Optimizing Interventions to Control Emerging Infectious Diseases

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OPTIMIZING INTERVENTIONS TO CONTROL EMERGING INFECTIOUS DISEASES

COREY M. PEAK

A Dissertation Submitted to the Faculty of The Harvard T.H. Chan School of Public Health in Partial Fulfillment of the Requirements for the Degree of Doctor of Science in the Department of Epidemiology Harvard University Boston, Massachusetts.

May 2017
OPTIMIZING INTERVENTIONS TO CONTROL EMERGING INFECTIOUS DISEASES

Abstract

Inherent uncertainties surrounding emerging and re-emerging infectious diseases pose unique challenges to control efforts. Concurrent with the acceleration of disease emergence in recent decades, advances in modern computational methods have enabled new approaches to optimize interventions for disease control. In this dissertation, we leverage mathematical modeling and novel data sources to reveal new approaches to designing and evaluating strategies for controlling cholera, Ebola, and several other communicable diseases.

In Chapter 1, we use a mathematical model to demonstrate the impact, and interaction, of key factors which cause vaccine-derived herd immunity to wane over time. We demonstrate that oral cholera vaccines can be powerful tools for quickly protecting a population for a period of time that depends critically on vaccine coverage, vaccine efficacy over time, and the rate of population turnover through human mobility. We use these findings to show that pre-emptive vaccination may best be targeted at intermediate-mobility settings and through a strategy that blends routine vaccination with mass campaigns.

In Chapter 2, we develop a quantitative framework for comparing the control performance of quarantine and symptom monitoring of contacts with suspected exposure to an infectious disease. We use a mathematical model of seven case study diseases to show
how intervention choice is influenced by the natural history of the infectious disease, its inherent transmissibility, and the intervention feasibility in the particular healthcare setting. We use this information to identify the most important characteristics of the disease and setting that need to be characterized for an emerging pathogen in order to make an informed decision between quarantine and symptom monitoring of individuals.

In Chapter 3, we broaden the previous chapter’s discussion on quarantine by focusing on quarantines and other travel restrictions applied to large groups. Historically, the impact of such interventions on human mobility have proven difficult to measure, but we demonstrate that new approaches using mobile phone data can provide the necessary information in near real-time. We use mobile phone data from Sierra Leone to reveal that travel restrictions had an enormous and easily measurable impact on human travel during the 2014-5 Ebola epidemic.
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To Olive Magnolia Peak
INTRODUCTION

Inherent uncertainties surrounding emerging and re-emerging infectious diseases pose unique challenges to control efforts. Concurrent with the acceleration of disease emergence in recent decades, advances in modern computational methods have enabled new approaches to optimize interventions for disease control. In this dissertation, we leverage mathematical modeling and novel data sources to reveal new approaches to designing and evaluating strategies for controlling cholera, Ebola, and several other communicable diseases.

In Chapter 1, we use a mathematical model to demonstrate the impact, and interaction, of key factors which cause vaccine-derived herd immunity to wane over time. We demonstrate that oral cholera vaccines can be powerful tools for quickly protecting a population for a period of time that depends critically on vaccine coverage, vaccine efficacy over time, and the rate of population turnover through human mobility. We use these findings to show that pre-emptive vaccination may best be targeted at intermediate-mobility settings and through a strategy that blends routine vaccination with mass campaigns.

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CHAPTER 1

Prolonging Herd Immunity to Cholera via Vaccination: Accounting for Human Mobility and Waning Vaccine Effects

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ABSTRACT

Background

Oral cholera vaccination is an approach to preventing outbreaks in at-risk settings and controlling cholera in endemic settings. However, vaccine-derived herd immunity may be short-lived due to interactions between human mobility and imperfect or waning vaccine efficacy. As the supply and utilization of oral cholera vaccines grows, critical questions related to herd immunity are emerging, including: who should be targeted; when should revaccination be performed; and why have cholera outbreaks occurred in recently vaccinated populations?

Methods and Findings

We use mathematical models to simulate routine and mass oral cholera vaccination in populations with varying degrees of migration, transmission intensity, and vaccine coverage. We show that migration and waning vaccine efficacy strongly influence the duration of herd immunity while birth and death rates have relatively minimal impacts. As compared to either periodic mass vaccination or routine vaccination alone, a community could be protected longer by a blended “Mass and Maintain” strategy. We show that vaccination may be best targeted at populations with intermediate degrees of mobility as compared to communities with very high or very low population turnover. Using a case study of an internally displaced person camp in South Sudan which underwent high-coverage mass vaccination in 2014 and 2015, we show that waning vaccine direct effects and high population turnover rendered the camp over 80% susceptible at the time of the cholera outbreak beginning in October 2016.
Conclusions

Oral cholera vaccines can be powerful tools for quickly protecting a population for a period of time that depends critically on vaccine coverage, vaccine efficacy over time, and the rate of population turnover through human mobility. Due to waning herd immunity, epidemics in vaccinated communities are possible but become less likely through complementary interventions or data-driven revaccination strategies.
INTRODUCTION

Vaccination campaigns with sufficiently high efficacy and coverage can ideally achieve herd immunity in the population, an emergent state in which sustained transmission becomes unlikely.[1–3] Herd immunity is not permanent, however, and is expected to wane over time via short-lived vaccine efficacy and an influx of susceptible, unvaccinated individuals. Due to a reliable efficacy profile and high attainable coverage, killed oral cholera vaccines (kOCV) can generate powerful herd protection effects.[4,5] In 2012, the World Health Organization (WHO) created a kOCV stockpile to facilitate vaccine usage in three settings: (1) humanitarian crises at high risk of cholera importation and transmission; (2) high-endemicity “hot spots”; and (3) cholera outbreaks.[6] As the stockpile approaches its fifth year, evaluation of its management must address uncertainties in sustainability and long-term strategy, particularly regarding the duration of herd immunity (DHI) in these three settings.

Regarding the first setting, kOCVs can be a quick stopgap measure to protect cholera-prone dynamic populations such as refugee camps,[7] but it remains unclear how much time is “bought” by vaccination before longer-term solutions such as water, sanitation, and hygiene promotion are necessary. Second, feasibility and economic analyses of vaccination in endemic settings are strongly influenced by the frequency of revaccination.[8] Third, it remains to be seen how strongly, and in what direction, population mobility should be considered when prioritizing target populations for vaccination.

These are not merely hypothetical concerns. Beginning in October 2016, the Bentiu Protection of Civilians (PoC) Camp in South Sudan sustained a cholera outbreak despite
high-coverage mass vaccination campaigns in both 2014 and 2015.[9,10] Consequently, questions have emerged about the utility of vaccination and the expected risk of outbreaks, particularly in dynamic populations where cholera often breaks out.[11] Modeling studies of other diseases (e.g., [12–16]) suggest a suite of factors which may have contributed to the camp’s susceptibility to an outbreak, including waning vaccine efficacy, the influx of susceptible displaced people, an extremely high birth rate, and resettlement of vaccinated individuals. However, the relative contributions of these factors and their implications for vaccination strategy in the future are not clear.

Here we examine the implications of vaccine waning and human mobility on herd immunity over time in non-endemic settings, providing new insights related to the risk of outbreaks in vaccinated populations. Using mathematical models, we compare how well several common vaccination strategies sustain herd immunity and we demonstrate the non-monotonic relationship between migration rate and the projected impact of pre-emptive vaccination. We analyze data from the Bentiu PoC Camp to quantify the impact of expected drivers of waning herd immunity and assess whether they are sufficient to explain the vulnerability of the camp to the observed outbreak.
METHODS

Model

We developed mathematical models of a well-mixed population that is being targeted with vaccination. The population compartments of principal interest for this study are individuals who are fully susceptible to disease, $S$, and those who were vaccinated $n$-months ago, $V_n$ (Figure 1.1). To account for the observation that kOCV direct effects do not tend to wane exponentially,[17] we created an ensemble of $n$ monthly stages ($V_1, V_2, ..., V_n$), which collectively generate an Erlang-distribution for the duration of time in the $V$-ensemble.[18,19] We set the mean time residing in any $V_n$ compartment to 30.5 days; therefore, susceptible individuals move after vaccination to compartment $V_1$ for an average of one month, then to $V_2$ for an average of one month, and so forth.
Figure 1.1 Mathematical model framework.

Susceptible individuals ($S$) can become vaccinated ($V_1$) and proceed through each monthly vaccine compartments ($V_1, V_2, \ldots, V_n$). Individuals enter the system through birth and immigration (top arrow) and leave the system through death and emigration (grey arrows). The force of infection for individuals in a compartment $V_i$ is reduced by a factor of $1 - VE(i)$ according to a leaky model of vaccine action. Disease progression compartments for exposed but not yet infectious (E), infectious (I), and recovered (R) are shown, but are not explicitly modeled due to the focus of this study on vaccine-derived herd immunity.
The system of ordinary differential equations was solved using the *deSolve* package[20] in the statistical software program R (version 3.2.4). All code used to generate this paper can be found at [https://github.com/peakcm/cholera](https://github.com/peakcm/cholera).

**Vaccination Strategies**

Vaccination is implemented according to two approaches: mass and routine. We model mass vaccination as a large fraction of individuals moving into the $V_1$ compartment on a particular day, possibly recurrently (e.g., annually). Routine vaccination moves a substantially smaller fraction of individuals into the $V_1$ compartment every day. In each approach, vaccine priority is given first to susceptible individuals, $S$, then those who were vaccinated the longest time ago (i.e., $V_n$, then $V_{n-1}$, and so on until reaching the allotted number of vaccines for that day). In addition to mass vaccination and routine vaccination, we test a blended “Mass and Maintain” strategy in which one-time mass vaccination is followed by routine vaccination. See supplemental materials for mathematical details on modeling mass vaccination transition rates.

Currently, a complete kOCV course includes two doses administered approximately two weeks apart.[6] However, because the timescale of interest for this study is measured in years, not days, we assume mass vaccination campaigns elapse over one day and provide protection instantaneously. Furthermore, for generalizability across disease systems, we focus on the number of vaccine courses rather than the number of actual vaccines.

We parameterized the time-varying vaccine efficacy, $VE(t)$, of kOCV (whole-cell with B-subunit) using estimates from a large clinical trial in Bangladesh.[17,21] To provide monthly estimates of vaccine efficacy, $VE(t)$, we linearly interpolated between 6-month
point estimates with efficacy after the 5th year assumed to be zero, as the estimated mean efficacy becomes negative. Therefore, our last $V_n$ compartment before returning to full susceptibility is at 60 months ($V_{60}$).

**Human mobility**

We assume individuals emigrate from the population at a rate that is equal for all compartments. The total population size, $N(t)$, is held constant by offsetting emigration with an equal rate of immigration, unless otherwise noted. Our main results assume that incoming migrants bring neither vaccine-derived nor naturally-acquired immunity into the population.

We estimated migration rates from three example settings where kOCVs have been used, including: (1) a ‘stable’ urban population; (2) a highly mobile urban population; and (3) a displaced person setting with intermediate mobility. First, to represent a stable urban population, we estimate a migration rate of $\frac{1}{20 \text{ years}}$ (i.e., an average residence time of 20 years) from the observation that only 9% of an OCV study population in Calcutta, India, changed in the two years following vaccination in 2006.[22] Secondly, to represent a highly mobile urban population, we estimate a migration rate of $\frac{1}{2 \text{ years}}$ from the observation that 58% of a study population in Dhaka, Bangladesh, had relocated over two years.[23] Thirdly, to represent a displacement camp with intermediate mobility, we estimate a resettlement rate of $\frac{1}{4.3 \text{ years}}$ in the Bentiu PoC Camp in South Sudan in the period from February to October 2016, during which the International Organization on Migration (IOM) reports a rather stable population of 104,000 people and approximately 2,000 monthly
individuals both entering the camp and resettling from the camp (Figure S1.1) [http://www.iomsouthsudan.org/tracking/].

Outcome Measurements

We define the duration of herd immunity (DHI) as the amount of time following a vaccination campaign with an effective reproductive number, $R_e$, below one. We calculate

$$
R_e(t) = X(t) \times R_0
$$

where $X(t)$ is the proportion of the population susceptible at time $t$,

$$
X(t) = \frac{S(t) + \sum_{i=1}^{n} V_i(t)(1 - VE(i))}{N(t)}.
$$

Due to the special behavior of deterministic models, when a simulation asymptotically approaches $R_e(t) = 1$ from below, we define DHI as the time until $R_e(t) \geq 0.99$.

Using the effective reproductive number, $R_e(t)$, we estimate the probability of the community sustaining an outbreak given the introduction of a single case. When $R_e > 1$, the final epidemic size tends to follow a bimodal distribution with a probability of sporadic die-out and a probability of a large epidemic. Using a recent method for computing epidemic final size distributions,[24] we find the threshold of 10 cases is a reasonable cutoff size such that a large outbreak is henceforth very likely for sizeable values of $R_e$ (Figure S1.2). We therefore define an outbreak as more than 10 cases and, by assuming a Poisson distribution of secondary infections (mean = $R_e$), we can calculate the probability
of an outbreak of more than \( y \) cases initiated by a single infectious case using the Borel-Tanner distribution:[25,26]

\[
Pr(Y > y) = 1 - \sum_{i=1}^{y} \frac{1}{(i-1)!} i^{i-2} R_e^{i-1} e^{-iR_e}.
\]

**Mobility-informed vaccination targeting**

To assess the role of mobility on the optimal pre-emptive targeting of kOCVs, we simulate a setting with migration rates ranging from zero, representing a closed population, to a very high value of \( \frac{1}{1\text{ year}} \) (i.e., an average residence time of one year). Since we focus here on an at-risk population in a non-endemic setting, our outcome of interest is the cumulative probability of sustaining a cholera outbreak that was seeded by an imported case, which equals one minus the probability of having no outbreaks greater than \( y \) cases:

\[
C = 1 - \prod_{t=1}^{D} (1 - Pr(Y > y))^{l_{mig}}
\]

where \( D \) is the duration of follow-up time in days, \( y \) is the minimum outbreak size, and \( l_{mig} \) is the expected number of infected individuals who migrate into the population in one day. \( l_{mig} \) is calculated by:

\[
l_{mig} = \pi N (e^m - 1),
\]
where \( \pi \) is the probability an incoming migrant is infected, \( N \) is the size of the targeted population, \( m \) is the daily migration rate, and therefore the daily number of incoming migrants equals \( N(e^{mt} - 1) \) where \( t = 1 \) day. We assume each imported case has an independent probability of starting an outbreak of more than \( y \) cases given the effective reproductive number \( R_e(t) \) on that day \( t \).

We measure the difference between the cumulative outbreak probability, \( C \), over \( D \) days in the absence of vaccination as compared to the first \( D \) days following mass vaccination. A larger difference suggests a more impactful vaccination intervention. For our main results, we focus on a setting with moderate transmissibility \( (R_0 = 1.5) \) [27,28] and set the probability that a migrant is infected, \( \pi \), equal to \( \frac{1}{N} \), which simplifies Equation 5 to \( I_{mig} = (e^m - 1) \) (see supplementary materials).

**Bentiu PoC Camp Case Study**

We examine the suspected drivers of waning herd immunity in a well-described outbreak in the Bentiu PoC Camp in South Sudan. Of the three million persons targeted for health resources in broader South Sudan, including the Bentiu PoC Camp, UNFPA expects 335 deliveries per day, which equates to birth rate of approximately \( \frac{1}{24.4 \text{ years}} \) [29] We assumed this to be our demographic turnover rate as a conservatively high estimate.

We estimated population susceptibility over time, \( X(t) \), in six scenarios (Table 1.1). In the “observed” scenario, we used empirical measures of four key drivers of waning herd immunity, specifically: the birth/death rate of \( \frac{1}{24.4 \text{ years}} \); an empirical distribution of efficacy over time, \( VE(t) \); a camp resettlement rate of \( \frac{1}{4.3 \text{ years}} \) (i.e., an average camp residence time
of 4.3 years) which is balanced by an equal rate of entries for a net-zero impact on $N(t)$; and a dynamic population size, $N(t)$, driven by net growth or shrinkage through camp entries or exits. We compare this scenario with counterfactual scenarios that eliminate at least one of these drivers and will therefore increase DHI. We constructed a composite counterfactual scenario in which: the birth/death rate was set to zero; vaccine efficacy was held constant at its maximum value (70.3%) for all time since vaccination; the camp resettlement rate was set to zero; and the population size was held constant at approximately the level observed during the outbreak (100,000). To isolate the impact of each driver of waning herd immunity, we run simulations where one driver is set to the “observed” condition while the other three drivers are set to their counterfactual condition to remove their influence (Table 1.1).
Table 1.1. Relative contribution of four potential drivers of waning herd immunity in Bentiu PoC Camp.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Vaccine Efficacy $VE(t)$</th>
<th>Population Size $N(t)$</th>
<th>Birth &amp; Death Rate</th>
<th>Resettlement Rate</th>
<th>Percent Susceptible on Oct 16, 2016 * $X(t)$</th>
<th>Difference in Percent Susceptible $\Delta X(t)$</th>
<th>Attributable Percent</th>
</tr>
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<tr>
<td>Composite Counterfactual</td>
<td>70.3%</td>
<td>100,000</td>
<td>0</td>
<td>0</td>
<td>34.4%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Only $VE(t)$ waning</td>
<td>Empirical</td>
<td>100,000</td>
<td>0</td>
<td>0</td>
<td>58.2%</td>
<td>23.8%</td>
<td>34.9%</td>
</tr>
<tr>
<td>Only $N(t)$ changes</td>
<td>70.3%</td>
<td>Empirical</td>
<td>0</td>
<td>0</td>
<td>56.6%</td>
<td>22.2%</td>
<td>32.6%</td>
</tr>
<tr>
<td>Only Births &amp; Deaths</td>
<td>70.3%</td>
<td>100,000</td>
<td>0</td>
<td>1/24.4 years</td>
<td>38.1%</td>
<td>3.7%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Only Resettlement</td>
<td>70.3%</td>
<td>100,000</td>
<td>0</td>
<td>1/4.3 years</td>
<td>52.9%</td>
<td>18.5%</td>
<td>27.1%</td>
</tr>
<tr>
<td>‘Observed’</td>
<td>Empirical</td>
<td>Empirical</td>
<td>1/24.4 years</td>
<td>1/4.3 years</td>
<td>80.8%</td>
<td>46.3%</td>
<td>--</td>
</tr>
</tbody>
</table>

* October 16, 2016 is the date of the first cholera case reported from the outbreak in the Bentiu PoC Camp
To assess the relative importance of each driver of waning herd immunity in this case study, we calculate a measure of attributable percent. For a scenario $i$ that isolates one driver, we measure the proportion susceptible ($X(t)_i$) on October 16, 2016, the start of the observed outbreak. To compare scenarios, we calculate the difference between estimates of the proportion susceptible at the start of the outbreak under scenario $i$ with estimates in the composite counterfactual scenario,

$$[6] \quad \Delta X(t)_i = X(t)_i - X(t)_{composite}. $$

Finally, we calculate the percent of waning herd immunity attributable to each driver ($AR\%$),

$$[7] \quad AR\% = 100 * \frac{\Delta X(t)_i}{\sum \Delta X(t)_i}. $$

In order to estimate the probability of an outbreak given introduction of a cholera case using the population susceptibility over time, $X(t)$, we must estimate the basic reproductive number, $R_0$. Following frameworks[30,31] recently applied to cholera in South Sudan,[32] we retrospectively estimate the time-varying reproductive number using daily case reports, which we extract from Cholera Situation Reports from the South Sudan Ministry of Health,[33] and an expected generation interval distribution, which we assume to follow a discretized gamma distribution with median of 5 days.[32] This method assumes uniform mixing, no imported cases after the first case, and no missing data.
Maximum likelihood estimation procedures were implemented in the statistical software program R using the \textit{R0} package.[34]
RESULTS

*Dynamics of population susceptibility and herd immunity*

Following mass vaccination with 100% coverage, population susceptibility, \( X(t) \), quickly increases over time in the presence of high migration rates and short-lived vaccine efficacy (Figure 1.2A, solid line). Even with a hypothetical perfect vaccine that retains complete protection indefinitely, high migration rates can drive population susceptibility near 100% within 9-10 years (Figure 1.2B, solid line). Between three primary drivers causing herd immunity to wane, namely migration, waning efficacy, and demographic turnover through births and deaths, we find that the first two are substantially more influential than either the birth or death rate, which are each typically much slower processes. As compared to rates of birth and death set to zero, even pessimistic estimates of a life expectancy of 40 years result in negligible differences in the proportion of the population susceptible (Figure S1.3).
Figure 1.2. Dynamics of population susceptibility and herd immunity.

Dynamics following mass vaccination (100% coverage) with kOCV (left column) or a hypothetical vaccine with VE=1 indefinitely (right column). (A-B) Population susceptibility increases over time in the presence of migration rates of \( \frac{1}{2 \text{ years}} \) (solid line), \( \frac{1}{20 \text{ years}} \) (dashed line), and zero (dotted). (C-D) The effective reproductive number changes over time with \( X(t) \) differently for settings with basic reproductive numbers of 2 (red), 1.5 (green), and 1 (blue). (E-F) The probability that a single case sparks and outbreak of more than 10 cases. Birth and death rates are set to zero in each simulation.
Following kOCV vaccination with 100% coverage in a population with high migration, we estimate the vaccine-derived DHI to be approximately 0.47 years when $R_0 = 2$, 0.98 years when $R_0 = 1.5$, and 4.06 years when $R_0 = 1$ (Figure 1.2C, solid lines). These durations increase to 1.07 years, 1.89 years, and 5.16 years, respectively, in the presence of low migration rates instead (Figure 1.2C, dashed lines). As expected, DHI is reduced when vaccine coverage is less than 100%, and, depending on both the coverage and $R_0$, herd immunity is sometimes unattainable (Figure S1.4).

Achieving herd immunity is a key theoretical threshold, but in reality an outbreak is possible below the threshold and is not guaranteed above the threshold.[35] Mass vaccination reduces, but not eliminates, the probability that an imported case sparks an outbreak for a duration of time that depends critically on the migration rate and how vaccine efficacy wanes over time (Figure 1.2E-F). For example, even though herd immunity is lost within just 0.47 years in a high migration setting when $R_0 = 2$ (Figure 1.2C, solid red line), the outbreak probability is kept below 50% for twice as long (Figure 1.2E, solid red line).

*Optimizing revaccination with “Mass and Maintain” strategies*

We considered several operational strategies for sustaining herd immunity through vaccination alone. In a hypothetical population of size $N$ with $R_0 = 1.5$ and a high rate of migration ($\frac{1}{2\,years}$), mass vaccination every year or every two years with 100% coverage of susceptible individuals can render herd immunity for 3.5 or 2.8 years, respectively, before depleting a fixed vaccine allotment of $3N$ full courses (Figure 1.3A). If these vaccines are instead allotted on a daily basis through routine vaccination, DHI can be extended to 4.4
years (Figure 1.3B). However, recurring mass campaigns have diminishing returns per vaccine once herd immunity is achieved; meanwhile routine vaccination alone requires a long period of time to build-up herd immunity. We therefore find that a blended “Mass and Maintain” strategy that complements a single mass vaccination campaign with subsequent routine vaccination can maintain herd immunity longer than either strategy alone (Figure 1.3C), both for this example and for a wide range of settings with various migration rates and $R_0$ values (Table S1.1).
Figure 1.3. Revaccination strategies to maximize DHI.

(A) Recurring mass vaccination events (arrows) with 100% coverage of susceptible people every year (dashed line) or two years (dotted line) is shown to periodically achieve then lose herd immunity, designated by the horizontal line at $R_o = 1$. Faded horizontal bars show times with herd immunity under each strategy and the total DHI is annotated to the right of each. (B) Routine vaccination of 2.4% (green), 3.6% (teal), or 4.8% (purple) of the population per month achieve herd immunity for 0, 4.4, and 4.3 years, respectively. (C) A "Mass and Maintain" strategy with one-time vaccination at 75% coverage followed by routine vaccination of 2.4% (green), 3.6% (teal), or 4.8% (purple) of the population per month can render herd immunity for 1.6, 5.2, and 4.3 years, respectively. The following are held constant for all simulations: population size = 10,000; maximum vaccine courses = 30,000; $R_o = 1.5$; migration rate = $\frac{1}{2 \text{ years}}$; and birth and death rates = $\frac{1}{40 \text{ years}}$. 

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23
Optimizing pre-emptive mass vaccination by targeting intermediate mobility settings

In addition to the importance of migration on DHI, one may posit that communities with higher migration rates are also more likely to have cholera imported. In order to optimize pre-emptive kOCV impact in at-risk settings, there is a tradeoff between targeting low-mobility communities, where herd immunity may last for a long time but cholera introduction is rare, and high-mobility communities, where the opposite is expected. We find that communities with intermediate levels of migration may experience the largest vaccine-derived decrease in outbreak risk sparked by an imported case (Figure 1.4). For example, the migration rate recorded in the Bentiu PoC Camp in mid-2016 is near the optimal condition for maximizing the impact of a single mass vaccination campaign in the 4-6 year time horizon, assuming $R_0 = 1.5$. If one is more interested in shorter time horizons since vaccination, the migration rate that maximizes vaccine impact favors mobile communities, similar to some urban areas in Dhaka, Bangladesh.[23] Sensitivity analyses suggest that intermediate mobility rates (e.g., between those observed in Dhaka and Calcutta) generally maximize vaccine impact, but the optimal migration rate is slower in settings that have a larger population size, a higher transmission potential ($R_0$), or where a higher fraction of incoming migrants are infected (e.g., due to high-burden neighbors) (Figure S1.5). Conversely, settings with small population size, low transmission potential, and whose migrants have a small probability of being infectious require very high migration rates in order to garner much baseline risk of cholera importation and outbreak.
Figure 1.4. Vaccine targeting optimized in settings with intermediate rates of migration.

Vaccine impact, as measured by the difference in the cumulative probability of an outbreak comparing a mass kOCV campaign (coverage 100%) versus no vaccination, is shown to reach maxima (triangles) at intermediate levels of mobility (x axis). The time since vaccination (colored lines) modifies these maxima. Grey dashed lines denote the estimated migration rates for Calcutta, Bentiu PoC Camp, and Dhaka. In this example, $R_0 = 1.5$ and the average probability that a migrant is infected is $1/N$, where $N$ is the population size.
**Bentiu PoC Camp Case Study**

The Bentiu PoC Camp grew from 4,291 occupants in February 2014 to a peak of 140,101 in December 2015 and then converged to approximately 104,000 in May 2016 (Figure 1.5A). Assuming a cholera-naïve population before vaccination, we estimate that at its lowest point, just after vaccination in June 2015, 37% of the population remained susceptible to cholera before increasing to 81% on October 16, 2016, when the first cholera case was detected (Figure 1.5B). By December 1, 2016, we estimate that only 40.5% of camp residents had ever been vaccinated, which closely matches a WHO/IOM survey performed that month that reported kOCV coverage of 40%.[33]
Figure 1.5. Bentiu PoC Camp case study.

(A) Reported population size of the Bentiu PoC Camp (blue line), approximate number of people vaccinated assuming two-dose coverage (green bars), and monthly case counts from October to January (inset grey bars). IOM began reporting entries and exits in December 2015, which are represented by the faint green and red ribbons around the blue line. (B) The proportion susceptible over time (green line) decreases due to mass vaccination events and increases over time since vaccination. (C) The probability that a single case sparks an outbreak of more than 10 cases increases with $X(t)$ and $R_0$, as represented by line color: $R_0=1$ (blue); 1.5 (green); 1.8 (black); and 2 (red).
Using case reports and assuming a fixed generation interval distribution, we estimate the mean effective reproductive number, \( R_e(t) \), exceeded unity for approximately two months following the first case, with a maximum likelihood estimate of 1.45 (1.18-1.75) (Figure S1.6). Using the population fraction susceptible of 0.81 estimated above, we calculate a basic reproductive number, \( R_0 \), of approximately 1.80 in this setting in the absence of vaccination (Equation 1). These findings are within the range of estimates derived from South Sudan in 2014.[32] Assuming this pre-vaccination estimate of \( R_0 \), we find that after vaccination the probability of an outbreak first exceeded 50% in May 2016 and reached 57% when the outbreak began in October (Figure 1.5C, black line). Using a “Mass and Maintain” strategy including vaccination of 100% of individuals migrating into the camp after the second mass vaccination campaign, we estimate that only 52% of the population would have been susceptible on the date the first case was reported in the camp, which is low enough to generate herd immunity at the time (assuming \( R_0 = 1.80 \))(Figure S1.7).

The drivers of waning herd immunity in this population, from strongest to weakest, were short-lived vaccine efficacy, population growth, camp resettlement rate, and lastly births and deaths (Table 1.1, Table S1.2). In the counterfactual scenario lacking these drivers, we would expect that as few as 34% of the population were susceptible on the day of the first reported cases in Bentiu PoC, which would render herd immunity even if \( R_0 \) was as high as 3.
DISCUSSION

Vaccination can rapidly protect a population at risk of a cholera outbreak, but the duration of vaccine-derived herd immunity depends critically on vaccine coverage, waning vaccine efficacy, and a net influx of susceptible people through population mobility. In our case study of the Bentiu PoC Camp, we find that these drivers are sufficient to explain the vulnerability of this population to an outbreak despite two recent high-coverage vaccine campaigns. Therefore, disease re-emergence does not imply vaccine failure and can be avoided by data-driven revaccination strategies or by scaling-up long-term solutions while under the temporary cover of vaccination. Our results provide key time windows during a population can expect to resist a cholera outbreak even if the pathogen were to be introduced. We developed an interactive tool to facilitate implementation of these results for a user-defined setting (https://coreypeak.shinyapps.io/herd_protection_estimator/).

One practical implementation of the “Mass and Maintain” vaccination strategy in a camp setting can include a one-time mass vaccination campaign followed by routine vaccination of new members of the population, such as births and new entries. Population sub-groups with high vulnerability and mobility, such as coastal fishing communities,[36] may also benefit from the “Mass and Maintain” vaccination strategy targeted at seasonal influxes of migrants such as new fishermen. In an urban or open population, such as Dhaka or Calcutta, routine identification of new members becomes more challenging, but performance of the WHO Expanded Programme on Immunization in cholera endemic regions like Bangladesh are promising.[37] Recent work has also shown serological triggers for periodic mass vaccination can be an effective alternative method to maintain herd immunity to measles.[38]. For cholera specifically, there is a need for more research
into cross-sectional markers of immunity which can inform risk profiling, revaccination timing, and, if stratified by age, the impact of mass vaccination.[39]

Current guidelines for the optimal use of the kOCV stockpile recommend targeting “areas with important population movements.”[40] Mobility is recognized as an important driver of the performance of vaccination strategies to control ongoing cholera outbreaks.[41] Here, we focus on pre-emptive vaccination of at-risk communities to show the competing effects of high mobility on expected vaccine impact. In order to operationalize the finding that vaccination may be most impactful for populations with intermediate degrees of mobility, data on migration rates from sources such as censuses or mobile phone call data records must be collected to define “intermediate” mobility for a given context.[42]

Our results depend on several simplifying assumptions. By modeling a well-mixed population, we are assuming no heterogeneity in contact patterns or local reproductive numbers. In reality, we expect diseases, especially those like cholera with environmental transmission dynamics, to exhibit substantial spatial heterogeneity in transmission intensity.[43] These differences become crucial if, as we may expect, migration occurs at higher rates into sub-regions with higher transmission potential due to confounders like poverty and temporary housing. In that case, we would expect DHI to decrease, the probability of an outbreak to increase, and the routine vaccination of migrants to become even more crucial.

Our model assumes a leaky mode of vaccine action, whereby vaccination reduces the disease susceptibility of each recipient. Our calculation of proportion susceptible, \( X(t) \), is robust to other assumptions regarding the method by which vaccine effects wane,
namely: time-dependent failure in “take,” corresponding to an all-or-nothing response; and
time-dependent failure in “degree,” corresponding to a leaky vaccine response (Figure S1.8).[44] Our parameterization of a waning leaky vaccine aligns with prevailing interpretations[17] of the clinical trial data,[21] but alternative possible explanations for changes in vaccine efficacy over time in a clinical trial are difficult to rule-out, such as frailty, loss to follow up, and random variability.[45]

The migration rates estimated from Dhaka, Bentiu, and Calcutta are intended for benchmarking purposes and do not imply that migration rates are either constant or generalizable to the whole city or region. Indeed, we would expect to retain herd immunity longer after vaccination for a given migration rate if the rate was calculated in a population which included a stable sub-group of permanent residents and a small, highly mobile sub-group of temporary residents.

Cholera vaccine efficacy has been shown to vary by age of recipient,[17,21] however for simplicity and lack of detailed data we do not model this age structure. If children respond poorly to kOCV and are members of a mass vaccination campaign, we would expect herd immunity to wane more quickly, and especially so if children are disproportionate sources of transmission. Furthermore, over the course of an outbreak, we may expect the relative contributions of different age groups to differ, which can have important consequences on vaccine impact and targeting.[46] For simplicity, we focus on pre-emptive vaccination of a generalized population without previous exposure to cholera.

The model we present is not limited to cholera or other diseases with only short-duration or leaky vaccines (e.g., the typhoid capsular polysaccharide vaccine [47]). The phenomenon of waning herd immunity also has strong implications on disease control
strategies that include mass vaccination or “mop up” vaccination, such as measles[48] and yellow fever.[49] For yellow fever in particular, fractional vaccine doses have been used to extend vaccine supply under the assumption that vaccine efficacy of fractional doses lasts at least one year.[50] Following the mass vaccination of 25 million people in Angola and the Democratic Republic of the Congo, routine vaccination may be the most efficient way to henceforth sustain herd immunity in these populations, should this be the goal. Human mobility and waning herd immunity are key considerations for when these urban populations should be revaccinated.

Herd immunity is a key target for the control of vaccine-preventable diseases and can be monitored over time using information on the vaccine efficacy and population turnover rates. We show this information is essential for optimizing revaccination strategies, targeting vaccine stockpiles, and explaining re-emergence of outbreaks in recently vaccinated populations.
**SUPPLEMENTAL INFORMATION**

*Vaccination transition rate calculation*

In the simplest case whereby vaccination occurs at the onset of the study, we initialize the model with compartment $V_1$ equal to the number of vaccine recipients and subtract these from the $S$ compartment. This approach suffices for one-time mass vaccination, but we must explicitly model vaccination transition rates for recurrent mass vaccination and routine vaccination. Assuming $n_V$ vaccines are available for use on a given day, the transition rate ($\nu_S$) from $S$ to $V_1$ is calculated by:

$$\nu_S = S \cdot -\ln \left(1 - \min \left(0.99, \frac{n_V}{S} \right) \right).$$

When the number of vaccines allocated on a given day is much smaller than the number of susceptible individuals eligible to receive vaccination (e.g., $\frac{n_V}{S} < 0.1$), then the logarithmic adjustment term $-\ln \left(1 - \min \left(0.99, \frac{n_V}{S} \right) \right)$ will approach $\frac{n_V}{S}$ and therefore the transition rate $\nu_S$ will approximately equal the number of vaccine courses available (i.e., $\nu_S \approx n_V$) (Figure S1.9, dashed line).

However, when a substantial fraction of the population is to receive mass vaccination on a single day (e.g., $n_V > 0.1 \cdot S$), the number of vaccine courses available, $n_V$, increasingly becomes a poor estimate for the transition rate, $\nu_S$, needed to move the appropriate number of individuals into $V_1$. Therefore, the logarithmic adjustment term $-\ln \left(1 - \min \left(0.99, \frac{n_V}{S} \right) \right)$ inflates the transition rate and allows the deterministic solver to move the desired number of individuals into $V_1$ (Figure S1.9, solid line). For computational tractability, we assume the vaccine campaign coverage, $\frac{n_V}{S}$, does not exceed 99%.
When the number of available vaccines, $n_V$, exceeds the number of individuals in the $S$ compartment, then vaccines are then given first to those who were vaccinated the longest time ago (i.e., $V_{48}$ first, then $V_{47}$, and so on).

**Vaccination Targeting in Intermediate Mobility Settings**

In order to calculate the expected impact of vaccination on reducing the probability of an outbreak sparked by an imported case, we must assume individuals migrating into the population are infected with cholera with a certain probability ($\pi$). As described in Methods and Materials, we set $\pi$ equal to $\frac{1}{N}$ for our main results, which simplifies Equation 5 to $I_{mig} = (e^m - 1)$ For main text Figure 1.4, we consider a population of size 10,000 and therefore $\pi = \frac{1}{10,000} = 0.0001$. This value for $\pi$ is consistent with a rough estimate of the average fraction of the population infectious on a given day during large recent epidemics in Zimbabwe (2008-2009) and Haiti (2010-2015) (Table S1.3).

We present a sensitivity analysis of the optimal migration rate with values of $\pi$ between 0.00001 and 0.001 (an order of magnitude larger and smaller than the main result presented) and $R_0$ ranging from 0.75 to 3. We find when $R_0$ and $\pi$ are large, representing a setting that has high transmission potential and a high influx of migration from cholera-affected neighbors, the impact of vaccination over a 4-year time horizon is optimized when migration is slow (i.e., the average residence time increases) (Figure S1.5, blue). Conversely, high migration rates will tend to optimize the impact of vaccination in settings where transmission potential is low and a small proportion of migrants are infected (Figure S1.5, red). Because the population size, $N$, and the fraction of migrants infected, $\pi$,
are coupled in Equation 5, the variables behave similarly and therefore the optimal migration rate tends to decrease as the population size increases.

*Interactive Online Supplement*

The interactive online supplement can be found at: [https://coreypeak.shinyapps.io/herd_protection_estimator/](https://coreypeak.shinyapps.io/herd_protection_estimator/). To account for seasonal forcing, the transmission parameter ($\beta$) is allowed to vary with each day ($t$) according to a sinusoidal function $\beta(t) = 1 + f \times \cos(\tau + 2\pi \times t / 365)$ where $f$ is the magnitude of seasonal forcing and $\tau$ is a frameshift parameter accounting for the time of initial vaccination campaign ($\tau=0$ if vaccination occurs at the peak transmission season, $\tau=\pi$ if vaccination occurs at the trough of transmission season). Therefore, we assume an annual cycle, but note that some regions such as Dhaka may exhibit biannual cycles.\[52\]
Table S1.1. Sensitivity analysis of revaccination strategy optimization.

Comparison of the performance of Routine, Mass, and Mass and Maintain vaccination strategies with respect to DHI in a population of size 10,000, a vaccine supply of 30,000 courses, and the following operational parameters: routine vaccination of between 2 and 16 courses per day; mass vaccination coverage between 0 and 100% of susceptible individuals; and mass vaccination frequency between annual and every 3 years.

<table>
<thead>
<tr>
<th>$R_0$</th>
<th>Migration Rate (years$^{-1}$)</th>
<th>Optimal Strategy</th>
<th>DHI (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25</td>
<td>0</td>
<td>Mass and Maintain</td>
<td>18.3</td>
</tr>
<tr>
<td>1.50</td>
<td>0</td>
<td>Mass and Maintain</td>
<td>10.0</td>
</tr>
<tr>
<td>2.00</td>
<td>0</td>
<td>Mass and Maintain</td>
<td>5.1</td>
</tr>
<tr>
<td>2.50</td>
<td>0</td>
<td>Mass and Maintain</td>
<td>3.0</td>
</tr>
<tr>
<td>1.25</td>
<td>1/20</td>
<td>Mass and Maintain</td>
<td>17.9</td>
</tr>
<tr>
<td>1.50</td>
<td>1/20</td>
<td>Mass and Maintain</td>
<td>8.8</td>
</tr>
<tr>
<td>2.00</td>
<td>1/20</td>
<td>Mass and Maintain</td>
<td>4.8</td>
</tr>
<tr>
<td>2.50</td>
<td>1/20</td>
<td>Mass and Maintain</td>
<td>3.2</td>
</tr>
<tr>
<td>1.25</td>
<td>1/4.3</td>
<td>Mass and Maintain</td>
<td>12.2</td>
</tr>
<tr>
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<td>1/4.3</td>
<td>Mass and Maintain</td>
<td>5.8</td>
</tr>
<tr>
<td>2.00</td>
<td>1/4.3</td>
<td>Mass and Maintain</td>
<td>4.1</td>
</tr>
<tr>
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<td>1/4.3</td>
<td>Mass and Maintain</td>
<td>2.6</td>
</tr>
<tr>
<td>1.25</td>
<td>1/2</td>
<td>Mass and Maintain</td>
<td>9.1</td>
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<td>1/2</td>
<td>Mass and Maintain</td>
<td>4.7</td>
</tr>
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<td>2.00</td>
<td>1/2</td>
<td>Mass and Maintain</td>
<td>3.5</td>
</tr>
<tr>
<td>2.50</td>
<td>1/2</td>
<td>Mass and Maintain</td>
<td>1.4</td>
</tr>
<tr>
<td>1.25</td>
<td>1/1</td>
<td>Mass and Maintain</td>
<td>4.8</td>
</tr>
<tr>
<td>1.50</td>
<td>1/1</td>
<td>Mass and Maintain</td>
<td>2.2</td>
</tr>
<tr>
<td>2.00</td>
<td>1/1</td>
<td>Mass and Maintain</td>
<td>1.5</td>
</tr>
<tr>
<td>2.50</td>
<td>1/1</td>
<td>Mass and Maintain</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Table S1.2. Magnitude of potential drivers of waning herd immunity in Bentiu PoC Camp using Backward Selection.

Backward removal of drivers reveals the same order of influential drivers as the forward selection of drivers (Table 1.1). In order of decreasing importance, these are vaccine efficacy, population size, resettlement, and births/deaths.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Vaccine Efficacy (VE(t))</th>
<th>Population Size (N(t))</th>
<th>Birth &amp; Death Rate</th>
<th>Resettlement Rate</th>
<th>Percent Susceptible on Oct 16, 2016 (X(t))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Counterfactual</td>
<td>70.3%</td>
<td>100,000</td>
<td>0</td>
<td>0</td>
<td>34.4%</td>
</tr>
<tr>
<td>Remove Only (VE(t)) waning</td>
<td>70.3%</td>
<td>Empirical</td>
<td>1 (\frac{1}{24.4 \text{ years}})</td>
<td>1 (\frac{1}{4.3 \text{ years}})</td>
<td>70.5%</td>
</tr>
<tr>
<td>Remove Only (N(t)) changes</td>
<td>Empirical</td>
<td>100,000</td>
<td>1 (\frac{1}{24.4 \text{ years}})</td>
<td>1 (\frac{1}{4.3 \text{ years}})</td>
<td>71.8%</td>
</tr>
<tr>
<td>Remove Only Births &amp; Deaths</td>
<td>Empirical</td>
<td>Empirical</td>
<td>0</td>
<td>1 (\frac{1}{4.3 \text{ years}})</td>
<td>79.6%</td>
</tr>
<tr>
<td>Remove Only Resettlement</td>
<td>Empirical</td>
<td>Empirical</td>
<td>1 (\frac{1}{24.4 \text{ years}})</td>
<td>0</td>
<td>73.3%</td>
</tr>
<tr>
<td>Observed</td>
<td>Empirical</td>
<td>Empirical</td>
<td>1 (\frac{1}{24.4 \text{ years}})</td>
<td>1 (\frac{1}{4.3 \text{ years}})</td>
<td>80.8%</td>
</tr>
</tbody>
</table>
### Table S1.3. Review of attack rates in select large recent epidemics.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Cases Reported$^1$</th>
<th>Population$^2$ (thousands)</th>
<th>Attack Rate (per thousand)</th>
<th>Daily Proportion Infectious$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Annual</strong></td>
<td><strong>Weekly Average</strong></td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>2008</td>
<td>60,055</td>
<td>13,495</td>
<td>4.45</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>2009</td>
<td>68,151</td>
<td>13,721</td>
<td>4.97</td>
<td>0.10</td>
</tr>
<tr>
<td>Haiti</td>
<td>2010</td>
<td>179,379</td>
<td>10,000</td>
<td>17.93</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>2011</td>
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<td>10,145</td>
<td>33.54</td>
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<td></td>
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<td>112,076</td>
<td>10,289</td>
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<td></td>
<td>2013</td>
<td>58,809</td>
<td>10,431</td>
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</tr>
<tr>
<td></td>
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<td>10,572</td>
<td>2.62</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>36,045</td>
<td>10,711</td>
<td>3.37</td>
<td>0.06</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Crude Average</strong></td>
<td>10.43</td>
</tr>
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</table>

1 [http://gamapserver.who.int/gho/interactive_charts/cholera/atlas.html](http://gamapserver.who.int/gho/interactive_charts/cholera/atlas.html)
2 [https://esa.un.org/unpd/wpp/](https://esa.un.org/unpd/wpp/)
3 Assuming an average duration of infectiousness of 3.5 days,[47] half the weekly average cases would be infectious on a given day.
Figure S1.1. Bentiu PoC Camp population estimates over time.

In order to simulate the Bentiu PoC Camp, we separated the IOM population estimates (black line) into four segments (separated by vertical dashed lines). During the first segment from February 2014 to June 2014, we assumed linear population growth (blue line). During the second segment from June 2014 to December 2015, we simulated exponential growth at a rate of $\frac{1}{1.21 \text{ years}}$. During the third segment from December 2015 to May 2015, we assumed exponential decay at a rate of $\frac{1}{1.21 \text{ years}}$. During the fourth and final segment beginning May 2015, we assumed population size was constant. The use of exponential and constant segments allowed for population size to change dynamically within a compartmental model framework, and provided population estimates that were visually reasonable. Our model simulations began on June 15, when vaccination first occurred.
Figure S1.2. Final epidemic size distribution and choice of cutoff.

The final epidemic size distribution in a population of 1000 is monotonically decreasing when $R_0$ equals 0.9 (red) and follows a bimodal distribution when $R_0$ equals 1.2 (yellow), 1.5 (green), 1.8 (blue), and 2.5 (black). The inset shows a cutoff of 10 cases can discriminate large and small outbreaks with high sensitivity, but specificity can be low with low values of $R_0$. 
Figure S1.3. Changes in the proportion of the population susceptible ($X(t)$) as a function of years since vaccination in the presence of non-zero birth rates.

As per Figure 1.2A-B, but with the addition of high birth/death rates ($\frac{1}{40\,years}$) and the Whole Cell vaccine profile (without the B-subunit). Even conservatively fast rates of birth and death ($\frac{1}{40\,years}$) are slow compared to the rates of vaccine efficacy waning and high ($\frac{1}{2\,years}$) or low ($\frac{1}{20\,years}$) migration, and therefore have little impact.
Figure S1.4. Duration of herd immunity (DHI) as a function of vaccine coverage and basic reproductive number.

For both the whole cell and whole cell (with B-subunit) kOCVs, DHI is maximized in settings with high vaccine coverage and low basic reproductive numbers. Migration rates are set to zero. Uncolored regions never obtain herd immunity.
Figure S1.5. Vaccine targeting sensitivity to $R_0$ and the fraction of migrants infected, $\mu$.

With increases in $R_0$ or the fraction of migrants infected, $\mu$, the optimal migration rate decreases from the fastest tested rate, $\frac{1}{\text{1 year}}$ (red), to the slowest tested rate, $\frac{1}{\text{40 years}}$ (blue).

Contour lines denote average residence time in years from case studies in Dhaka (2), Bentiu (4.3), and Calcutta (20). For each simulation, the population size, $N$, is set to 10,000.
Figure S1.6. Time-dependent reproductive number ($R_t$) and daily cholera case counts in Bentiu PoC Camp between October, 2016, and January, 2017.

Using the daily case counts (grey bars) and a generation interval with median of 5 days and following a gamma distribution with shape=0.5 and rate=0.1 as per ref [32], we report a mean time-dependent reproductive number (red line) above unity for nearly two months.

95% confidence intervals are shown in pink.
Figure S1.7. Time-dependent proportion susceptibility, $X(t)$, in the Bentiu PoC Camp in the presence of a Mass and Maintain vaccination strategy.

As per Figure 1.5B, with an additional dashed line indicating a counterfactual scenario whereby vaccines were administered to 100% of the estimated 55,628 new entries to the camp after the second mass vaccination campaign. With this strategy, population susceptibility on October 16, 2016 is 0.52 (dashed line), as compared to 0.81 in the absence of the Mass and Maintain strategy (solid green line).
Figure S1.8. Calculation of $X(t)$ is robust to vaccine efficacy waning due to time-dependent failures in “take” or “degree.”

Vaccine efficacy waning that is due to a time-dependent failure in “take” (i.e., an “All or Nothing” vaccine waning) (left panel) retains a constant $VE(t)$ (dashed lines) while the number of individuals in the $V(t)$ ensemble decreases over time (dotted lines) from 75% to 0% using a theoretical example vaccine. For a time-dependent failure in “degree” (i.e., a leaky vaccine waning) (right panel), individuals remain in the $V(t)$ ensemble, but vaccine efficacy wanes from 75% to 0%. The proportion susceptible over time, $X(t)$, calculated by Equation 5 is identical for both modes of action (solid lines).
**Figure S1.9. Demonstration of logarithmic adjustment for transition rates.**

As the desired fraction of individuals to be vaccinated in a single day increases (x axis), the vaccination transition rate with the logarithmic adjustment (see supplementary materials) moves the accurate fraction of the population into the $V_1$ compartment (solid line) while a transition rate that is simply equal to just the number of vaccines to be used (dashed line) does not move enough individuals into $V_1$. 
REFERENCES


33. Republic of South Sudan Ministry of Health. Situation Report #103 on Cholera in South Sudan [Internet]. 2017. Available:


CHAPTER 2

A Quantitative Comparison of Non-Pharmaceutical Interventions for Containing Emerging Epidemics

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Yonatan H. Grad 3, 4
Caroline O. Buckee 1

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4 Division of Infectious Diseases, Brigham and Women’s Hospital, Harvard Medical School
ABSTRACT

Strategies for containing an emerging infectious disease outbreak must be non-pharmaceutical when drugs or vaccines for the pathogen do not yet exist or are unavailable. The success of these non-pharmaceutical strategies will depend not only on the effectiveness of isolation measures but also on the epidemiological characteristics of the infection. However, there is currently no systematic framework to assess the relationship between different containment strategies and the natural history and epidemiological dynamics of the pathogen. Here, we compare the effectiveness of quarantine and symptom monitoring, implemented via contact tracing, in controlling epidemics using an agent-based branching model. We examine the relationship between epidemic containment and the disease dynamics of symptoms and infectiousness for seven case study diseases with diverse natural histories including Ebola, Influenza A, and Severe Acute Respiratory Syndrome (SARS). We show that the comparative effectiveness of symptom monitoring and quarantine depends critically on the natural history of the infectious disease, its inherent transmissibility, and the intervention feasibility in the particular healthcare setting. The benefit of quarantine over symptom monitoring is generally maximized for fast-course diseases, but we show the conditions under which symptom monitoring alone can control certain outbreaks. This quantitative framework can guide policy-makers on how best to use non-pharmaceutical interventions and prioritize research during an outbreak of an emerging pathogen.
INTRODUCTION

The global burden of emerging infectious diseases is growing and prompts the need for effective containment policies (1–3). In many cases, strategies must be non-pharmaceutical, as targeted drugs or vaccines for the pathogens are unavailable. Among the various containment strategies, isolation of ill and potentially infectious patients is one of the most intuitive, relying on the tracing the contacts of known cases. Contacts with symptoms can then be hospitalized or isolated, but policy makers must also decide how best to handle contacts that do not meet the case definition for infection. Two strategies have historically been used in the instance of a potentially infected but symptom-free contact: quarantine and symptom monitoring.

Quarantine of potentially infected contacts during an epidemic is highly conservative with respect to efficacy, but it comes at a high cost. Costs associated with quarantine policies range from direct (e.g., implementation expenses and the restriction of personal liberties) to indirect (e.g., stigmatization of health workers and sometimes interruption of financial and trade markets) (4–8). A less conservative but substantially cheaper and more socially palatable approach is active symptom monitoring of contacts. In this strategy, health workers check on contacts one or two times a day and isolate them if symptoms occur (see definitions in Methods).

Given the importance of rapid decision making in the event of novel emerging pathogens, and the potentially devastating consequences of poor containment strategies, quantitative guidelines are urgently needed for deciding whether quarantine is, according to Gates et al., at worst "counterproductive" or at best "one of the few tactics that can reduce its spread" (9). Current guidance on the use of quarantine or symptom monitoring
is ad hoc, frequently distributed across several resources for a given disease (see Table S2.1 for a review of select diseases), and lack the generalizability required for rapid decision-making for novel pathogens and leading to confusion during implementation (10–12). During the Severe Acute Respiratory (SARS) epidemic, broad quarantine interventions were applied in Taiwan and subsequently abandoned (13). Furthermore, we are aware of no framework that considers the implementation setting as a factor for intervention choice or performance, despite its obvious importance. Indeed, the United States Centers for Disease Control and Prevention (CDC) implicitly recognized the value of implementation setting by differentiating its international response, where quarantine was performed (14), and its domestic response, where symptom monitoring was recommended (15, 16).

The success of these approaches is not simply a reflection of the efficiency of their implementation but crucially depend on the biology and natural history of the pathogen in question. Previous theoretical work by Fraser, et al. (17) summarized these dynamics into a measure of the proportion of infections by asymptomatic infection ($\theta$) and the basic reproductive number ($R_0$), defined as the average number of infections generated by an infectious individual in a fully susceptible population. Subsequent work has explored the interaction between disease characteristics [e.g., super-spreading (18)] and the performance of interventions [e.g., travel screening (19)], but the recent Ebola epidemic demonstrated that at least two large questions remain (7). Firstly, what is the role of symptom monitoring as an alternative to quarantine, and secondly, how does this choice depend on the characteristics of the disease, the setting, and their interactions?

Here we develop an agent-based branching model that accommodates realistic distributions of disease characteristics and maintain the infector-infectee correlation
structure necessary for interventions targeted via contact tracing. To assess diseases with a wide range of natural histories that have the potential for causing sudden, severe epidemics, we consider case studies of seven known pathogens: Ebola; hepatitis A; influenza A; Middle East respiratory syndrome (MERS); pertussis; SARS; and smallpox. We identify which disease characteristics and intervention attributes are most critical in deciding between quarantine and symptom monitoring, and provide a general framework for understanding the consequences of isolation policies during emerging epidemics.
RESULTS

*Intervention Effectiveness Depends on Disease Epidemiological Dynamics*

To assess the impact of quarantine and symptom monitoring, we developed a general mathematical model of disease transmission and interventions targeted via contact tracing (Figure 2.1). The model structure accommodates five key metrics of intervention performance in a given setting (Table 2.1). We used particle filtering to generate parameter sets consistent with seven case studies of outbreak-prone pathogens (see *Methods* and Table 2.2).
Figure 2.1. Schematic of the natural history of disease and the timing of interventions.

Beginning on the left with the infection event, one progress through a latent period ($T_{LAT}$) before becoming infectious for $d_{INF}$ days with late peak infectiousness $\tau_\beta$. For diseases A, B, and C, symptoms are respectively shown to emerge before, concurrent with, and after onset of infectiousness. We show here an individual who is traced shortly after infection and is placed under symptom monitoring or quarantine after a short delay $D_{CT}$. 
### Table 2.1. Intervention Parameters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Example Intervention Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optimal</td>
</tr>
<tr>
<td>Isolation Effectiveness</td>
<td>$\gamma$</td>
</tr>
<tr>
<td>Fraction of contacts traced</td>
<td>$P_{CT}$</td>
</tr>
<tr>
<td>Fraction of traced contacts who are truly infected</td>
<td>$P_{INF}$</td>
</tr>
<tr>
<td>Delay in tracing a named contact</td>
<td>$D_{CT}$</td>
</tr>
<tr>
<td>Delay from symptom onset to isolation</td>
<td>$D_{SM}$</td>
</tr>
<tr>
<td>Delay from symptom onset to health seeking behavior</td>
<td>$D_{HSB}$</td>
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Table 2.2. Disease parameters.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inputs from Published Estimates</th>
<th>Parameters fit via Sequential Monte-Carlo method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basic Reproductive Number $R_0$</td>
<td>Serial Interval (days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incubation Period $T_{INC}$ (days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latent period offset $T_{OFFSET} = T_{LAT} - T_{INC}$ (days)</td>
</tr>
<tr>
<td>Ebola</td>
<td>1.83 (20) [1.72, 1.94]</td>
<td>13.36 (20) [2.66, 38.8]</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>2.25 * [2, 2.5]</td>
<td>26.72 (21) [20.7, 33.8]</td>
</tr>
<tr>
<td>Influenza A</td>
<td>1.54 (23) [1.28, 1.80]</td>
<td>2.20 (21) [0.63, 3.76]</td>
</tr>
<tr>
<td>MERS</td>
<td>0.95 (25) [0.6, 1.3]</td>
<td>7.62 (26) [2.48, 23.3]</td>
</tr>
<tr>
<td>Pertussis</td>
<td>4.75 † [4.5, 5]</td>
<td>19.26 (27) [3.61, 57.2]</td>
</tr>
<tr>
<td>SARS</td>
<td>2.9 (29) [2.2, 3.6]</td>
<td>8.32 (29) [1.59, 19.2]</td>
</tr>
<tr>
<td>Smallpox</td>
<td>4.75 † [4.5, 5]</td>
<td>15.54 (30) [9.98, 24.2]</td>
</tr>
</tbody>
</table>

Median (Reference); [95% CI]

* Sequential Monte-Carlo boundary condition reached
† Assumed.
Unimpeded exponential epidemic growth in our branching model (red in Figure 2.2A) can be reduced by the increasingly conservative interventions of health-seeking behavior, symptom monitoring, and quarantine. Under a given intervention policy, we estimate the effective reproductive number \( R_0 \) as the average number of infections generated by an infectious individual in the population (Figure 2.2B).
Figure 2.2. Model dynamics and output for influenza A.

(A) Each line designates one model run initiated with 100 infectious individuals in generation 1 and submitted to either no intervention (red), health seeking behavior (teal), symptom monitoring every day (gold), or quarantine (blue) at generation 3. (B) Each point designates the simulated effective reproductive number from one model run with input reproductive number (x axis) between one and five. Loess curves are shown as heavier lines.
We find the effectiveness of symptom monitoring and quarantine in controlling a disease in a particular setting depends critically on its biological dynamics (e.g. latent and infectious periods) and transmissibility ($R_0$) (Figure 2.3A). Holding transmissibility constant ($R_0$ arbitrarily set to $2.75\pm0.25$), biological dynamics alone strongly influence the effectiveness of quarantine and especially symptom monitoring, as seen by the wide spread in $R_5$ (Figure 2.3B).
Figure 2.3. Infection control performance depends on disease biological dynamics and inherent transmissibility ($R_0$).

(A) The effective reproductive number under symptom monitoring (x-axis) and quarantine (y-axis) for 100 simulations of each disease when the basic reproductive number is set to published values [See Panel C, diamonds]. (B) As in (A), but the basic reproductive number ($R_0$) is set to for all diseases to 2.75 ($\pm$ 0.25). (C) Disease-specific mean basic reproductive number (diamond) and the mean effective reproductive numbers under symptom monitoring (triangle) and quarantine (circle). The length of the horizontal line therefore equals the absolute comparative effectiveness $R_S - R_Q$. 
In simulations with high intervention performance settings (Table 2.1), diseases such as MERS and Ebola could be controlled (i.e., \( R_e < 1 \)) with either quarantine or symptom monitoring; diseases such as hepatitis A with only quarantine; but diseases such as pertussis require additional interventions in order to reduce the effective reproductive number below one, due in large part to pre-symptomatic infectiousness (Figure 2.3C). Absolute comparative effectiveness \((R_s - R_Q)\) varies widely by disease, as demonstrated by the line length in Figure 2.3C. Relative comparative effectiveness \(\frac{R_s - R_Q}{R_s}\) also varies widely, with quarantine reducing \(R_s\) by over 65% for influenza A and hepatitis A and by less than 10% for pertussis (Figure S2.1). The reader can explore results from landscapes with different intervention performance settings and disease transmissibility in the interactive supplement (https://coreypeak.shinyapps.io/InteractiveQuarantine).

**Categorizing Disease Control Frontiers**

In order to compare the effectiveness of symptom monitoring and quarantine, one must select an appropriate metric to compare \(R_s\) and \(R_Q\). We therefore categorized intervention response heterogeneity into four control quadrants (Figure 2.3A). In quadrant I, where neither intervention is sufficient to prevent epidemic growth, the relative difference \(\frac{R_s - R_Q}{R_s}\) can distinguish whether quarantine is merited or could be paired with other strategies to achieve control. Because quarantine is by definition the more conservative intervention, simulation results in quadrant II occur only stochastically. In quadrant III, where both interventions are sufficient and the number of prevented cases can be more directly estimated, the distinguishing metric was the absolute difference
$R_s - R_Q$ and its inverse ($\frac{1}{R_s - R_Q}$), which can be interpreted as the number of contacts that must be quarantined in order to prevent one additional case over symptom monitoring (an analog of “number needed to treat”). In quadrant IV, where quarantine but not symptom monitoring can control the disease, quarantine would be strongly considered as the minimum sufficient strategy to prevent exponential epidemic growth.

The following two sections aim to identify which disease characteristics and intervention performance metrics most strongly influence these differences in response to quarantine and symptom monitoring.

**Ranking of epidemiological characteristics by importance for containment feasibility**

The comparative effectiveness of quarantine and symptom monitoring is strongly influenced by differences in the infection’s natural history. We measured partial rank correlation coefficients to examine which biological characteristics in particular are most influential after controlling for the other characteristics (*Methods*). As demonstrated by strongly negative partial rank correlation coefficients in Figure 2.4, increasing the duration of infectiousness ($d_{INF}$) and elongating the latent period offset ($T_{OFFSET}$) reduced the differences between quarantine and symptom monitoring, thereby making the interventions more similar. Other factors, such as overdispersed heterogeneity of the basic reproductive number ($\kappa$), did not influence the average effect of symptom monitoring and quarantine, as reflected by a coefficient of nearly zero. However, at a given effective reproductive number, overdispersion does decrease the average number of generations until extinction, as predicted (Figure S2.2) (18). Longer incubation periods ($T_{INC}$) increased the preference for quarantine, as seen by the positive partial rank correlation coefficient.
for both absolute and relative comparative effectiveness. However, the length of the incubation period does not generally influence comparative effectiveness per quarantine day because the number of days in quarantine ($d_Q$) increases as the incubation period lengthens (Figure S2.3).
Figure 2.4. Influence of disease characteristics and intervention performance metrics.

Partial rank correlation coefficients (x-axis) measuring the influence of disease characteristics and intervention performance metric (rows) on the absolute (red) and relative (green) comparative effectiveness of quarantine and symptom monitoring, pooled for all case study diseases. The 95% confidence intervals from 100 bootstrapped samples are represented by error bars.
Frequently, the most pressing concerns are whether control (i.e. $R_0 < 1$) is achievable and what would be the least invasive intervention to achieve control. Figure 2.5 shows frontiers where control of an Ebola-like disease requires increasingly invasive interventions, moving from health-seeking behavior, to symptom monitoring, to quarantine, the most invasive. Figure 2.5A shows how this frontier is influenced by the inherent transmissibility ($R_0$) and timing of the latent period relative to the incubation period ($T_{OFFSET}$), with all other characteristics similar to Ebola. When $R_0$ is large and symptoms emerge long after infectiousness (e.g., $T_{OFFSET} > 0$), even quarantine is insufficient to control the disease with optimal intervention performance. However, we observe that when transmissibility is relatively low (e.g., $R_0 < 2.5$), control of this hypothetical disease can be achieved even if infectiousness precedes symptoms by several days (Figure 2.5A) or if a substantial fraction of transmission events occur during presymptomatic or asymptomatic infection (adapting the framework of (17)) (Figure 2.5B).
Figure 2.5. Minimally invasive interventions sufficient to control a hypothetical disease.

(A) Points represent simulations where health-seeking behavior (teal), symptom monitoring (gold), or quarantine (blue) were the minimally sufficient intervention to bring $R_e$ below 1. Disease characteristics drawn from Ebola except symptoms are assumed to precede infectiousness by up to 10 days ($X = -10$ days) or emerge up to 10 days after infectiousness onset ($X = +10$ days). (B) As in (A), but the x-axis is transformed to represent the proportion of infections that occur prior to symptoms in a analogous way to Fraser, Riley, et al.(17)
Ranking of intervention performance metrics by importance for containment feasibility

Policy makers facing an epidemic must also consider the expected performance of interventions, since the effectiveness of targeted control policies will depend on their feasibility within a particular healthcare system. Generally, we found the benefit of quarantine over symptom monitoring increases with better intervention performance (i.e. larger fraction of contacts traced \( P_{CT} \), better isolation effectiveness \( \gamma \), and shorter delays in tracing a contact \( D_{CT} \) (Figure 2.4). However, the effectiveness of symptom monitoring approached that of quarantine when the delay between symptom onset and isolation \( D_{SM} \) is shortened, due either to more frequent symptom monitoring or more sensitive detection of symptoms followed by prompt isolation.

While these patterns were highly consistent across the case study diseases, some intervention performance metrics were particularly influential in the presence of certain disease characteristics. For example, diseases with short incubation periods \( T_{INC} \) such as influenza A were strongly influenced by delays in tracing a contact \( D_{CT} \) (Figure S2.3).
DISCUSSION

A key strategy to controlling the spread of infectious diseases focuses on tracing the contacts of infected individuals, with the goal of limiting subsequent spread should those contacts become infectious. Here, we compare the effectiveness of the two primary non-pharmaceutical interventions targeted via contact tracing: symptom monitoring and quarantine. We show that the interventions are not equivalent and that the choice of which intervention to implement to achieve optimal control depends on the natural history of the infectious disease, its inherent transmissibility, and the intervention feasibility in the particular healthcare setting.

Our results show that the benefit of quarantine over symptom monitoring is maximized for fast-course diseases (short duration of infectiousness and a short latent period compared to the incubation period), and in settings where isolation is highly effective, a large fraction of contacts are traced, or when there is a long delay between symptom onset and isolation. Our findings are consistent with Fraser, Riley, et al. (17) that both inherent transmissibility and the proportion of transmission from asymptotically infected individuals are key epidemiological parameters for the feasibility of control via quarantine.

In addition to identifying parameters that differentiate quarantine and symptom monitoring, our results also characterize parameter spaces where symptom monitoring, not just quarantine, is sufficient for containment of an emerging epidemic. Given the high costs and poor scalability of quarantine, symptom monitoring is likely to be a key intervention for future epidemic containment.
Our results support the retention of quarantine as a live-option for Ebola, SARS, MERS, smallpox, and influenza strains with pandemic potential, (12) but only if control is infeasible through symptom monitoring (i.e. $R_Q < 1 < R_s$). We find that the incremental benefit of quarantine over symptom monitoring is small for Ebola and SARS, but relatively large for smallpox, for which reemergence would instigate a maximum response, and influenza, for which short duration of infectiousness ($d_{INF} \approx 1\text{-}3 \text{ days}$) and some pre-symptomatic infectiousness ($T_{OFFSET} < 0$) render symptom monitoring a generally ineffective intervention – particularly in settings with slow contact tracing ($D_{CT} >> 0$) and symptom identification ($D_{SM} >> 0$). For pandemic influenza strains (which are expected to have higher $R_0$ than the seasonal influenza strains shown here) or if circumstances arise such that MERS transmissibility increases substantially, quarantine may be necessary to control these diseases (Figure 2.3B). In general, we find that a reduction in the fraction of contacts who are ultimately traced will decrease the preference for quarantine over symptom monitoring, therefore supporting the previous findings that quarantine was inefficient for a respiratory disease like SARS (31). Our results demonstrate that response recommendations must consider the healthcare setting of implementation as well as disease-specific nuances; therefore, decision tools that incorporate the context and epidemiology of an outbreak are likely to be more useful than one-size-fits-all guidelines.

Although our results focus on the early stages of an outbreak, contact tracing, symptom monitoring, and quarantine are often key tools for end-stage epidemic control and elimination. As the effective reproductive number decreases below one (e.g. via depletion of susceptible individuals, complementary interventions, seasonality, etc.), our results suggest the preference for quarantine also decreases (Figure 2.4). However, one
must consider aspects such as geographic containment, public compliance, and, if the availability of resources lags the epidemic curve, a possible resource-per-case surplus that may enable the more conservative and costly approach of quarantine.

Our results suggest that symptom monitoring could effectively control an outbreak of a new Ebola-like disease, even when infectiousness precedes symptoms and interventions are not perfectly implemented. Because perfect interventions are not always necessary, these results support the conclusion of Cetron et al. (32) that the optimal containment strategy may allow “partial or leaky quarantine” in order to increase the fraction of contacts who participate.

We propose that the most influential parameters should be prioritized for early characterization during an outbreak (33) and should be modeled with conservative consideration of parameter uncertainty, including both real diversity and measurement error. Our framework identifies the key infection-related parameters to define and can form the basis of cost-benefit analyses. Such data-driven decision-making will be critical to determining the optimal public health strategies for the inevitable next epidemic.
METHODS

Definitions

“Contact Tracing” is the process of identifying and assessing people who have been exposed to a disease (34, 35). Contacts who are symptomatic when traced are immediately placed in isolation; those who are not symptomatic are placed under either quarantine or symptom monitoring. Here, we model “forward” contact tracing whereby an infected individual names contacts they may have infected (34).

“Isolation” is the separation of a symptomatic individual believed to be infected (34). By reducing the number of risky contact events, isolation reduces disease transmission when infectiousness coincides at least partly with symptoms.

“Quarantine” is the separation of an individual who is believed to be exposed, but is currently not ill (34). If an individual becomes symptomatic, they will be isolated and receive healthcare.

“Symptom Monitoring” is the assessment of symptoms at regular intervals of an individual believed to be exposed, but not ill. If symptoms are detected, the individual is placed in isolation (34). Although they may be encouraged to avoid interpersonal contacts, an individual under symptom monitoring is not separated from others and therefore does not experience a reduction in risky contacts until symptoms are detected.

“Health Seeking Behavior” is the act of seeking healthcare during the presentation of symptoms, leading to isolation. Practically, this intervention could be a health education campaign that prompts individuals to self-identify illness and seek effective isolation. This intervention, which accelerates isolation in a manner separate from contract tracing, provides a comparative care standard for our analysis.
Model

Individuals in our branching model progress through a Susceptible-Exposed-Infectious-Recovered (SEIR) disease process. We focus our analysis on the early epidemic phase of an emerging infectious disease, assuming no substantial depletion of susceptibles within the first few generations of transmission.

Following infection, the number of days before onset of infectiousness and onset of symptoms are the latent period ($T_{LAT}$) and incubation period ($T_{INC}$), respectively (Figure 2.1). Because symptoms, pathogen concentration, and behavior of the patient can change throughout the course of disease (36), we allow relative infectiousness to vary with time $\tau$ since onset of infectiousness ($\beta_{\tau}$).

The recent SARS and Ebola epidemics highlighted that hospital isolation does not always contain transmission; we therefore allow isolation effectiveness ($\gamma$) to vary to reflect different settings (17, 37, 38). The fraction of contacts who are traced ($P_{CT}$) can be less than 1, encompassing symptomatic infectors who fail to recall contacts, asymptomatic “silent” infection events, reluctance to report contacts, and challenges in identifying contacts, especially for airborne transmission routes. Imperfections and uncertainties in risk profiling can reduce the fraction of traced contacts that are truly infected ($P_{INF}$) (16, 31). Delays in tracing a contact ($D_{CT}$) can arise for numerous reasons, including intractable roads, low mobile phone penetration, and personnel limitations. The delay between symptom onset and isolation ($D_{SM}$) specifically applies to individuals under symptom monitoring and is influenced by the frequency of monitoring, delays in recognizing sometimes unreliable clinical features, and delays in prompt isolation upon symptom detection.
Simulation

We draw disease characteristics for each simulated individual from disease-specific input distributions. During each hour $\tau$ of infectiousness, an individual infects a number of new individuals drawn from a Poisson distribution [or, if super-spreading factor $\kappa < 1$, a negative binomial distribution (18)](Figure S2.4 and Table S2.2) with mean equal to the product of the expected number of onward infections for the individual ($R_0$) and the relative infectiousness $\beta_\tau$ where $\sum_{\tau=1}^{d_{INF}} \beta_\tau = 1$ (Figure S2.5). We assume time-varying relative infectiousness follows a triangular distribution with time of peak infectiousness ($\tau_\beta$) occurring anywhere between the onset and end of infectiousness, inclusively.

We record both the day of transmission and the infector for each transmission event, and draw disease characteristics for each newly infected individual. An individual is identified by contact tracing with probability $P_{CT}$ at the earlier time of either when their infector is isolated or the time of the transmission event if infection occurs while the infector was isolated. After an operational lag time of $D_{CT}$ days, a contact is placed under quarantine, symptom monitoring or, if already symptomatic, isolation. An individual in isolation or quarantine has their infectiousness reduced by a factor $\gamma$ for the remainder of their disease. An individual under symptom monitoring is isolated $D_{SM}$ days after symptom onset. A full description of the model process can be found in SI Text.

Parameterization

As compared to characteristics related to the natural history of symptoms and illness, key aspects of the natural history of infectiousness tend to be harder to observe and measure (39). Therefore, we use a Sequential Monte Carlo particle filtering algorithm (40,
to create a joint probability space of the time offset between the latent period and incubation period ($T_{OFFSET} = T_{LAT} - T_{INC}$), time of peak infectiousness ($\tau_\beta$), and duration of infectiousness ($d_{INF}$). From an uninformative prior distribution of each parameter bounded by published observations, we simulate five infection generations of 500 initial individuals and record the simulated serial interval (i.e., the time between symptom onset in infector-infectee pairs). Parameter sets are resampled with importance weights determined by the degree to which the distribution of simulated serial intervals match published serial interval distributions, using the Kolmogorov-Smirnov test of the difference between cumulative distribution functions (Table 2.2 and Figure S2.6) (42, 43).

Holding the incubation period distribution constant, we fit an offset for the latent period ($T_{OFFSET}$) for several reasons, including consistency with CDC methods for disease characterization (28), the biological expectation of these timings both being linked to pathogen load, and to parsimoniously limit each characteristic to one interpretable parameter. For the duration of infectiousness ($d_{INF}$), we fit the upper bound of a uniform distribution with a lower bound of 1 day. To allow for variable infectiousness during this duration, we assume a triangular distribution of relative infectiousness $\beta_\tau$ and fit the time of peak infectiousness ($\tau_\beta$). A full description of the model parameterization can be found in the SI Text.

Analysis

Partial rank correlation coefficients are calculated to identify the most influential disease characteristics (e.g. duration of infectiousness) and intervention performance metrics (e.g. isolation effectiveness). To maximize coverage of the parameter space we
allowed fractional parameters \((γ, P_{CT}, P_{INF}, k)\) to range from 0 to 1, delays \((D_{CT}, D_{SM})\) to range from 0 to 7 days, \(R_0\) to range from 1 to 5, and the incubation period \((T_{INC})\) to be shrunk by up to 50% or stretched by up to 150%.

We draw 1,000 samples from the joint-parameter space from the particle filtering method and measure \(R_0, R_Q,\) and \(R_S\) for each disease. We compare the effectiveness of symptom monitoring and quarantine by the absolute difference \((R_S - R_Q)\) and the relative difference \(\frac{R_S - R_Q}{R_S}\). We calculate the number of days an infected individual was in quarantine but not yet infectious \((d_Q)\) as surrogate for the marginal cost of quarantine over symptom monitoring. As abstract surrogates for cost-effectiveness, we calculate the absolute difference per quarantine day \((R_S - R_Q)/d_Q\) and relative difference per quarantine day \(\frac{R_S - R_Q}{R_S}/d_Q\) and present these results in Figures S2.1 and S2.3. More concrete measures of cost-effectiveness would require economic and social considerations that are outside the scope of this paper.

When risk profiling is imperfect (i.e. \(P_{INF} < 1\)), uninfected individuals may be mistakenly traced as contacts and placed under symptom monitoring or quarantine. We assume that contacts who had suspected exposure but are not actually infected are followed for a length of time set up the 95th percentile incubation period \((T_{INC}^{95})\), at which point health authorities may conclude the contact was not infected after all. Values of \(P_{INF} < 1\) change the number of days in quarantine to \(d_{Q} = \left( d_Q + T_{INC}^{95} \left( \frac{1}{P_{INF}} - 1 \right) \right)\).
**SUPPLEMENTAL INFORMATION**

**Disease model.** The model simulates a branching network of infected individuals only. An individual $i$ is assigned characteristics sampled from distributions defined for each disease (Table S2.2). The incubation period ($T_{INC}$), i.e. the time from infection to symptom onset, is drawn from published distributions (Table 2.2). The duration of infectiousness ($d_{INF}$), time of peak infectiousness ($\tau_\beta$), and time offset between the ends of the latent and incubation periods ($T_{OFFSET}$) are drawn from the joint posterior distribution generated by the sequential Monte-Carlo (SMC) particle filtering method described in SI Text, Parameterization via SMC. For clarity, we describe the method for an individual $i$, but the following process is repeated for an initial population of 1,000 individuals who each initiate distinct trees.

The expected number of onward infections by individual $i$, $R_{0i}$, is distributed over each hour $\tau$ of disease $R_{\tau i} = \beta_{\tau i} R_{0i}$, where $\beta_{\tau i}$ is the relative infectiousness of individual $i$ on hour $\tau$ since the onset of infectiousness such that $\sum_{\tau=0}^{d_{INF}} \beta_{\tau i} = 1$ (Figure S2.5). For parsimony and ease of interpretation, we assume $\beta_{\tau i}$ follows a discretized triangle distribution with a peak value at time $\tau_{\beta i}$ drawn from the SMC posterior and rounded to the nearest hour. In other words, infectiousness is linearly increasing from 0 to the peak of $\beta_{\tau i}$ at time $\tau_{\beta i}$ and linearly decreasing from the peak to the end of the period of infectiousness. When $0 < \tau_{\beta i} \leq d_{INF}$, $\beta_{\tau i}$ is defined by a piecewise function according to whether $\tau$ is in the period before the peak of infection ($\tau \leq \tau_{\beta i}$) or $\tau$ is after the peak of infection:
$$\beta_{\tau_i} = \begin{cases} \frac{\tau}{\rho_i}, & \text{if } \tau \leq \tau_{\beta_i} \\ \frac{\omega_i(d_{INF_i} - \tau)}{\rho_i}, & \tau > \tau_{\beta_i} \end{cases}.$$ 

Infectiousness after the peak is scaled by $\omega_i$, which is the negative of the slope of the post-peak infectiousness line:

$$\omega_i = \frac{\tau_{\beta_i}}{d_{INF_i} - \tau_{\beta_i}}.$$ 

In order to normalize $\beta_{\tau_i}$ to sum to 1, each piecewise component is divided by $\rho_i$, which is defined as the sum of infectiousness before the peak, at the peak, and after the peak:

$$\rho_i = \left( \sum_{\tau=0}^{\tau_{\beta_i}} \tau \right) + \left( \omega_i \sum_{\tau=\tau_{\beta_i}+1}^{d_{INF_i}} (d_{INF_i} - \tau) \right).$$ 

Under the condition of linearly increasing infectiousness (peak infectiousness at $\tau_{\beta_i} = d_{INF_i}$), $\beta_{\tau_i}$ simplifies to:

$$\beta_{\tau_i} = \frac{\tau}{\sum_{\tau=0}^{d_{INF_i}} \tau}.$$ 

Under the condition of linearly decreasing infectiousness (peak infectiousness at $\tau_{\beta_i} = 0$), $\beta_{\tau_i}$ is defined by:

$$\beta_{\tau_i} = \frac{d_{INF_i} - \tau}{\sum_{\tau=0}^{d_{INF_i}} \tau}.$$
The total number of infections \((N_i)\) generated by individual \(i\) is drawn from a negative binomial distribution with mean equal to the total expected number of infections \((E(N_i) = R_{0i})\) generated by individual \(i\) and dispersion factor \(\kappa\). If \(\kappa = 1\), the negative binomial distribution reduces to a Poisson distribution with rate \(\lambda = R_{0i}\). If \(\kappa < 1\), the number of infections generated per case will be overdispersed to simulate super-spreading (Figure S5).

If individual \(i\) generates infections (i.e., \(N_i > 0\)), then each infection generated is assigned to a particular time \(\tau\) drawn from a random sample \(\tau \in \{0, 1, \ldots, d_{INF_i}\}\) that is weighted by \(R_{\tau_i}/R_{0i}\) so that hours of high infectiousness are more likely to have larger values of \(N_{\tau_i}\). Therefore, each individual \(i\) has a vector of \(\langle N_{0i}, N_{1i}, \ldots, N_{d_{INF_i}} \rangle\) of onward infections that occur during each hour \(\tau\) of their infectiousness.

A new individual \(j\) is generated for each onward infection \(N_{\tau_i} \geq 1\). Disease characteristics for individual \(j\) are drawn as above and are set to begin at the time of infection of individual \(j\).

Each individual \(j\) will be traced with probability \(P_{CT}\). If traced, individual \(j\) is placed under symptom monitoring or quarantine after an operational lag time of \(D_{CT}\) days. The lag time occurs after the earlier of: (1) isolation of individual \(i\) or (2) removal of individual \(i\) from the disease system upon recovery or death. We assume individuals granted access to the quarantine or isolation room will be logged and given the same attention as contacts traced through epidemiological interview and will therefore will begin monitoring or quarantine at the time of the infection control breach or transmission event.

Next we determine the time of isolation for individual \(j\). If time of symptom onset for individual \(j\) occurs before individual \(j\) is traced, individual \(j\) is immediately isolated.
Otherwise, time of isolation for individual \( j \) depends on whether symptom monitoring or quarantine is used. Under symptom monitoring, isolation of individual \( j \) occurs a delay \( D_{SM} \) days after symptom onset. Note that for contacts checked twice-daily, \( D_{SM} \sim \text{unif}(0, 0.5) \).

Upon isolation, the hourly expected number of onward infections is reduced to \( R_{tj} = (1 - \gamma)\beta_{tj} \tau_{0j} \) where \( \gamma \) is effectiveness of isolation with support \([0, 1]\). If individual \( j \) is under quarantine, then \( R_{tj} \) is reduced by \((1 - \gamma)\) beginning at the time individual \( j \) is traced.

**Parameterization via SMC.** We used the following method to generate parameter sets that are consistent with the published serial interval and incubation period distributions for each case study disease. The objective of this procedure is not explicitly parameter inference, for which raw data and disease-specific nuance is necessary, but rather a range of parameters to reflect the heterogeneity of each disease in a common framework. Data-informed incubation period and serial interval distributions were collected through a literature review. Sequential Monte-Carlo (also known as particle filtering) methods were used to estimate the joint distribution of three disease parameters \((T_{OFFSET}, d_{INF}, \text{and } \tau_{\beta})\) using knowledge of the incubation period and serial interval distributions.

Here we assume that the latent period for an individual ends some time \((T_{OFFSET})\) before \((T_{OFFSET} < 0)\) or after \((T_{OFFSET} > 0)\) the onset of symptoms. Therefore, \( T_{OFFSET} \) is a translation of the incubation period distribution. We assume a uniform distribution of duration of infectiousness from 1 day to \( d_{INF} \), by hour. We assume the distribution of relative infectiousness to follow a triangle distribution with a peak at time \( \tau_{\beta} \), which ranges
from 0 (indicating infectiousness is linearly decreasing) to 1 (indicating infectiousness is linearly increasing).

The steps are as follows:

i. Use the “lhs” package in R to create a Latin Hypercube sample of 1000 parameter sets \( \theta_1, \theta_2, \ldots, \theta_{1000} \) consisting of \( T_{OFFSET}, d_{INF} \), and \( \tau_\beta \), which are bounded by the range of the parameter values found in the literature (Table 2.2),

ii. Draw a parameter set \( \theta_l = \theta_1 \)

iii. Under parameter set \( \theta_l \), run the branching epidemic model beginning with 500 distinct infections under a situation with no interventions.

iv. Use the two-sample “ks.test” function in R to calculate the Kolmogorov-Smirnov (\( KS_i \)) test statistic comparing the empirical distribution of simulated serial intervals to the published serial interval distribution (Figure S2.6).

v. Repeat steps (iii-iv) for each parameter set \( \theta_l = \theta_2, \theta_3, \ldots, \theta_{1000} \).

vi. Set an adaptive threshold \( KS^* \) equal to 80% of the maximum \( KS_i \) among the 1000 parameter sets above.

vii. Create a set of 1000 \( \theta_{\text{candidate}} \) parameter sets by selecting a weighted sample with replacement from all parameter sets \( \theta_l \) with \( KS_l \leq KS^* \). Weights are proportional to \( \frac{1}{KS_i} \).

viii. Perturb each \( \theta_{\text{candidate}} \) by between 0% and 2% (uniformly) of the initial parameter value range.
ix. Repeat steps (ii)-(viii) until the median KS is within 10% of each of the previous two rounds.

It is widely known that generation intervals are difficult to observe in nature, but challenges also arise in measurements of generation intervals in simulations. For example, generation time distributions may change over the course of an epidemic due to depletion of the susceptible individuals. Our method of direct observation of simulated serial intervals is restricted to the exponential growth period of an epidemic, as produced by a branching model. However, the potential for the length of generation intervals to be underestimated near the peak of an epidemic can cause a downward bias in the published serial intervals upon which our parameterization methods are based. Therefore, this downward bias can result in a bias towards “faster” disease parameters (namely, a leftward bias in $T_{OFFSET}$, $d_{INF}$, and $\tau_\beta$). Such a bias would reduce the simulated effectiveness of all interventions considered in this chapter.
Table S2.1. Review of Currently Recommended Practice.

For each of contact tracing (CT), isolation (I), symptom monitoring (SM), and quarantine (Q), recommendations are color-coded as follows: recommended (green); conditional recommendation (yellow); explicitly not recommended (red); and position unidentified (grey).
Table S2.1 (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>CCDM (10)</th>
<th>CDC</th>
<th>WHO</th>
<th>Discussion</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola</td>
<td>CT</td>
<td>I</td>
<td>SM</td>
<td>Symptom monitoring is a powerful intervention for Ebola. The incremental benefit of quarantine is small for Ebola. Since quarantine is still the more conservative intervention, it should still be a live-option for a setting where control is possible with quarantine but not symptom monitoring (i.e., $R_Q &lt; 1 &lt; R_S$), or where compliance with symptom checks is low.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>CT</td>
<td>I</td>
<td>SM</td>
<td>With the availability of vaccines, our findings are not intended to influence Hepatitis A control approaches. Symptom monitoring would have little impact. Quaranite can be effective but very costly due to the challenge of identifying contacts (i.e., $P_CT$ and $P_INF &lt; 1$) and due to the long time individuals would need to be quarantined (i.e., $T_LAT$ and $d-INF$ are long).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pandemic or Novel Influenza A</td>
<td>CT</td>
<td>I</td>
<td>SM</td>
<td>Evidence of pre-symptomatic infectiousness ($T_OFFSET &lt; 0$) and short duration of infectiousness (short $d-INF$) render symptom monitoring ineffective. Forward contact tracing must be rapid (short $D_CT$ and $D_SM$) to keep up with this fast-course disease. Especially for pandemic influenza strains with higher $R_0$, quarantine of contacts should be retained as a possible intervention after careful consideration of the feasibility of control through other means.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERS</td>
<td>CT</td>
<td>I</td>
<td>SM</td>
<td>Our findings support established recommendations for symptom monitoring of contacts exposed to MERS, which has so far shown limited human-to-human transmissibility ($R_0 \sim 1$). If circumstances arise such that transmissibility increases substantially, reassessment of quarantine may be warranted due to the inability of symptom monitoring to achieve control.</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertussis</td>
<td>CT</td>
<td>I</td>
<td>SM</td>
<td>Due to the availability of vaccination and post-exposure prophylaxis, neither quarantine nor symptom monitoring are recommended for Pertussis. However, if either quarantine or symptom monitoring were to be considered under a particular circumstance, the latter is a similarly efficacious and more socially palatable choice.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS</td>
<td>CT</td>
<td>I</td>
<td>SM</td>
<td>Symptom monitoring is a powerful intervention for SARS. The incremental benefit of quarantine is small for SARS. If control can be achieved in a particular context through symptom monitoring and complementary interventions (e.g., social distancing, personal protective equipment, etc.), then control and extinction are likely without needing to resort to quarantine, especially considering the super spreading tendencies of SARS.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smallpox</td>
<td>CT</td>
<td>I</td>
<td>SM</td>
<td>There is a sizable incremental benefit of quarantine over symptom monitoring for smallpox. In the event of a suspected smallpox outbreak, quarantine, as opposed to symptom monitoring, may serve as a conservative intervention alongside post-exposure vaccination.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Q</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table S2.2. Confirmation of overdispersion parameterization.

The offspring distribution for each of 100,000 infectious individuals was recorded for three durations of infectiousness (1, 10, and 100 hours) as well as three levels of dispersion (1, 0.1, and 0.01). The input $R_0$ was set to 2 and individuals generated a mean of approximately 2 offspring per case in each simulation. As expected, the standard deviation in the number of offspring generated increased as the dispersion factor decreased (i.e., super-spreading increased), and within each level of dispersion (e.g., 1, 0.1, and 0.01), the standard deviation was approximately equal regardless of how many hours of infectiousness an infector had.

<table>
<thead>
<tr>
<th>$d_{INF}$ (hours)</th>
<th>Hourly $R_0$</th>
<th>Dispersion Factor “k”</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
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<td>2</td>
<td>1</td>
<td>2.00</td>
<td>1.42</td>
</tr>
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<td>0.2</td>
<td>1</td>
<td>2.00</td>
<td>1.41</td>
</tr>
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<td>2.00</td>
<td>1.41</td>
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<tr>
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<td>0.1</td>
<td>2.01</td>
<td>4.47</td>
</tr>
<tr>
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<td>0.02</td>
<td>0.1</td>
<td>1.96</td>
<td>4.43</td>
</tr>
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<td>2</td>
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<td>2.03</td>
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<td>0.01</td>
<td>2.07</td>
<td>13.72</td>
</tr>
</tbody>
</table>
**Figure S2.1. Relative comparative effectiveness and cost-effectiveness.**

The relative comparative effectiveness varies widely by disease, with quarantine reducing $R_S$ by >65% for influenza A and hepatitis A and by <10% for pertussis. However, due to a much shorter incubation period of influenza A versus hepatitis A (Table 2.2), the relative cost-effectiveness measured by the reduction per day of quarantine (outlined bars) is substantially higher for influenza A than hepatitis A.
Figure S2.2. Number of generations until extinction decreases in the presence of overdispersion.

As the dispersion factor (k) decreases (i.e., creating more super-spreading), the average number of generations (red square) before extinction of a single infectious case with an $R_0$ of 0.75 is 1.43 for $k=1$, 0.26 for $k=0.1$, and 0.036 for $k=0.01$. Each point indicates the number of generations (y axis, jittered for visibility) until a transmission tree initiated by a single case is contained. 95% confidence intervals shown in brackets.
Figure S2.3. Partial rank correlation coefficients for all outcomes.

Partial rank correlation coefficients (x-axis) measuring the influence of disease characteristics and intervention performance metrics (rows) on the impact, comparative effectiveness, and comparative cost-effectiveness of the interventions under study. Disease-specific estimates are shown with colored bars and pooled estimates with larger grey bars. For example, increasing the delay in tracing a named contact DCT has a generally small effect negative effect on RS-RQ when pooled across diseases (large grey bar), but for influenza A specifically (purple bar), DCT has a rather large negative effect on RS-RQ. Note that pooled estimates for comparative cost-effectiveness are not available due to non-monotonic relationships across diseases.
Figure S2.4. Demonstration of overdispersion parameter (k).

In a system with 100,000 agents, as the dispersion parameter (k) decreases (i.e., creating more super-spreading), the variance of the number of infections generated by each infectious individual increases while the mean is approximately constant at the input value of 2.
Key time points in the distribution of infectiousness include the peak ($\tau_\beta$) and duration ($d_{INF}$) of infectiousness.
Figure S2.6. Demonstration of the Kolmogorov-Smirnov distance for SMC paramterization method.

The parameter set in Panel A generates serial intervals (bars, blue line) that are poorly explained by the reference serial interval distribution (green line), generating a KS score of 0.25. A later iteration of the SMC algorithm generated parameter set (B) in which the generated serial intervals are more consistent with the reference serial interval (same green line).
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CHAPTER 3

Measuring the Impact of Travel Restrictions during Emergencies using Mobile Phone Data: Lessons from Ebola

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Andrew Tatem 2,4
Erik Wetter 2,5
Xin Lu 2,6
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Elaine Weidman-Grunewald 7
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ABSTRACT

Regional travel restrictions such as quarantines are principal strategies to contain emerging infectious diseases such as Ebola, but their actual impact on human mobility is difficult to measure using traditional methods. However, new “big data” approaches using mobile phone data can in theory provide exactly this type of information in near real-time. Here, we use mobile phone data from Sierra Leone to demonstrate that travel restrictions had an enormous and easily measurable impact on human travel during the 2014-5 Ebola epidemic. We find substantial differences in effect size across the country and, subsequently, travel returned to normal levels once restrictions were lifted. We conclude that the effects of travel restrictions can be large, targeted, reversible, and measurable in near real-time. With appropriate anonymization protocols, mobile phone data should play a central role in guiding and monitoring interventions for epidemic containment.
MAIN TEXT

Travel restrictions are principle strategies for containing the spatial spread of emerging epidemics, and are particularly important in the highly connected world of the 21st century. Indeed, population mobility was one of the main reasons why the scale of the 2014-2015 West African Ebola epidemic dwarfed all previous Ebola epidemics; the virus was able to quickly disperse throughout the region, outstrip containment efforts, and rapidly reach areas capable of sustaining transmission. In an effort to control and eliminate Ebola from Sierra Leone, a strict set of travel restrictions were instituted, including international border closures, district quarantines, and national "Stay at Home" lockdowns (Figure 3.1A). At the time, travel restrictions were strongly criticized by the international medical community as reactionary, draconian, and even counter-productive (1, 2). In order to understand either the desired effects of these interventions on Ebola transmission, or the extent of possible side effects, we must first measure their impact on travel.
Figure 3.1. Mobile phone data reveal travel anomalies during the elimination phase of Ebola in Sierra Leone.

(A) The timespan of mobile phone data (green) include: the late stage of the national epidemic curve (bars); Operation Northern Push (blue); and one of the two national lockdowns (red). (B) The daily number of trips between Freetown and Magbema, the largest chiefdom in the northern district of Kambia, reveal significant negative anomalies during the 2015 national lockdown and suggest a downward trend during Operation Northern Push. (C) The daily number of positive (grey) and negative (black) anomalies detected amongst all chiefdom pairs with at least 1,000 cumulative trips. Full details are provided in the SM. (D) District heterogeneity in the reduction of travel during the national lockdown as compared to a control period. Each dot represents 25 total Ebola cases, the dashed border outlines Magbema chiefdom, and the black borders outline the districts targeted during Operation Northern Push. Districts containing the largest cities (circles) and the capital (star) experienced the largest response to the lockdown.
Figure 3.1. (Continued)
Although policies at a national-scale are fundamental for containment, the impact of travel restrictions on individual behaviors have until recently been very challenging to measure, with most analyses focusing on changes to passenger volumes during international air traffic restrictions (3). Furthermore, during an emergency, evaluation of travel restrictions would ideally take place in near real-time in order to assess whether they are reducing travel. New “big data” approaches to measuring mobility patterns using mobile phone call detail records (CDRs) can in theory provide exactly this type of information, and repeated requests by the international community to release CDRs during the outbreak highlight their potential for monitoring travel patterns during an emergency (4, 5).

We conducted a retrospective analysis of CDRs from over 1.6 million subscribers of a leading mobile operator in Sierra Leone between March 20th and July 1st in 2015, during which several travel restriction policies were implemented in an effort to eliminate Ebola. We show that these travel restrictions in Sierra Leone had a significant, measurable impact on travel patterns and we reveal regional heterogeneity in the size of the impact. This Policy Forum demonstrates that CDRs are an important source of near real-time information about how travel patterns change during an epidemic, and what impact national quarantine and travel policies have on journeys of different distances.

Lessons from Ebola in Sierra Leone

In total, the 2014-2015 epidemic of Ebola virus disease led to 28,610 documented cases in West Africa, nearly half of which occurred in just Sierra Leone (14,122 cases) (http://apps.who.int/ebola/ebola-situation-reports). In May 2014, the virus was brought
across the porous border with Guinea into Sierra Leone by attendants of a burial and quickly spread throughout the country’s Eastern region. By September 1st, cases were identified in the capital city, Freetown, and 59 of the 149 chiefdoms (6), the administrative unit below the thirteen districts and four regions. To contain the epidemic spread, the government and military enforced travel restrictions that included a national “Stay at Home” lockdown from September 19-21 and quarantines targeted in areas of high transmission amidst the highly heterogeneous landscape.

The epidemic peaked in December 2014 and by March 2015 the country launched the “Zero Ebola Campaign” to achieve elimination. To initiate this campaign, the Government of Sierra Leone organized a second national lockdown from 06:00 on Friday, March 27, until 18:00 on Sunday, March 29, 2015 (Figure 3.1A) (7). During this 60-hour intervention, individuals throughout the country were instructed to “Stay at Home” while approved health workers performed home visits and active case finding, eventually discovering ten previously undocumented Ebola cases (8). An 80% decrease in the number of clinic walk-ins was recorded in the capital, Freetown, but this observation is reportedly due to an increase in ambulance activity and remains to our knowledge the only measurement of changes to mobility during the lockdown (8).

We analyzed CDRs for each subscriber to locate their principle chiefdom location on each day they placed or received at least one phone call. For each possible chiefdom pair (A, B), we generated a time-series of the daily number of individuals who relocate from chiefdom A to chiefdom B (Figure 3.1B). Using an anomaly detection algorithm for time-series data (https://github.com/twitter/AnomalyDetection), we observed large, consistent dips in travel between chiefdoms in Sierra Leone during the 2015 national lockdown.
(Figure 3.1C). This simple, non-parametric method can be used for real-time monitoring of travel restriction interventions and population displacement. All our analyses were robust to alternative definitions of “trips”, minimum travel distance, and excluding travel involving the capital city, Freetown (see Supplementary Materials (SM)).

To measure the size of the lockdown effect, we conducted crossover and time-series analyses. First, we compared the travel behavior for individuals during the national lockdown to their “control” behavior during the preceding and following weekends (SM). During the lockdown, we recorded a 53% decrease in the proportion of subscribers who were mobile (i.e., placed/received calls at ≥2 towers at least 10km apart) and a 66% decrease in the mean distance traveled by those users. We found this effect to be particularly pronounced in highly populated chiefdoms (Figure 3.1D) (Spearman’s rho = 0.31, P < 0.01). This effect can be quantified in near real-time with only one week of pre-intervention data.

To control for confounding factors like Ebola burden, we conducted a time-series analysis using the common family of ARIMA models (SM). This method again showed a substantial decrease in travel during the lockdown, especially for long-distance trips. We measure a 31.2% decrease in trips of up to 15 kilometers, a 46.0% decrease in trips of 15-30 km, and a remarkable 76.2% decrease in trips over 30 km. Importantly, we measured no increase in travel during the days immediately following the lockdown, which suggests that individuals did not compensate for the lockdown by increasing travel later.

Community participation in the national lockdown appeared to be higher in populations that experienced higher Ebola burdens. Specifically, we measured a 28.7% boost in intervention effect size for each additional 100 Ebola cases reported in either
chiefdom (per 100,000 population). This effect modification could be due to differences such as intervention compliance, advertising, or enforcement. This finding supports the feasibility of implementing a strategy that is simultaneously national in scope while also maximizing the benefits in affected regions and minimizing the collateral costs in low-burden regions.

In addition to the national lockdown, another key intervention for Ebola elimination was Operational Northern Push, during which two northern districts of Sierra Leone with relatively high recent incidence were targeted with a range of interventions, including a 12-hour curfew from beginning at 18:00 each night (9). Using the same time-series model as before, we detect a decrease in travel into targeted chiefdoms (-6.0%, \( P < 0.01 \)) but no change in travel out of targeted chiefdoms \( P > 0.05 \). These results importantly demonstrate the potentially asymmetric nature of travel restrictions and the ability for CDRs to distinguish a decrease in travel into the target zone from the routine outward flow of individuals.

The spatial resolution of our data is limited by the density of cell towers, which is sparse in some regions of Sierra Leone but closely matches population densities (Figure S3.1). While socioeconomic status may be related to phone use (10) and disease burden (11), we have not seen evidence indicating differences in travel behavior to an extent that would change the overall results.

Policy Implications

These findings provide strong evidence that CDRs can be a valuable source of information about the impact of travel restriction policies during an emergency. It also
highlights that lockdowns in Sierra Leone strongly reduced travel, despite controversy.

CDRs are routinely collected and provide an ideal source of near real-time data on human mobility during an emergency. However, strong regulatory guidelines that protect individual privacy must be considered. The ethics and logistics of how mobile phone operators should provide access to these data, and to whom, are vital conversations for the international community to engage in before we face new pandemics, such as unprecedented and hyper-local travel advisories in response to Zika (12).
SUPPLEMENTAL INFORMATION

Materials and Methods

1. Data and sources

1.1 Ebola Cases

Daily Ebola suspected, confirmed, and total cases between May 2014 and September 2015 were compiled and made publicly available by Fang et al (6). Our primary results depend on confirmed cases, defined according to the diagnostic criteria developed by WHO (13).

1.2 Call Detail Records (CDR)

Anonymous Call Detail Records (CDRs) from a leading mobile operator in Sierra Leone from March 20th to July 1st, 2015 were made available in partnership with Ericsson. All identifiers were removed and subscribers were given a study-specific hashed ID that was not provided to the analysis team. Data included the timestamp of each call event and the managing tower number. A separate file with the Latitude and Longitude of each tower ID was provided by Ericsson. Tower placement closely follows population density (Figure S3.1).

CDRs have been used before to study mass human movements (14, 15), disease dynamics (16–18), and more. For this class of data, the spatial resolution is limited by the tower density and other factors such as terrain. The range of the towers were estimated at 10km. During surge activity or when a tower is offline, nearby towers may manage a call. These events are not recorded in our data and are a source of noise that is not expected to be informative or produce a bias in a known direction.
A single mobile phone tower typically has three cells, each covering a span of 120-degrees. For ten of these tower panel groups, the Cell ID was shared between the 3g tower network and the 2g tower network and located in different chiefdoms. The available data structure does not allow for discrimination for which tower managed the call. To err on the side of under-estimating mobility, we therefore assumed the call was managed at the tower that minimized the distance to the next tower. We additionally repeated analysis dropping all events from towers without precisely known locations and found the results were stable.

1.3 Travel Restrictions

A list of travel restrictions deployed between May 2014 and September 2015 was identified by searching academic literature, news media outlets, reliefweb (www.reliefweb.int/disaster/ep-2014-000041-gin), WHO situation reports (www.who.int/csr/disease/ebola/en), National Ebola Response Centre (NERC) reports (www.nerc.sl), and reviewing collated resources such as (http://goo.gl/zplmSy). The principle travel restrictions studied here are the 2015 national lockdown and Operation Northern Push.

The 2015 national lockdown began at 06:00 on March 27 and ended at 18:00 on March 29, with minimal breaks such as for Friday prayers and Palm Sunday church service. Essential workers were exempted, including health workers, staff involved in the Zero Ebola Campaign, fuel station workers, and others (7). All other individuals were asked to stay at home, even those living in districts with no recent transmission (19). While security personnel were directed to insist on ID cards for essential workers, the NERC stated the
following regarding enforcement: “It is expected that Sierra Leoneons will do the right thing and voluntarily stay at home during 27th to 29th March” (19).

Operation Northern Push began on June 16 2015 with a suite of interventions targeted at the two northern districts of Port Loko and Kambia, where the recent Ebola burden remained high (9). During Phase 1, curfews were instituted from 18:00 to 6:00 each day.

2. Anomaly Detection

2.1 Time Series Data Structure

Time series are very powerful longitudinal data formats and typically comprise of counts recorded at equally spaced points in time. In order to reduce the dimensionality of mobile phone CDRs, we define the location of each unique subscriber as the chiefdom containing the towers that managed the majority of calls by that subscriber on that day. Ties were given to the chiefdom of the first call. Each subscriber therefore has a sequence of locations, with possible gaps on each day when that subscriber had no calling events recorded. Our primary analysis only considers trips as the change in a subscriber’s assigned location on day $t$ and $t+1$. Secondary analyses allow the subscriber’s location to carry forward up to three days.

We aggregated the number of anonymous subscribers relocating from chiefdom $A$ on day $t$ to $B$ on day $t+1$ as the number of trips between these locations on day $t$. Thus, each directional chiefdom pair has a number of trips on each day from March 20th to June 30th, 2015. These data are commonly referred to as panel data, where each directional chiefdom pair is a panel (Figure S3.2).
2.2 Method

We used the open-source R package AnomalyDetection (https://github.com/twitter/AnomalyDetection). The algorithm underlying this package builds upon a generalized Extreme Studentized Deviate (ESD) many-outlier procedure (20). Seasonality and long-term trends are decomposed, allowing for detection of positive and negative deviants of statistically significant magnitude. We applied this algorithm to each directional chiefdom pair (“panel”) and recorded the date and direction of each anomaly detected.

3. Crossover Window Analysis

3.1 Data structure

Three time windows were selected to represent the exposure period (weekend 06:00 March 27 to 18:00 March 29), a control window the preceding weekend (06:00 March 20 to 18:00 March 22), and a control window the following weekend (06:00 April 3 to 18:00 April 5). We recorded the sequence of towers visited by each subscriber that appears in any of the three time windows.

3.2 Method

3.2.1 Distance Measurements

Subscribers were labeled “stationary” if all towers used by that subscriber were within a 10 kilometer (km) radius of the first tower. This distance was reduced to 3 km and 0 km for sensitivity analysis. As expected, the number of individuals labeled “mobile”
increases as the minimum distance decreases, but the intervention effect remains stable (see Section 6.2).

The primary metric used to measure distance traveled by non-stationary individuals is the sum of inter-tower distances. Thereby, individuals who place all their calls from the same tower will register a distance of zero, and if placing calls at a sequence of towers \{A, B, C, A, D\}, their distance traveled is the sum of distance A-B, B-C, C-A, and A-D. The distance between tower geolocations was calculated in kilometers using ArcGIS (World Geographic Survey 1984 projection).

To account for overlapping coverage, we repeated this measurement after setting equal to zero any inter-tower distances of less than a certain distance. We tested threshold distances of 0, 3, and 10 km. The most conservative of these choices to underestimate travel, 10 km, was chosen for the main results.

We present results below using a second metric for distance, the convex hull area (see Sections 6.1 and 6.3). This calculation was performed using the sp package in R and functionally measures the area of a polygon that encloses the locations of all towers used by that individual (imagine a rubber band stretched around each tower) \(21, 22\). To convert to square kilometers, each unit of longitude and latitude at this location is approximately 110km. Therefore, a square spanning one unit of latitude and one unit of longitude represents approximately \((110\text{km})^2= 12,100\text{ square-km}\)

3.2.2 Down-sampling Methods

The number of calls placed during the lockdown was 22-26% lower than during the control windows (see Section 6.3). Therefore, we down-sampled the control window call
activity to address whether the differences in stationarity during the intervention was due to reduced call activity. During the control window preceding the intervention (i.e. March 20-22), 6,882,636 calling events were observed, which is 22.4% lower than the 5,343,388 events during the intervention window. During the second control window (i.e., April 3-5), 7,221,813 calling events were observed, which is 26.0% lower (1 - 5343388/7221813). Therefore, each calling event in control window preceding and following the intervention had a probability of remaining equal to 77.6% and 74.0%, respectively.

3.2.3 Pairwise Analysis Methods

As these data are paired by subscriber, we used McNemar's test of whether there is an overall increase or decrease in stationarity between the control and exposure windows. Because distance metrics are continuous, we used the paired t-test of means to test if the mean distance traveled differed between control and exposure windows (see Section 6.5).

4 Time Series Analysis

4.1 Time-series data structure

Using the data format described above (Section 2.1), we adapted the time series panel data structure for R developed by Christopher Adolph (23). For each directional chiefdom pair (“panel”), we used the lagpanel function of the simcf R package to generate lagged and differenced time series necessary to assess stationarity (24).

4.2 Method

4.2.1 Model Structure
To quantify the magnitude of the impact of travel restrictions, we fit an Autoregressive Integrated Moving-Average (ARIMA) model. Because we have a stationary time series (see Section 4.2.2), our model reduces to an ARMA process and allows us to directly estimate the number of trips between chiefdom pairs on each day, instead of the first or second differences that are sometimes needed to establish stationarity. When used to assess the impact of a brief intervention, such methods are commonly referred to as “Intervention Analysis” (25). Following the framework of ref (26), the time series $Y_{(i,j),t}$ of trips from chiefdom $i$ to chiefdom $j$ on day $t$ is given by

$$\log Y_{(i,j),t} = N_{(i,j),t} + m_{(i,j),t} + \varepsilon_{(i,j)}$$

where $N_{(i,j),t}$ is modeled as some ARMA process for chiefdom pair $(i,j)$ were there no intervention (see Section 4.2.2), $m_{(i,j),t}$ is the change in the expected number of trips for pair $(i,j)$ on day $t$ by an exogenous intervention (Table S3.1), and $\varepsilon_{(i,j)} \sim N(0, \sigma^2)$ is a random intercept for each chiefdom pair.

### 4.2.2 ARIMA Parameters $(p,d,q)$

The flexible family of ARIMA models allows for periodicity as well as long-term trends (i.e., non-stationarity). The parameters of an ARIMA model are typically defined as $(p,d,q)$, where $p$ is the order of autoregression, $d$ is the number of differences needed to achieve stationarity, and $q$ is the order of moving average terms (26).

We used the `auto.arima` R function in the R package `forecast` to identify a range of $(p,d,q)$ parameters to consider for the $N_{l,t}$ function (see Section 4.2.1) (27). We found that the maximum likelihood set of $(p,d,q)$ for each panel was $\leq 2$ for $p$ and $q$ and $\leq 1$ for $d$ in 94.6% of chiefdom pairs. Next we calculated for each panel the AIC of each combination
\((p,d,q)\) in this range. Calculating the mean AIC across panels, we found very poor support for \(d>0\), therefore confirming visual inspections that the time series are stationary within the 100 days of data available. The highest level of support was found for \((p,d,q)\) equal to \((1,0,2)\), \((1,0,1)\), and \((2,0,2)\). The parameters \((p=1,d=0,q=2)\) were used to generate the main results and we repeated our analyses with each other combination of \(p\) and \(q\) between 0 and 2 (see Section 7.5).

4.2.3 Model Construction in R

Once the data are in structure described above (see Supplemental Methods section 4.1), we can fit each model using the \(lme\) function of the \textit{nlme} R package \((28)\). We define our outcome as the log-transformed count of trips. We define fixed effects for each variable described above (Section 4.2.1), including effect modification terms. We define random intercepts for each directional chiefdom pair to implicitly account for different degrees of average traffic between two chiefdoms without explicitly needing to generate a gravity model or lose degrees of freedom estimating a fixed effect for each pair. We defined the order of autoregression \((p)\) and moving averages \((q)\) using the \textit{corARMA} function, also in the \textit{nlme} R package.

Supplementary Results

5 Anomaly Detection

5.1 Impact of minimum trips required

Our primary results restrict the anomaly detection analysis to chiefdom pair travel edges with at least 1,000 cumulative trips. Figure S3.3 illustrates that very similar results
were generated by reducing this restriction to only 100 cumulative trips (i.e., approximately 1 per day). The number of chiefdom pair travel edges with at least 100 cumulative trips is 1,234, which is over twice as many as edges with at least 1,000 trips (523).

### 5.2 Impact of excluding the capital and largest city, Freetown

Figure S3.4 shows how our results are qualitatively unchanged when all travel edges beginning or ending in the Western Area (which includes Freetown) are removed. In this analysis, 436 pairs remain.

### 5.3 Impact of Lockdown on subsequent anomaly detection

To ensure that the lockdown anomalies did not substantially affect the latter number of anomalies observed, we repeated the analysis beginning March 30, 2015 (Figure S3.5). We find very few anomalies are detected relative to the 523 pairs assessed.

### 6. Crossover Window Analysis

#### 6.1 Main Results

In our primary analysis, we measured the number of users who placed all calls within a 10 km radius during a control or intervention window. Only users with at least 2 calls placed in each window were eligible, because stationarity is impossible to assess using only one calling event.

We show that the fraction of subscribers who are stationary during the intervention window is significantly higher than during the control windows (Table S3.2). Furthermore, the mean distance traveled, measured by either the total inter-tower distance or the convex

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hull area (see section 3.2.1), showed between 3-fold and 11-fold differences between the intervention and control windows.

6.2 Impact of minimum detected travel distance

To assess the sensitivity of our results to the choice of a 10 km buffer around towers, we repeated our analysis using a 3 km buffer and again with no buffer. The results are qualitatively similar, with the 10 km buffer generating the most conservative odds ratio (OR) estimates, which we expect because small travel distances are unobserved and therefore any changes in them due to the intervention are also unobserved (Table S3.3).

6.3 Impact of down-sampling number of calling events

The number of calling events was significantly lower during the lockdown. In order to assess if the change in stationarity was a result of decreased calling activity, we down-sampled calls during the control periods to match the number of calls during the intervention. The results were essentially preserved (Table S3.4), and again when the number of calls during control periods were down-sampled 50% further and yielded similar results (not shown).

6.4 Impact of minimum number of calling events

In order to document changes in location within the intervention or control windows, subscribers must record at least two calling events. In order to test the sensitivity of our results to the cutoff of ≥2 events, we show that the findings are similar when the restriction increases to at least 5, or 10, events (Table S3.5).

6.5 Paired Tests of individual changes in travel
6.5.1 McNemar’s test of changes in stationarity

Our main results show a large increase in the proportion of subscribers who are stationarity during the intervention window as compared to the control windows. Using the user identification number, we can track individual users who are present in at least two windows. Table S3.6 shows the number of users who were stationary in the control period before the intervention but mobile during the intervention (green square, upper right quadrant) or mobile during the control period before the intervention and mobile during the intervention (green square, lower right quadrant). The ratio of these “discordant” pairs are used to generate the McNemar Odds Ratio and test for statistical differences between the two time windows (Table S3.7).

Under the null hypothesis of no intervention effect, we would expect that the count of discordant pairs in each direction to approximately balance. Comparing our two control windows, we find an odds ratio of 0.94, which is near the null value of 1, but due to very large sample sizes, still significantly different (Table S3.7). The intervention period showed a substantial and consistent decrease in mobility as compared to each of the control periods (0.212 and 0.213).

6.5.2 Paired t-test of changes in distance traveled

The distance traveled by individuals was significantly lower during the intervention period as compared to the control periods. Using the primary metric of sum inter-tower distance, we estimate a mean 9.15 km and 9.16 km decrease during the intervention as compared to the control periods before and after, respectively (Table S3.8). If we restrict our analysis to individuals who were mobile during one or both windows, the difference increases by two- to five-fold.
Using the alternative metric of convex-hull area, we find qualitatively similar results. The distance traveled by individuals was again significantly lower during the intervention period as compared to the control periods (Table S3.9). We estimate a nearly 60 square km decrease in convex-hull area during the intervention as compared to the control periods. This difference again grows 3- to 5-fold when we restrict our analysis to only those subscribers who were mobile in one or both windows.

### 6.6 Effect Modification by Chiefdom Population Size

We used Spearman rank correlation tests to non-parametrically assess a possible association between the percent reductions in distance traveled during the intervention windows as compared to the control windows. We measured a significant, positive coefficient comparing the size of the impact to the log-transformed chiefdom population size in the home location given to each subscriber based on their most-used tower (Figure S3.6). Nearly identical results were observed when comparing the intervention window to the control window on the following weekend (Spearman's rho = 0.30 [95% CI: 0.09, 0.49]).

Freetown, the capital and largest city, is more than twice as populous as the next biggest chiefdoms. We repeated our analyses after removing this outlier and found the positive correlation was reduced, but still significant for both the pre- and post- control windows (Spearman's rho = 0.24 [0.02, 0.44] and 0.23 [0.02, 0.43], respectively).

### 7. Time Series Analysis

#### 7.1 Main Results
Our primary mixed-effects time series model utilizes an ARMA correlation structure of \((1,2)\). Table S3.10 shows the results of this model, which are robust to changes in ARMA correlation structure and other changes in the following sections. Travel decreased by 26.9% for trips less than 15km and more strongly for longer trips. Incidence is measured as the cumulative number of cases in the source and destination chiefdoms divided by the total population in those chiefdoms. It is shown to be an independent predictor of lower travel \((p=0.0081)\) and an important effect modifier of the lockdown magnitude. Similar patterns were observed for longer distances. During the three days following the lockdown ("Lockdown Control A") and during the weekend following the lockdown ("Lockdown Control B"), we measure no increase in travel to compensate for the lockdown, but instead a slight 3-5% decrease in travel \((P < 0.05)\).

7.2 Exclude Freetown

With its large population size, key economic and political role, and high density of towers, Freetown is expected to strongly influence the observed travel patterns. Table S3.11 presents results excluding all trips originating from, or leading to, Freetown to demonstrate the robustness of our results.

7.3 Alternative definition of trips

Our primary results define trips as the change in location for an individual from day \(t-1\) to day \(t\). We relaxed this assumption to allow individuals to carry-forward their location such that an individual who had no recorded phone activity on day \(t-1\) can record a trip on
day \( t \) if they had a different location on day \( t-2 \) (Table S3.12). We similarly repeated this where trips can occur between day \( t-3 \) and \( t \).

### 7.4 Alternative ARIMA parameters

Our primary results utilize a correlation structure according to an ARIMA(1,0,2) model, but parameters (1,0,1) received similarly strong support across panels and generated similar results (Table S3.13).
**Figure S3.1. Distribution of population densities and Airtel towers in Sierra Leone.**

Thick borders denote districts and thin borderlines demarcate chiefdoms. Due to the resolution of Ebola case data, Western Area Urban is counted as one chiefdom (including the capital, Freetown), and Western Area Rural as another.
Figure S3.2. Panel data for all trips from the two largest cities, Freetown (Top) and Bo (Bottom).

Each line represents the log-transformed number of subscribers relocating to that destination chiefdom throughout time. The large decrease in travel corresponds to the March 27-29 lockdown. Note that chiefdoms between 1000-1999 are in the Eastern Region, 2000-2999 in the Northern Region, 3000-3999 in the Southern Region, and 4000-4999 in the Western Region.
Figure S3.3. Travel anomalies detected when minimum trip count is reduced from 1,000 (Figure 3.1C, main text) to 100.
Figure S3.4. Travel anomalies detected after excluding Freetown.
Figure S3.5. Using only data after the lockdowns, the number of travel anomalies remains small.
Figure S3.6. The reduction in travel during the intervention window as compared to the control window (the previous weekend) increased with population size of the “home” chiefdom of each user.
## Table S3.1. Parameters included in $m_{(i,j),t}$.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable Name</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L_t$</td>
<td>National stay-at-home Lockdown</td>
<td>$L = \begin{cases} 1, &amp; t \in (March 27, 28, 29) \ 0, &amp; otherwise \end{cases}$</td>
</tr>
<tr>
<td>$NP_{i,t}$</td>
<td>Operation Northern Push</td>
<td>$NP_i = \begin{cases} 1, &amp; i \text{ is in Kambia or Port Loko and } t \geq June 16 \ 0, &amp; otherwise \end{cases}$</td>
</tr>
<tr>
<td>$NP_{j,t}$</td>
<td>Operation Northern Push</td>
<td>$NP_j = \begin{cases} 1, &amp; j \text{ is in Kambia or Port Loko and } t \geq June 16 \ 0, &amp; otherwise \end{cases}$</td>
</tr>
<tr>
<td>$D_{ij}^{mid}$</td>
<td>Inter-chiefdom distance between 15 and 30 km</td>
<td>$D_{ij}^{mid} = \begin{cases} 1, &amp; \text{inter-chiefdom distance is 15 to 30 km} \ 0, &amp; \text{otherwise} \end{cases}$</td>
</tr>
<tr>
<td>$D_{ij}^{long}$</td>
<td>Inter-chiefdom distance greater than 30 km</td>
<td>$D_{ij}^{long} = \begin{cases} 1, &amp; \text{inter-chiefdom distance is greater than 30 km} \ 0, &amp; \text{otherwise} \end{cases}$</td>
</tr>
<tr>
<td>$I_t$</td>
<td>Cumulative Ebola incidence up to time $t$ in chiefdoms $i+j$ per 100,000 population</td>
<td></td>
</tr>
</tbody>
</table>
Table S3.2. Main results from crossover window analysis.

<table>
<thead>
<tr>
<th></th>
<th>Users</th>
<th>Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Calls</td>
<td># Users</td>
</tr>
<tr>
<td>Control (Pre-)</td>
<td>6,882,636</td>
<td>532,267</td>
</tr>
<tr>
<td>Intervention</td>
<td>5,343,388</td>
<td>480,469</td>
</tr>
<tr>
<td>Control (Post-)</td>
<td>7,221,813</td>
<td>544,568</td>
</tr>
</tbody>
</table>
Table S3.3. Results are robust to changes in the minimum travel distance.

<table>
<thead>
<tr>
<th>Minimum travel distance</th>
<th>Fraction Stationary</th>
<th>OR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (Pre-)</td>
<td>Intervention</td>
<td>Control (Post-)</td>
</tr>
<tr>
<td>0 km</td>
<td>0.368</td>
<td>0.527</td>
<td>0.381</td>
</tr>
<tr>
<td>3 km</td>
<td>0.652</td>
<td>0.840</td>
<td>0.670</td>
</tr>
<tr>
<td>10km</td>
<td>0.827</td>
<td>0.932</td>
<td>0.835</td>
</tr>
</tbody>
</table>
### Table S3.4. Results are robust to down-sampling of control periods to reflect the number of calling events in the intervention period.

<table>
<thead>
<tr>
<th>Down-sample Fraction</th>
<th>Users</th>
<th>Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Active Subscribers Remaining</td>
<td># Stationary</td>
</tr>
<tr>
<td>Control (Pre-) Downsampled</td>
<td>22.4%</td>
<td>495,707</td>
</tr>
<tr>
<td>Intervention</td>
<td>N/A</td>
<td>480,469</td>
</tr>
<tr>
<td>Control (Post-) Downsampled</td>
<td>26.0%</td>
<td>422,827</td>
</tr>
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</table>
Table S3.5. Results are robust to changes in the minimum number of calling events required for eligibility.

<table>
<thead>
<tr>
<th>Minimum # Calls</th>
<th>Fraction Stationary</th>
<th>OR</th>
<th>Intervention is Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (Pre-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>0.827</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>0.782</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>0.737</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention (Post-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.932</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.916</td>
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</tr>
<tr>
<td></td>
<td>0.903</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control (Avg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.835</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.795</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>0.756</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>is Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.831</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>0.788</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.747</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.359</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.341</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.317</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table S3.6. The number of subscribers stationary or mobile in each window.

<table>
<thead>
<tr>
<th>Intervention Window</th>
<th>Stationary Users</th>
<th>Mobile Users</th>
<th>Control (Pre-)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stationary Users</td>
<td>Mobile Users</td>
<td></td>
</tr>
<tr>
<td>Control (Pre)</td>
<td>360,506</td>
<td>12,750</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60,229</td>
<td>14,233</td>
<td></td>
</tr>
<tr>
<td>Control (Post)</td>
<td>305,871</td>
<td>11,060</td>
<td>346,449</td>
</tr>
<tr>
<td></td>
<td>51,875</td>
<td>12,607</td>
<td>45,426</td>
</tr>
</tbody>
</table>

|                     | Stationary Users | Mobile Users |
|---------------------|------------------|--------------|----------------|
| Control (Pre)       |                  |              |                |
| Control (Post)      |                  |              |                |
Table S3.7. The McNemar Odds Ratio comparing stationarity during each combination of time windows.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention versus Control (Pre-)</td>
<td>0.212</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intervention versus Control (Post-)</td>
<td>0.213</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Control (Pre-) versus Control (Post-)</td>
<td>0.940</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
**Table S3.8. Paired T-Tests of differences in each individual’s inter-tower distance traveled during each time window.**

<table>
<thead>
<tr>
<th></th>
<th>Intervention versus Control (Pre-)</th>
<th>Intervention versus Control (Post-)</th>
<th>Control (Pre-) versus Control (Post-)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Diff</td>
<td>95% CI</td>
<td>Mean Diff</td>
</tr>
<tr>
<td>All Subscribers</td>
<td>-9.15 km</td>
<td>-9.27, -9.02</td>
<td>-9.16 km</td>
</tr>
<tr>
<td>Mobile in at least 1 window</td>
<td>-46.95 km</td>
<td>-47.54, -46.36</td>
<td>-46.26 km</td>
</tr>
<tr>
<td>Mobile in both windows</td>
<td>-18.10 km</td>
<td>-19.52, -16.67</td>
<td>-17.09 km</td>
</tr>
</tbody>
</table>

* $P = 0.0005$. For all other tests, $P < 0.0001$. 
### Table S3.9. Paired T-Tests of differences in each individual’s convex-hull distance traveled during each time window.

<table>
<thead>
<tr>
<th></th>
<th>Intervention versus Control (Pre-)</th>
<th>Intervention versus Control (Post-)</th>
<th>Control (Pre-) versus Control (Post-)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Diff 95% CI</td>
<td>Mean Diff 95% CI</td>
<td>Mean Diff 95% CI</td>
</tr>
<tr>
<td>All Subscribers</td>
<td>-59.05 km² -60.52, -57.57</td>
<td>-58.26 km² -59.84, -56.67</td>
<td>-5.56 km² -7.35, -3.77</td>
</tr>
<tr>
<td>Mobile in at least 1 window</td>
<td>-299.0 km² -306.4, -291.7</td>
<td>-290.2 km² -298.0, -282.3</td>
<td>-21.3 km² -28.3, -14.3</td>
</tr>
<tr>
<td>Mobile in both windows</td>
<td>-208.0 km² -227.4, -188.7</td>
<td>-182.4 km² -201.2, -163.6</td>
<td>-25.4 km² -39.0, -7.68*</td>
</tr>
</tbody>
</table>

*P = 0.0035. For all other test, P < 0.0001.
Table S3.10. Results of a mixed effects ARIMA(1,0,2) model estimating the log-transformed trip count between chiefdom pairs.

Chiefdom pairs are restricted to those with an average of at least 10 trips per day. Values are shown after exponentiation. AIC=39387.56.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lockdown</td>
<td>-0.269</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Incidence (per 1000 pop)</td>
<td>-0.104</td>
<td>0.0081</td>
</tr>
<tr>
<td>Distance (15-30km)</td>
<td>-0.254</td>
<td>0.0084</td>
</tr>
<tr>
<td>Distance (&gt;30km)</td>
<td>-0.265</td>
<td>0.0055</td>
</tr>
<tr>
<td>Operation Northern Push (destination)</td>
<td>-0.064</td>
<td>0.0003</td>
</tr>
<tr>
<td>Operation Northern Push (source)</td>
<td>-0.048</td>
<td>0.0088</td>
</tr>
<tr>
<td>Lockdown Control A</td>
<td>-0.056</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown Control B</td>
<td>-0.029</td>
<td>0.0155</td>
</tr>
<tr>
<td>Interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lockdown*Incidence</td>
<td>-0.379</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown*Distance (15-30km)</td>
<td>-0.196</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown*Distance (&gt;30km)</td>
<td>-0.637</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table S3.11. Results of a mixed effects ARIMA(1,0,2) model estimating the log-transformed trip count between chiefdom pairs, excluding Freetown.

Chiefdom pairs are restricted to those with an average of at least 10 trips per day. Values are shown after exponentiation. AIC=33397.21.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lockdown</td>
<td>-0.272</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Incidence (per 1000 pop)</td>
<td>-0.101</td>
<td>0.0090</td>
</tr>
<tr>
<td>Distance (15-30km)</td>
<td>-0.170</td>
<td>0.0535</td>
</tr>
<tr>
<td>Distance (&gt;30km)</td>
<td>-0.264</td>
<td>0.0032</td>
</tr>
<tr>
<td>Operation Northern Push (destination)</td>
<td>-0.064</td>
<td>0.0024</td>
</tr>
<tr>
<td>Operation Northern Push (source)</td>
<td>-0.048</td>
<td>0.0093</td>
</tr>
<tr>
<td>Lockdown Control A</td>
<td>-0.059</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown Control B</td>
<td>-0.052</td>
<td>0.0057</td>
</tr>
<tr>
<td><strong>Interaction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lockdown*Incidence</td>
<td>-0.383</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown*Distance (15-30km)</td>
<td>-0.174</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown*Distance (&gt;30km)</td>
<td>-0.620</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table S3.12. Results of a mixed effects ARIMA(1,0,2) model estimating the log-transformed trip count between chiefdom pairs, allowing for location to be carried forward up to 2 days (left columns) or up to 3 days (right columns).

Chiefdom pairs are restricted to those with an average of at least 10 trips per day. Values are shown after exponentiation. AIC = 38304.31 and 37442.37, respectively.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$t$-2 to $t$</th>
<th></th>
<th>$t$-3 to $t$</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>P-value</td>
<td>Value</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Main Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lockdown</td>
<td>-0.248</td>
<td>&lt;0.0001</td>
<td>-0.238</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Incidence (per 1000 pop)</td>
<td>-0.108</td>
<td>0.0036</td>
<td>-0.112</td>
<td>0.0019</td>
</tr>
<tr>
<td>Distance (15-30km)</td>
<td>-0.250</td>
<td>0.0078</td>
<td>-0.277</td>
<td>0.0024</td>
</tr>
<tr>
<td>Distance (&gt;30km)</td>
<td>-0.357</td>
<td>&lt;0.0001</td>
<td>-0.362</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Operation Northern Push (destination)</td>
<td>-0.048</td>
<td>0.0042</td>
<td>-0.046</td>
<td>0.0054</td>
</tr>
<tr>
<td>Operation Northern Push (source)</td>
<td>-0.038</td>
<td>0.0272</td>
<td>-0.023</td>
<td>0.1668</td>
</tr>
<tr>
<td>Lockdown Control A</td>
<td>-0.062</td>
<td>&lt;0.0001</td>
<td>-0.068</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown Control B</td>
<td>-0.033</td>
<td>0.0021</td>
<td>-0.037</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Interaction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lockdown*Incidence</td>
<td>-0.370</td>
<td>&lt;0.0001</td>
<td>-0.333</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown*Distance (15-30km)</td>
<td>-0.155</td>
<td>&lt;0.0001</td>
<td>-0.134</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown*Distance (&gt;30km)</td>
<td>-0.587</td>
<td>&lt;0.0001</td>
<td>-0.545</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table S3.13. Results of a mixed effects ARIMA(1,0,1) model estimating the log-transformed trip count between chiefdom pairs.

Chiefdom pairs are restricted to those with an average of at least 10 trips per day. Values are shown after exponentiation. AIC = 39400.55.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lockdown</td>
<td>-0.270</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Incidence (per 1000 pop)</td>
<td>-0.106</td>
<td>0.0061</td>
</tr>
<tr>
<td>Distance (15-30km)</td>
<td>-0.253</td>
<td>0.0085</td>
</tr>
<tr>
<td>Distance (&gt;30km)</td>
<td>-0.264</td>
<td>0.0057</td>
</tr>
<tr>
<td>Operation Northern Push (destination)</td>
<td>-0.064</td>
<td>0.0002</td>
</tr>
<tr>
<td>Operation Northern Push (source)</td>
<td>-0.048</td>
<td>0.0075</td>
</tr>
<tr>
<td>Lockdown Control A</td>
<td>-0.055</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown Control B</td>
<td>-0.029</td>
<td>0.0145</td>
</tr>
<tr>
<td>Lockdown*Incidence</td>
<td>-0.379</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown*Distance (15-30km)</td>
<td>-0.196</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lockdown*Distance (&gt;30km)</td>
<td>-0.638</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
REFERENCES


