseases is currently one of the most parsimonious models for spatial epidemic spread. This model uses distance-weighted, population size-dependent coupling to estimate host movement and disease incidence in metapopulations. The model captures overall measles dynamics in terms of underlying human movement in pre-vaccination England and Wales. In spatial models, edges often present a special challenge. Therefore, to test the model’s robustness, we analyzed gravity model predictions of measles persistence for coastal cities in England and Wales. Results show that, although predictions are accurate for inland towns, they significantly underestimate coastal persistence. We examine incidence, outbreak seasonality, and public transportation records, to show that the model’s inaccuracies stem from an underestimation of contacts per individual along the coast. We rescue this predicted ‘edge effect’ by increasing coastal contacts to approximate the number of per capita inland contacts. These results illustrate the impact of ‘edge effects’ on epidemic metapopulations in general and demonstrate directions for the refinement of spatiotemporal epidemic models.
Introduction

The dynamic clockwork of measles epidemics is relatively well understood [1, 2]. Measles is a highly infectious virus and, in pre-vaccine developed countries, the strong acquired immunity following infection led to an average age of infection of around 5 years [1, 3]. In both historical and current measles outbreaks, a brief primary infection followed by lifelong immunity results in violent epidemics. These epidemics extinguish themselves by depleting susceptible numbers, as hosts move irreversibly through susceptible-infected-recovered (SIR) classes. Subsequent epidemics start only when susceptible density has increased over time via births, resulting in repeated epidemic cycles interspersed with deep troughs of little or no measles incidence [4] (fig. 2.S1b). Seasonal patterns in aggregation and transmission can also force the timing and magnitude of these epidemic sequences [5], and this has been captured clearly in historical records of measles incidence for many countries [2].

Measles data from pre-vaccination England and Wales (1944-64) highlight spatial patterns in outbreaks and, therefore, also indirectly reveal patterns in human movement [6, 7]. A key driver of measles spatiotemporal dynamics is a threshold local population size, or critical community size (CCS), below which pre-vaccination measles fails to persist and goes stochastically extinct (‘fade out’) between outbreaks. Epidemics in populations smaller than this threshold are subsequently reintroduced from other patches of a metapopulation. The CCS for measles in pre-vaccination England and Wales is estimated at approximately 300,000 individuals [8]. Outbreaks begin in cities that exceed the CCS, called ‘core’ cities and extend away from them, in traveling waves of infection...
These outward traveling waves identify core cities as epidemic drivers. The ‘coupling’ between patches quantifies the contact between them, which results in their degree of epidemic synchrony.

From previous studies, we understand that measles dynamics in London, as well as most of England and Wales, were driven by increased contact rates for children at the beginning of school terms [5]. These increases in contact rates led to higher transmission rates and ‘forced’ major biennial (every other year) epidemics. Susceptible density built up via births during non-epidemic years.

Despite complex geographic patterns of human habitation and movement (e.g. [9]), the simple gravity model appears to provide a fair approximation to many features of viral transmission. The gravity model parameterizes both the extent to which people move to large towns compared to small ones, and the spatial localization of their movements. These movements can occur for any reason and the model ignores geographic features such as desirability of each location as a vacation/weekend destination and the availability of public transportation. Moreover, it implicitly treats inland communities in a different fashion than coastal towns because neighboring communities surround inland towns whereas water partially surrounds coastal towns. To better understand the applicability and limitations of the gravity model, we were prompted by Savill et al. [10] to ask how well the model predicts coastal dynamics, as they point out that these are true ‘edges’ and therefore, are a unique case and a robust test of spatial models. We start with a simplified scenario: an artificial metapopulation with equidistant and equivalently sized
inland and coastal towns arranged in a regular geometric shape. We use this simple system to analyze the model’s predictions along the edges. Next, we study a more complex and realistic system using actual spatial, demographic, and epidemic data from England and Wales. We compared predicted and observed patterns of measles persistence in coastal locations to those of inland locations.

Methods

Local and Regional Scale Models

Within towns and cities (patches), hosts move from Susceptible (S) to Infected (I) to Recovered (R) classes irreversibly (full details and parameter values are given in [11]). We use a Time-series SIR model as follows:

\[
S_{t+1} = S_t - I_{t+1} + births_t, \quad \text{Equation 1}
\]

\[
\lambda_t = \frac{\beta_t S_t I_t^\alpha}{N_t}, \quad I_{t+1} = \text{Poisson}(\lambda_t), \quad \text{Equation 2}
\]

Here, \(\beta_t\) is the seasonally varying transmission rate, estimated from reported measles incidence. The parameter \(\alpha\), when slightly less than unity (as here), is a factor that converts from continuous to discrete time [12]. Each time step is two-weeks long to reflect the average infectious period of the measles virus. Cases enter the infected class at the beginning of a time step. Two weeks later, they exit the infected class and enter the recovered class in the next time step. We define a fadeout as one biweek (a two-week interval) with zero cases reported in a location. In any one location, the absence of a fadeout signifies a possible unbroken local chain of transmission and we assume measles has persisted locally. Conversely, cases following a fadeout, or local extinction, indicate that the virus was locally reintroduced.
Reintroductions occur when the movement of individuals results in transmission events between patches. In order to quantify this movement, we calculate patch connectivity using a gravity model [2, 7]. Specifically, we represent the expected movement of individuals from patch \( j \) to patch \( i \) as:

\[
j \rightarrow i = \frac{\Theta N_i^{\tau_1} N_j^{\tau_2}}{D_{ij}^\rho}
\]

*Equation 3*

Here, \( N_i \) and \( N_j \) are the population sizes of towns \( i \) and \( j \), respectively, \( D_{ij} \) is the Euclidean distance between towns \( i \) and \( j \), \( \rho \) is an exponent describing the decay of flux with distance, \( \tau_1 \) and \( \tau_2 \) are immigration and emigration exponents, respectively, and \( \Theta \) is a coefficient of spatial coupling. Movement between patches is most likely to occur over short distances and towards patches with large populations. Xia *et al.* [7] used a spatially explicit metapopulation model for England and Wales with gravity coupling to estimate the coefficients as \( \rho = 1, \tau_1 = 1, \tau_2 = 1.5 \), and \( \Theta = 4.54 \times 10^{-9} \text{ km / person}^{1.5} \text{ / biweek.} \)

Savill *et al.* [10] examined the 2001 UK foot and mouth disease epidemic and determined that Euclidean distance was a better predictor for transmission risk than shortest or quickest route. While transportation of infectious materials likely occurred over roads in the foot and mouth epidemic, multiple transmission routes over long distances made Euclidean distance a significantly better predictor of simple spatial transmission risk. For these reasons, we use Euclidean distance here.

This gravity framework successfully captures the overall defining features of pre-vaccination measles dynamics in England and Wales, particularly the relationship
between measles persistence and spatial synchrony with local population size and isolation [7]. Disease models with similar distance-weighted size-dependent coupling have recently been used to capture spatiotemporal epidemic spread successfully in a number of other systems [10, 13-16].

**Simple Case: Artificial Metapopulation Model**

We created a metapopulation with one core city (a city which exceeds the CCS) surrounded by many cities below the CCS (fig. 2.1a). Our intentions with this simple artificial population were to isolate and identify the effects of placement along an edge by holding population size and distance to core city constant and equal between edge and non-edge patches. This metapopulation included 27 cities along the edge of the system that were all equal in size and equidistant from the core city. The metapopulation also included an equivalent set of 27 non-edge cities, or inland patches, also equal in size and equidistant from the core city. We introduced a simulated measles epidemic into this artificial metapopulation. We ran the simulation for 5000 biweeks and used the predictions from the final 4000 biweeks. We chose an $R_0$ value of ~30, invariant of community size ([11] their figure 8 and p. 180) and an alpha slightly less than unity. We gradually increased the coupling strength from .005 to .02 (the value fit for this parameter falls within this range) and used seasonal term time forcing, as observed in the data. We compared the model predictions for disease persistence and outbreak correlation to the core city between these edge and inland cities from our artificial metapopulation.
Actual Case: England and Wales Metapopulation

Our data consist of biweekly reported measles cases, population size, and birth rate from each of 952 towns in England and Wales (fig. 2.2a) from 1944 to 1964. We used latitude and longitude coordinates to determine the Euclidean distance between each pair. We defined coastal towns as those within 5 km of the edge of the island and we identified 184 of these.

To investigate edge effects in England and Wales, we first fit the gravity model (equation 3) to fortnightly data for measles from 1944 to 1964 for all 952 towns in England and Wales. The gravity model parameters ($\Theta$, $\tau_1$, $\tau_2$, and $\rho$) were estimated by a combination of short and long term predictions, as described by Xia et al. [7] and discussed above. (For a more detailed description of the gravity model fit, see [7].) We ran gravity model simulations for twenty-one consecutive years with each year consisting of 26 biweeks in order to test the null hypothesis that the simulated persistence and dynamics of coastal towns and non-coastal towns of the same size would be similar.

Seasonality

We considered the possibility that coastal cities may reach peak densities (and therefore have elevated contact rates) during the summer months, when travelers are preferentially drawn to the coast [17]. To investigate the impact of specific coastal seasonality on measles epidemics, we compared coastal outbreak seasonality to inland outbreak seasonality from the data. We compared the average timing and duration of actual epidemic peaks and troughs for the entire 21-year period.
Public Transportation

While there are no specific records of human movement to and from the coastline during the time period studied, we used annual public transportation passenger volume from this time in England and Wales [18]. As a proxy for contact rates, we analyzed these data for interesting patterns or anomalies, with respect to each coastal town’s population size and location. We were unable to obtain bus passenger volume, road use data or any seasonal movement data, which would have complemented annual train passenger data to more completely show movement patterns.

Results

Simple Case: Artificial Metapopulation Model

The gravity formulation uses distance and population size to capture complex patterns of human movement in a relatively crude way. These movements are important because they drive epidemic spread between patches of metapopulations. To understand how the model specifically treats edges of metapopulations, we used an artificial metapopulation with ‘edge’ and ‘non-edge’ towns that were similar in size (all but the ‘core’ were below the CCS) and equidistant from the core city (fig. 2.1a). It is important to note that each coastal town we identified in England and Wales was below the CCS and therefore too small to sustain a continuous chain of measles transmission in the absence of re-introductions. We introduced a simulated measles epidemic into our artificial metapopulation and focused on the model’s predictions of persistence in ‘edge’ towns and the equivalent ‘non-edge’ towns.
In our artificial metapopulation, the model predicts that edge town epidemics stochastically fade out more frequently than inland town epidemics. The edge towns have fewer contacts and re-introductions than inland towns due to the predicted movement of individuals within a gravity model framework. Reduced contacts would lead to a difference in fadeout frequency between edge and inland towns. These edge town epidemics are also less correlated with the core city than are the inland town epidemics, another likely result of reduced contacts (fig. 2.1b). Figure 2.1 illustrates this ‘edge effect’ by using our simple model core-satellite disease metapopulation [7] to show that locations along the edge of the system are predicted to experience a smaller flux of infective sparks than their inland counterparts. We are confident that the increased fadeouts and reduced correlation along the edge were due to reduced contacts because solely increasing the per capita contacts for towns along the edge is sufficient to result in comparable fadeouts between edge and inland equivalents (fig. 2.1c, 2.1e) and to increase edge epidemic correlation with the central core town (fig. 2.1b, 2.1d).

**Actual Case: England and Wales Metapopulation**

England and Wales provide an excellent opportunity to explore how a gravity model applies to measles and real coastal towns, or ‘edges.’ The ocean surrounding Great Britain was a relatively impenetrable geographic barrier that was unlikely to introduce many measles cases, relative to the impact of inland child movement. This allows us to observe a fairly autonomous epidemic system to analyze the true edge effects of human movement in a metapopulation and epidemics on an island (fig. 2.2a).
The gravity model predicted a significantly greater difference in fadeouts for coastal towns in England and Wales than for inland towns (corrected for population size) than we observed in the data (fig. 2.2b and 2.2c, fig. 2.S1). These model predictions show a greater bias than was seen in both our simulated metapopulation and simple coastal system models. Importantly, model predictions showed no spatial bias or geographic clustering of overestimated fadeouts (fig. 2.S2). This indicates that the basic gravity metapopulation is unable to capture the relatively high level of stochastic persistence seen in coastal measles. We now explore possible extrinsic and mechanistic epidemiological explanations for this discrepancy.

**Seasonality**

The epidemic seasonality of coastal and inland towns was not significantly different; the epidemics both began and peaked at similar times during the same years, which correspond to school terms (fig. 2.3a). The similar timing of epidemics implies that contact rates between inland and coastal locations were high enough to cause inland core cities to spark coastal epidemics. Extremely low contact rates between inland and coastal towns would have resulted in highly uncorrelated measles epidemics along the coast of England and Wales, relative to inland town epidemics. The data show that these contact rates were higher than predicted by the gravity model because the inland and coast were in epidemic synchrony.
Public Transportation

These data revealed no abnormal relationship between train use and measles persistence that could not be explained by population size, a component that the gravity model already considers (fig. 2.S3 and fig. 2.4). We also saw no explanatory spatial patterns in the passenger train volume.

Model Adjustments

Although we found no statistically significant difference between train use and population size (fig. 2.S3b and 2.S3c), we adjusted the spatial coupling coefficient for only the coastal towns with passenger train volume that exceeded 10,000 passengers per week (which we categorized as high train use) and repeated the simulations. We used least squares to compare our adjusted model predictions to the data for the 109 coastal cities with high train use (fig. 2.S3a and fig. 2.4a). We found that increasing the basic coupling parameter (Θ) by 1.3 times the initial fitted value allowed the model to more accurately predict the fadeouts along the coast. The model simulations with this adjustment did not significantly overestimate the total number of coastal fadeouts (fig. 2.4b and 2.4c).

The volume of passenger traffic clearly highlights the mobility of individuals in England and Wales at this time. In order to model this level of host mobility, we repeated the model simulations with another adjustment. We optimized the gravity model to reflect equal numbers of individual contacts in coastal and inland towns. The data suggested a conservation of contacts created a more accurate map of social space over geographic
space. We addressed this by minimizing the difference of the sum of squares between
adjusted model predictions and the data. For all 184 coastal towns, we found the
simulations fit best when we increased the spatial coupling by 1.3 times our initial \( \Theta \) value. With this adjustment, the model simulations no longer showed a bias towards
coastal fadeouts and predictions more accurately matched the observed fadeout rate
distribution (fig. 2.2c and fig. 2.S1).

**Discussion**

In this study, we demonstrate a discrepancy between modeled and observed coastal
epidemics and we ask what drives this breakdown of the gravity model assumptions.
Because our question address spatial transmission, detailed human movement data to
parallel the epidemic time series would be ideal for comparison but these are not
available, particularly for children, during the 1940s and 50s [3]. Instead, we used local
population heterogeneities to test the gravity model predictions of epidemic persistence
and synchrony.

Our initial, basic gravity model may have incorrectly predicted coastal persistence for
two possible reasons. First, the towns along the coast may have had contact rates that
were different from those of inland towns. For example, we considered the possibility
that coastal locations may have experienced relative isolation-by-distance and low
contact rates for most of the year, alternating with high contact rates during the summer
months, due to travelers [17]. In inland towns, contact rates are highest at the beginning
of each school term, when epidemics take place. Cyclic demographic flux could cause
the model to underestimate seasonal movement and coastal contacts, resulting in overestimated fadeout rates caused by not considering summer cases and predicting only school term epidemics, sparked by core cities. In this situation, coastal towns would show measles outbreaks in the summer, unique from the rest of the island, where contact rates and epidemics rise and peak during the school term. The data do not show this.

If coastal towns showed epidemic seasonality that indicated summer outbreaks, this would imply that they were somewhat isolated from inland towns and were not influenced by inland epidemic cycles as a result of unique contact rates. However, our analysis shows that measles epidemics in coastal towns followed the term time forcing of large inland cities and coastal towns were not at all isolated from inland towns. Therefore, the data show us that coastal epidemic cycles were likely driven by core cities, which were only found inland, indicating that coastal and inland towns did not have different seasonal contact rates (fig. 2.3a). It has further been shown that the coast was an attractive location for suburban residences year round, as well as for seasonal holidays [19], not a continuously isolated edge as the model predicted in both our simulated ‘artificial metapopulation model’ and our England and Wales simulations. The data clearly show that coastal towns did not have reduced contact rates with inland towns.

A second possible reason that the gravity model overestimated fadeouts along the coast is that coastal and inland per capita contact rates are relatively similar. The distance-weighted, size-dependent spatial coupling element of the basic gravity model will always predict lower overall contact rates for coastal than for inland towns. Because coastal
towns are partially surrounded by water, they have fewer populations at close proximity (small $D_{ij}$ in equation 3), which greatly impacts the flux of infection between towns. However, if each coastal town averages approximately the same number of contacts per capita as inland locations (as the public transportation data suggest in fig. 2.S3), and the model is unable to map social space over geographic space by assuming the opposite, then the prediction of reduced contacts along the coast would create a false “edge effect” of increased fadeouts. It is both unrealistic and counterintuitive to assume reduced individual coastal contacts; living along the coast does not reduce the need, for example, for medical attention, commerce, or social companionship. If observed contact rates are reasonably similar between coastal and inland towns, the model will underestimate contacts, transmission, and persistence along the coast. In this case, the observed coastal epidemic seasonality would not differ from inland seasonality and it does not in this system.

If host mobility resulted in high contact rates along the coast year-round, even for distant cities, this would result in multiple measles introductions during local epidemics troughs. While these introductions would not have sparked new measles epidemics because of low susceptible density resulting from regular biennial outbreaks, they would have sparked isolated cases and led to decreased fadeout rates in coastal towns. However, it is very difficult to determine actual contact rates; even though we were able to obtain passenger train use volume, we did not have bus or road use data. Further, even with all those data, we would still fail to quantify the actual movement of children. Thus, while our train use
data give us a good idea of host mobility and train use by town size, it is still only a vague approximation of the contacts we are actually interested in.

In the gravity model, the spatial coupling coefficient ($\Theta$, equation 3) represents the amount of human movement from one town to another; as $\Theta$ increases, contacts increase and spatial synchrony increases. Based on our model predictions, the spatial coupling parameter estimation fits inland towns well but underestimates the connectivity of coastal towns.

In figure 2.4b, we compare the residuals of the fadeouts on population size between the observed data, initial gravity model predictions, adjusted gravity model predictions for high train use coastal towns, and adjusted gravity model predictions for all coastal towns. Although the high train use adjustment gravity model predicts a slight bias towards coastal fadeouts, it corrects for most of the bias in the initial, unadjusted gravity model predictions and more accurately reflects the observed data. When we increased the coastal spatial coupling coefficient to more accurately map social space over geographic space for the purpose of increasing coastal contact rates, the adjustment corrected for the model’s bias of reduced coastal contacts and increased coastal fadeouts (fig. 2.1d and 2.1e, fig. 2.2c, and fig. 2.3).

**Conclusions**

Contact from core cities to coastal regions introduced isolated measles cases during the troughs between epidemics. These stochastic introductions did not lead to out-of-phase
epidemics along the coast; instead they resulted in low levels of cases, or persistence [20]. When this occurred, coastal towns did not fade out as the model predicted because of the model’s inaccurate assumption that locations at the edge of a system have reduced contact rates because of their spatial position. The observed data do not support this assumption, implying that (at least childhood) behavior and movement in this landscape do not isolate geographic edges.

The adjustments we have shown here crudely illustrate the gravity model’s potential to accommodate spatial heterogeneities and host behavior in stochastic metapopulations by identifying important geographic features, which can influence host mixing behavior and affect disease transmission [21]. The spatial coupling coefficient for edges can be increased when host mobility results in reduced isolation-by-distance.

In realistic landscapes, habitats often include variation in accessibility, land quality and resource availability. Populations establish centers and edges with respect to these features. The methods presented here can be applied as a first step to understanding disease dynamics and host movement across heterogeneous landscape peripheries. Dissecting the applied implications of these results is an important area for future work, especially in developing countries [22]. It is clear that more sophisticated methods need to be developed to address these specific issues with spatial models but these findings make a satisfactory first step in identifying the problem and exploring solutions.
Author Contributions

Conceived and designed the experiments: BG OB NB YX. Performed the experiments: NB YX. Analyzed the data: BG NB YX. Contributed reagents/materials/analysis tools: BG OB NB YX. Wrote the paper: NB.

References

Figure 2.1. Simulated metapopulation for edge analysis
(a) The spatial distribution of towns (all dots), the large black dot represents a core city or central town (analogous to London) and the edge towns in red (analogous to coastal towns) have inland towns in navy (analogous to any non-edge towns) that are equidistant from the central town and similar in size.
(b), (c) The model always predicts a reduced correlation coefficient and an increased fadeout rate between an edge town and the central town than between a similar inland town and the central town. The bias is significant, although it looks slight here, and is even stronger in the real model predictions for England and Wales (fig. 2.2b and 2.3b)
(d), (e) This can be corrected by increasing the coupling strength ($\Theta$ in equation 3).
Figure 2.2. The model predicts more coastal fadeouts than observed for England and Wales
(a) Map of England and Wales showing the location of each of the 952 towns included in this study. Green points with white outlines are inland towns, pink points are coastal towns. Area of each point is correlated to population size.
(b) Total number of fadeouts against population size as observed (top) and as predicted by gravity model (bottom). In the data, the coastal fadeouts (pink) are distributed among the inland fadeouts (green). In the model predictions, the coastal fadeouts are clustered near the top of the inland distribution.
(c) Boxplots showing coastal (pink) and inland (green) pairs of residuals of fadeouts on population size. Left: observed; center: gravity model predictions; right: gravity model predictions with spatial coupling increased for the entire coast.
Figure 2.3  Epidemic Seasonality: Inland and Coastal

(a) The biennial epidemic seasonality does not differ between the inland towns (dark green line indicates inland seasonal mean, light gray shading is +/- one standard deviation) and the coast (magenta line indicates coastal seasonal mean and pink shading is +/- one standard deviation); both peak at the same times and the cycle repeats every two years. Time is shown as biweeks on the x-axis, where 26 biweeks are equal to one year.

(b) The biennial outbreaks in London, the largest city in this system, drive the cycles of England and Wales. Susceptibles are depleted during large outbreaks and accumulate during epidemic troughs until the next outbreak. Major peaks occur at the beginning of the school term every second year. Time is shown as biweeks on the x-axis, where 26 biweeks are equal to one year.
Figure 2.4 Adjustments to gravity model using train use data

(a) Map of England and Wales. Red dots show coastal locations, size of dots reflects amount of train use, black dots in the center of red dots indicate train use > 10,000 weekly passengers.

(b) Left Panel: Left shows data, right shows initial gravity model predictions, gray = coast, black = inland. Right Panel: Left shows model predictions with increased spatial coupling along entire coast, right shows model with increased spatial coupling for towns along coast with >10,000 weekly train passengers (red), gray = coast, black = inland.

(c) Total number of fadeouts against log population size as predicted by gravity model when the spatial coupling coefficient is increased for only the coastal towns which average >10,000 weekly train passengers per week. This adjustment results in an even distribution of coastal fadeouts (red), as they appear in the data. Initial model predictions show coastal fadeouts are clustered along the top of the distribution (fig. 2.2b).
Residuals from ‘proportion of fadeouts against log population size’ against log population size

The center panel (b) shows that the gravity model predicts a strong bias for coastal towns of all population sizes to fadeout more than the data show (a). The panel on the right (c) shows that our model adjustment corrects for this bias and the distribution of predicted coastal fadeouts is similar to that of inland towns. Inland in dark green, coast in magenta.
Figure 2.S2  Spatial distribution of coastal fadeouts from model predictions
Navy points show coastal towns that the model predicts will fade out more than the average number of predicted fadeouts. Yellow points show the towns that are predicted to fade out less than the average number of predicted fadeouts. The navy points are found along all sections of the coast and do not reveal any spatial pattern. Similarly, the yellow points show no spatial clustering. This shows that the model is not spatially biased in its predictions. The size of each point is proportional to population size.
Measles on the Edge: Coastal Heterogeneities and Infection Dynamics
Supplementary Material 2.3
Measles persistence, population size, and train use along the coast

Figure 2.S3  Measles persistence, population size, and train use along the coast
(a) Left: Train use against log population size for each coastal town. Size of point reflects relative persistence. Right: Relative Persistence against train use, size of points reflect population size.
(b) The top two panels show the data. Left: Log of population size is strongly correlated with persistence. Right: The effect of train use on the residuals of persistence on population size is not significant (p = .08). The bottom two panels show the gravity model predictions. Left: Log of population size is strongly correlated with persistence. Right: The effect of train use on the residuals of persistence on population size is not significant (p = .08).
Chapter 3

Measles hotspots and epidemiological connectivity in Niger
Epidemiology and Infection (submitted)

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Abstract

Though largely controlled in developed countries, measles remains a major public health issue in many areas of Asia and Africa. Transmission patterns are rooted in human mixing behavior across spatial scales. Identifying spatial interactions that contribute to recurring epidemics will help define and predict outbreak patterns. Problematically, our current understanding of the spatio-temporal dynamics of measles is largely based on pre-vaccination industrialized countries. Using spatially explicit reported cases from recent measles outbreaks in Niger, we explore regional variations in host movement and contact patterns relating to measles outbreaks. Previously studied measles systems emphasize the importance of school terms and population size in measles transmission. We find that critical elements of spatial disease dynamics in Niger are agricultural seasonality, transnational contact clusters, and roads networks that facilitate connectivity. These results highlight the need to understand locally specific patterns of seasonality, demographic characteristics, and spatial heterogeneities to inform vaccination policy.
**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 analyse 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 developed countries, and are often used as a paradigm for acute immunizing infections [6-11]. Previous studies have shown that the 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) had relatively low birth rates and showed highly synchronized, regular biennial epidemics forced by the seasonal aggregation of children in schools [10, 11]. Local persistence of the infection through epidemic troughs occurred above a critical community size (CCS) of around 250000-400000 inhabitants [13]. Below this threshold measles routinely went stochastically extinct during troughs (see supplementary material, fig. 3.S1a). 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 two-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 traveling waves [10].

In contrast to the highly connected towns in England and Wales, the most 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. 3.1a), however at more refined spatial scales, weekly incidence reveals highly irregular outbreaks [14](fig. 3.1b). 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 unlikely 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 approximately 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 is clearly a key issue in understanding the local epidemic patterns [14].

The vast majority of Niger’s employment is agriculturally related and the annual rainy season dictates agricultural production and labor [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 posited that the epidemic patterns reflect how individuals tend to live in lower density agricultural areas during the rainy season and higher density urban centres during
the dry season [16, 18] such that seasonal fluctuations in population density determines seasonal transmission rates. This behavioral mechanism is analogous to how aggregation of school children during term times forced the epidemic timing of measles in England and Wales but Ferrari et al. show the result of the agricultural cycles in Niger is dramatically stronger seasonality in transmission [10, 11, 14, 19].

Unlike the British Isles, Niger shares borders with seven countries within a larger region in which measles is also a 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 Niger shares a border 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 use geographic proxies for movement and migration. Specifically we use 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 estimate 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. 3.S1a). 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 a defined period of time and within national boundaries [27] and individuals who are not in the country during an SIA are not vaccinated as part of the SIA nor are SIAs coordinated between neighboring 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 be a reliable signal of measles’ spatial transmission across Niger’s borders.

To explore whether the hotspots highlighted by the SIAs are the result of consistent, high connectivity during non-SIA years, we compare the length of the interepidemic periods (number of consecutive weeks with zero reported measles cases) from the full time series from these hotspots to those of all the other districts. Cases reported after a local extinction result from introductions through immigration. Therefore, long interepidemic periods indicate very few immigration events, low connectivity, and very few introductions of measles while short interepidemic periods indicate frequent immigration events, high connectivity, and frequent measles introductions (fig. 3.3c)[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 reintroductions of measles.

**Methods**

*Reported Cases*

We obtained weekly reported measles cases from 1995-2005 (fig. 3.1b) [14] as well as for 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]. Underreporting is likely during this
period [14] (see analysis in supplementary material 3.2). Reported measles incidence from 2006-2007 was not obtained.

**Total Fadeouts and Population Size**

We refer to more than two consecutive weeks with zero reported cases as interepidemic periods and define each 2 week period with zero reported cases as a fadeout. Due to the infectious period of measles (about 2 weeks), we eliminate 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 reintroductions 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. 3.S1a). 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 test for spatial autocorrelation in the residuals from the linear fit of the proportion of zeros on
population size by calculating Moran’s I with neighbors 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 supplementary immunization activities (SIAs) in Niger [31]. The 2004 SIA was a ‘catch up’ campaign to immunize individuals from 6 months to 15 yrs old [5] and in 2007 a ‘follow up’ SIA was conducted, targeting children from 6 months to 5 years old. The SIAs of 2004 and 2007 achieved 99% and 100% coverage, respectively [5, 15]. The SIAs reduced the overall density of susceptibles in a population and thereby halted local chains of transmission and highlighted spatial connectivity by flagging likely imported cases [28, 29].

We calculate 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 identify districts with more reported cases for population size than the national mean following both SIAs as ‘hotspots’ for measles reintroductions. We analyse the spatial clustering of the hotspots using a Moran’s test as described above with hotspots treated as a binary variable (i.e. 1 = district is identified as a hotspot, 0 = district is not identified as a hotspot).

Rates of Reintroductions

We use local measles extinctions to gain information on spatial connectivity and human movement [11] and examine whether the results from the analysis on post-SIA cases for
population size in 2005 and 2008 agree with the length of interepidemic periods by population size from 1995-2004 [11]. Using a Cox proportional hazard regression model, we fit the length of the interepidemic periods as waiting times to determine the hazard rate of reintroductions (similar to [26]) (fig. 3.3c). Specifically, population size is the independent variable, interepidemic lengths is the response variable, and hotspots are indicator functions. Accounting for population size, we compare the reintroduction rates of the hotspots identified by the post-SIA analysis against 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 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 v0.9 (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 ($R^2 = 0.31$) (fig. 3.2a). We identified 19 districts that have negative residuals from the regression of fadeouts on population size, indicating that these districts have a disproportionate number of measles introductions (fig. 3.2a). A line fit to the data excluding Niamey (fig. 3.2a, point on far right) revealed these same 19 districts with negative residuals. Our analysis revealed that these eleven districts are spatially clustered in the central southern portion of Niger (Moran I statistic = 0.30 and $p < 0.01$) (fig. 3.2b). Having identified these locations, we explore their epidemic importance and spatial distribution.

Reported Cases Following Vaccination Campaigns

We use 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 of measles introductions due to human movement patterns [28, 29]). We find 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 clustered: all six are found along or near the central southern border of Niger (fig. 3.3a) (Moran I statistic = 0.174 and $p < 0.05$). Each of these districts also contains segments of primary roads (fig. 3.4). We next determine whether these hotspots were epidemically significant for ten years of reported cases when SIAs did not occur (1995-2004).
Rates of Reintroductions

The length of interepidemic 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 rate of reintroductions (p < 0.0001, Cox proportional hazard regression model) in the districts, indicating that reintroductions are more likely in highly populated districts. We further find that the six hotspots, identified from post-SIA cases, have a significantly higher rate of reintroductions relative to population size than do the other 32 districts for 1995-2004 (p < 0.01, Cox proportional hazard regression model) (fig. 3.3b).

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. 3.4).

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. 3.2a). This lack of local persistence throughout Niger highlights the importance of migration for the regional persistence of measles.

Overall, measles is more persistent in more populous regions of Niger. The outliers to this relationship reveal valuable information about spatial connectivity and disease introductions (fig. 3.2a)[11]. We find that six districts clustered along the south central
border of Niger tend to have more reintroductions of measles than expected from their population size in both SIA and non-SIA years. These six districts all lie along primary roads (fig. 3.4) and are likely to receive disproportionate numbers of migrants.

It is worth noting that the northern-most 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 Nigeria; a formerly nomadic Taureg population also resides here. This district is likely 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 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 metapopulation [38]. Connections like this 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 likely 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
These states contain dense urban areas and have a high burden of measles [22, 23] (fig. 3.4).

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. 3.4).

**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 metapopulation. This emphasizes that 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 metapopulation with an epidemic core that likely 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 metapopulation to interrupt measles
transmission. This phenomenon is hardly specific to Niger; transnational movements between countries that are economically linked have 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 success 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 regime [14], the spatial coupling of a core-satellite metapopulation is likely 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 identify epidemically important contact clusters, ideally across multiple infections, and apply surveillance and intervention measures to the identified metapopulation for maximum effectiveness. Identifying these contact clusters and understanding the extent of local movements will help 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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**Declaration of interest**

None.

**Author Contributions**

The paper was conceived by N.B, M.J.F, O.N.B. and B.T.G. Statistical analyses were designed and conducted by N.B and M.J.F. Spatial analyses were designed and conducted by N.B., C.M., and A.T. Data collection was coordinated by A.D., R.F.G., A.T., and C.M. The paper was written by N.B. with help from B.T.G., R.F.G., M.J.F., and O.N.B. All authors discussed the results and edited the manuscript.

**References**


FEWS NET. Africa Data Dissemination Service.


Figure 3.1. (a) The seasonality of measles is always in anti-phase with the rainy season (red is mean reported cases in Niger, blue is mean rainfall in mm in Niger). (b) Reported cases from 1995-2005 arranged from west to east. Notice that the large outbreaks occur in different years between the eastern and western districts. Red = low or zero cases, Yellow = high cases. Note the irregular periodicity of the outbreaks in Niamey as indicated by vertical black arrow in b.
Figure 3.2. (a) Fadeouts and population size from 1995-2005. Districts with the fewest fadeouts per population size are shown in gray. Only fadeouts of more than one week are included. Size of dots is related to mean length of interepidemic period, colors indicate positive (black) or negative (gray) residuals from fit of total number of fadeouts on population size. (b) Districts with negative residuals (gray) are primarily clustered along the central southern border.
Figure 3.3. (a) Hotspots following both SIAs. These six districts (in gray) 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 reintroductions from 1995-2004 (gray) than all other districts (black) \((p < 0.01)\) and may have the strongest connections to a measles reservoir or ‘core’ in Nigeria. (c) Introduced cases end interepidemic periods and therefore determine their length. Infrequent or few introductions (grey arrows) produce long interepidemic periods (left) whereas frequent or many introduced cases produce short interepidemic periods (right).
Figure 3.4. 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).
Supplementary Material 3.1

Figure 3.S1. Here we show the classic relationship between population size and number of fadeouts as seen in pre-vaccination England and Wales from 1944-1964. Yellow line indicates CCS [1].

Supplementary Material 3.2

To account for underreporting, we repeat our analysis on interepidemic length using a minimum of four consecutive weeks with zero cases to define a fadeout. Here, interepidemic periods are consecutive weeks with zero cases that exceed four weeks. The spatial patterns seen from these analyses are nearly identical to ones found for two-week fadeouts. Thus, we can be fairly certain that these patterns are real spatial signatures as a result of epidemic connectivity and not an artifact of underreporting.

Using four-week long fadeouts, we plot number of fadeouts against population size ($R^2 = 0.2832$) and map the residuals (above, size of points is correlated to mean length of interepidemic periods). The negative and positive residuals are spatially autocorrelated (Moran I statistic = 0.214 and $p = 0.02$) (above, right).

As in the main text, we use a Cox proportional hazard regression model with the length of the interepidemic periods as a waiting time to determine the hazard rate of reintroductions (similar to [1]) (fig. 3.3c). Specifically, population size is the independent variable, interepidemic lengths is the response variable, and hotspots/not
hotspots are factors (same hotspots as in the main text as these were defined by post-SIA incidence, not fadeouts). Accounting for population size, we compare the reintroduction rates of the hotspots identified by the post-SIA analysis against all the other districts.

We again find that population size is strongly negatively correlated on the rate of reintroductions (p < 0.0001, independent variable from Cox proportional hazard regression model), indicating that reintroductions are more likely in highly populated districts. We further find that the six hotspots, identified by high numbers of post-SIA cases, have a significantly higher rate of reintroductions relative to population size than do the other 32 districts for 1995-2004 (p < 0.03, factor from Cox proportional hazard regression model). This means that the hotspots (above, grey) have significantly shorter waiting time to reintroductions than do non-hotspot districts (above, black) when fadeouts are defined as four weeks to account for underreporting.

References

Chapter 4

Spatial Dynamics of Meningitis in Niger: observed patterns in comparison with measles

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Abstract

In Africa, meningococcal meningitis outbreaks occur only during the dry season. Previous analyses from Niger suggest that fluctuations in population density influence the seasonality of measles. We propose that seasonal host aggregation and migration similarly affect the strong seasonality seen in meningitis incidence. Although climatic factors are widely believed to play a role in meningitis seasonality, here we specifically focus on the less examined role of human density and movement.

A strong environmental component to meningitis dynamics would lead to a correlation with the proposed causal environmental factors, such as rainfall, wind, and humidity. Although this is true at broad spatial scales, our analysis shows that at local scales, spatial patterns of meningitis incidence are clustered along primary roads and migration corridors. We further show that districts in Niger with high measles reintroduction rates also have high meningitis reappearance rates.

In spite of the biological and epidemiological differences between the two diseases, similar spatial patterns emerge from the dynamics of both. This analysis enhances our current understanding of regional contact patterns and disease dynamics and can be used to identify important areas in meningitis surveillance for early detection and vaccination.
Introduction

Measles and meningitis are directly transmitted human diseases that are both significant public health issues in West Africa [1-3]. While the relatively simple dynamics of measles are fairly well understood, the more complex epidemiology of meningitis has been difficult to grasp completely.

*Measles* is a completely immunizing infection with an inexpensive vaccine that confers lifelong immunity. Susceptible individuals become infected through direct contact with aerosolized particles from an infected individual and remain infected for about two weeks before they recover fully with lasting immunity against future infections such that measles largely infects only children. There are no long-term viral shedders, or antigenically distinct strains; individuals simply progress irreversibly through susceptible, infected, and recovered classes. The resulting simple, recurrent patterns have made measles an ideal system for studying the dynamics of acute immunizing infections [1, 2]. High levels of routine vaccination have successfully interrupted endemic measles transmission from many regions of the world [3], though it continues to persist in areas of Africa and Asia where only patchy vaccine coverage is achieved [4].

In pre-vaccine developed countries, outbreaks occurred at regular intervals with strong spatial synchrony [5]. Births replenish the supply of susceptibles during the interspersed troughs, or periods of low cases or no cases. By definition, local persistence of measles through endemic troughs occurs above a *critical community size* (CCS), which is influenced by birth rates, vaccination rates, and seasonality in transmission [6]. Below this threshold, measles routinely goes stochastically extinct (fades out) during troughs.
(fig. 4.S1a) and subsequent cases are the result of reintroductions. The CCS for measles has been observed consistently as 250,000-400,000 for pre-vaccine developed countries.

In Niger the combination of very high birth rates, patchy routine vaccine coverage, and very strong seasonal transmission appears to increase the CCS by an order of magnitude from that of pre-vaccine developed countries [7]. The magnitude of epidemics varies greatly between years and districts but outbreaks occur only during the dry season (fig. 4.1a) when local population density is thought to be highest, favoring transmission [7]. Spatially measles appears to be consistently reintroduced along frequently used travel routes [8].

*Meningococcal meningitis* (meningitis), caused by the bacterium *Neisseria meningitidis*, is transmitted similarly to measles: susceptible individuals are infected by direct contact with aerosolized particles from infected individuals. Unlike measles, the duration of infection can vary greatly and the progression between susceptible, infected, and recovered classes is not unidirectional. Meningococcal meningitis immunity wanes and recovered individuals return to the susceptible class [9, 10] such that meningitis infects a broad age range of individuals, predominantly those between 2 and 30 yrs of age [11-13]. Contributing to the loss of immunity, meningitis has antigenically unique serogroups of bacterial meningitis, each with some broad regional specificity. Within serogroups, there are different subtypes, which likely have low levels of cross immunity [10].

Additionally, asymptomatic carriers of *Neisseria meningitidis* are known to exist and thought to be important in transmission of meningococcal disease [14]. Unfortunately, transmission rates throughout carriage are poorly understood. The proportion of carriers
in the population has also been difficult to assess, with estimates ranging from 3-30% [12]. Estimates on the duration of carriage vary between an estimated half-life of 3 months [15] and an upper bound of ten months [16] (note that these do not consider host or pathogen variation and longer-term carriage can neither be refuted nor supported [12]).

Although meningitis cases occur worldwide, the highest rates of incidence are found in the meningitis belt in Africa [17, 18]. This is a sub-Saharan region that experiences approximately 300-1100 mm of rainfall per year [19]. Locations in this belt are environmentally similar and reported cases show strong annual seasonality: cases peak during the dry season and decrease abruptly when the rainy season begins (fig. 4.1a).

Much work has been done showing that the onset and intensity of meningitis epidemics within the African belt could be strongly influenced by environmental factors [20, 21]. Although the specific factors that control the onset of epidemics are somewhat unidentified [11] the broad geographic range and seasonal incidence of meningitis in Africa are linked to environmental components, particularly rainfall, humidity, and wind [20-24]. The mechanism behind the environmental affect is unknown but one widely believed idea is that the seasonal peaks are caused by the dry dusty winds of the Harmattan. Debris inhaled during this season are thought to scratch and prime the throat for bacterial colonization, leading to increased susceptibility to meningitis infection [11, 20].

While environmental factors influence the broad range of meningitis and likely define the African belt, these factors alone do not explain the local spatial variation in incidence and prevalence within the meningitis belt. Spatial variation at this scale is extremely
important in early outbreak detection and for evaluating surveillance and vaccination strategies.

Across the African belt, the magnitude of meningitis outbreaks is highly erratic and unpredictable from year to year [22-24]. Because the pathogen changes and immunity wanes within approximately three years [9, 11], vaccination in the meningitis belt is done reactively based on case surveillance [25], rather than prophylactically, as with measles.

Due to the unpredictable nature of meningitis, a stockpile of the polysaccharide vaccine is always on hand but the supply is very limited. It is distributed reactively based on case surveillance. Although this may change with the introduction of a new vaccine, effective and efficient allocation of the vaccine has been one of the greatest challenges in meningitis control in Africa. As with any infection, early vaccination (before the epidemic peaks) slows transmission in the initial stages of the epidemic and provides the greatest reduction in morbidity and mortality.

Meningitis epidemics in the belt progress steadily and the disease is severe with a 10% mortality rate and a 20% rate of causing lifelong debilitating effects on survivors. Thus, understanding the causes of meningitis epidemics and developing a tool to predict the timing and location of future outbreaks in the African belt is a major public health priority.

*Host Movement and Disease Dynamics*

Measles has a relatively short infectious period (~ 2 weeks) and is highly transmissible, allowing it to invade easily and move quickly through populations. Local extinctions occur during the rainy season throughout much of Niger [26] and end with
reintroductions [27], generally along primary roads in highly connected areas, possibly through (transnational) movement of infected individuals [8]. Although movement and reintroductions almost certainly occur throughout the year, epidemics take place only during the dry season, likely due to increased levels of host density and, therefore, pathogen transmission [7]. Measles appears to be most frequently reintroduced in districts with highly used routes (i.e. primary roads) [8].

Meningitis is a slow progressing disease with a long infectious period and long-term asymptomatic carriers. Even in the absence of incidence, during periods with zero reported cases, the disease may not be locally extinct during the rainy season. Thus, it does not necessarily require reintroductions for subsequent cases. Instead, cases are thought to reappear wherever a favorable combination of climate and demography are found [17, 24]. Therefore, with the exception of large groups of displaced individuals [11], it is not thought that host movement and density are extremely important in the onset of seasonal meningitis outbreaks. Consequently, one might not expect spatial patterns of reappearance along routes of movement in highly connected populations, as is found with measles, or seasonal transmission that favors high host density.

Using detailed spatiotemporal data for meningitis in Niger, we reevaluate this paradigm by exploring the roles of population movement and density in meningitis dynamics by comparing spatial patterns of fadeouts and reintroductions of measles cases with spatial patterns of absences and reappearances of meningococcal meningitis cases. Bharti et al (2009)[8] analyzed spatial patterns of measles fadeouts and reintroduction rates to identify epidemically important districts within Niger [2, 6]. Using a similar analysis, we identify districts of potential epidemic importance in meningitis dynamics by the absence
of new cases during the troughs between epidemics. We also determine reintroduction rates by district for measles [8, 27] and reappearance rates by district for meningitis as an additional measure of epidemic importance.

Methods

Reported Cases

Weekly reported measles cases from 1995-2004 [7] from 35 districts and 3 urban districts (38 total districts) in Niger were obtained from the Ministry of Health of Niger [28]. Weekly reported meningitis cases from 1985-2005 from the same 38 total districts in Niger were obtained from a national surveillance system from the World Health Organization (WHO) [29]. Because of the severity of meningitis infection, underreporting of cases is thought to be negligible throughout the meningitis belt.

Total Fadeouts and Population Size

For more than two consecutive weeks with no cases, each week with zero reported cases was defined as a fadeout (consistent with [8]). Due to the infectious period of measles (about two weeks), single weeks with zero reported cases were not considered ‘fadeouts’ because they do not necessarily imply a broken chain of transmission. Consecutive fadeouts were referred to as interepidemic periods. For consistency, the same two-week threshold was used to define an absence of meningitis, although the same biological reason does not apply due to long-term carriage and infection. We return to this point in the discussion. For meningitis, consecutive absences were also referred to as interepidemic periods.
A negative relationship between the proportion of zeroes (or the number of fadeout weeks in the time series) and population size for measles has been previously shown [2, 6] during this study period for measles in Niger [7, 8] (fig. 4.S1a). This comparative analysis focused on the residuals from that predicted relationship for both measles and meningitis. Districts with the fewest fadeouts relative to population size (negative residuals) had more introductions and appearances than expected and may be epidemically important for the regional spread of each disease. Districts with negative residuals for both diseases may reflect their importance in spatial coupling and connectivity. These districts were referred to as potential hotspots and this analysis focused on those districts.

*Rates of Reintroduction and Reappearance*

To inversely measure the *reintroduction* rates from the length of interepidemic periods, the length of local disease extinctions was measured. This provides insight on spatial connectivity and human movement [27]. Using a Cox proportional hazard regression model, the length of the interepidemic periods was fit as a waiting time to determine the hazard rate of reintroduction for measles (similar to [27] and as in [8] for measles) (fig. 4.S1b). The same was done to determine the rate of *reappearance* for meningitis. Accounting for population size, the reintroduction and reappearance rates for measles and meningitis, respectively, were compared for the potential hotspots to those of all the other districts for each disease.
Environment and Settlement data

Niger’s district population sizes were obtained from the official census reports from Niger.

Daily rainfall estimates were obtained from 2003 to 2008 from NOAA’s Climate Prediction Center’s CPC Morphing Technique [30]. These were aggregated and smoothed to create an annual rainfall signature.

ESRI shapefiles for administrative boundaries were obtained from Global Administrative Areas v0.9 (GADM) [31].

Results

Seasonal Incidence

The seasonal incidence of these two diseases is very similar; both peak during the dry season and decrease at the onset of the rainy season. Meningitis decreases more severely than measles although neither decreases due to the depletion of susceptibles (fig. 4.1a) [7, 8, 22-24].

Spatial Correlation

Despite marked differences between the natural history and environmental dependence of measles and meningitis, we find that the correlation by distance for measles (regional synchrony = 0.31(0.26,0.37)) and meningitis (regional synchrony = 0.35(0.26,0.43)) in Niger are very similar (fig. 4.1b).
Population Size and Fadeouts

The relationship between population size and total number of fadeouts/absences showed an overall similar negative relationship for measles ($R^2 = 0.305$) [7, 8] and meningitis ($R^2 = 0.517$) (fig. 4.2a and b, also see supplementary material fig. 4.S2). This pattern is expected for measles [6] but not necessarily for meningitis if long-term carriage during interepidemic periods generates strong local persistence [32]. Even more remarkable, the residuals from these relationships (i.e. correcting for population size) are highly correlated for the two diseases ($R^2 = 0.45$, fig. 4.2d); in other words, relatively high or low persistence of the two diseases occurs in the same districts.

To detect relative ‘hotspots’ for disease reintroduction, we identify districts with negative residuals of fadeouts/absences residuals for both diseases [2]. We identify 19 districts with negative residuals of measles fadeouts on population size [8] (fig. 4.2a), and 17 districts with negative residuals of meningitis absences on population size (fig. 4.2b). We find 15 districts with negative residuals of fadeouts/absences on population size for both diseases (fig. 4.2c), and focus on these as joint potential hotspots.

Rates of Reintroduction and Reappearance

The length of interepidemic periods provides an inverse measure of the rate of re-introduction of measles and reappearance of meningitis for each district [27] (fig. 4.S1b). Not surprisingly, population size is negatively correlated with the rate of reintroductions/reappearances by district for both diseases ($p < 0.01$ for measles; $p < 0.01$ for meningitis)(fig. 4.2e), indicating that reintroductions and reappearances are more likely in more populous districts. However we also find that the 15 districts classified as
“joint potential hotspots” (negative residuals of fadeouts/absences on population size for both diseases, gray in fig. 4.2c) have a significantly higher rate of reintroductions/reappearances relative to population size for both diseases than do the other 23 districts (p < 0.01 for measles, p < 0.01 for meningitis) (fig. 4.2e).

Discussion

Comparative approaches to epidemiology, such as the present analysis, can strengthen our understanding of spatiotemporal risks for human diseases [33]. Here we find that the seasonal incidence of meningitis is very similar to that of measles (fig. 4.1a). It has been clearly shown that measles dynamics are strongly influenced by birth rates and seasonal aggregation of the host population (such as school terms [34] and possibly agricultural cycles [7]), but not directly by environmental factors. In contrast, it is widely believed that meningitis dynamics are determined by environmental components and epidemic complexities [17, 20]. However, rates of meningitis carriage do not vary markedly by season [13, 15] and the transmission of Neisseria meningitidis between hosts does not appear to be enhanced by environmental factors in the meningitis belt [15], possibly indicating non-environmental triggers. Transmission rates for both measles and meningitis peak when population density is thought to be increasing [7], which would enhance the spread of a directly transmitted pathogen.

Spatially, meningitis and measles also exhibit very similar patterns. The correlation of incidence by distance (fig. 4.1b) is unexpectedly similar for these two infections with very different epidemiology and time scales. Most striking is the highly correlated spatial
pattern of zero cases, both in absolute terms and when correcting for population size (fig. 4.2a-d).

The overwhelming similarity between the spatial distribution of the hotspots (districts with negative residuals of fadeouts/absences on population size for each disease) for measles and meningitis as well as the similar rates of reintroduction/reappearance for both diseases suggests that meningitis moves in a way similar to measles such that connectivity, human movement, and host aggregation could play a more important role in the spatial dynamics of meningitis than previously considered.

It is important to note that the complex epidemiology of meningitis makes zero cases difficult to interpret. Zero cases represent an absence of incidence but not necessarily a broken chain of transmission, due to possible long-term carriage. However, reported cases following zeroes indicate reappearances and districts with an abundance of reappearances are certainly epidemically important.

In analyzing the dynamics of meningococcal meningitis, previous and ongoing studies have identified a pattern of a primary acute respiratory viral infection followed by secondary bacterial disease [35-37]. In these cases, a primary viral infection may either increase susceptibility to, or exacerbate the severity of, a later bacterial infection. Interestingly, a specific relationship between influenza and Neisseria meningitidis has been shown in various settings [35-38].

Although these influenza-meningitis associations were all found outside the meningitis belt and little is definitively known regarding influenza incidence in Niger, there are indications that the seasonality of influenza is similar to that of meningitis [39](Viboud,
pers. com.). Future work can address this hypothesis and influenza surveillance may ultimately provide valuable insight for understanding meningitis seasonality. An acute infection (such as influenza) would likely show spatial patterns similar to measles and could ‘lead’ meningitis down the same spatial paths, thus explaining the nearly identical ‘hotspots’, an idea we can explore further with mathematical models. If meningitis in Africa lags influenza or another acute infection, identifying this pattern would be an important step towards understanding a mechanism for the seasonality of meningitis and the role of population density, and may provide some predictive power for outbreaks in the meningitis belt.

Conclusions

Although environmental factors such as rainfall, humidity, and wind are likely to be important large-scale determinants of meningitis outbreaks [20-24], we suggest that these do not explain the full extent of spatial and temporal variation in the seasonal outbreaks of meningitis within the African belt. We consider the possibility that human density and movement may be directly affecting the dynamics of meningitis.

The striking similarities between the overall patterns of measles and meningitis reinforce previous suggested patterns of human movement and suggest that human movement and density may influence the epidemiology of meningitis, an important point for improving control measures. Although these results are preliminary, this is, to the best of our knowledge, the strongest evidence to date for a density effect in meningitis dynamics.

This study brings us one step closer to understanding the spatiotemporal dynamics of meningitis epidemics in the African belt. The next step in this analysis will use dynamic
models for measles and meningitis to interpret these results while taking into account the complexities of meningitis, including environmental drivers, predisposing infections, strain structure, and asymptomatic carriage.

Author Contributions

The paper was conceived by N.B., H.B., and B.T.G. Statistical analyses were designed and conducted by N.B and B.T.G. The paper was written by N.B. with help from H.B., B.T.G., R.F.G., and A.D. All authors discussed the results and edited the manuscript.

References


Figure 4.1: (a) Seasonal outbreaks of meningitis (red) align with those of measles (grey) and both are strongly out of phase with rainfall (blue). Solid lines are mean values, shaded areas are +/- 1 standard deviation. (b) Pair wise correlation by distance for all districts for reported meningitis incidence (red, regional synchrony = 0.35(0.26,0.43)) and reported measles incidence (black, regional synch = 0.31(0.26,0.37)) are very similar.
Figure 4.2: (a) Number of fadeouts weeks per year against population size for each district for meningitis. Grey line is best-fit line. Grey points are districts with negative residuals. (b) Same as a for measles. (c) Map of Niger showing all 38 districts, including 3 urban districts. The 15 districts that have negative residuals for both measles and meningitis are shown in grey. (d) Residuals from a plotted against residuals from b, grey points are the 15 joint potential hotspots (grey districts from c), size of points correlates to district population size. (e) Residuals of mean length of interepidemic periods on population size for the 15 joint potential hotspots (grey districts from c) in grey (on right in each plot) and all other districts in black (on left in each plot) for meningitis (left) and measles (right).
Supplementary Material

4.S1. Fadeouts and Interepidemic periods (adapted from [1])

Figure 4.S1. (a) This figure illustrates the classic relationship between population size and number of measles fadeouts as seen in pre-vaccination England and Wales from 1944-1964. Red line indicates critical community size (CCS) [2]. (b) Schematic showing the relationship between interepidemic periods and reintroductions for measles. Introduced cases end interepidemic periods and therefore determine their length. Infrequent or few introductions (red arrows) produce long interepidemic periods (left) whereas frequent or many introduced cases produce short interepidemic periods (right) [3, 4].

References

Supplementary Material 4.2

Niamey

It is interesting to note that for the largest city, Niamey, meningitis absences against population size lie along the best-fit line (fig. 4.S2a, far right point with arrow) while this same city shows far more fadeouts than expected for measles (fig. 4.S2b, far right point with arrow). There are two possible explanations for this. First, routine measles vaccine coverage in Niamey is high relative to other districts in Niger [1], resulting in a comparatively low density of susceptibles for measles. In contrast, for meningitis, due to waning immunity, which leads to a broad age range of infection [2], and reactive meningitis vaccination, we expect the relative density of susceptibles for meningitis in Niamey to be higher than for measles.

Second, the seasonal forcing of measles transmission is much stronger in Niamey than in most other districts in Niger [3]. In contrast, the seasonality of meningitis incidence appears to be strong in all districts throughout the country (fig. 4.1a). Currently, we do not have enough data to know exactly why Niamey shows a fadeout pattern for measles different from its pattern of meningitis absences while most other districts show similar patterns for both diseases. To tease apart these two hypotheses, future work will require additional data on vaccination and reported cases for both diseases, as well as mathematical models to address variation in transmission.

References

Chapter 5

Calibrating measles transmission rates and relative population density using a novel satellite imagery approach

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Abstract

A fundamental challenge in infectious diseases dynamics is calibrating transmission rates and population density. Transmission rates are difficult to measure but can be estimated from incidence data in some cases. Local population density can be as difficult to assess, especially in some developing country contexts. Although difficult to measure directly for many countries, stable population density has been estimated indirectly using Defense Meteorological Satellite Program (DMSP) Operational Linescan System (OLS) nighttime lights data. Here, we present a method for measuring dynamic (seasonal) relative population density fluctuations in Niger. With eleven years of spatially explicit reported measles cases, we have the unique opportunity to combine data on estimated relative seasonal transmission rates with a novel method using night-lights brightness to measure dynamic density in three major cities in Niger. Overall, we find that transmission rates are positively correlated with night-lights brightness, which is a proxy for population density. This method has the potential to be a powerful tool in understanding and managing infectious disease in areas where detailed demographic and epidemiological data are lacking, particularly some of the most disease-affected areas of the world.
**Introduction**

Determining a relationship between pathogen transmission and population density is a basic challenge in disease dynamics [1-3]. Characterizing transmission rates is an important prerequisite to understanding the impact of control measures such as vaccination [1]. The relationship of transmission and population density can also give insights into the fundamental dynamics of epidemics. For example, if transmission rate and population size scale linearly (slope > 0 when both log transformed), this indicates density dependent transmission; a slope of 1 would indicate mass action mixing [4]. Although transmission rates are generally difficult to measure, they can be estimated from sufficiently good long-term incidence data [5, 6] or serology [1]. Host density is also very challenging to measure outside of experimental contexts [7]. The difficulty in gathering sufficiently detailed data regarding patterns of host aggregation makes it very difficult to test hypotheses involving population density.

Cyclic variations in pathogen incidence (seasonal and longer period multiennial) provide a potentially useful tool for evaluating the relationship between population density and transmission rates. Here, we focus on seasonal cycles, which are a frequently observed characteristic of many host-pathogen systems [8, 9]. While the dynamic implications of complex patterns of seasonal dynamics have been studied thoroughly [10, 11], the (biological or demographic) mechanism underlying seasonal patterns in incidence is often not known [8, 9]. This is the case for a number of well-studied, globally prevalent, seasonal infections of humans [8, 9, 12, 13].
Previous studies have described four categories of causes for seasonal cycles of infections: 1) seasonal variation in the survival of the pathogen outside the host (such as cholera [14, 15]), 2) seasonal variation in host immune function (suggested but not shown for bacterial meningitis in Africa [16]), 3) seasonal changes in vector (or non-human host) abundance (as in malaria [17]), and 4) seasonal changes in host behavior (seal aggregation and phocine distemper virus (PDV) [4], aggregation of children in schools and childhood infections, such as measles [18]) [9]. To address the relationship between density and transmission, we present a method to indirectly measure seasonal changes in population density.

Certainly the best examples of seasonal host aggregation leading to seasonal incidence in human infections are childhood diseases. Specifically, in pre-vaccination England and Wales, the seasonal crowding of children in classrooms increased transmission rates of measles and caused epidemics to occur during school terms [18]. The same mechanism has also been shown to cause seasonal peaks of incidence for a variety of childhood diseases in other systems [19].

Measles epidemics in Niger show even stronger seasonal dynamics than the classic England and Wales paradigm [20]. Niger experiences alternating rainy and dry seasons with one rainy season per year. Measles outbreaks consistently occur only during the dry season [20]. Although the magnitude of outbreaks varies greatly from year to year, the timing of epidemics is extremely consistent. The economy and work force of Niger are largely agriculturally dependent [21, 22]. It is not uncommon for individuals to travel seasonally for work [22, 23]. Previous studies have put forth a hypothesis that Niger’s seasonal cycles of measles are caused by fluctuations in population density; individuals
tend to live in low-density agricultural areas during the rainy season and many relocate to high-density urban areas during the dry season [20].

To capture seasonal transmission rates phenomenologically, epidemiologists often model transmission as a function of time [9, 24]. These models use static measures of population density, along with time-varying contact rates [25].

Static estimates of average spatial population density can be obtained from high-resolution imagery. In particular, a long time series of high-resolution satellite images of nighttime lights from the Defense Meteorological Satellite Program (DMSP) Operational Linescan System (OLS) has been used for defining stable patches of consistently high population density [26, 27]. These images show lights from human settlements. The stable patches of lights from several images are used to create a composite image to define stable urban areas or areas of consistently high population density. A previous study added a dynamic component, using a few serial nighttime lights images to detect changes in levels of occupancy before and after a single defined event [28].

Here, we present a novel method for assessing seasonal fluctuations in population density using many serial images of DMSP OLS nighttime lights from Niger’s urban centers. We measure brightness as a proxy for relative urban density over time and investigate seasonal patterns of fluctuations in radiance. We apply this method to three major cities in Niger to test the hypothesis that seasonal fluctuations in rainfall trigger seasonal fluctuations in host density in Niger. We then compare patterns of seasonal density as measured by a proxy to relative measles transmission, as estimated from eleven years of reported cases [5].
The method presented here considers transmission rate as a function of local population density, for which we determine fluctuations over time, thus addressing the causal mechanism for changes in transmission. This calibration of extensive seasonal disease data against host population density fluxes will address a fundamental goal in disease dynamics. This tool has the potential to become extremely useful in areas of sparse demographic and epidemiological data and high disease burden.

Methods

Nighttime lights and associated data

Daily rainfall estimates were obtained from 2003 to 2008 from the National Oceanic and Atmospheric Administration’s (NOAA) Climate Prediction Center’s (CPC) Morphing Technique [29](CMORPH). These were aggregated and smoothed to create an annual rainfall signature (fig. 5.1c).

To classify whether nighttime lights images were taken during the rainy season, the rainy season was defined as the date by which continuous days of rainfall consistently began based on daily rainfall values from CMORPH. Rainfall consistently began between day 122 and 145 and stopped between day 266 and 284. None of the 22 nightlights images used for this analysis were taken on or during dates of seasonal uncertainty; the cut-off points for the rainy season were surrounded by several days of ‘buffer’ (grey shading, fig. 5.1).

DMSP-OLS images from the F16 sensor were used for this analysis. DMSP satellites orbit at low altitude (550 km) and provide high-resolution visible and near-infrared images to visualize settlement lights and detect cloud cover. These images are
approximately 1 km spatial resolution (0.00833 decimal degrees). The F16 OLS sensor was launched at the end of 2003 and remains operational today. To ensure comparability and minimize contamination of nighttime lights from F16 images, only images that were taken under low moon conditions between 7 pm and 10 pm with no cloud cover over the three urban areas of interest were used. Twenty-two images that fit these criteria were identified for this analysis.

For each of the three urban areas, the extent of the stable urban area was identified using the Global Rural Urban Mapping Project (GRUMP) urban extents shapefile in ArcGIS, obtained from the Center for International Earth Science Information Network (CIESIN) [30]. The gridding system of the night light imagery was overlaid and the centroid of each urban extent nightlights pixel was calculated. The brightness and near infrared (NIR) values were extracted for each centroid of each image. Images with exceptionally high NIR values were excluded because these indicate cloud contamination, which obstructs the view of settlement lights. For each image, the average brightness value per pixel across all pixels was calculated within each stable urban extent (fig. 5.1a). Raw values of brightness were used for all analyses.

The brightness values were tested for normality using a Shapiro-Wilk test (large p-values indicate a normal distribution; small p-values indicate a non-normal distribution). To determine whether non-rainy seasons were brighter than rainy seasons for each city, an analysis of variance (ANOVA) was conducted with city and season as explanatory variables and brightness values as the response variable. To test for seasonal differences in brightness within each city, individual t-tests were conducted (for each city) and the
significance level was adjusted using a Bonferroni correction to control for the overall error rate.

**Measles transmission**

Weekly reported measles cases from 1995-2005 from 35 districts and 3 urban districts (38 total districts) [20] in Niger were obtained from the Ministry of Health of Niger [31]. National birth rate and population size by district were also obtained [31].

Estimated relative transmission rates of measles in Niger were taken from [5](fig. 5.1b). The methods are paraphrased here. The entire manuscript is included as appendix A.

The seasonal fluctuation in transmission rate for each reporting district was estimated by fitting the TSIR model of Finkenstadt and Grenfell [6] to eleven years of reported measles incidence. Incidence was aggregated into two-week intervals to reflect the average infectious generation time for measles. As in [32], first the unobserved time series of susceptible individuals was reconstructed as the residuals from the relationship between the cumulative reported incidence and the cumulative births (discounted by the vaccination rate) [20, 33].

The TSIR model [6] fits the time varying transmission rate as an unknown constant multiplied by a seasonally varying scaling factor. The seasonally varying component was modeled as a piecewise constant function with 13 (i.e. 4-week intervals) levels from January 1 to December 31. The parameters of the TSIR model were estimated from the reconstructed susceptible time series and the reported incidence, corrected for underreporting [20], using least squares [6, 32]. Because the absolute value of the
seasonal transmission rate is likely to be biased by the unknown vaccination rate, the seasonality is shown as the range of the seasonally varying scaling factor.

The relationship between relative transmission rates of measles and brightness values for each city was assessed for correlation.

**Results**

The brightness values are fairly normally distributed (Shapiro-Wilk test p-value = 0.1854). The overall patterns for brightness, transmission, and rainfall are qualitatively similar for all three cities (fig. 5.1).

Overall brightness is higher during the non-rainy season than it is during the rainy season across all cities (ANOVA, p-value < 0.001). Within each city, the trend is consistent and the difference is significant in Niamey and Zinder (Niamey, Maradi, and Zinder t-test p-value < 0.1, p-value < 0.2, and p-value < 0.05, respectively, after Bonferroni correction) (fig. 5.2).

Relative transmission rate is positively correlated to brightness for each city, and most strongly for Maradi ($R^2 = 0.286, 0.534, 0.367$ for Niamey, Maradi, Zinder, respectively) (fig. 5.3).

**Discussion**

This is a preliminary application of a new approach to calibrating populating density fluctuations against seasonal transmission rates of measles. Our results suggest that the method works qualitatively, in that urban densities are higher during the non-rainy seasons when compared to the rainy season. Using brightness as a proxy for relative
population density, we show that transmission scales with urban brightness. This provides a mechanistic link to the observed pattern of seasonal swings in transmission. In the rest of this section, we interpret these results and discuss further applications and limitations of this method as well as future work developed from this analysis.

As mentioned earlier, models of seasonal (or otherwise cyclic) disease incidence will often model seasonal transmission rate (or contact rate) as a function of time while holding population density constant [25]. The method presented here shows that relative transmission rate varies as a function of population size. This addresses the host aggregation mechanism causing seasonal dynamics of measles and shows that this system exhibits density-dependent transmission.

Seasonal migration in this region, and in Niger specifically, has been ethnographically studied and is known to occur. Unfortunately, the sample sizes for these studies are often small and the prevalence of these movements has not been well documented [23]. Using nighttime lights imagery allows us to see the large scale of these movements, as documented in the three biggest cities of Niger.

Disease data are reported by district, which can encompass large areas with multiple types of land cover and highly varied population densities. The three urban districts included in this analysis are the only disease reporting districts that include only a small area of land with basically a single type of land cover (urban). Having disease data at this detailed spatial scale allows us to directly compare estimated transmission rates to measured values of brightness. Thus, disease data reported at finer spatial scales would
enable us to apply this method to more areas to explore correlations between transmission rates and brightness.

The method developed here can potentially be used extensively in areas with high levels of agricultural dependence and the presence of directly transmitted infections, which describes many of the world’s most heavily disease burdened regions. This approach could also be greatly beneficial to explore dynamics of directly transmitted diseases thought not to be highly density dependent, for example meningococcal meningitis in the meningitis belt of Africa (chapter 4). Environmental causes, not host density, are widely believed to be the primary cause of meningitis outbreaks in this region [16, 34].

Population density and, more importantly, patterns of fluctuations in population density highlight important nonlinearities in contact rates, which greatly affect the transmission of directly transmitted infections. Assessing these fluctuations is an important step towards understanding the disease dynamics of Niger and similarly affected areas.

Limitations of this method

It is unlikely that these nighttime lights brightness values have a true linear relationship with population density; the exact shape of this relationship varies from one location to the next, affected by everything from surrounding land cover [26] to wealth asset indicators [35] and national level socio-economic indicators [36, 37]. Additionally, heavily urbanized areas can cause sensor saturation [38]. Without a doubt, the relative relationship within each city holds true such that higher brightness values per pixel indicate more people [38, 39], but the exact shape of this correlation varies and has not been determined specifically for these three cities.
Many areas with high disease burden may also lack a stable supply of electricity. This becomes particularly problematic when these instabilities display seasonally regular outages (e.g. loss of electricity during heavy rains). In areas where regular electric outages are experienced, nighttime lights radiance would not be a valid method for determining relative fluctuations in population density.

Fluctuations in population density in urban areas imply the movement of individuals into urban areas and out of other locations. This implies that some areas should show decreased brightness as brightness increases in urban areas. Unfortunately, it is not possible to detect low-density settlement lights and these images do not provide the resolution necessary to visualize changes in brightness outside of highly populated areas.

As populations become more industrialized, they become less perturbed by seasonal factors. Essentially, such populations are less susceptible to demographic changes caused by environmental perturbations. Thus, host population density fluctuates less drastically in industrialized, non-agricultural areas making the use of this method fairly specific to non-industrialized, agriculturally dependent areas. Additionally, even within such areas, these fluctuations are slightly less informative for pathogens that exhibit frequency dependent transmission, as do many vector-borne or sexually transmitted infections [1, 3].

While the population size of each town played an important role in the regional dynamics of measles in England and Wales, it did not have a large impact on the local dynamics. The relationship between the transmission rates of measles in England and Wales and the population size of each town shows density independent transmission (a negative scaling
of transmission rate and population size) [40]. This appears to contradict the present results; however, the UK results may be because the meaningful measure of density is school class size, which varied seasonally but not very strongly between large and small urban areas.

Future work

We note that these three cities in Niger have differing relative transmission curves of measles (fig. 5.1b). Although the timing of outbreaks is consistent throughout Niger, the amplitude is not. The seasonal amplitude of measles transmission is very strong in the largest urban center, Niamey [20], while it is considerably weaker in Maradi and Zinder [5]. Our future work will investigate whether variations in seasonal amplitude can be captured in seasonal images of nighttime lights. For this analysis, we have acquired additional images for Niamey, Maradi, and Zinder.

While measles is prevalent throughout West Africa, the disease dynamics vary widely throughout the region. In a well-documented example, Niakhar, Senegal experiences regular, annual cycles of measles [41]. Mathematically, this indicates that the seasonal swings in transmission in Niakhar are not as extreme as the seasonal swings in cities in Niger [5, 20]. Mechanistically, we would expect this to be the result of less severe seasonal fluctuations in population density in Senegal. This hypothesis could be tested with the application of this method, allowing us to compare the differing measles dynamics of two locations and measuring seasonal fluctuations of population density via seasonal patterns of brightness.
Conclusions

To our knowledge, this is the first documented study measuring seasonal fluctuations in population density, directly or indirectly, in Niger. This is also the first application of serial nighttime lights imagery to estimate seasonal patterns of fluctuations in population density. This method has the potential for wide-reaching applications in areas with low resolution demographic and census data and high disease burden.

Author Contributions

The paper was conceived by N.B. and A.T. Statistical analyses were designed and conducted by N.B., M.F., and B.G. Data collection was coordinated by A.T. and M.F. The paper was written by N.B. All authors discussed the results and edited the manuscript.

References


Figure 5.1

A) Brightness values for urban areas by day of year. B) Relative transmission rates for urban areas calculated from reported cases over eleven years. C) Annual rainfall in mm calculated from five years of daily rainfall measures. In all, gray shaded areas are between rainy and non-rainy seasons; days between vertical dashed grey lines indicate rainy season.
Figure 5.2

Brightness by season for each city. Grey box plots are rainy season brightness; black box plots are non-rainy season brightness. Width of box plots correlates to number of observations.
Figure 5.3

Relative transmission rate against brightness for each city. Grey points are brightness values from images taken during the rainy season; black points are brightness values obtained from images taken during non-rainy seasons. Black line is best-fit line. From left to right, $R^2$ values are 0.286, 0.534, and 0.367.
Chapter 6

Discussion and Conclusions

Introduction

Spatiotemporal spread of infection has long been considered a critical process in understanding the dynamics and control of infectious diseases [1-3]. This thesis focused on the impact of variation in rates of human movement between and within population subunits over space, using analyses of epidemiological and demographic data with dynamic and statistical models.

Each of the chapters in this thesis explored different aspects of host movement and connectivity in real space. Over the course of this thesis, the chapters investigated patch connectivity in a historical disease system as well as a current one. These chapters also analyzed host movement over large spatial scales between districts, towns, or patches, as well as host mixing across small spatial scales within cites. Throughout this study, each analysis explored mechanisms underlying disease dynamics stemming from variations in human movement and aggregation across space and time.

For the remainder of this discussion, I will review and synthesize the results from each chapter and discuss the areas of future work that have developed from the work presented in this thesis.
Retrospectus

I began this work with an analysis of the well-understood, highly studied system of measles in pre-vaccination England and Wales [2, 4-8] and focused on spatial heterogeneities in epidemic connectivity between subunits of a metapopulation (chapter 2). Here I showed that a spatial model that accurately predicted measles dynamics throughout England and Wales broke down along the edges of the system. Coastal towns showed fewer fadeouts than the model predicted. In this case, the model had predicted reduced between-patch host connectivity for coastal towns relative to inland towns. I showed that the number of fadeouts for coastal towns was fewer than predicted because hosts displayed conservation in connectivity, meaning that individuals traveled more or farther than their inland counterparts, thus maintaining a higher level of connectivity to other towns and greater influx of measles than was predicted by the model.

In chapter 3, I shifted the focus to the dynamics of measles in present-day Niger, where the burden of infectious disease is substantial and data are not as complete [9, 10]. Still interested in human movement between towns, I compared the number of fadeouts (corrected for population size) for each district in Niger, the number of cases per district following mass vaccination campaigns, and the rate of reintroductions for these districts [11]. I showed that districts with more cases following mass vaccination also had significantly higher rates of reintroductions, suggesting elevated rates of connectivity for certain districts. I suggested that this could be due to heterogeneities in accessibility; the presence of primary roads placed these districts along highly used routes of movement. I also noted that in Northern Nigeria, just south of these districts and along these primary
roads, is a large dense urban center with low measles vaccine coverage and high measles incidence. I proposed that this dense population center might serve as a measles reservoir, making Niger a satellite population for measles whose regional fadeouts are rescued by reintroductions via transnational movements. This emphasizes the importance of regional approaches in public health policy making.

In chapter 4, I used a comparative approach to assess the spatial heterogeneities in epidemic connectivity in Niger between districts and diseases. Specifically, I compared the relatively well understood dynamics of measles, as revealed in chapter 3, with meningococcal meningitis, a very different infection biologically and a major killer in the region. This approach was used for two reasons: first, to compare patterns of spatial connectivity of these diseases and second, to evaluate the effects of density dependence on meningitis transmission in the African belt. I showed that the same districts show high levels of persistence and elevated rates of reintroductions for both diseases. The result was surprising, given the strong belief that meningitis dynamics in the region are largely determined by environmental drivers and occasional strain introductions [12] [13]. This analysis is the first to document a host population mixing and density effect for meningococcal meningitis. It also underlines the conclusions of chapter 3 and the role of population movement on the persistence and spatial dynamics of directly transmitted infections.

Finally, in chapter 5, I analyzed seasonally varying epidemic connectivity (host mixing) within districts for three major cities in Niger. Transmission rates and host density are
difficult to estimate in any context and particularly so in low income nations with high disease burden. Therefore, the ability to calibrate density and transmission estimates in a few areas, such as Niger, provides a potentially powerful tool for other less documented areas. Here, I presented a method to measure seasonal variations in population density indirectly by using high-resolution satellite images of nighttime lights. I showed that brightness was consistently greater during non-rainy seasons than during the rainy season, indicating higher population density. I then demonstrated a positive correlation between seasonal urban brightness values and relative measles transmission rates. This indicates that the mechanism underlying the seasonal timing of measles outbreaks is an increase in population density in the three cities analyzed here. This is a novel approach to a fundamental challenge in infectious diseases that also addresses a serious concern in public health. This method has the potential for widespread future applications in disease management because it determines a mechanism for seasonal incidence, which is commonly seen but poorly understood.

**Future work**

Up to this point I have shown how host movement between districts in Niger can explain the spatial patterns of measles and meningitis. I have also shown how changes in host density within cities in Niger can explain the temporal patterns of measles incidence. Future work will continue developing mechanistic models to understand the impact of spatial coupling on the dynamics and control of human diseases.
Returning to the foundation of epidemic geography, primary studies asked how diseases traveled over space by detailing exactly how hosts moved across space [14]. These studies explicitly mapped out host movement patterns in the context of disease.

As mathematical modeling became an integral part of epidemiology and disease dynamics, phenomenological representations of human movement started to replace a mechanistic approach. Many models relied on simplified explanations of human movement, such as isotropic dispersal kernels, to generalize movement across space and predict the spatial and temporal spread of infections.

As we gather new data from new places, we will increasingly find examples where simplified models of human movement will not accurately capture the spatial dynamics of diseases. In these situations, it is necessary to revisit the roots of epidemic geography by returning to mechanistic questions. Armed with new methods and modern technology, we can investigate explicit patterns of movements. By understanding these, we can create robust predictions of disease dynamics across spatial scales. Below, I discuss fruitful areas for future work along these lines.

*Local mixing*

Focusing first on small scales, future work should consider the hypothesis that prevailed throughout the latter chapters of this thesis: agriculturally dependent populations may move in seasonally dependent ways such that they will consistently aggregate during the non-growing season, favoring the transmission of directly transmitted pathogens. In this
case, we focused primarily on measles and rainfall in Niger but this can be expanded to all of Africa. If agricultural cycles are the key to driving seasonal dispersal and aggregation patterns, this could be seen in measles incidence throughout agriculturally dependent areas; measles would be seen out of phase with the growing season in agriculturally dependent areas. If this correlation is seen frequently within Africa, and in other parts of the world, several methods can be used to gain a mechanistic understanding of this relationship.

First, using high-resolution nighttime lights images, as in the method presented in chapter 5, one could assess this hypothesis of seasonal density in various African cities. As with all methods, there are limitations to this one and this will not work in non-urban areas. Thus, the increase in urban density can be evaluated but not with an accompanying decrease in rural density.

Additionally, the potential for explicit, individual-level data on movements grows daily, as cellular phones become more popular and widely used throughout Niger. Previous studies have shown that detailed movement data collected from cellular phone use have been greatly beneficial in understanding specific human movements [15]. By tracking hosts, one can track the movement of the pathogens they carry with them. In a region like West Africa, where movement is undocumented, poorly understood, and clearly important in regional disease dynamics, cell phone usage to track actual movements would be invaluable in understanding the region’s epidemiology. This method is effective within cities and between towns and countries. One could compare data
collected from cell phones to data from urban nighttime lights. A comparison between these two independent data sources from this region would provide a more complete picture of human movement and greatly benefit epidemiological studies.

The rainy season shifts with latitude across Africa such that at any point in time, it will be the growing season in one location and the non-growing season in another location. Many economies in Africa are currently agriculturally dependent. For an infection like measles, this means that the disease could persist regionally by following the growing season in both space and time. This would be possible via host movement between towns and countries.

*Regional movement*

On a larger spatial scale, I return to the idea of host movement between towns and across national borders. When considering the movement of people, we must focus on transport networks and accessibility, understanding the specific way in which an individual could arrive at one point from another. Using road networks, land cover, and slope, a map of movement likelihood could detail a network of connectivity. Such a model would use a more realistic set of rules to predict the way people move. Estimating host movement from one town to another in this way would undoubtedly be more complex than a dispersal kernel prediction but would likely also be more realistic. Underlining this point, several recent studies have mechanistically analyzed movement across spatial scales in the absence of epidemic data [15-17]. In the coming years, as the global economy continues to change the means of production and rapidly alter growing markets,
the changes will no doubt affect the ways and the reasons individuals move. As local economies change and connectivity and movement are altered, mechanistic models will likely outperform phenomenological models in their ability to respond to these changes and predict the new patterns to emerge. Certainly, these inevitable changes will impact the spread of disease in important and unexpected ways, highlighting the importance of developing adaptable tools.

One method to understand the movement of pathogens by hosts is by using genetic sequence data [18, 19]. Using a pathogen with a known mutation rate, one can evaluate the movement of mutations and strains through time and space. The sources of reintroductions and reappearances of measles and meningitis could be identified in space and time, revealing details of host movement and contact. This type of work is already being done for malaria in Africa with very interesting results [20] but such analyses for measles, meningitis, and other infections as well would be extremely informative, particularly for disease management in Africa and other areas of high disease burden.

Another interesting area for growth in this field is related to improved surveillance data of human infections in West Africa. In chapter four, I mentioned a possible relationship between influenza and meningitis in the African meningitis belt. Influenza infection increases host susceptibility to subsequent meningitis infection, either resulting in symptomatic cases or increasing the severity of symptomatic cases. This relationship has been studied in other regions of the world but unfortunately, influenza cases are not recorded in Niger because influenza infection is not considered as serious as many others.
pathogens in the region (Grais, pers. comm.). A potential association between influenza and the very deadly infection meningitis shows how one infection can play an important role in the dynamics of another, perhaps without even interacting directly [20-23]. In this situation, the spatial spread of meningitis is pre-determined by influenza, an acute immunizing infection that very closely mirrors the movement of hosts. Spatially explicit influenza incidence could clarify human movement between towns and countries and possibility predict meningitis incidence.

**Summary**

Overall, this work highlights the importance of adding mechanism to models of human movement and the spatiotemporal spread of disease. As long-term epidemic data are collected from various locations around the world, we will find an increasing number of systems where the simple assumptions of distance-decay dispersal kernels from phenomenological models will not apply. Understanding the mechanisms of host movement should serve to increase a model’s adaptability and predictive power. Such models can be validly extrapolated to other infectious diseases and are not particularly restricted to directly transmitted or completely immunizing infections. Access to novel and existing demographic and epidemiological data sets is crucial to advancing this important field.

**References**


Appendix

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

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M. Ferrari, A. Djibo, R. Grais, N. Bharti, B. Grenfell, O. Bjornstad

Introduction

Measles is the exemplar for the study of the non-linear dynamics of infectious disease (Bolker and Grenfell 1993, Grenfell et al. 1994, Earn et al. 2000, Keeling and Grenfell 2002, Conlan et al. 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 and Grenfell 1993, Earn et al. 2000, Rohani et al. 2002) and long-term persistence of immunizing childhood infections such as measles (Keeling and Grenfell 1997, Conlan et al. 2007). Even very weak seasonal fluctuations in transmission rates interact with then epidemic clockwork to generate stable annual cycles of incidence (Aron and Schwartz 1984, Bauch and Earn 2003, Dushoff et al. 2004). The birthrate governs the accumulation of susceptible individuals in the troughs between outbreaks, and high birthrates can lead to over compensating cycles, multi-annual dynamics, and deterministic chaos (Earn et al. 2000).

While many pathogens exhibit behavior characteristic of seasonally forced cycles, the explicit mechanism of seasonal forcing has rarely been identified. Seasonality in water-borne (e.g. cholera) and vector-borne pathogens (e.g. malaria) is well understood; however, teasing out the cause of seasonality for directly transmitted pathogens has
proved 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 and Clarkson 1982, Schenzle 1984, Finkenstadt and 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 and 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 and Viboud 2009) and meningitis (Broutin et al. 2007), ranging from seasonal fluctuations in susceptibility, to environmental drivers, to abundance of non-human hosts (Altizer et al. 2006, Grassly and 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 density and a concomitant decline in measles transmission rates. Guyer and McBean (1981) suggested that the same mechanism explained 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” of 300-500,000 inhabitants (Bartlett 1957, Keeling and Grenfell 1997, Bjørnstad et al. 2002b, Grenfell et al. 2002, Conlan et al. 2007). These large cities then serve as local reservoirs that can seed outbreaks in smaller municipalities following local extinction, giving rise to traveling 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 centers across Niger, strong seasonality in measles transmission rates drive local instability of measles dynamics and impact 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 above general 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 critical community size 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.
Methods

We analyzed weekly case reports of measles from the Ministry of Health of Niger from January 1, 1995 to December 31, 2005. The country of Niger is divided into 38 administrative units; 34 districts and 4 urban centers (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 centers (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-center 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 3 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 colored regions in Figure A.2D). The former 2 regions tend to have large outbreaks that are more correlated within than between regions (Figure A.1C; Bharti et al (in review)). The latter is characterized by much more episodic measles outbreaks (Figure A.1C). We also considered an alternative regional grouping that divides the arrondissement of Tahoua into east and western departments (allocated to the Niamey and Maradi regions respectively) and the results we present are robust to the alternative grouping (Suppl. Figure A.4).
We estimate the seasonal fluctuation in transmission rate for each reporting district by fitting the Time series Susceptible-Infected-Recovered (TSIR) model of Finkenstadt and Grenfell (2000) to the reported incidence aggregated into two week intervals because it is the average infectious generation time for measles. Following (Bjørnstad et al. 2002a) 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 not be susceptible to measles, we discounted the reported birth rate (51.73 births/1000) by an assumed 70% 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 50-85% 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 supplementary material).

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 degrees of freedom (Bjørnstad et al. 2002a). The TSIR model of Finkenstadt and Grenfell (2000) fits the time varying transmission rate as an
unknown constant multiplied by a seasonally varying scaling factor. We modeled 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 and Grenfell 2000, Bjørnstad et al. 2002a). 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 range of the seasonally varying scaling factor.

To explore the effect of climatic factors and human aggregation on seasonality we fit the estimated amplitude of 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 official 1995 census report from Niger.

We explore the interaction between seasonality and the critical community size for measles by simulating measles dynamics using the TSIR model with a 2-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 $\beta_1$ is the mean transmission rate and $\beta_2$ controls the amplitude of seasonality (London and Yorke 1973). In all simulations we scaled $\beta_1$ relative to population size to give the same average $R_0$ 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 $\beta$, ranging from 0.1 to 0.8. At each parameter combination we simulated 200 years of measles incidence with a small immigration rate of $\sim$10 infected individuals per year. After a burn-in period of 150 years, we measured persistence as the proportion of years with two consecutive bi-weeks of 0 incidence.

We additionally conducted simulations using the estimated seasonality for the 38 districts and urban centers 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.

**Results**

At the national scale, measles in Niger show regular annual outbreaks (Figure A.1A) that are strongly out of phase with the annual rainy season (Figure A.1B). 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 A.1B,C). At the sub-national scale, measles dynamics in the 38 districts and urban centers 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.
Despite large variation in the amount of rain across the country (ranging from 190 mm/year in the south to 5 in the North), the timing of measles outbreaks is highly correlated across the rainfall gradient (Figure A.1C).

The shape of the seasonal forcing of measles transmission is roughly consistent across the country (Figure A.2A-C). There is strong variation, however, in the amplitude of the seasonal fluctuation. The sparsely populated northern and eastern districts show consistently smaller amplitude forcing than did the southern and western districts. Within the southern and western districts, the highest seasonal amplitudes were associated with the densely populated urban centers of Niamey (in the west) and Maradi (in the east) (Figure A.2D). Districts with high seasonal amplitude tended to cluster around the major urban centers in Niamey, Maradi, and Zinder (Figure A.2D). The overall trend in seasonal amplitude follows the dominant north-south rainfall gradient and total annual rainfall is positively correlated with seasonal amplitude (Figure A.3A). However, that pattern is not consistent within each of the 3 regions of the country. Indeed, in the western districts surrounding Niamey the amplitude of seasonal forcing is negatively correlated with rainfall \((p<0.05)\), and in the districts surrounding Maradi, the relationship is not statistically significant \((p<0.05)\) (Figure A.3A).

The amplitude of seasonal forcing was strongly positively correlated with the population size in each department or urban center (Figure A.3B) across the entire country. This pattern also holds within the 3 regions of Niger; the linear relationship is significant in the western region containing Niamey \((p<0.05)\) and the southern region containing Maradi and Zinder (excluding the department of Magaria, which is a marked outlier; \(p<0.05)\) (Figure A.3B). 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 (Figure A.S3)

The Magaria outlier has an estimated range of seasonal forcing of 0.34, the lowest
in the country, despite a relatively large population of 400,000 (Figure A.3A). 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 review), 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 A.1C), 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 critical community size for the long-term persistence
of measles cycles (Figure A.4A). 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
pattern is the same, though less smooth due to variation in the shape of the seasonal
forcing (Figure A.4B). 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 in predicted to fadeout locally
at least once 50 years in most of the Nigerien districts, the likelihood of local extinction
is, on average, lower for districts of moderate size (Figure A.4B inset). Indeed, the proportion of years with a local fadeout increases in the three largest districts (including Niamey, the largest). 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.

**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 likely the ultimate determinant of human settlement and aggregation in Niger, population size is the most consistent predictor of measles seasonality across the country (Figure A.3A,B). Thus, the pattern of seasonality is consistent with the hypothesis that seasonal transmission is driven by the aggregation of people in cities during the dry season (Guyer and McBean 1981). This is further congruent with the prior observations of aggregations in school classrooms driving transmission rates of childhood infections in Western Europe (Fine and Clarkson 1982, Gomes et al. 1999, Deguen et al. 2000, Finkenstadt and Grenfell 2000) and North America (London and Yorke 1973).

Seasonal forcing of measles transmission can have strong consequences for the predictability and stability of both local (Bolker and Grenfell 1993, Keeling and Grenfell 1997, Earn et al. 2000, Rohani et al. 2002, Conlan et al. 2007) and regional dynamics (Bolker and 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 A.1C), reducing the stability due to synchronous extinction risk (Grenfell et al. 1995, Keeling et al. 2004).

Pre-vaccination England and Wales is perhaps the best-studied seasonally forced epidemic metapopulation (Grenfell and 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 that ~300,000 people to smaller municipalities that tended to experience local fadeouts in the inter-epidemic troughs (Grenfell and Bolker 1998, Grenfell et al. 2001, Xia et al. 2004). In Niger, however, 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 (Bharti et al (in prep)). Since no single region in Niger appears to be able to act as a reservoir for measles through the dry season, the connectivity between regions, and perhaps beyond the national borders (Bharti et al (in prep), (Yameogo et al. 2005)), 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 review), as is seen, for example, in the dynamics of meningitis (Bharti et al, in prep). Thus, to the extent that it is logistically possible, control strategies aimed at measles eradication should consider the coordination of vaccination activities at the regional scale.

References


NOAA National Weather Service. 2009. NOAA CPC Morphing Technique ("CMORPH").


Figure A.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 to the mean monthly rainfall in Niamey (red). Shaded regions give +/- 2 standard errors. C) Logarithm of weekly reported measles incidence for all 35 districts and 3 urban centers 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 A.2).
Figure A.2. A) Estimated seasonal forcing of measles transmission rate (x10 for display) for the 11 districts and the city of Niamey corresponding to the red shaded area below. The curves were smoothed for presentation. The raw curves are presented in the supplementary material. B) Same as A, for the 18 districts and the cities of Maradi and Zinder shown in green below. C) Same as A, for the 6 districts shown in blue below. D) Map of the departments and urban centers of Niger with the estimated range of the seasonal forcing (x10 for display) shown for each.
Figure A.3. A) Estimated range of seasonal forcing for the 38 departments and urban centers as function of mean annual rainfall during the period 2003-2006. Colors indicate the three regions (see map in Figure A.2). Solid lines are the regression fit for each region. Urban centers are shown as solid points. The department of Magaria, which is a strong outlier and was excluded from the analysis, is indicated. B) Estimated range of seasonal forcing for the 38 departments and urban centers as function of district population size (colors and lines are as in A).
Figure A.4. Probability of measles fadeout as a function of population size and the amplitude of seasonal forcing. A) Sinusoidal forcing; red indicates high probability of 2 consecutive time periods with 0 measles incidence within each year, white indicates low probability of 2 consecutive time periods with 0 measles incidence. The grey dashed box indicates the approximate parameter range for panel 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. The inset shows the proportion of years without fadeouts for the 38 districts of Niger (grey dots). Curves are the best-fit quadratic function with (red, solid) and without (dashed, blue) Niamey.
Supplementary material A.1

Figure A.S1. Raw (black) and smoothed (red) estimates of seasonal forcing for 38 districts and urban centers in Niger.
Supplementary material A.2

To evaluate the potential bias in the amplitude of the seasonal fluctuation in transmission rates introduced by unknown increase in vaccine uptake over time we simulated seasonally forced measles dynamics under the TSIR model with vaccine uptake gradually increasing from 60% to 80%, the likely range of vaccine coverage in Niger. We simulated 50 years of measles dynamics, with vaccine coverage increasing linearly over that period and fit the TSIR model using the true vaccine coverage and assuming the mean vaccine coverage, 70%, over that time period. The simulated transmission rates varied seasonally as a sin function with a period of one year; $1+\theta \cos(t/2\pi)$. We fit the seasonal fluctuation for simulations with seasonal amplitude, $\theta$, for 10 values over the range 0.2 to 0.6, which roughly corresponds to weak seasonality, as in pre-vaccination London, and high seasonality, as in Niamey (Ferrari et al. 2008). For each levels of seasonal amplitude we fit the TSIR model and estimated the seasonal amplitude for 50 simulation runs.

Our simulations show that the estimated range of the seasonal fluctuation in transmission rates for the increasing vaccination simulations was strongly correlated with that estimated assuming the mean vaccination rate (Figure A.S2). Assuming constant vaccination tends to over estimate the true seasonal amplitude, but the relationship is linear, indicating that the relative estimates of seasonal amplitude should be comparable.
Figure A.S2. Estimates of the seasonal amplitude under the assumption constant vaccination (y-axis) compared to the true, increasing vaccine uptake (x-axis). Each point indicates the estimates from a single simulation run. Colors and symbols indicate different levels of true seasonal amplitude (circles = 0.20-0.38, triangles=0.42-0.60). The black line indicates the one-to-one line.
Figure A.3. A) Estimated range of seasonal forcing for the 38 departments and urban centers as function of mean annual rainfall during the period 2003-2006. Colors indicate the 3 regions shown in the above map. Solid lines are the regression fit for each region. Urban centers are shown as solid points. The department of Magaria, which is a strong outlier and was excluded from the analysis, is indicated. B) Estimated range of seasonal forcing for the 38 departments and urban centers as function of district population size (colors and lines are as in A).
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