TITLE

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

AUTHORS

Corey M Peak[1], Lauren M Childs[1], Yonatan H Grad[2,3], Caroline O Buckee[1*]

AFFILIATIONS

1. Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston MA 02115 USA
2. Department of Immunology and Infectious Diseases, Harvard TH Chan School of Public Health, Boston, MA 02115
3. Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115

*To whom correspondence should be addressed: cbuckee@hsph.harvard.edu

**ABSTRACT**

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. The success of these non-pharmaceutical strategies will not only depend on the effectiveness of quarantine or other isolation measures, but also on the epidemiological characteristics of the infection. There is currently no systematic framework to assess the relationship between different containment strategies and the natural history and epidemiological dynamics of the pathogen, however. 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 to contain emerging outbreaks and prioritize research during an outbreak of a novel pathogen.

## 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. 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 characterized for an emerging pathogen in order to make an informed decision between quarantine and symptom monitoring.

## 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, and relies on targeting individuals by 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 who do not meet the case definition for infection. Two strategies have historically been used in the case of a potentially infected but symptom-free contact: quarantine and symptom monitoring.

Quarantine of potentially infected contacts is a highly conservative approach to epidemic containment. However, there are substantial costs associated with quarantine policies, ranging from direct costs, like implementation expenses and the restriction of personal liberties, to indirect costs, including 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, moving the contacts to isolation if symptoms occur (see definitions in *Methods*). Given the importance of rapid decision making in the event of novel emerging pathogens such as Ebola, and the potentially devastating consequences of poor containment strategies, quantitative guidelines are urgently needed.

The recent Ebola epidemic in West Africa highlights the uncertainties surrounding the relationship between non-pharmaceutical interventions and both disease biological

74 dynamics and the intervention setting [7]. Recommendations by the United States Centers for
75 Disease Control and Prevention (CDC) implicitly recognized the importance of the
76 implementation setting by differentiating its international response, where quarantine was
77 prioritized [9], and its domestic response, where symptom monitoring was prioritized [10,11].
78 During the Severe Acute Respiratory (SARS) epidemic, broad quarantine interventions
79 were applied in Taiwan and subsequently abandoned [12]. These recent epidemics exemplify
80 the urgent need for evidence-based guidelines on how to decide whether quarantine of an
81 infectious disease is, according to Gates et al, at worst "counterproductive" or at best "one
82 of the few tactics that can reduce its spread" [13].
83 The success of these approaches is not simply a reflection of the efficiency of their
84 implementation, however, but crucially depend on the biology and natural history of the
85 pathogen in question. Disease stages are typically divided into those describing the
86 symptom history of the individual (e.g., the incubation period and duration of symptoms)
87 and the temporality of that individual's infectiousness to others (e.g., the latent period and
88 duration of infectiousness). Studies of epidemic dynamics typically focus solely on the
89 latter, but the interaction between the two has important consequences for how diseases
90 spread and the impact of interventions such as ring vaccination [14], travel screening [15], and
91 symptom monitoring. To examine the relationship between epidemiological dynamics of a
92 pathogen and non-pharmaceutical containment strategies, we develop an agent-based
93 branching model that accommodates dynamics of symptoms and infectiousness and allows
94 interventions to be targeted via contact tracing. To assess diseases with a wide range of
95 natural histories that have the potential for causing sudden, severe epidemics, we consider
96 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 clear, general framework for understanding the consequences of isolation policies during an epidemic of known or novel pathogens.

## 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 five key metrics of intervention performance in a given setting (**Table 1**). We used particle filtering to parameterize seven case studies of outbreak-prone pathogens (see *Methods* and **Table S1**).

**Fig 2** illustrates model dynamics for two infections with different epidemiological characteristics, Ebola and influenza A, showing the range of epidemic outcomes resulting from different interventions for a given $R_0$ value. Unimpeded exponential epidemic growth in our branching model (red) can be reduced by the increasingly conservative interventions of health-seeking behavior (teal), symptom monitoring (gold), and quarantine (blue) (**Figs 2A-B**). 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. The effective reproductive number under symptom monitoring ($R_S$), quarantine ($R_Q$), and the absolute difference between the two ($R_S - R_Q$) increases with $R_0$ and differs by disease (**Figs 2C-D**).

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 ($R_0$) (**Fig 3a**). 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 3b**).

124 In simulations with high intervention performance settings (i.e., 90% isolation
125 effectiveness, 90% of contacts traced within one day, and symptoms monitored daily),
126 diseases such as MERS and Ebola could be controlled (i.e., $R_e < 1$) with either quarantine or
127 symptom monitoring; diseases such as hepatitis A with only quarantine; but diseases such
128 as pertussis require additional interventions in order to reduce the effective reproductive
129 number below one, due in large part to pre-symptomatic infectiousness (**Fig 3c**). The
130 absolute comparative effectiveness ($R_S - R_Q$) varies widely by disease, as demonstrated by
131 the line length in **Fig 3c.** The relative comparative effectiveness ($\frac{R_S - R_Q}{R_S}$) also varies widely,
132 with quarantine reducing $R_S$ by over 65% for influenza A and hepatitis A and by less than
133 10% for pertussis (**Fig S1**). The reader can explore results from landscapes with different
134 intervention performance settings and disease transmissibility in the **interactive**
135 **supplement** (https://coreypeak.shinyapps.io/InteractiveQuarantine).
136

137 **Categorizing Disease Control Frontiers**

138 In order to compare the effectiveness of symptom monitoring and quarantine, one
139 must select an appropriate metric to compare $R_S$ and $R_Q$. We therefore categorized
140 intervention response heterogeneity into four control quadrants (**Fig 3a**). In quadrant I,
141 where neither intervention is sufficient to prevent epidemic growth, the relative difference
142 $\frac{R_S - R_Q}{R_S}$ can distinguish whether quarantine is merited or could be paired with other
143 strategies to achieve control. Because quarantine is by definition the more conservative
144 intervention, simulation results in quadrant II occur only stochastically. In quadrant III,
145 where both interventions are sufficient and the number of prevented cases can be more

146 directly estimated, the distinguishing metric was the absolute difference $R_S - R_Q$ and its
147 inverse ($\frac{1}{R_S - R_Q}$), which can be interpreted as the number of contacts that must be
148 quarantined in order to prevent one additional case over symptom monitoring (an analog
149 of "number needed to treat"). For the example of SARS, Day et al. propose that mass
150 quarantine may be unnecessary because effective symptomatic isolation alone would
151 sufficiently control the disease (hence placing the disease in quadrant III) [8]. In quadrant IV,
152 where quarantine but not symptom monitoring can control the disease, quarantine would
153 be strongly considered as the minimum sufficient strategy to prevent exponential epidemic
154 growth.

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

158

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

160 The comparative effectiveness of quarantine and symptom monitoring is strongly
161 influenced by differences in the infection's natural history. We measured partial rank
162 correlation coefficients to examine which biological characteristics in particular are most
163 influential after controlling for the other characteristics (*Methods*). As demonstrated by
164 strongly negative partial rank correlation coefficients in **Fig 4**, increasing the duration of
165 infectiousness ($d_{INF}$) and elongating the latent period ($T_{OFFSET}$) reduced the differences
166 between quarantine and symptom monitoring, thereby making the interventions more
167 similar. Other factors, such as overdispersed heterogeneity of the basic reproductive
168 number ($\kappa$), did not influence the average effect of symptom monitoring and quarantine, as

169 reflected by a coefficient of nearly zero. Longer incubation periods ($T_{INC}$) increased the
170 preference for quarantine, as seen by the positive partial rank correlation coefficient for
171 both absolute and relative comparative effectiveness. However, the length of the incubation
172 period does not generally influence comparative cost-effectiveness because the number of
173 days in quarantine ($d_Q$) increases as the incubation period lengthens (**Fig S2**).

174 Frequently, the most politically and economically pressing concerns are whether
175 control (i.e. $R_e < 1$) is logistically achievable and what would be the least invasive
176 intervention to achieve control. **Fig 5** shows frontiers where control of an Ebola-like
177 disease requires increasingly invasive interventions, moving from health-seeking behavior
178 (teal), to symptom monitoring (gold), to quarantine (blue), the most invasive. **Fig 5a** shows
179 how this frontier is influenced by the inherent transmissibility ($R_0$) and timing of the latent
180 period relative to the incubation period ($T_{OFFSET}$), with all other characteristics similar to
181 Ebola. When $R_0$ is large and symptoms emerge long after infectiousness (e.g., $T_{OFFSET} > 0$),
182 even quarantine is insufficient to control the disease with optimal intervention
183 performance. However, we observe that when transmissibility is relatively low (e.g.,
184 $R_0 < 2.5$), control of this hypothetical disease can be achieved even if infectiousness
185 precedes symptoms by several days (**Fig 5a**) or if a substantial fraction of transmission
186 events occur before symptom onset (adapting the framework of [16]) (**Fig 5b**).

187

188 **Ranking of intervention performance metrics by importance for containment**
189 **feasibility**

190 Policy makers facing an epidemic must also consider the expected performance of
191 interventions, since the effectiveness of targeted control policies will depend on their

192 feasibility within a particular healthcare system. Generally, we found the benefit of
193 quarantine over symptom monitoring increases with better intervention performance (i.e.
194 larger fraction of contacts traced ($P_{CT}$), better isolation effectiveness ($\gamma$), and shorter delays
195 in tracing a contact ($D_{CT}$) (**Fig 4**). However, the effectiveness of symptom monitoring
196 approached that of quarantine when the delay between symptom onset and isolation ($D_{SM}$)
197 is shortened, due either to more frequent symptom monitoring or more sensitive detection
198 of symptoms followed by prompt isolation.
199 While these patterns were highly consistent across the case study diseases, some
200 intervention performance metrics were particularly influential in the presence of certain
201 disease characteristics. For example, diseases with short incubation periods ($T_{INC}$) such as
202 influenza A were strongly influenced by delays in tracing a contact ($D_{CT}$) (**Fig S2**).
203
204

205 **DISCUSSION**

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

214 Our results show that the benefit of quarantine over symptom monitoring is
215 maximized for fast-course diseases (short duration of infectiousness and a short latent
216 period compared to the incubation period), and in settings where isolation is highly
217 effective, a large fraction of contacts are traced, or when there is a long delay between
218 symptom onset and isolation. This delay ($D_{SM}$) not only captures ineffective symptom
219 monitoring, but also the potential for symptoms to be masked for a period of time through
220 biological (e.g., natural disease progression or self-medication with anti-pyretics) or
221 behavioral (e.g., avoidance) mechanisms. In contrast, the widely-discussed "super
222 spreading" disease characteristic did not independently impact the comparative
223 effectiveness of interventions after holding the mean $R_0$ constant. However, this
224 characteristic could remain important to understand disease control during early, highly
225 stochastic stages of emergence [17]. Our findings are consistent with Fraser, Riley, et al. [16]
226 that both inherent transmissibility and the proportion of transmission from

227 asymptomatically infected individuals are key epidemiological parameters for the
228 feasibility of control via quarantine.

229 In addition to identifying parameters that differentiate quarantine and symptom
230 monitoring, our results also characterize parameter spaces where symptom monitoring,
231 not just quarantine, is sufficient for containment of an emerging epidemic. Given the high
232 costs and poor scalability of quarantine, symptom monitoring is likely to be a key
233 intervention for future epidemic containment.

234 Although our results focus on the early stages of an outbreak, contact tracing,
235 symptom monitoring, and quarantine are often key tools for end-stage epidemic control
236 and elimination. As the effective reproductive number decreases below one (e.g. via
237 depletion of susceptible individuals, complementary interventions, seasonality, etc.), our
238 results suggest the preference for quarantine also decreases (**Fig 4**). However, one must
239 consider aspects such as geographic containment, public compliance, and, if the availability
240 of resources lags the epidemic curve, a possible resource-per-case surplus that may enable
241 the more conservative and costly approach of quarantine.

242 Our results suggest that symptom monitoring could effectively control an outbreak
243 of a new Ebola-like disease, even when infectiousness precedes symptoms and
244 interventions are not perfectly implemented. Because perfect interventions are not always
245 necessary, these results support the conclusion of Cetron et al. [18] that the optimal
246 containment strategy may allow "partial or leaky quarantine" in order to increase the
247 fraction of contacts who participate.

248 The case study diseases were selected to demonstrate a broad range of natural
249 histories and are not intended to represent all candidates for quarantine and symptom

250 monitoring. Furthermore, the selected diseases have a diverse set of transmission routes,
251 including bodily fluid, fecal-oral, and airborne, which will influence the contact networks
252 and traceability of contacts. In our framework, a reduction in the fraction of contacts who
253 are ultimately traced will decrease the preference for quarantine over symptom
254 monitoring, therefore supporting the previous findings that quarantine was inefficient for a
255 respiratory disease like SARS [19].

256 We do not consider group quarantines or other non-pharmaceutical interventions
257 implemented *en masse*. For such interventions as targeting all airplane passengers
258 returning from an affected region, the time at which symptom monitoring or quarantine
259 are initiated is not necessarily linked to the timing of their infector, so does not require the
260 correlation structure of our branching model. The effectiveness and efficiency of
261 quarantine, like any intervention, improves with better targeting, hence the case for mass
262 quarantine would require additional considerations for multisectoral cost-effectiveness [4].
263 We propose that the most influential parameters should be prioritized for early
264 characterization during an outbreak [20] and should be modeled with conservative
265 consideration of parameter uncertainty, including both real diversity and measurement
266 error. Our framework identifies the key infection-related parameters to define and can
267 form the basis of cost-benefit analyses. Such data-driven decision-making will be critical to
268 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 [30]. 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 [31].

"Isolation" is the separation of a symptomatic individual believed to be infected [30]. 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 [30]. 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 [30]. 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 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.

292

293 **Model**

294 Individuals in our branching model progressed through a Susceptible-Exposed-
295 Infectious-Recovered (SEIR) disease process. We focus our analysis on the early epidemic
296 phase of an emerging infectious disease, assuming no changes to herd immunity within the
297 first few generations of transmission.

298 Following infection, the number of days before onset of infectiousness and onset of
299 symptoms are the latent period and incubation period, respectively (**Fig 1**). Because
300 clinical symptoms, pathogen concentration, and behavior of the patient can change
301 throughout the course of disease [21], we allowed relative infectiousness to vary with time τ
302 since onset of infectiousness ($\beta_\tau$). The effective reproductive number in the presence of
303 health seeking behavior, symptom monitoring, and quarantine are respectively $R_{HSB}$, $R_S$, and
304 $R_Q$.

305 The recent SARS and Ebola epidemics highlighted that hospital isolation does not
306 always contain transmission, and we therefore allowed isolation effectiveness (γ) to vary to
307 reflect different settings [16,22,23]. The fraction of contacts who are traced ($P_{CT}$) can be less
308 than 1, encompassing symptomatic infectors who fail to recall contacts, asymptomatic
309 "silent" infection events, reluctance to report contacts, and challenges in identifying
310 contacts, especially for airborne transmission routes. Imperfections and uncertainties in
311 risk profiling can reduce the fraction of traced contacts that are truly infected ($P_{INF}$) [11,19].
312 Delays in tracing a contact ($D_{CT}$) can arise for numerous reasons, including intractable
313 roads, low mobile phone penetration, and personnel limitations. The delay between
314 symptom onset and isolation ($D_{SM}$) specifically applies to individuals under symptom

315 monitoring and is influenced by the frequency of monitoring, delays in recognizing
316 sometimes unreliable clinical features, and delays in prompt isolation upon symptom
317 detection.
318
319 **Simulation**
320 We drew disease characteristics for each simulated individual from disease-specific
321 input distributions. During each hour τ of infectiousness, an individual infected a number of
322 new individuals drawn from a Poisson distribution (or, if super-spreading factor $\kappa \neq 1$, a
323 negative binomial distribution [17]) with mean equal to the product of the expected number
324 of onward infections for the individual ($R_0$) and the relative infectiousness $\beta_\tau$ where
325 $\sum_{\tau=1}^{d_{INF}} \beta_\tau = 1$. We assumed time-varying relative infectiousness follows a triangular
326 distribution with time of peak infectiousness ($\tau_\beta$) occurring anywhere between the onset
327 and end of infectiousness, inclusively.
328 We recorded both the day of transmission and the source of each new infection for
329 each new transmission event, and drew disease characteristics for each newly infected
330 individual. An individual was identified by contact tracing with probability $P_{CT}$ at the earlier
331 time of either when their infector is isolated or the time of the transmission event if
332 infection occurred while the infector was isolated. After an operational lag time of $D_{CT}$ days,
333 a contact was placed under quarantine, symptom monitoring or, if already symptomatic,
334 isolation. An individual in isolation or quarantine had their infectiousness reduced by a
335 factor γ for the remainder of their disease. An individual under symptom monitoring was
336 isolated $D_{SM}$ days after symptom onset. A full description of the model process can be found
337 in **S1 Appendix**.

338

339 **Parameterization**

340 As compared to characteristics related to the natural history of symptoms and
341 illness, key aspects of the natural history of infectiousness tend to be harder to observe and
342 measure [24]. Therefore, we used a Sequential Monte Carlo particle filtering algorithm [25,26] to
343 create a joint probability space of the time offset between the latent period and incubation
344 period ($T_{OFFSET} = T_{LAT} - T_{INC}$), time of peak infectiousness ($\tau_\beta$), and duration of
345 infectiousness ($d_{INF}$). From an uninformative prior distribution of each parameter
346 bounded by published observations, we simulated five infection generations of 500 initial
347 individuals and recorded the simulated serial interval (i.e., the time between symptom
348 onset in infector-infectee pairs). Parameter sets were resampled with importance weights
349 determined by the degree to which the distribution of simulated serial intervals matched
350 published serial interval distributions, using the Kolmogorov-Smirnov test of the difference
351 between cumulative distribution functions (**Table S1**) [27,28]. After perturbation, the process
352 was repeated until convergence, which we defined to be when the median Kolmogorov-
353 Smirnov statistic was within 10% of the previous two iterations. This cutoff criterion was
354 chosen to balance the objectives of finding a stationary posterior set of particles while
355 preserving some of the heterogeneity in input parameters.

356 Holding the incubation period distribution constant, we fit an offset for the latent
357 period ($T_{OFFSET}$) for several reasons, including consistency with CDC methods for disease
358 characterization [29], the biological expectation of these timings both being linked to
359 pathogen load, and to parsimoniously limit each characteristic to one interpretable
360 parameter. For the duration of infectiousness ($d_{INF}$), we fit the upper bound of a uniform

361 distribution with a lower bound of 1 day. To allow for variable infectiousness during this
362 duration, we assume a triangular distribution of relative infectiousness $\beta_\tau$ and fit the time
363 of peak infectiousness ($\tau_\beta$). A full description of the model parameterization can be found
364 in the **S2 Appendix.**
365
366 **Analysis**

367 Partial rank correlation coefficients were calculated to identify the most influential
368 disease characteristics (e.g. duration of infectiousness) and intervention performance
369 metrics (e.g. isolation effectiveness). In order to remove dependence between the
370 parameters jointly fit through the particle filtering method above, we used Latin Hypercube
371 Sampling to draw 5,000 sets from each marginal posterior parameter distribution
372 independently. To maximize coverage of the parameter space we allowed fractional
373 parameters ($\gamma$, $P_{CT}$, $P_{INF}$, $k$) to range from 0 to 1, delays ($D_{CT}$, $D_{SM}$) to range from 0 to 7 days,
374 $R_0$ to range from 1 to 5, and the incubation period ($T_{INC}$) to be shrunk by up to 50% or
375 stretched by up to 150%.

376 Using 1,000 samples drawn from the joint-parameter space from the particle
377 filtering method, we measured $R_0$, $R_Q$, $R_S$, and $R_{HSB}$ for each disease. We compared the
378 effectiveness of symptom monitoring and quarantine by the absolute difference $R_S - R_Q$
379 and the relative difference $\frac{R_S - R_Q}{R_S}$. We calculated the number of days an infected individual
380 was in quarantine but not yet infectious ($d_Q$) as surrogate for the marginal cost of
381 quarantine over symptom monitoring. As surrogates for cost-effectiveness, we calculate the

absolute difference per quarantine day $(R_S - R_Q)/d_Q$ and relative difference per quarantine day $\left(\frac{R_S - R_Q}{R_S}\right)/d_Q$ and present these results in Fig S1 and S2.

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. Such events may be conceptualized as false positives and will decrease $P_{INF}$; conversely, individuals who were infected but not traced are false negatives and will decrease $P_{CT}$. 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 $\widehat{d_Q} = \left(d_Q + T_{inc}^{95}\left({}^{1}/_{P_{inf}} - 1\right)\right)$.

**ACKNOWLEDGEMENTS**

CMP, LMC, and COB were supported by Cooperative Agreement U54GM088558 from the National Institute Of General Medical Sciences. CMP was also supported by National Research Service Award T32AI007535-16A1. YHG was supported by the National Institutes of Health (K08-AI104767) and the Smith Family Foundation. The content is solely the responsibility of the authors and does not necessarily represent the 433 official views of the National Institute Of General Medical Sciences or the National Institutes of 434 Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors thank Colin Worby for helpful statistical discussions.

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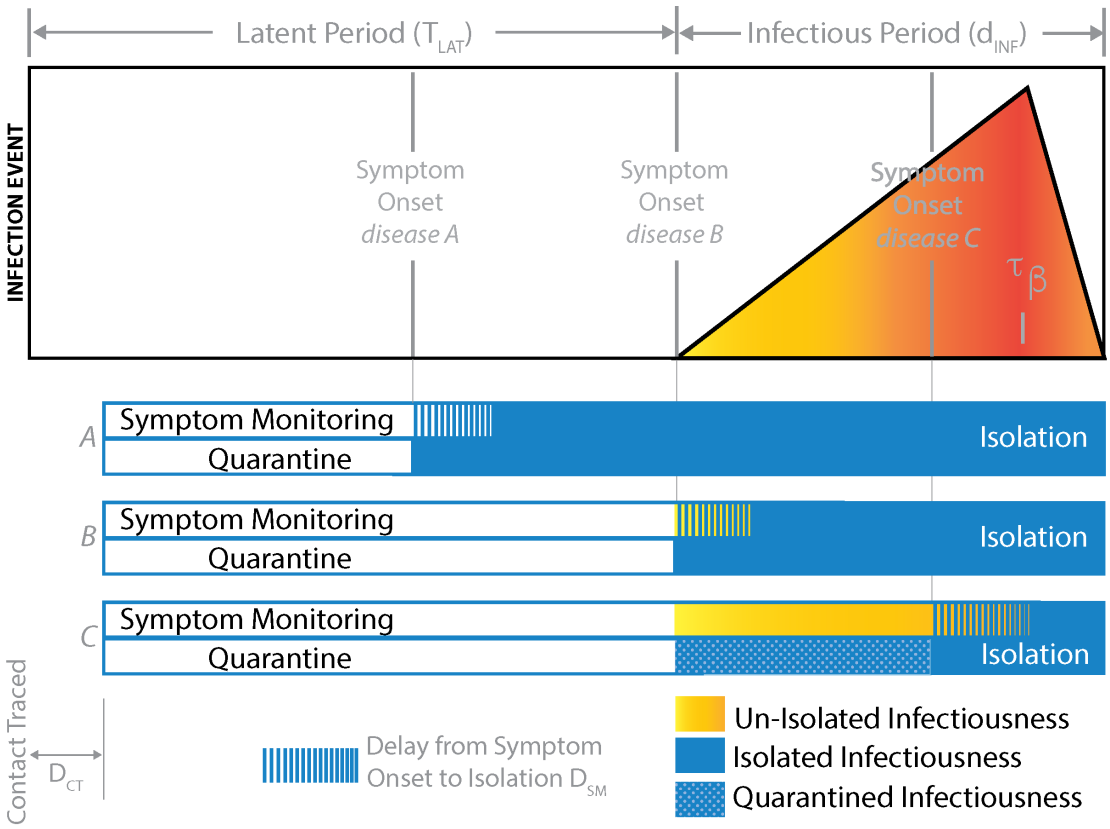


**Fig 1. Schematic of the natural history of disease and the timing of interventions.** Beginning on the left with the infection event, one progress through a latent period ($T_{LAT}$) before becoming infectious for $d_{INF}$ days with late peak infectiousness $\tau_\beta$. For diseases A, B, and C, 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 $D_{CT}$.

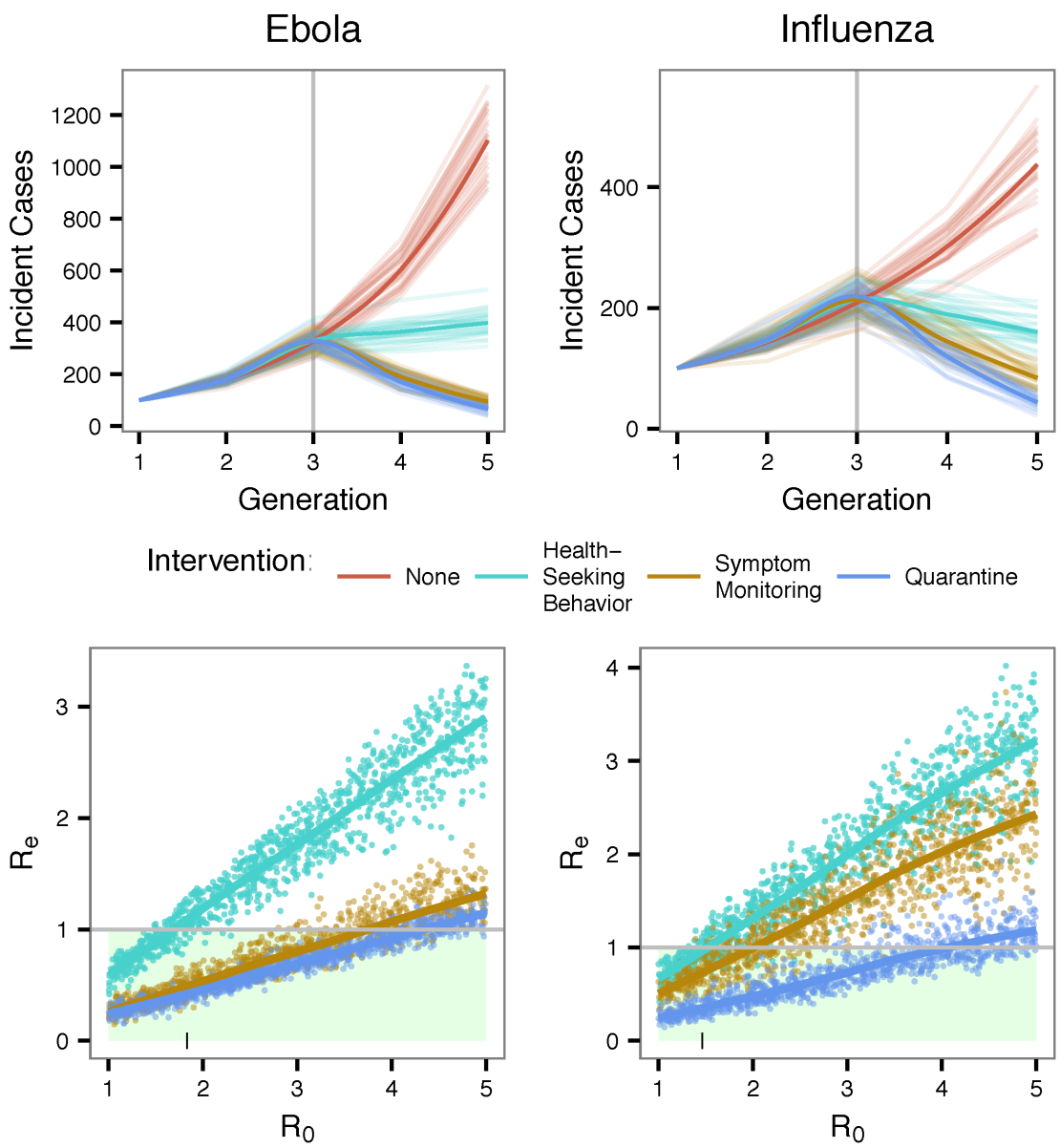


**Fig 2. Model dynamics and output for two exemplar diseases: Ebola and influenza A.** Each line in the panels (A) and (B) designates one model run initiated with 100 infectious individuals in Generation 1 and submitted to either no intervention (red), health seeking behavior (teal), symptom monitoring 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

526 asterisk denoting the input R for panels (A) and (B) (1.83 and 1.46, respectively). Loess
527 curves are shown as heavier lines. Here, symptom monitoring performs similarly to
528 quarantine for Ebola control, but not for influenza A. Note the independent y-axes.
529

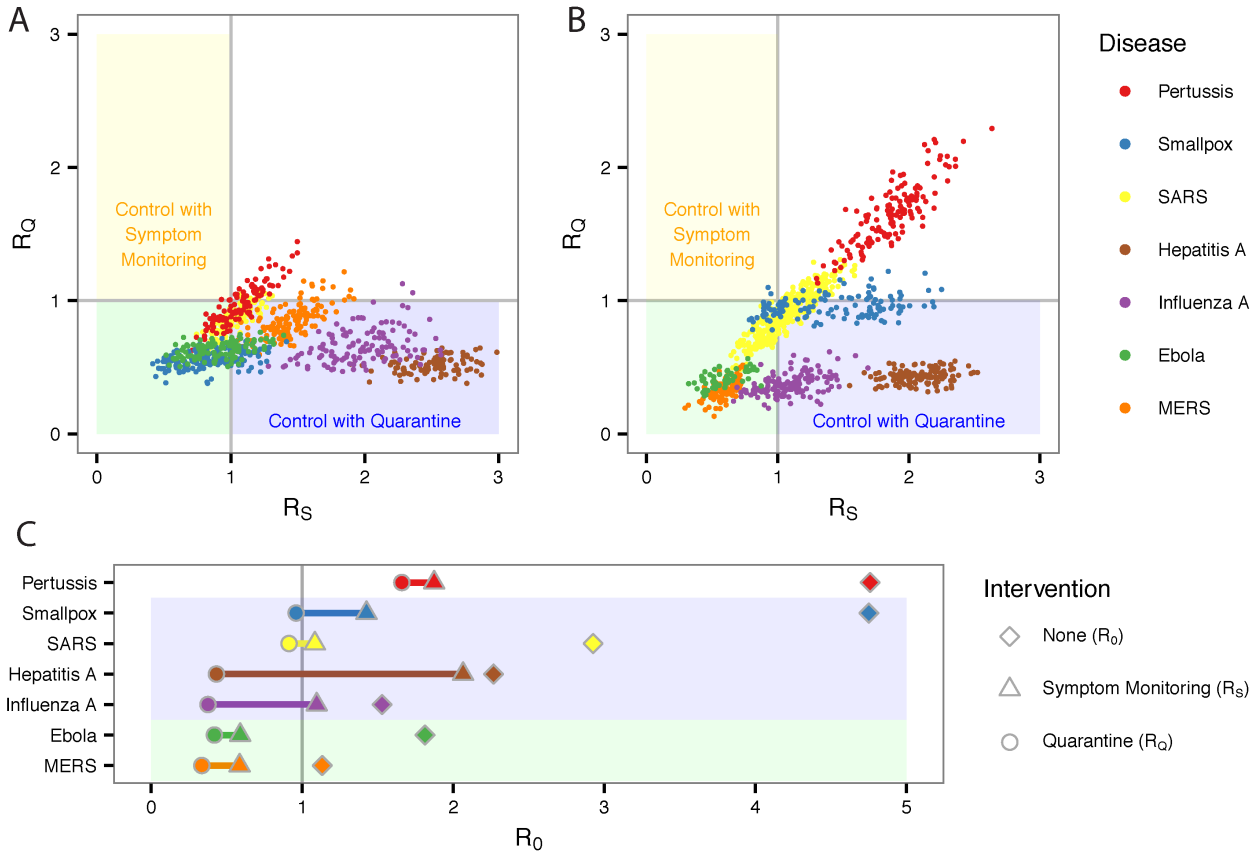


**Fig 3. Infection control performance depends on disease biological dynamics and inherent transmissibility ($R_0$).**

(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 $R_S - R_Q$.

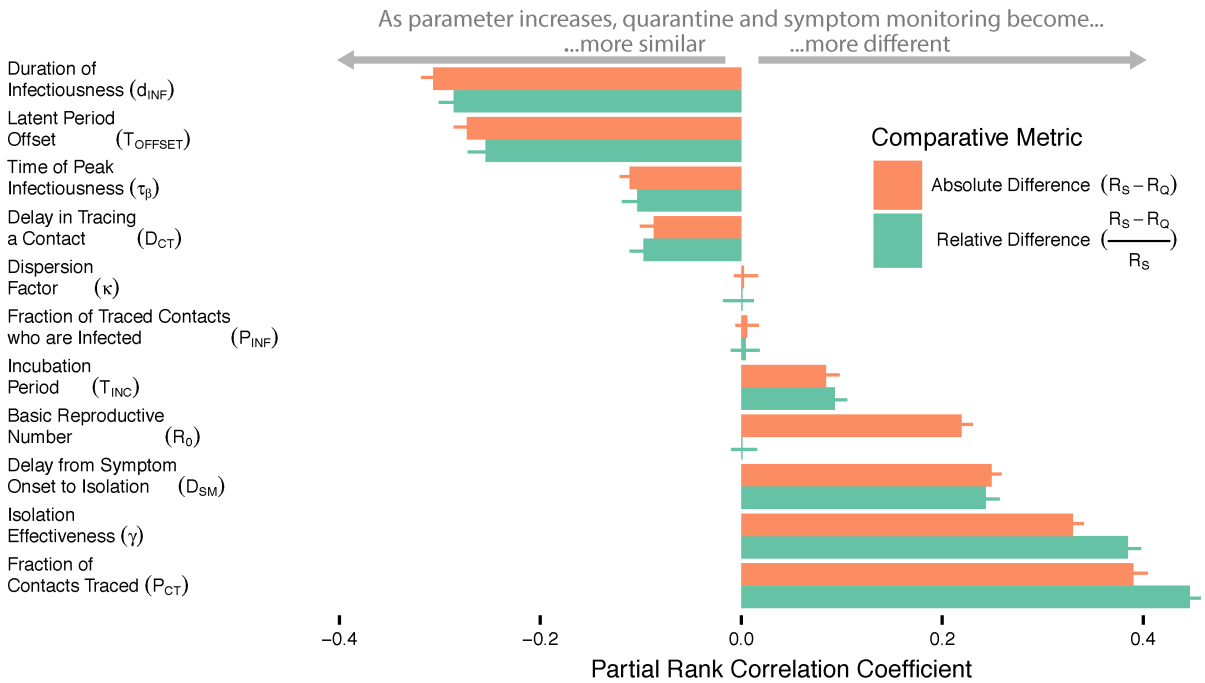


**Fig 4. Influence of disease characteristics and intervention performance metrics.** Partial rank correlation coefficients (x-axis) measuring the influence of disease characteristics and intervention performance metric (rows) on the absolute (red) and relative (green) comparative effectiveness of quarantine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

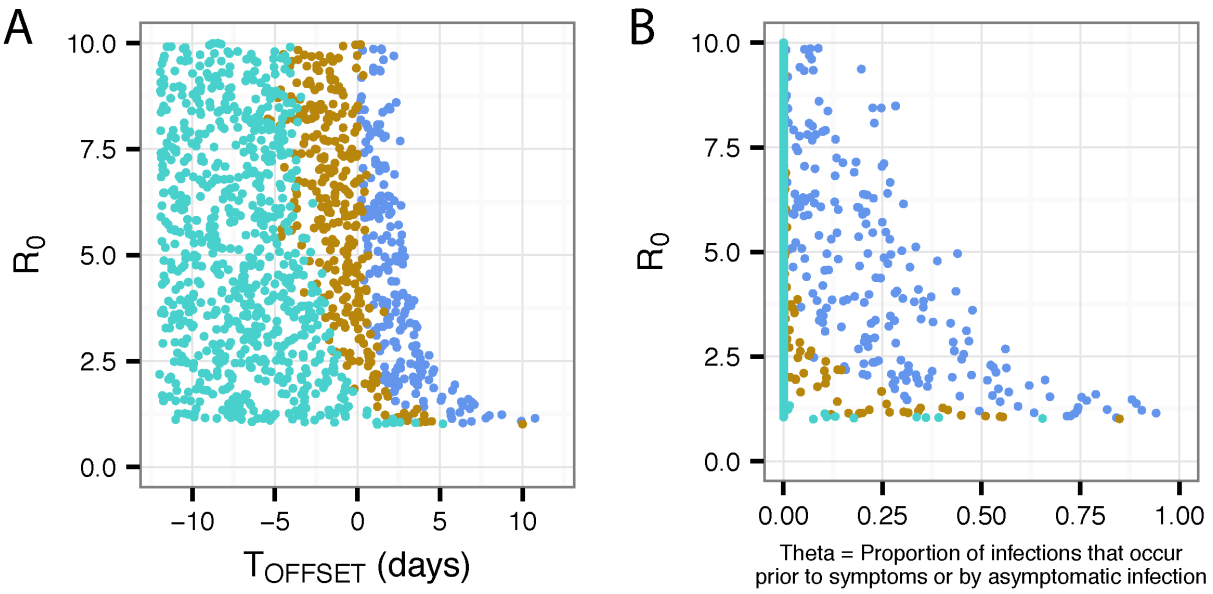


**Fig 5. Minimally invasive interventions sufficient to control a hypothetical disease.** (A) Disease characteristics drawn from Ebola except symptoms are assumed to either: precede infectiousness by up to 10 days (X = -10 days); coincide with infectiousness onset (X = 0 days); or emerge up to 10 days after infectiousness onset (X = +10 days). 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. (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 2004 [16]. Interventions are in an optimal setting with all contacts being traced immediately, no infections occur during isolation, and symptom monitoring is performed twice per day.

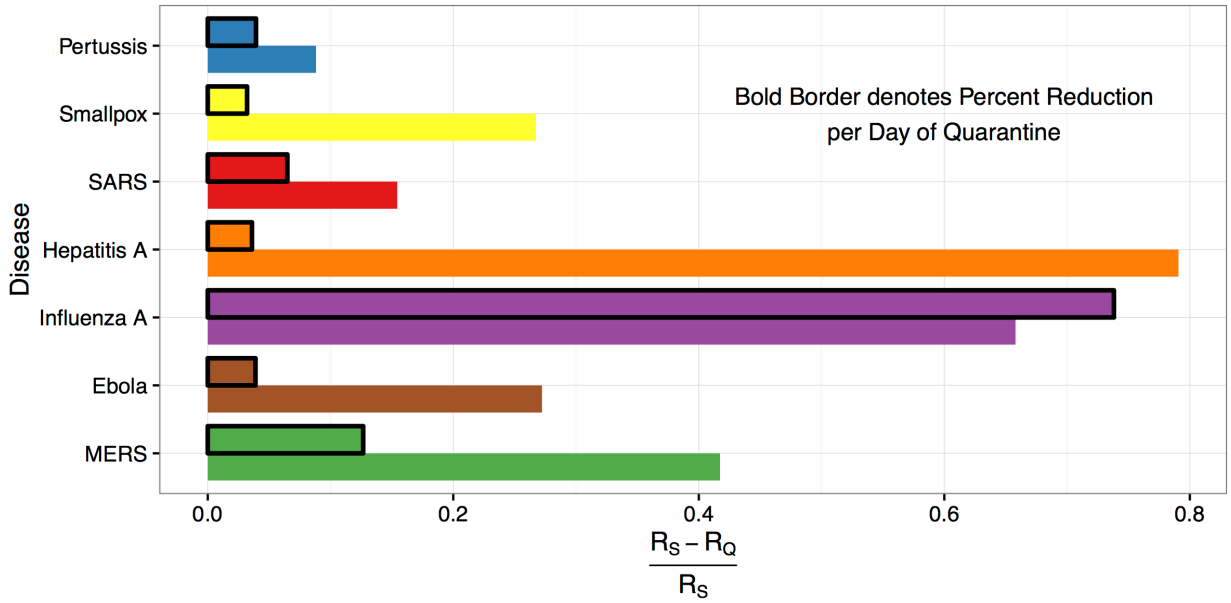


**Fig S1. Relative comparative effectiveness and cost-effectiveness.** The relative comparative effectiveness varies widely by disease, with quarantine reducing $R_S$ by >65% for influenza A and hepatitis A and by <10% for pertussis. However, due to a much shorter incubation period of influenza A versus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

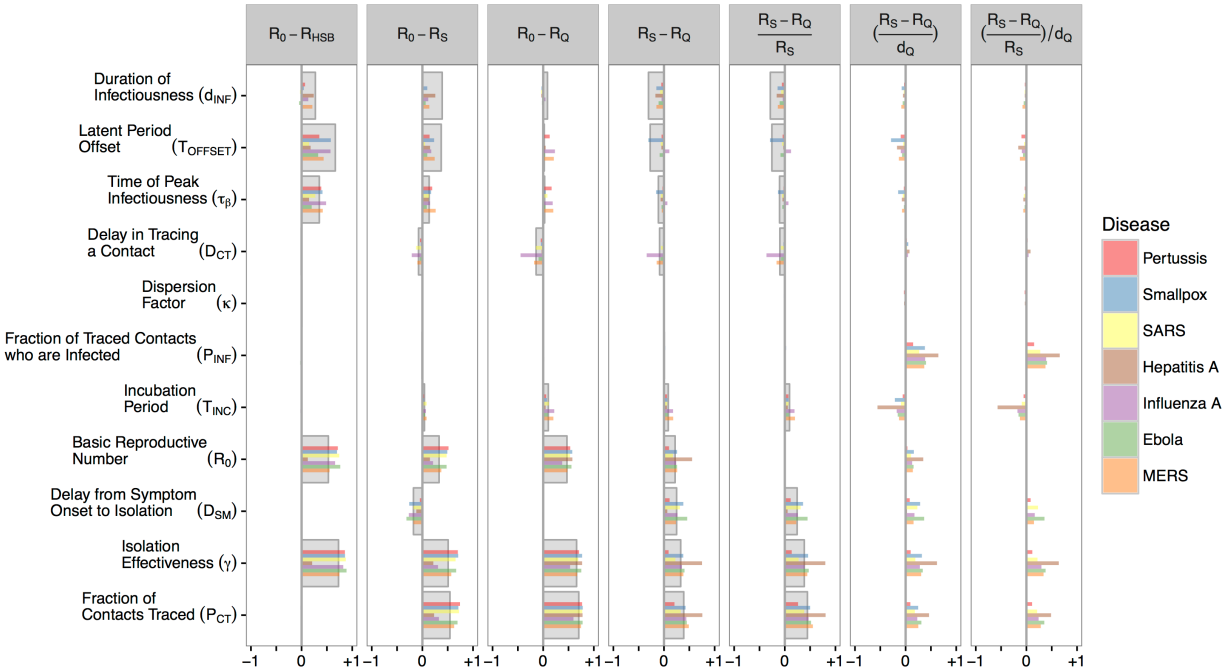


**Fig S2. Partial rank correlation coefficients for all outcomes.** Partial rank correlation coefficients (x-axis) measuring the influence of disease characteristics and intervention performance metrics (rows) on the impact, comparative effectiveness, and comparative cost-effectiveness of the interventions under study. Disease-specific estimates are shown with colored bars and pooled estimates with larger grey bars. For example, increasing the delay in tracing a named contact $D_{CT}$ has a generally small effect negative effect on $R_S$-$R_Q$ when pooled across diseases (large grey bar), but for influenza A specifically (purple bar), $D_{CT}$ has a rather large negative effect on $R_S$-$R_Q$. Note that pooled estimates for comparative cost-effectiveness are not available due to non-monotonic relationships across diseases.

**Table S1.** 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 $\tau_\beta$ |
| Ebola | 1.83 (1.72, 1.94) [33] | 13.36 (2.66, 38.8) [34] | 7.87 (0.93, 28.2) [33] | 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) [35,36] | 29.11 (24.6, 34.1) [37] | -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) [38] | 2.20 (0.63, 3.76) [35,39] | 1.40 (0.63, 3.10) [40] | -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) [41] | 7.62 (2.48, 23.3) [42] | 5.20 (1.83, 14.7) [42] | -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) [43] | 7.00 (4.00, 10.0) [29] | -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) [44] | 8.32 (1.59, 19.2) [44] | 4.01 (1.25, 12.8) [40] | 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) [45] | 11.83 (8.47, 16.5) [45] | 0.03 (-1.80, 1.68) | 8.45 (1.37, 20.0) | 0.32 (0, 0.97) |

Median (95% CI)

* Assumed

** Sequential Monte-Carlo boundary condition reached

## 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 S1**). The duration of infectiousness ($d_{INF}$), time of peak infectiousness ($\tau_\beta$), 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 $\tau$ of disease $R_{\tau_i} = \beta_{\tau_i} R_{0_i}$, where $\beta_{\tau_i}$ is the relative infectiousness of $i$ on hour $\tau$ such that $\sum_{\tau=0}^{d_{INF}} \beta_\tau = 1$. For parsimony and ease of interpretation, we assume $\beta_\tau$ follows a triangle distribution with a peak value at time $\tau_\beta$ 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 ($N_{\tau_i}$) generated by individual $i$ at hour $\tau$ is drawn from a negative binomial distribution with mean equal to $R_{\tau_i}$ and dispersion factor $\kappa$ 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 $\tau \epsilon \langle 0,1, \dots, d_{INF_i} \rangle$. 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 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 $j$. 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 $\gamma$ 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 $\tau_\beta$) 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 $\tau_\beta$, 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 $\tau_\beta$ 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 th1e 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 $\tau_\beta$ independent distributions from Θ.