Comparing nonpharmaceutical interventions for containing emerging epidemics

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Strategies for containing an emerging infectious disease outbreak must be nonpharmaceutical when drugs or vaccines for the pathogen do not yet exist or are unavailable. The success of these nonpharmaceutical strategies will depend on not only the effectiveness of isolation measures but also 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 policymakers on how best to use nonpharmaceutical interventions and prioritize research during an outbreak of an emerging pathogen.

epidemiology | quarantine | active symptom monitoring | contact tracing | infectious disease dynamics

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 nonpharmaceutical, because 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 of the contacts of known cases. Contacts with symptoms can then be hospitalized or isolated, but policymakers 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 instance of a potentially infected but symptom-free contact: quarantine and symptom monitoring.

Quarantine of currently healthy but 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 (definitions are 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 (9), at worst "counterproductive" or at best "one of the few tactics that can reduce its spread." Current guidance on the use of quarantine or symptom monitoring is ad hoc, is frequently distributed across several resources for a given disease (Table S1 has a review of select diseases), and lacks the generalizability required for rapid decision making for novel pathogens, leading to confusion during implementation (10–12). During the severe acute respiratory syndrome (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 US 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 depends 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 (θ) 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., superspreading (18)] and the performance of interventions [e.g., travel screening (19)], but the recent Ebola epidemic showed that at least two large questions remain (7).

Significance

Quarantine and symptom monitoring of contacts with suspected exposure to an infectious disease are key interventions for the control of emerging epidemics; however, there does not yet exist a quantitative framework for comparing the control performance of each intervention. Here, we use a mathematical model of seven case-study diseases to show how the choice of intervention 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 considered for an emerging pathogen to make an informed decision between quarantine and symptom monitoring.

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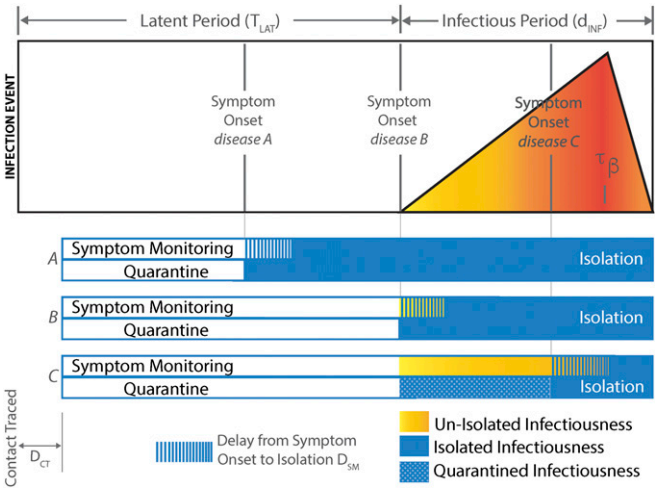

Fig. 1. Schematic of the natural history of disease and the timing of interventions. Beginning on the left with the infection event, one progresses through a latent period (T_{LAT}) before becoming infectious for d_{INF} days with late peak infectiousness τ_β. For diseases A–C, symptoms are shown to emerge before, concurrent with, and after onset of infectiousness, respectively. We show here an individual who is traced shortly after infection and placed under symptom monitoring or quarantine after a short delay D_{CT}.

First, what is the role of symptom monitoring as an alternative to quarantine? Second, 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 (Fig. 1). The model structure accommodates six key metrics of intervention performance in a given setting (Table 1). We used particle filtering to generate parameter sets consistent with seven case studies of outbreak-prone pathogens (*Methods* and Table 2).

Unimpeded exponential epidemic growth in our branching model (red in Fig. 2*A*) 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_e) as the average number of infections generated by an infectious individual in the population (Fig. 2*B*).

We find that 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) (Fig. 3*A*). Holding transmissibility constant (R_0 arbitrarily set to 2.75 ± 0.25), biological dynamics alone strongly influence the effectiveness of quarantine and especially symptom monitoring as seen by the wide spread in R_S (Fig. 3*B*).

In simulations with high-intervention performance settings (Table 1), diseases such as MERS and Ebola could be controlled (i.e., $R_e < 1$) with either quarantine or symptom monitoring while diseases such as hepatitis A could be controlled with only quarantine. However, diseases such as pertussis require additional interventions to reduce the effective reproductive number below one in such a setting (Fig. 3), in large part because of presymptomatic infectiousness (Table 2). Absolute comparative effectiveness ($R_S - R_Q$) varies widely by disease as shown by the line length in Fig. 3*C*. Relative comparative effectiveness $[(R_S - R_Q)/R_S]$ also varies widely, with quarantine reducing R_S by over 65% for influenza A and hepatitis A and 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 at https://coreypeak.shinyapps.io/InteractiveQuarantine.

Categorizing Disease Control Frontiers. To compare the effectiveness of symptom monitoring and quarantine, one must select an appropriate metric to compare R_S and R_Q. We categorized intervention response heterogeneity into four control quadrants (Fig. 3*A*). In quadrant I, where neither intervention is sufficient to prevent epidemic growth, the relative difference $(R_S - R_Q)/R_S$ 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 $[1/(R_S - R_Q)]$, which can be interpreted as the number of contacts who must be quarantined 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.

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 shown by strongly negative partial rank correlation coefficients in Fig. 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 (κ), 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

Table 1. Intervention parameters

Parameter name	Variable	Example performance: Optimal	Example performance: High
Isolation effectiveness	γ	1	0.9
Fraction of contacts traced	P_{CT}	1	0.9
Fraction of traced contacts who are truly infected	P_{INF}	1	0.5
Delay in tracing a named contact	D_{CT}	0.25 ± 0.25 d	0.5 ± 0.5 d
Delay from symptom onset to isolation	D_{SM}	0.25 ± 0.25 d	0.5 ± 0.5 d
Delay from symptom onset to health-seeking behavior	D_{HSB}	Disease-dependent ~unif(0, d_{INF})	

Table 2. Disease parameters

Parameter name	Inputs from published estimates: Basic reproductive no. R_0	Inputs from published estimates: Serial interval (d)	Inputs from published estimates: Incubation period T_{INC} (d)	Parameters fit via sequential Monte Carlo method: Latent period offset $T_{OFFSET} = T_{LAT} - T_{INC}$ (d)	Parameters fit via sequential Monte Carlo method: Maximum duration of infectiousness d_{INF} (d)	Parameters fit via sequential Monte Carlo method: Time of peak infectiousness τ_β (range = 0–1)
Ebola						
Median (reference)	1.83 (20)	13.36 (20)	7.87 (20)	0.33	11.95	0.10
[95% CI]	[1.72, 1.94]	[2.66, 38.8]	[0.93, 28.2]	[0,* 1.01]	[10.0, 17.0]	[0, 0.37]
Hepatitis A						
Median (reference)	2.25†	26.72 (21)	29.11 (22)	−5.33	13.38	0.35
[95% CI]	[2, 2.5]	[20.7, 33.8]	[24.6, 34.1]	[−7.57, −3.26]	[3.16, 19.2]	[0, 0.98]
Influenza A						
Median (reference)	1.54 (23)	2.20 (21)	1.40 (24)	−0.23	2.99	0.49
[95% CI]	[1.28, 1.80]	[0.63, 3.76]	[0.63, 3.10]	[−0.76, 0.29]	[2.00, 4.87]	[0.02, 0.98]
MERS						
Median (reference)	0.95 (25)	7.62 (26)	5.20 (26)	−1.55	16.43	0.37
[95% CI]	[0.6, 1.3]	[2.48, 23.3]	[1.83, 14.7]	[−3.14, 0.02]	[9.59, 24.5]	[0.01, 0.96]
Pertussis						
Median (reference)	4.75†	19.26 (27)	7.00 (28)	−2.14	68.53	0.45
[95% CI]	[4.5, 5]	[3.61, 57.2]	[4.00, 10.0]	[−5.39, 0.78]	[49.5, 94.0]	[0.11, 0.88]
SARS						
Median (reference)	2.9 (29)	8.32 (29)	4.01 (24)	0.16	21.60	0.10
[95% CI]	[2.2, 3.6]	[1.59, 19.2]	[1.25, 12.8]	[0,* 0.67]	[14.9, 26.8]	[0, 0.46]
Smallpox						
Median (reference)	4.75†	15.54 (30)	11.83 (30)	0.03	16.96	0.32
[95% CI]	[4.5, 5]	[9.98, 24.2]	[8.47, 16.5]	[−1.80, 1.68]	[9.33, 25.5]	[0, 0.97]

*Sequential Monte Carlo boundary condition reached.
†Assumed.

number, overdispersion does decrease the average number of generations until extinction as predicted (Fig. S2) (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 (Fig. S3).

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, moving from health-seeking behavior to symptom monitoring to quarantine, the most invasive. Fig. 5*A* 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, 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 (Fig. 5*A*) or if a substantial fraction of transmission events during presymptomatic or asymptomatic infection (adapting the framework of ref. 17) (Fig. 5*B*).

Ranking of Intervention Performance Metrics by Importance for Containment Feasibility. Policymakers facing an epidemic must also consider the expected performance of interventions, because the effectiveness of targeted control policies will depend on their feasibility within a particular healthcare system. Generally, we found that 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 because of either more frequent symptom monitoring or more sensitive detection of symptoms followed by prompt isolation.

Although 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. S3).

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 nonpharmaceutical 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 with the incubation period), and in settings where isolation is highly effective, a large fraction of contacts is traced, or there is a long delay between symptom onset and isolation. Our findings are consistent with those of Fraser et al. (17) that both inherent transmissibility and the proportion of transmission from asymptomatically 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.

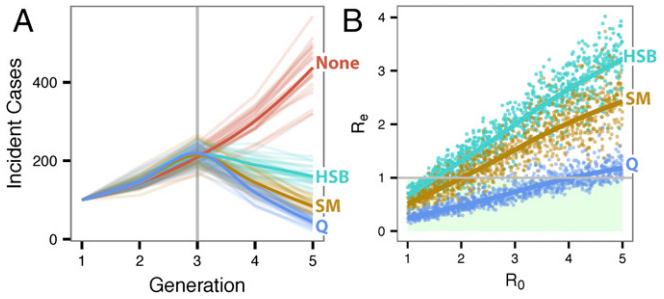

Fig. 2. Model dynamics and output for influenza A. (*A*) Each line designates one model run initiated with 100 infectious individuals in generation 1 and submitted to no intervention (red), health-seeking behavior (teal), symptom monitoring every day (gold), or quarantine (blue) at generation 3. (*B*) 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.

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 ($d_{INF} \sim$ 1–3 d) and some presymptomatic 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 (Fig. 3*B*). 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 show 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 that the preference for quarantine also decreases (Fig. 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" 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 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. "Isolation" is the separation of a symptomatic individual believed to be infected (34). "Quarantine" is the separation of an individual who is believed to be exposed but currently not ill (34). If an individual becomes symptomatic, he/she will be isolated and receive healthcare. "Symptom monitoring" is the assessment of symptoms at regular intervals of an individual believed to be exposed but who is not ill. If symptoms are detected, the individual is placed in isolation (34). "Health-seeking behavior" is the act of seeking healthcare during the presentation of symptoms, leading to isolation.

Model. Individuals in our branching model progress through a susceptible–exposed–infectious–recovered 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.

After infection, the numbers of days before onset of infectiousness and onset of symptoms are the latent period (T_{LAT}) and the incubation period (T_{INC}), respectively (Fig. 1). Because symptoms, pathogen concentration, and behavior can change throughout the course of disease (36), we allow relative infectiousness to vary with time τ since onset of infectiousness (β_τ).

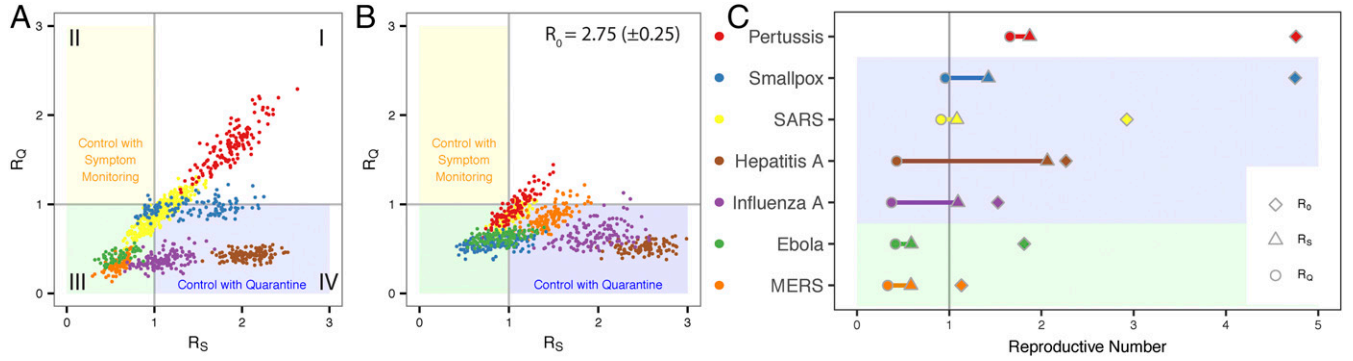

Fig. 3. Infection control performance depends on disease biological dynamics and inherent transmissibility (R_0). (*A*) The effective reproductive number under symptom monitoring (*x* axis) and quarantine (*y* axis) for 100 simulations of each disease when the basic reproductive number is set to published values (◇ in *C*). (*B*) The same as in *A*, but the basic reproductive number (R_0) is set for all diseases to 2.75 (±0.25). (*C*) Disease-specific mean basic reproductive number (◇) and the mean effective reproductive numbers under symptom monitoring (△) and quarantine (○).

The recent SARS and Ebola epidemics highlighted that hospital isolation does not always contain transmission; we, therefore, allow isolation effectiveness (γ) to vary to reflect different settings (17, 37, 38). The fraction of contacts who are traced (P_{CT}) can be less than one, encompassing symptomatic infectors who fail to recall contacts, asymptomatic "silent" infection events, and challenges in identifying contacts. Imperfections and uncertainties in risk profiling can reduce the fraction of traced contacts who are truly infected (P_{INF}) (16, 31). Delays in tracing a contact (D_{CT}) can arise for numerous reasons, including intractable roads 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 on symptom detection.

Simulation. We draw disease characteristics for each simulated individual from disease-specific input distributions. During each hour τ of infectiousness, an individual infects a number of new individuals drawn from a Poisson distribution [or if superspreading factor $\kappa < 1$, a negative binomial distribution (18)] (Fig. S4 and Table S2) 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 $\sum_{\tau=1}^{d_{INF}} \beta_\tau = 1$ (Fig. S5). We assume that 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 record both the day of transmission and the infector for each transmission event, and we 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 his/her 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 his/her infectiousness reduced by a factor γ for the remainder of his/her 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*, *Disease Model*.

Parameterization. Compared with 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, 41) to create a joint probability space of the time offset between the latent period and incubation period ($T_{OFFSET} = T_{LAT} - T_{INC}$), the time of peak infectiousness (τ_β), and the 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 matches published serial interval distributions using the Kolmogorov–Smirnov test of the difference between cumulative distribution functions (Table 2 and Fig. S6) (42, 43).

Holding the incubation period distribution constant, we fit an offset for the latent period (T_{OFFSET}) for several reasons, including consistency with the 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 d. 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 *SI Text*, *Parameterization via SMC*.

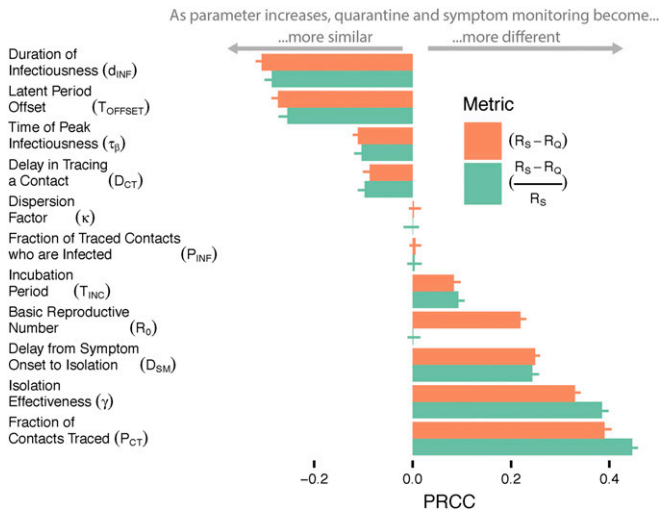

Fig. 4. Influence of disease characteristics and intervention performance metrics. Partial rank correlation coefficients (PRCCs; *x* axis) measuring the influence of disease characteristics and intervention performance metric (rows) on the absolute (red) and relative (green) comparative effectiveness of quarantine and symptom monitoring pooled for all case-study diseases. The 95% CIs from 100 bootstrapped samples are represented by error bars.

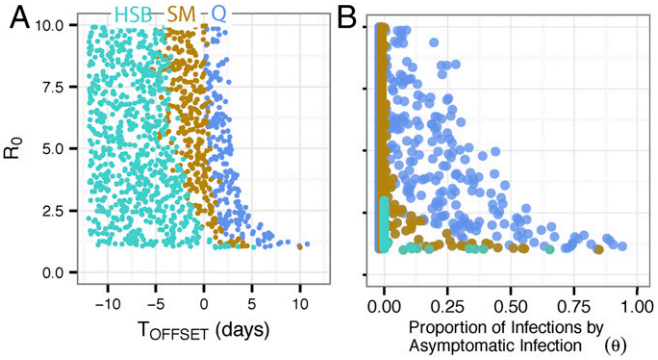

Fig. 5. Minimally invasive interventions sufficient to control a hypothetical disease. (*A*) Points represent simulations where health-seeking behavior (teal), symptom monitoring (gold), or quarantine (blue) was the minimally sufficient intervention to bring R_e below one. Disease characteristics drawn from Ebola, except symptoms, are assumed to precede infectiousness by up to 10 d ($X = -10$ d) or emerge up to 10 d after infectiousness onset ($X = +10$ d). (*B*) The same as in *A*, but the *x* axis is transformed to represent the proportion of infections that occurs before symptoms in an analogous way to Fraser et al. (17).

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}, and k) to range from zero to one, delays (D_{CT} and D_{SM}) to range from 0 to 7 d, R_0 to range from one to five, 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 [$(R_S - R_Q)/R_S$]. We calculate the number of days that an infected individual was in quarantine but was not yet infectious (d_Q) as a 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 $[(R_S - R_Q)/R_S]/d_Q$ and present these results in Figs. S1 and S3. 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 that the contact was not infected after all. Values of $P_{INF} < 1$ change the number of days in quarantine to $\widehat{d_Q} = (d_Q + T_{INC}^{95}(1/P_{INF} - 1))$.

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