TITLE

Containing Emerging Epidemics: a Quantitative Comparison of Quarantine and Symptom Monitoring

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ABSTRACT

Background

Strategies for containing an emerging infectious disease outbreak must be non-pharmaceutical when drugs or vaccines for the pathogens do not yet exist or are unavailable. However, little work exists to guide decisions between competing non-pharmaceutical strategies, as exemplified by the confusion about whether to employ quarantine or symptom monitoring during the recent Ebola epidemic in West Africa.

Methods

We compared the effectiveness of quarantine and symptom monitoring in controlling epidemics using an agent-based branching model that accommodates non-pharmaceutical interventions. We used Sequential Monte Carlo particle filtering methods to parameterize 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 quantify the key characteristics of an emerging disease that are most influential for determining the optimal intervention, given varying feasibility of its implementation.

Findings

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, or when there is a long delay between symptom onset and isolation. We find 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.

Interpretation

We establish a quantitative framework for guiding policy-makers in their decisions about how best to use non-pharmacological interventions to contain emerging outbreaks. Our method also provides guidelines for prioritizing research during an outbreak of a novel pathogen, by highlighting which aspects of the disease determine the epidemic potential of emerging pathogens.

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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 obvious, and relies on targeting individuals by tracing the contacts of those infected. Contacts with symptoms can then be hospitalized or isolated, but policy makers must also decide how best to handle contacts who do not meet the case definition for infection. Two strategies have historically been used in the case of a potentially infected but healthy contact: quarantine and symptom monitoring. Precise definitions of these interventions can be found in **Panel 1**.

The recent Ebola epidemic in West Africa highlighted the confusion about whether quarantine or symptom monitoring should be employed and under what circumstances [4]. For example, the US Centers for Disease Control and Prevention (CDC) recommendations differed between its international response, where quarantine was prioritized [5], and its domestic response, where symptom monitoring was prioritized [6,7]. Similar confusion was recorded during the Severe Acute Respiratory (SARS) epidemic, where broad quarantine interventions were applied in Taiwan and subsequently abandoned [8]. These recent epidemics highlight the urgent need for evidence-based guidelines on how to decide whether quarantine of an infectious disease is, according to Gates et al, at worst "counterproductive" or at best "one of the few tactics that can reduce its spread" [9].

Quarantine of potentially infected contacts is a highly conservative approach to epidemic containment. However, there are substantial costs associated with quarantine

78 policies, ranging from direct costs, like implementation expenses and the restriction of
79 personal liberties, to indirect costs, including stigmatization of health workers and
80 sometimes interruption of financial and trade markets [4,10–13]. A less conservative but
81 substantially cheaper and more socially palatable approach is active symptom monitoring
82 of contacts. In this strategy, health workers check on contacts one or two times a day,
83 moving the contacts to isolation if symptoms occur (see **Panel 1**). Given the importance of
84 rapid decision making in the event of novel emerging pathogens such as Ebola, and the
85 potentially devastating consequences of poor containment strategies, quantitative
86 guidelines are urgently needed.

87 Here, we develop a mathematical model to compare the performance of symptom
88 monitoring and quarantine of traced contacts in containing an emerging infectious disease.
89 We consider case studies of seven known pathogens with a wide range of natural histories
90 that have the potential for causing sudden, severe epidemics. We use these case studies to
91 examine the impact of isolation policies for diseases with diverse known epidemiological
92 characteristics, and to provide a generalizable approach to decision making in the event of
93 future epidemics. We identify which disease characteristics and intervention attributes are
94 most critical in deciding between quarantine and symptom monitoring, and provide a clear,
95 general framework for understanding the consequences of isolation policies during an
96 epidemic.

97 METHODS

98 **Model Structure**

99 We developed an agent-based branching model, which accommodates dynamics of
100 symptoms and infectiousness. Specifically, we considered the epidemiological
101 characteristics of infections including Ebola, hepatitis A, influenza A, Middle East
102 Respiratory Syndrome (MERS), pertussis, SARS, and smallpox. Individuals in our branching
103 model progressed through a Susceptible-Exposed-Infectious-Recovered (SEIR) disease
104 process. We focused our analysis on the early epidemic phase of an emerging infectious
105 disease, assuming no changes to herd immunity within the first few generations of
106 transmission.

107

108 **Model Inputs**

109 Following infection, the number of days before onset of infectiousness and onset of
110 symptoms are the latent period and incubation period, respectively (**Fig 1**). Because
111 clinical symptoms, pathogen concentration, and behavior of the patient can change
112 throughout the course of disease [20], we allowed relative infectiousness to vary with time τ
113 since onset of infectiousness (β_τ). The basic reproductive number (R_0) is defined as the
114 average number of infections caused by one infectious individual who is not isolated over
115 the course of disease in a susceptible population. To incorporate the idea that symptomatic
116 individuals are likely to seek care, regardless of contact tracing policies in place, we
117 included a "health seeking behavior" (HSB) intervention condition (Panel 1), where
118 individuals were assumed to seek care at a random time while symptomatic. The effective

reproductive number in the presence of health seeking behavior, symptom monitoring, and quarantine are respectively $R_{HSB,}$ $R_{S,}$ and R_Q.

The definitions of the five key intervention policy performance metrics are found in **Table 1**. The recent SARS and Ebola epidemics highlighted that hospital isolation does not always contain transmission, and we therefore allowed isolation effectiveness (γ) to vary to reflect different settings [21–23]. The fraction of contacts traced (P_{CT}) can be less than 1, encompassing symptomatic infectors who fail to recall contacts, asymptomatic "silent" infection events, or reluctance to report contacts. Imperfections in risk profiling can reduce the fraction of traced contacts that are truly infected (P_{INF}). For example, only 2 Ebola infections were recorded among 179 contacts traced in the United States [7]. 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}) applies only to individuals under symptom monitoring and is influenced by the frequency of monitoring and delays in prompt isolation upon symptom detection.

Simulation

We drew disease characteristics for each simulated individual from disease-specific input distributions. During each hour τ of infectiousness, an individual infected a number of new individuals drawn from a Poisson distribution (or, if super-spreading factor $\kappa \neq 1$, a negative binomial distribution[24]) with mean equal to the product of the expected number of onward infections for the individual (R_0) and the relative infectiousness β_τ where $\sum_{\tau=1}^{d_{INF}} \beta_\tau = 1$. We assumed time-varying relative infectiousness follows a triangular

distribution with time of peak infectiousness (τ_β) occurring anywhere between the onset and end of infectiousness, inclusively.

We recorded both the day of transmission and the infector for each new transmission event, and drew disease characteristics for each newly infected individual. An individual was identified by contact tracing with probability P_{CT} at the earliest time of the following: (a) their infector was isolated; (b) their infector recovered/died from disease; or (c) at the time of infection if the infector was isolated when the transmission event occurred. After an operational lag time of D_{CT} days, a contact was placed under quarantine, symptom monitoring or, if already symptomatic, isolation. An individual in isolation or quarantine had their infectiousness reduced by a factor γ for the remainder of their disease. An individual under symptom monitoring was isolated D_{SM} days after symptom onset. A full description of the model process can be found in **S1 Appendix**. **Fig 2** shows sample outputs for five simulated generations of transmission.

Parameterization

There is a general lack of published data on key characteristics including latent period, relative infectiousness, and duration of infectiousness, while some other characteristics, including the incubation period and serial interval, are generally estimable [25]. Therefore, we used a Sequential Monte Carlo particle filtering algorithm [26,27] 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 (τ_β), and duration of infectiousness (d_{INF}). From an uninformative prior distribution of each parameter bounded by published observations, we simulated five infection generations of 500 initial individuals and

recorded the simulated serial interval (i.e., the time between symptom onset in infector-infectee pairs). Parameter sets were resampled with importance weights determined by the degree to which the distribution of simulated serial intervals matched published serial interval distributions, using the Kolmogorov-Smirnov test of the difference between cumulative distribution functions (**Table 2**) [28,29]. After perturbation, the process was repeated until convergence, which we defined to be when the median Kolmogorov-Smirnov statistic was within 10% of the previous two iterations. This cutoff criterion was chosen to balance the objectives of finding a stationary posterior set of particles while preserving some of the heterogeneity in input parameters.

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 [30], 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 β_τ and fit the time of peak infectiousness (τ_β). A full description of the model parameterization can be found in the **S2 Appendix.**

Analysis

Partial rank correlation coefficients were calculated to identify the most influential disease characteristics (e.g. duration of infectiousness) and intervention performance metrics (e.g. isolation effectiveness). In order to remove dependence between the

parameters jointly fit through the particle filtering method above, we used Latin Hypercube Sampling to draw 5,000 sets from each marginal posterior parameter distribution independently. 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%.

Using 1,000 samples drawn from the joint-parameter space from the particle filtering method, we measured R_0, R_Q, R_S, and R_{HSB} for each disease. We compared 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 calculated 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 surrogates for cost-effectiveness, we calculate the absolute difference per quarantine day $\left(R_S - R_Q\right)/d_Q$ and relative difference per quarantine day $\left(\frac{R_S - R_Q}{R_S}\right)/d_Q$.

When risk profiling was imperfect (i.e. $P_{INF} < 1$), individuals who were not infected may have been mistakenly traced as contacts and placed under symptom monitoring or quarantine. We assumed that non-infected contacts were 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. This would change the number of days in quarantine to $\widehat{d_Q} = \left(d_Q + T_{inc}^{95}\left({}^{1}/_{P_{inf}} - 1\right)\right)$.

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212

RESULTS

The effectiveness of symptom monitoring and quarantine in controlling a disease in a particular setting depends critically on its transmissibility (R_0) and on its biological dynamics (e.g. latent and infectious periods) (**Fig 3a**). By holding transmissibility constant (R_0 arbitrarily set to 2·75±0·25), **Fig 3b** shows how biological dynamics alone strongly influence the effectiveness of quarantine and especially symptom monitoring, as seen by the wide spread in R_S.

When intervention performance is "high" (see **Table 1**), diseases such as MERS and Ebola can be controlled with either quarantine or symptom monitoring; diseases such as hepatitis A with only quarantine; and diseases such as pertussis require additional interventions, e.g. vaccination (**Fig 3c**). The absolute comparative effectiveness ($R_S - R_Q$) varies widely by disease, as demonstrated by the line length in **Fig 3c.** The 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 (**Fig S1**). The reader can explore results from landscapes with different intervention performance settings and disease transmissibility in the **interactive supplement** (https://coreypeak.shinyapps.io/InteractiveQuarantine).

When choosing between symptom monitoring and quarantine, one must consider the effective reproductive numbers under each intervention and choose an appropriate metric to compare these two values. We categorized intervention response heterogeneity into four control quadrants (**Fig 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"). For the example of SARS, Day et al. propose that mass quarantine may be unnecessary because effective symptomatic isolation alone would sufficiently control the disease (hence placing the disease in quadrant III) [13]. 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.

Influential Disease Characteristics

The comparative effectiveness of quarantine and symptom monitoring is strongly influenced by differences in the components of the infection's natural history. We examined which biological characteristics in particular are most influential. As demonstrated by strongly negative partial rank correlation coefficients in **Fig 4**, increasing the duration of infectiousness (d_{INF}) and elongating the latent period (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 (κ), did not influence the average effect of symptom monitoring and quarantine, as reflected by a partial rank correlation coefficient of nearly zero. 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 cost-effectiveness because the number of days in quarantine (d_Q) increases as the incubation period lengthens (**Fig S2**).

Frequently, the most pressing concerns are whether control (i.e. $R_e < 1$) is achievable and what would be the least invasive intervention to achieve control. **Fig 5** shows frontiers where control of an Ebola-like disease requires increasingly invasive interventions, namely health-seeking behavior (teal), symptom monitoring (gold), or quarantine (blue). **Fig 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 [see **Table 1**]. However, we observe that when transmissibility is relatively low (e.g., $R_0 < 2 \cdot 5$), control of this hypothetical disease can be achieved even if infectiousness precedes symptoms by several days (**Fig 5a**) or if a substantial fraction of transmission events occur before symptom onset (adapting the framework of [22]) (**Fig 5b**).

Intervention Performance Metrics

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 (γ), and shorter delays in tracing a contact (D_{CT}) (**Fig 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}) (**Fig S2**).

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 infected and infectious. Here we present the first study comparing the effectiveness of the two primary non-pharmacological interventions for a directly-transmitted infection, 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. This delay (D_{SM}) not only captures ineffective symptom monitoring, but also the potential for symptoms to be masked for a period of time through biological (e.g., natural disease progression or self-medication with anti-pyretics) or behavioral (e.g., avoidance) mechanisms. In contrast, the widely-discussed "super spreading" disease characteristic did not impact the comparative effectiveness of interventions, although this characteristic could remain important to understand disease control during early, highly stochastic stages of emergence [24]. Our findings are consistent with Fraser, Riley, et al. [22] that both inherent transmissibility and the proportion of

316 transmission from asymptomatically infected individuals are key epidemiological
317 parameters for the feasibility of control via quarantine.

318 Our results uniquely identify parameter spaces where symptom monitoring, not just
319 quarantine, is sufficient for containment of an emerging epidemic. Given the high costs and
320 poor scalability of quarantine, symptom monitoring is likely to be a key intervention for
321 future epidemic containment. Our results suggest that symptom monitoring could
322 effectively control an outbreak of a new Ebola-like disease, even when infectiousness
323 precedes symptoms and interventions are not perfectly implemented. Because perfect
324 interventions are not always necessary, these results support the conclusion of Cetron et al.
325 [31] that the optimal containment strategy may allow "partial or leaky quarantine" in order to
326 increase the fraction of contacts who participate.

327 We do not consider mass quarantines or other non-pharmaceutical interventions
328 done on a population level. For mass interventions, such as targeting all airplane
329 passengers returning from an affected region, the time at which symptom monitoring or
330 quarantine are initiated is not necessarily linked to the timing of their infector, so does not
331 require the correlation structure of our branching model. The effectiveness and efficiency
332 of quarantine, like any intervention, improves with better targeting, hence the case for
333 mass quarantine would require additional considerations for multisectoral cost-
334 effectiveness [10].

335 We propose that the most influential parameters should be prioritized for early
336 characterization during an outbreak and should be modeled with conservative
337 consideration of parameter uncertainty, including both real diversity and measurement
338 error. Our framework identifies the key infection-related parameters to define and can

339 form the basis of cost-benefit analyses. Such data-driven decision-making will be critical to
340 determining the optimal public health strategies for the inevitable next epidemic.
341

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343
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349

Panel 1: Definitions of interventions

Contact Tracing is the process of identifying and assessing people who have been exposed to a disease [33]. 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 [33]. 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 [33]. As soon as an individual is placed in quarantine, we assume they have the same reduction in risky contacts as in isolation. 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 [33]. Although they may be encouraged to avoid mass-gatherings or other specific events, 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 communications campaign that prompts individuals to self-identify their 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.

Panel 2. Research in context

Evidence before this study

We searched PubMed and Google Scholar on July 17, 2016, with the terms "quarantine" and "symptom monitoring" and "contact tracing". We did not find any studies that compare the impact on disease spread of quarantine and symptom monitoring of contacts. However, previous work has demonstrated how disease characteristics can strongly influence the effectiveness of non-pharmaceutical interventions such as isolation and quarantine [13,22,35] and traveler screening [36].

Added value of this study

We provide a formal mathematical framework for comparing the relative merits of quarantine and symptom monitoring targeted by contact tracing. We use this framework and a range of case study diseases to show how the natural history of the infectious disease, its inherent transmissibility, and the intervention feasibility in the particular healthcare setting all influence the comparative effectiveness of quarantine and symptom monitoring.

Implications of all available evidence

In certain circumstances, quarantine and/or symptom monitoring can be powerful non-pharmaceutical interventions for epidemic control. When choosing between these interventions, some aspects of the disease and setting are more influential than others and should therefore be prioritized when studying an emerging disease and modeled with a range of uncertainty for re-emerging diseases.

404 **Table 1.** Intervention Parameters

	Variable	Definition	Example Intervention Performance	
			Optimal	High
Isolation Effectiveness	γ	Proportion of infections prevented by isolation as compared to an individual never in isolation (R_0)	1	0·9
Fraction of contacts traced	P_{CT}	Proportion of infected contacts identified by infector	1	0·9
Fraction of traced contacts who are truly infected	P_{INF}	Proportion of individuals under quarantine or symptom monitoring who were truly infected before they were traced	1	0·5
Delay in tracing a named contact	D_{CT}	Number of days between nomination of a contact and monitoring or quarantine	0·25 days ± 0·25	0·5 days ± 0·5
Delay from symptom onset to isolation	D_{SM}	Number of days between symptom onset and isolation of an individual being symptom monitored	0.25 days ± 0.25	0.5 days ± 0.5

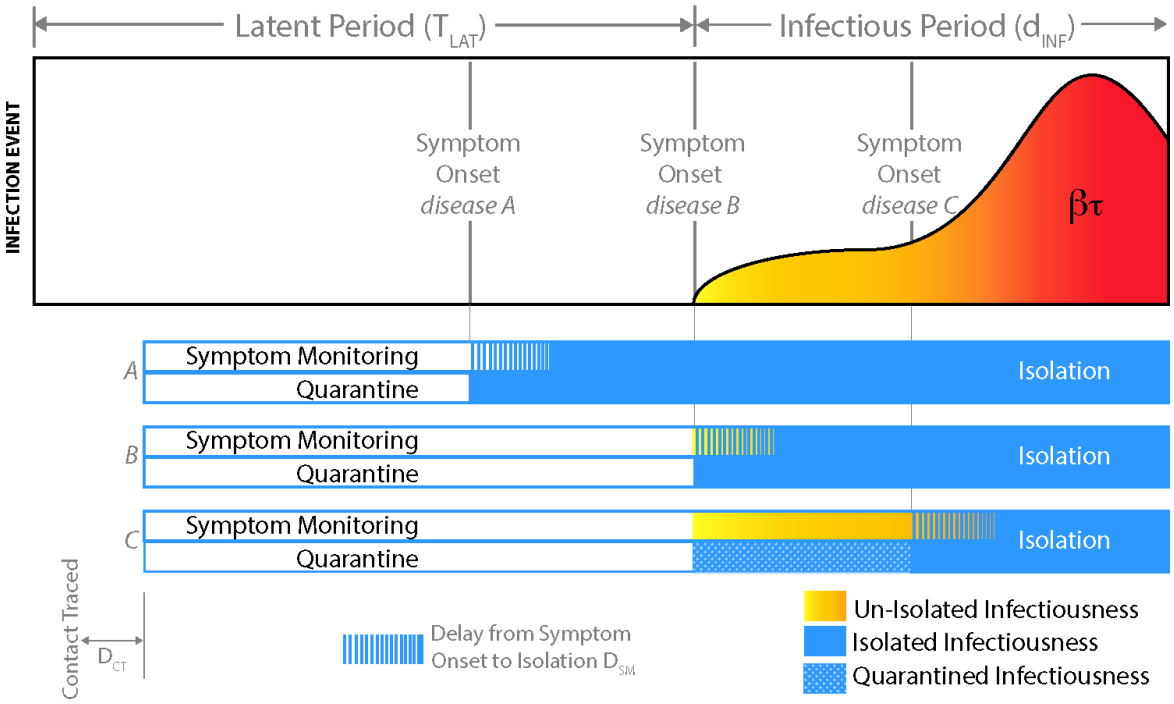
405

406 **Table 2.** Disease parameters

	Inputs			Parameters fit via Sequential Monte-Carlo method		
	Basic Reproductive Number R_0	Serial Interval (days)	Incubation Period T_{INC} (days)	Latent period offset $T_{OFFSET} = T_{LAT} - T_{INC}$ (days)	Mean duration of infectiousness $(1 + d_{INF})/2$ (days)	Time of peak Infectiousness τ_β
Ebola	1·83 (1·72, 1·94) [37]	13·36 (2·66, 38·8) [38]	7·87 (0·93, 28·2) [37]	0·33 (0**, 1·01)	6·53 (1·28, 13·7)	0·10 (0, 0·37)
Hepatitis A	2·25 (2, 2·5) *	26·72 (20·7, 33·8) [39,40]	29·11 (24·6, 34·1) [41]	-5·33 (-7·57, -3·26)	6·23 (1·22, 15·8)	0·35 (0, 0·98)
Influenza A	1·54 (1·28, 1·80) [42]	2·20 (0·63, 3·76) [39,43]	1·40 (0·63, 3·10) [44]	-0·23 (-0·76, 0·29)	1·88 (1·04, 3·84)	0·49 (0·02, 0·98)
MERS	0·95 (0·6, 1·3) [45]	7·62 (2·48, 23·3) [46]	5·20 (1·83, 14·7) [46]	-1·55 (-3·14, 0·02)	8·35 (1·37, 19·9)	0·37 (0·01 , 0·96)
Pertussis	4·75 (4·5, 5) *	19·26 (3·61, 57·2) [47]	7·00 (4·00, 10·0) [30]	-2·14 (-5·39, 0·78)	34·38 (2·67, 76·7)	0·45 (0·11, 0·88)
SARS	2·9 (2·2, 3·6) [15]	8·32 (1·59, 19·2) [15]	4·01 (1·25, 12·8) [44]	0·16 (0**, 0·67)	10·94 (1·50, 23·0)	0·10 (0, 0·46)
Smallpox	4·75 (4·5, 5) *	15·54 (9.98, 24.2) [48]	11.83 (8.47, 16.5) [48]	0.03 (-1.80, 1.68)	8.45 (1.37, 20.0)	0.32 (0, 0·97)

407 Median (95% CI)
408 * Assumed
409 ** Sequential Monte-Carlo boundary condition reached

410



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412 **Fig 1. Schematic of the natural history of disease and the timing of interventions.**

413 Beginning on the left with the infection event, one progress through a latent period (T_{LAT})

414 before becoming infectious for d_{INF} days with a varying degree of infectiousness β_τ. For

415 diseases A, B, and C, symptoms are respectively shown to emerge before, concurrent with,

416 and after onset of infectiousness. We show here an individual who is traced shortly after

417 infection and is placed under symptom monitoring or quarantine after a short delay D_{CT}.

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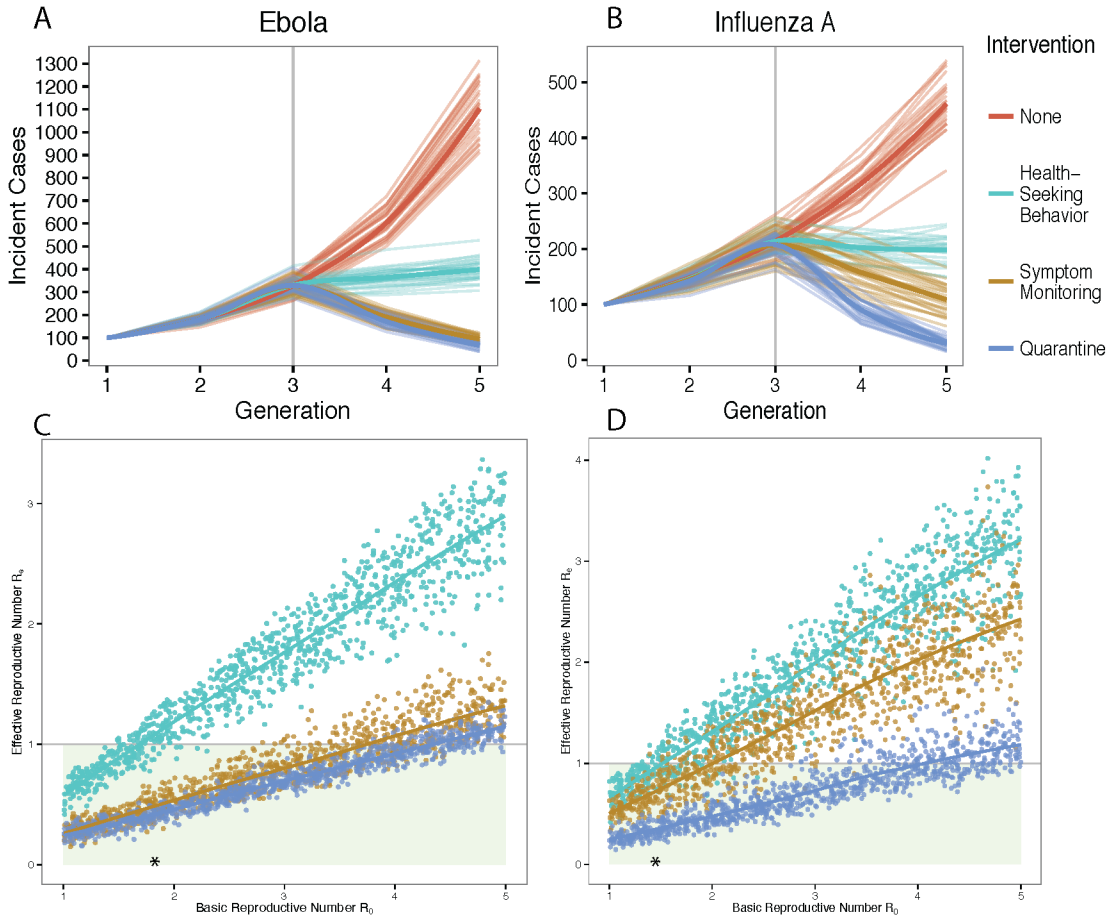


Fig 2. Model dynamics and output for two exemplar diseases: Ebola and Influenza A. Each line in the panels (A) and (B) designates one model run initiated with 100 infectious individuals in Generation 1 and submitted to either no intervention (red), health seeking behavior (teal), symptom monitoring every day (gold), or quarantine (blue) at Generation 3. Each point in panels C and D designates the simulated effective reproductive number from one model run with input reproductive number (x-axis) between 1 and 5, with the asterisk denoting the input R for panels (A) and (B) (1·83 and 1·46, respectively). Loess curves are shown as heavier lines. Here, symptom monitoring performs similarly to quarantine for Ebola control, but not for influenza A. Note the independent y-axes.

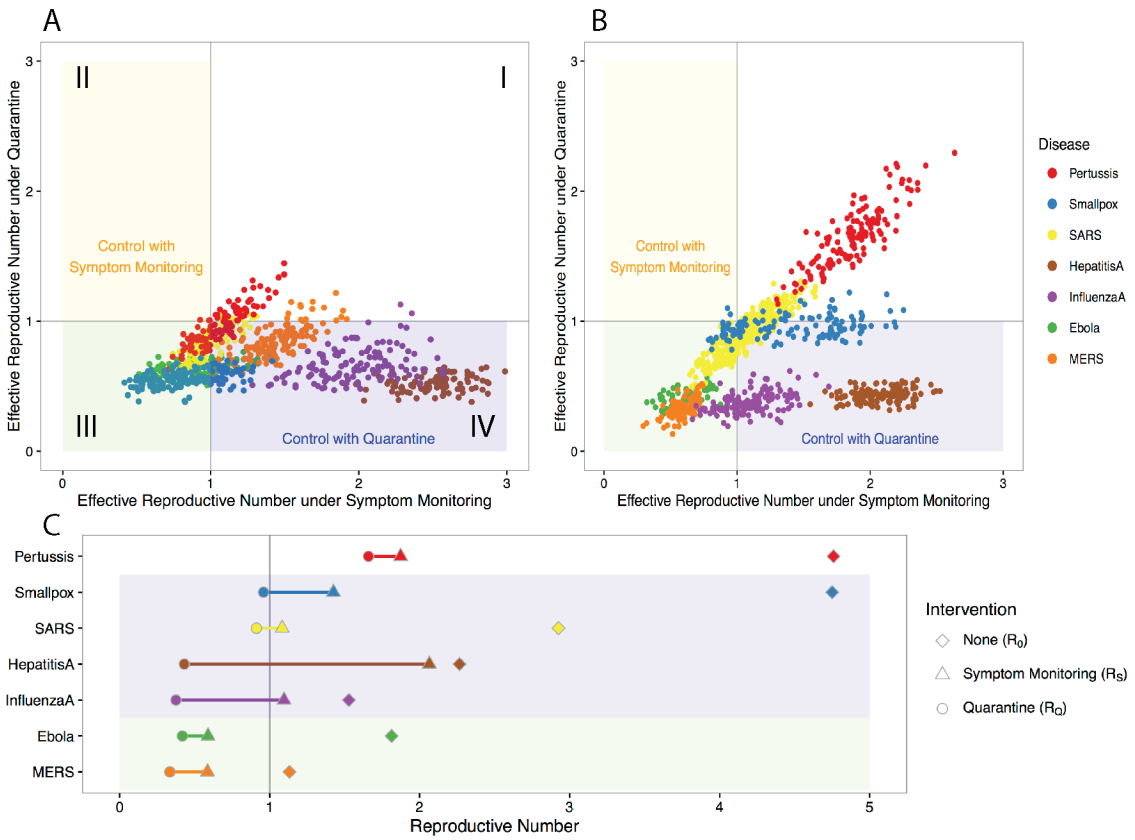


Fig 3. Infection control performance depends on disease biological dynamics and inherent transmissibility (R_0).

(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]. Quadrants indicate regions of control with (I) neither quarantine nor symptom monitoring, (II) only symptom monitoring, (III) either quarantine or symptom monitoring, and (IV) only quarantine. (B) As in (A), but the basic reproductive number (R_0) is set to for all diseases to 2·75 (+/- 0·25) to isolate inherent differences in biological dynamics. (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 $R_S - R_Q$.

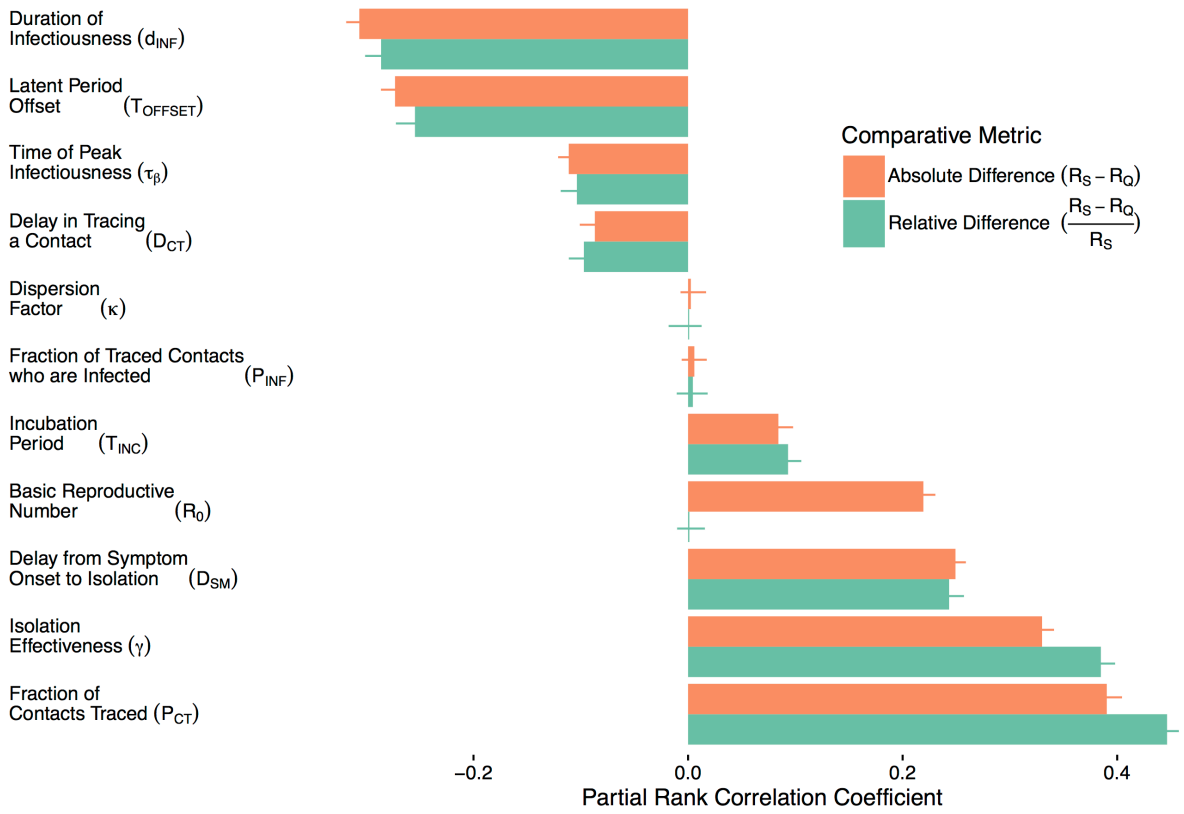
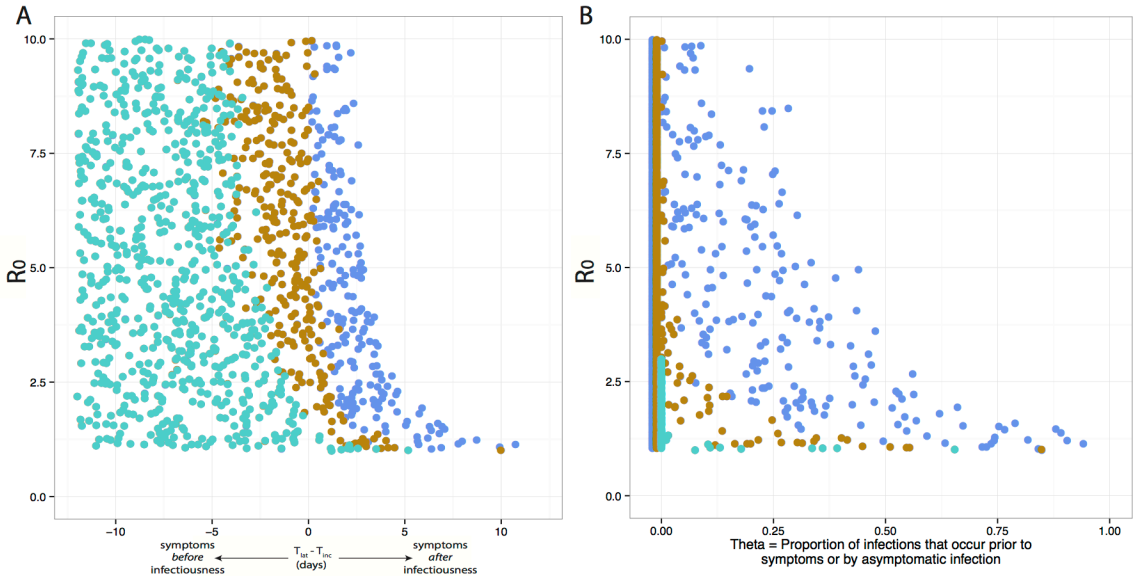


Fig 4. Influence of disease characteristics and intervention performance metrics.

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.



453

454 **Fig 5. Minimally invasive interventions sufficient to control a hypothetical disease.**

455 (A) Disease characteristics drawn from Ebola except symptoms are assumed to either:

456 precede infectiousness by up to 10 days (X = -10 days); coincide with infectiousness onset

457 (X = 0 days); or emerge up to 10 days after infectiousness onset (X = +10 days). Points

458 represent simulations where health-seeking behavior (teal), symptom monitoring (gold),

459 or quarantine (blue) were the minimally sufficient intervention to bring R_e below 1. (B) As

460 in (A), but the x-axis is transformed to represent the proportion of infections that occur

461 prior to symptoms in a analogous way to Fraser, Riley, et al 2004 [22]. Interventions are in

462 the "optimal" setting with all contacts being traced immediately, no infections occur during

463 isolation, and symptom monitoring is performed twice per day.

464

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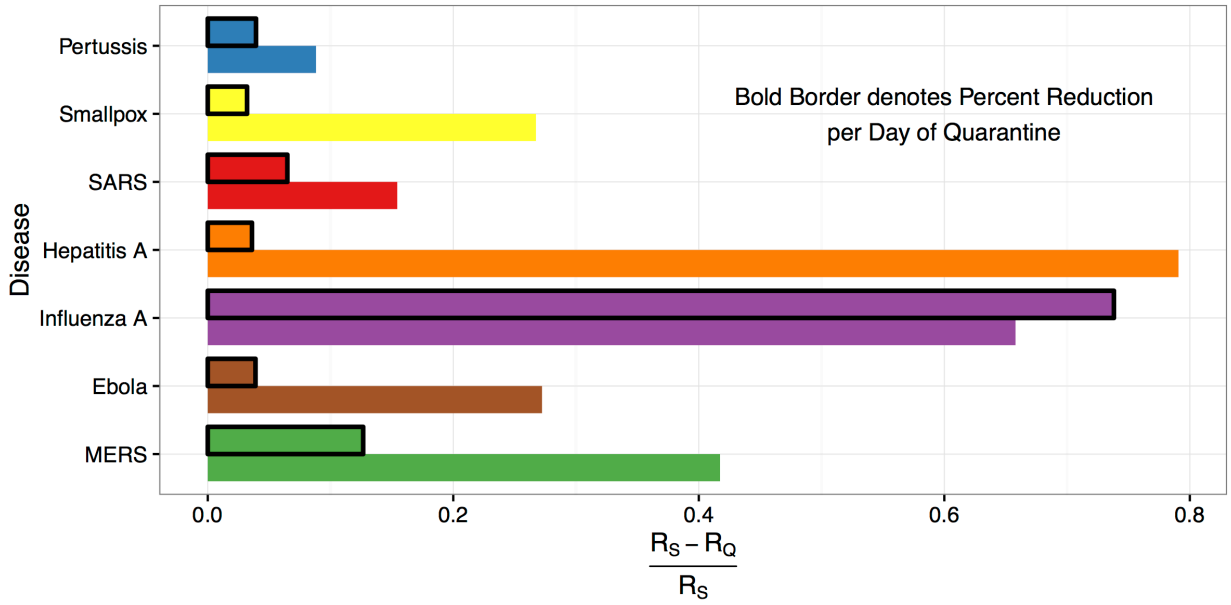
579 SUPPORTING INFORMATION
580



581
582 **Fig S1. Relative comparative effectiveness and cost-effectiveness.** The relative
583 comparative effectiveness varies widely by disease, with quarantine reducing R_S by >65%
584 for influenza A and hepatitis A and by <10% for pertussis. However, due to a much shorter
585 incubation period of influenza A versus hepatitis A (**Table 2**), the relative cost-
586 effectiveness (outlined bars) is substantially higher for influenza A than hepatitis A.

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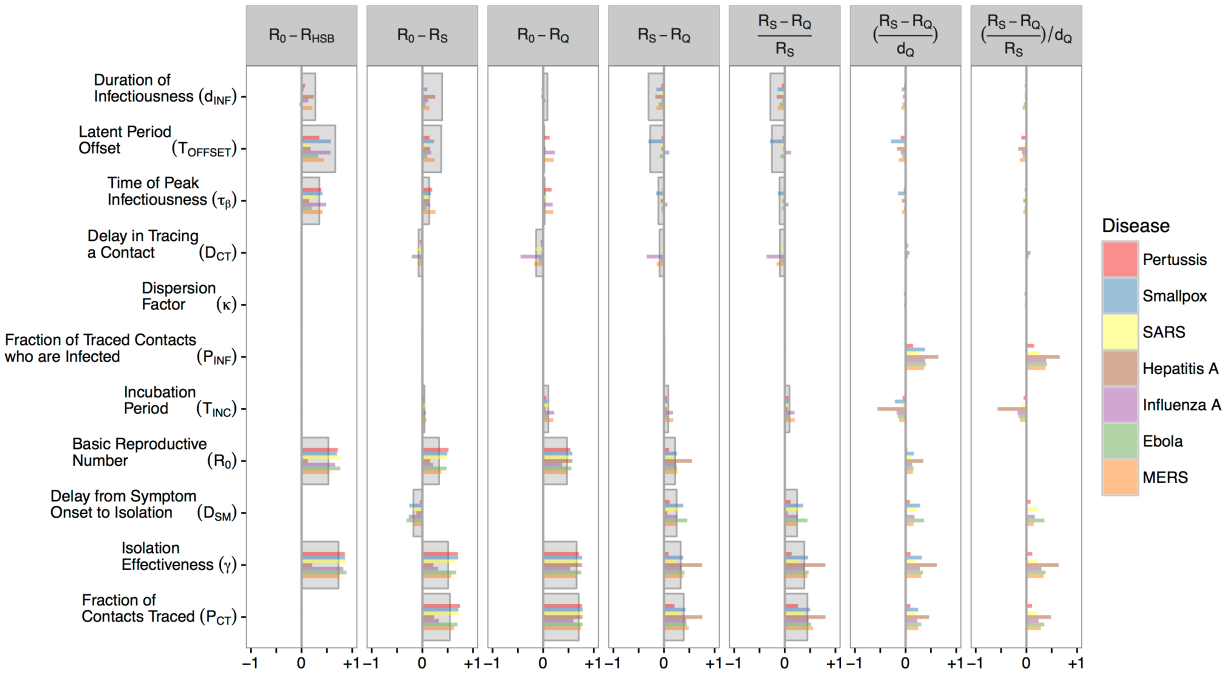

Fig S2. Partial rank correlation coefficients for all outcomes. Partial rank correlation coefficients (x-axis) measuring the influence of disease characteristics and intervention performance metrics (rows) on the impact, comparative effectiveness, and comparative cost-effectiveness of the interventions under study. Disease-specific estimates are shown with colored bars and pooled estimates with grey bars. Note that pooled estimates for comparative cost-effectiveness are not available due to non-monotonic relationships across diseases.

S1 Appendix. 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. The incubation period (T_{INC}), i.e. the time from infection to symptom onset, is drawn from published distributions (**Table 2**). The duration of infectiousness (d_{INF}), time of peak infectiousness (τ_β), and time offset between 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 **S2 Appendix**. 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 initiate distinct trees.

The expected number of onward infections by i, R_{0_i}, is distributed over each hour τ of disease $R_{\tau_i} = \beta_{\tau_i} R_{0_i}$, where β_{τ_i} is the relative infectiousness of i on hour τ such that $\sum_{\tau=0}^{d_{INF}} \beta_\tau = 1$. For parsimony and ease of interpretation, we assume β_τ follows a triangle distribution with a peak value at time τ_β drawn from the SMC posterior.

$$\beta_{\tau_i} = \begin{cases} \sqrt{\tilde{u}\, d_{INF}\, \tau_\beta} & , \quad if\ \tilde{u} < {}^{\tau_\beta}/_{d_{INF}} \\ d_{INF} - \sqrt{(1-\tilde{u})(d_{INF} - \tau_\beta)(d_{INF})} & , \quad otherwise \end{cases}$$

where $\tilde{u} \sim unif(0,1)$

The number of infections (N_{τ_i}) generated by individual i at hour τ is drawn from a negative binomial distribution with mean equal to R_{τ_i} and dispersion factor κ to capture super spreading tendencies. If $\kappa = 1$, the negative binomial distribution reduces to a Poisson distribution with rate $\lambda = R_{\tau_i}$.

Each individual i then has a vector of $\langle N_{0_i}, N_{1_i}, \dots, N_{d_{inf_i}} \rangle$ of onward infections that occur during each hour $\tau \in \langle 0,1, \dots, d_{INF_i} \rangle$. A new individual j is generated for each onward infection $N_{t_i} \geq 1$. Disease characteristics for j are drawn as above, adding the time of infection to the latent and incubation periods for j.

Contact j of infector i will be traced with probability P_{CT}. If traced, j is placed under symptom monitoring or quarantine with an operational lag time of D_{CT} days. The lag time occurs after the earlier of isolation or removal from the disease system upon recovery or death for individual i. We assume all contacts of an individual in hospital isolation are documented, so an individual j who was infected by an isolated individual i will be traced from the time of the transmission event.

Next we determine the time of isolation for j. If time of symptom onset for j occurs before j is traced, j is immediately isolated (**Panel 1**). Otherwise, time of isolation for j depends on whether symptom monitoring or quarantine is used. Under symptom monitoring, isolation of 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 $R_{t_j} = (1-\gamma)\beta_{t_j} R_{0_j}$ where γ is effectiveness of isolation with support $[0, 1]$. If j is under quarantine, then R_{t_j} is reduced by $(1-\gamma)$ beginning at the time j is traced.

S2 Appendix. Parameterization via Sequential Monte Carlo

The following parameterization method was repeated for each case study disease. 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}, and τ_β) using knowledge of the incubation period and serial interval distributions [28,29].

Here we assume that the latent period for an individual is 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}, allowing for partial days as well. We assume the distribution of relative infectiousness to follow a triangle distribution with a max at time τ_β, which ranges from 0, indicating infectiousness is linearly decreasing, to 1, indicating infectiousness is linearly increasing.

The steps are as follows:

i. Draw initial parameter set Θ consisting of T_{OFFSET}, d_{INF}, and τ_β from a Latin Hypercube sample bounded by the range of parameter values found in the literature (Note: d_{INF} is loosely bounded by symptom observations).
ii. Run the branching epidemic model under a situation with no interventions and measure the simulated serial intervals.
iii. Compare the simulated serial intervals to the published serial interval(s) in the literature using the Kolmogorov-Smirnov test statistic (KS).
iv. Draw a bootstrapped sample of $\Theta_{candidate}$ from Θ weighted by the KS statistic and restricted by an adaptive Θ threshold of (max KS in trial)*0.80
v. Perturb each $\Theta_{candidate}$ by up to 2% of the initial parameter value range
vi. Repeat steps (ii)-(v) until the median KS is within 10% of each of the previous two rounds.
vii. Generate an unweighted sample from final Θ joint probability space with replacement as the input parameter set for the case studies.
viii. To calculate partial rank correlation coefficients generate an unweighted sample with replacement from the parameter space of each of for T_{OFFSET}, d_{INF}, and τ_β independent distributions from Θ.