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Timely identification of optimal control strategies for emerging infectious diseases☆

Zhilan Feng a, Yiding Yang a, Dashun Xu a,1, Pei Zhang a,2, Mary Mason McCauley b, John W. Glasser b,∗

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Abstract

Background: Health authorities must rely on quarantine, isolation, and other non-pharmaceutical interventions to contain outbreaks of newly emerging human diseases.

Methods: We modeled a generic disease caused by a pathogen apparently transmitted by close interpersonal contact, but about which little else is known. In our model, people may be infectious while incubating or during their prodrome or acute illness. We derived an expression for $R_p$, the reproduction number, took its partial derivatives with respect to control parameters, and encoded these analytical results in a user-friendly Mathematica™ notebook. With biological parameters for SARS estimated from the initial case series in Hong Kong and infection rates from hospitalizations in Singapore, we determined $R_p$’s sensitivity to control parameters.

Results: Stage-specific infection rate estimates from cases hospitalized before quarantine began exceed those from the entire outbreak, but are qualitatively similar: infectiousness was negligible until symptom onset, and increased 10-fold from prodrome to acute illness. Given such information, authorities might instead have emphasized a strategy whose efficiency more than compensates for any possible reduction in efficacy.

Conclusions: In future outbreaks of new human diseases transmitted via close interpersonal contact, it should be possible to identify the optimal intervention early enough to facilitate effective decision-making.

1. Introduction

Early in 2003, a physician infected while treating patients with atypical pneumonia in Guangdong Province, China, infected other travelers in their Hong Kong hotel. On returning home to Singapore, Taiwan, Toronto, and Vietnam, they transmitted the pathogen causing the disease, later named severe acute respiratory syndrome (SARS), to local residents. Global spread of this hitherto unknown pathogen led WHO to issue travel advisories and some national health authorities to quarantine travelers from affected areas. As subsequent infections were largely nosocomial, hospital infection-control procedures were increasingly enforced. Absent knowledge of the onset of infectiousness, local authorities also quarantined community contacts.

Facing with an infectious disease of unknown etiology, policymakers acted quickly (Gerberding, 2003). Case-series were among the earliest sources of information (e.g., presenting symptoms, duration of distinguishable clinical stages, and outcomes). Upon isolation of the etiologic agent, experience with illnesses caused by related pathogens became germane. While these actions were thoughtful, in retrospect some were unnecessary. We have since developed a model with which policymakers could use similar information—which should be available in future outbreaks, especially of new diseases causing serious morbidity—to assess the likely impact of available interventions.

Because identifying infected people before they become ill is difficult, quarantine is inefficient; e.g., only 11 of 238 probable cases were identified before symptom onset in Singapore (Tan, 2005) and 24 of 480 in Taiwan (Hsieh et al., 2005). Isolating people with symptoms that may herald disease, especially if they might have been exposed to someone since diagnosed, would be more efficient. Impact is proportional to the product of efficiency and efficacy, which must exceed 1 − 1/ℛ0 for control, where ℛ0 is the average number of sufficiently intimate contacts for transmission while infectious. Consequently, infected people must be highly infectious or infectious long before becoming ill for quarantine to be a better strategy than simply encouraging those...
with early symptoms to seek care and ensuring their proper disposition.

To weigh possible interventions to control infectious disease outbreaks, modelers must faithfully represent transmission. Our model allows infected people to become infectious before or after becoming ill. It permits quarantine while asymptomatic or isolation on seeking medical care and being diagnosed, at rates and with efficiencies that depend on clinical stage. Because health communications could influence these social phenomena, our model also allows hospitalization rates during distinguishable clinical stages to evolve. How effectively cases are isolated, when authorities begin searching for their contacts, if ever, and the proportion found, also may vary temporally.

Policymaking is difficult enough with accurate and complete information, neither of which is available during outbreaks of new diseases. Using only the Hong Kong case series (Lee et al., 2003; Tsang et al., 2003) and admissions to Tan Tock Seng Hospital (TTSH) through 24 March, when quarantine began, we estimated that infected people were not particularly infectious until acutely ill, a consensus reached months later (WHO, 2003). As the distribution of infectiousness largely determines the intervention of choice (Fraser et al., 2004; Day et al., 2006), this information is critical.

Armed with such results, we might have dissuaded policymakers from quarantine, suggesting they instead encourage people with symptoms that might herald disease to seek care, especially if exposed to someone since diagnosed, and—if indicated—ensure their proper isolation. This would have minimized the number of non-infected individuals detained without substantially compromising efficacy. Besides recommending the most promising interventions in future outbreaks, we could revise early estimates of parameter values as additional or better information became available, monitor intervention impacts, and recommend changing course if necessary. This would ensure the best possible use of available public health resources and minimize social disruption.

The belief that quarantine contributed substantially to the control of SARS persists despite the modest number of secondary infections that could have been prevented (e.g., the product of roughly 0.9 secondary infections per probable case in Singapore and 11 probable cases quarantined—assuming perfect isolation and no competing risks—is roughly 10 cases). But modeling enables one to calculate final outbreak sizes with and without interventions conditional on others (i.e., to relax both assumptions). Moreover, 116 possible contacts per probable case were restricted, respectively (Tan, 2005; Pang et al., 2003). In Singapore and Beijing, 38 and 13 contacts per probable case were restricted, respectively (Tan, 2005; Pang et al., 2003). As others cared for these well, but unproductive people, the economic cost was enormous.

2. Methods

To assist in controlling other newly emerging diseases, we modeled a generic respiratory illness caused by pathogens transmitted by close interpersonal contact. To evaluate actual interventions for SARS, we estimated some biological parameters from the case series in Hong Kong, adjusted others to fit clinically diagnosed probable cases in Singapore, and calculated outbreak sizes under alternative scenarios. Motivated by the social cost of quarantine relative to its contribution to control in Singapore, we also derived analytical expressions policymakers could use with limited information to determine the most effective strategy for controlling future outbreaks of new human diseases.

2.1. Sojourn distributions

Because models are hypotheses, their predictions must be evaluated and the causes of any disparities identified and remedied (Quine and Ullian, 1970), especially before use to inform public policy. Because complex models are difficult to evaluate, Einstein advocated modeling as simply as possible (May, 2004). To simplify, modelers commonly assume individuals move among disease stages at constant specific rates, whereupon sojourns are exponentially distributed. A property of exponential distributions—that time spent in any stage is independent of time elapsed before entry—is inconsistent with the natural history of infectious diseases.

Depending on one’s purpose, this discrepancy between biology and mathematics may be inconsequential. But it affects conclusions about the impact of quarantine and isolation (Feng et al., 2007), public health interventions differing only in timing. The gamma distribution does not have the memory-less property, so is more realistic biologically (Wearing et al., 2005). Models with gamma distributed sojourns are equivalent to ones in which stages of duration \( T \) are composed of \( n \) sub-stages each with duration \( T/n \).

To illustrate the difference, Feng et al. (2007) use the expected remaining sojourn at time-in-stage \( s \), \( M_n(s) \). For the gamma distribution with \( n \geq 2 \),

\[
M_n(s) = \int_0^\infty \frac{p_n(t+s)}{p_n(s)} \, dt = \frac{1}{p_n(s)} \int_0^\infty p_n(t) \, dt = 1 - \sum_{k=0}^{n-1} \frac{(n/t)^k}{k!} \sum_{j=0}^{n-1} \frac{(j/t)^j}{j!}.
\]

As \( M_n(s) < 0 \) and \( \lim_{s \to \infty} M_n(s) \to T/n \), here \( T = 1/\theta \), evidently \( M_n(s) \) strictly decreases with stage time \( s \). When \( s \) is large, moreover, the expected remaining sojourn can be as small as \( T/n \). Hence, time remaining depends on time already spent. The gamma distribution \( [p_n(s) \text{ for } n \geq 2] \) thus provides a more realistic description of disease natural history than the exponential \( [p_1(s)] \), for which \( M_1(s) = T \) for all \( s \).

Feng et al. (2007) derived a system of ordinary differential equations from a general integral equation model suitable for evaluating quarantine and isolation by replacing the exponential with the gamma distribution. Our model resembles theirs (Fig. 1), but we distinguish the prodrome and acute respiratory phase and allow infected people to become infectious before or after becoming ill, at rates—products of contact rates and probabilities of transmission on contact—that may differ among stages.

![Fig. 1. Minimum states (susceptible, S; incubating, E; ill, I; immune, R) and state-transition processes (infection, \( \lambda \); progression to the prodrome, \( \alpha \); and through acute illness, \( \delta \); quarantine, \( \chi \); hospitalization, \( \phi \), required to represent control of emerging infectious diseases transmitted via close contact via non-pharmaceutical interventions.](image-url)
2.2. Empirical methods

Our model’s biological parameters derive mostly from observations of early SARS patients in Hong Kong (Lee et al., 2003; Tsang et al., 2003). We estimated time-varying control parameters by minimizing sums of squared differences between cumulative model hospitalizations, $y_{E} + \phi_{I} + \phi_{R}$—where $y_{E}$ are those hospitalized from quarantine and $\phi_{I}$ from successive symptomatic stages, denoted by subscripts—and probable cases admitted to Tan Tock Seng Hospital (TTSH). We estimated these parameters twice, once from the first 30 days of hospital admissions (Table 1), before quarantine began, and once from admissions during the entire outbreak (Table 2).

As we were uncertain of many parameter values, we chose either gamma or triangular distributions for Latin hypercube sampling (Table 3). From the literature just mentioned, we obtained mean values for $1/\gamma$, $1/\delta_{R}$ and $1/\delta_{E}$ of 6, 4, and 8 days, respectively. Because the gamma’s mean is the product of its parameters, here called $A$ and $B$, we know that $B = mean/A$. Note that $A = 1$ corresponds to the exponential distribution, and that the gamma’s variance decreases with increasing $A$. We chose $A = 3$ for all three distributions, and thus, $B = \frac{3}{2}$ for $\gamma$, $\delta_{R}$ and $\delta_{E}$, respectively. ($A = 3$ also corresponds to three sub-stages in these respective states.) As for their upper and lower values, we chose ones for which the area under the probability density function (pdf) in between was 95–98%. Similarly, for the gamma distributions of $\beta_{I}$, $\beta_{R}$ and $\beta_{E}$, we used our best estimates as means (Table 2). We chose $A$ values of 2, 2, and 3 (i.e., assumed the variance of $\beta_{E}$ and $\beta_{R}$ exceed that of $\beta_{I}$), so the $B$ values are $0.0487$, $0.152$, and $0.582$. Each range was again chosen so that the area under the pdf in between was 95–98%. Results are similar if the $A$ values are neither too large nor close to 1.

Next we stratified the area under the corresponding density function (pdf) into $M$ equally probable intervals (i.e., each having area $1/M$, where $M$ is at least $\frac{1}{4}$ the number of uncertain variables, $K$). Letting $x_{0}, x_{1}, \ldots, x_{M}$ be sub-interval end points, the parameter’s/pdf to be $f(x_{i})$, and its cumulative distribution function (cdf) to be $F(x_{i})$:

$$
\frac{1}{M} = \int_{x_{i-1}}^{x_{i}} f(x) dx = F(x_{i}) - F(x_{i-1}) \quad \text{for } i = 1, 2, \ldots, M
$$

Because $x_{0}$ is the lower limit of $f(x)$, the remaining $x_{i}$‘s can be obtained from $x_{i} = F^{-1} \left[ F(x_{i-1}) - 1/M \right], \; i = 1, \ldots, M$. Finally, we selected points at random from each interval. The $M$ samples drawn for each input parameter were paired randomly with the $M$ for another, those $M$ pairs were paired randomly again with the $M$ for a third, and so on. Random paring continued until samples of all $K$ input parameters had been paired to form an $M$ by $K$ table. We estimated the infectious stage-specific contributions to the realized reproduction number, $R_{0}$, using these $M$ sets of input parameters.

We compared final outbreak sizes with our best estimates of time-varying control parameters (i.e., quarantine and hospitalization rates and isolation efficiencies) in Singapore with hypothetical alternatives. Differences with and without interventions, or with advanced or delayed timing, are estimates of cases (and hence deaths) averted, conditional on others. Such assessments tacitly assume independence (e.g., quarantine of possible contacts did not affect the timeliness with which actual ones who developed compatible symptoms sought medical care). Social distancing may have increased with quarantine in Hong Kong (Lo et al., 2005), but synergistic population responses in Singapore were more likely due to very effective health communications.

3. Results

Our analytical results include an expression for the realized reproduction number $R_{0}$, its partial derivatives with respect to control parameters and relationship to $R_{0}$, the intrinsic reproduction number (Appendix A). A Mathematica$^{\text{TM}}$ notebook that evaluates these expressions for user-supplied parameter values, comparing the impact of non-pharmaceutical interventions on any disease transmitted by close contact, is available from the

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**Table 1**

| Parameter (i) | Estimates |
|---------------|-----------|
| $\beta_{I}$   | 0.032     |
| $\beta_{R}$   | 0.259     |
| $\beta_{E}$   | 0.084     |
| Two epochs    | $t < 3/14$| $t > 3/14$|
| $\rho_{E}$    | 0.049     |
| $\rho_{R}$    | 0.12      |
| $\rho_{I}$    | 0.133     |
| $\gamma$      | 1.5       |
| $\delta_{E}$  | 0.123     |
| $\delta_{R}$  | 0.72      |
| $\delta_{I}$  | 0.25      |
| $\phi_{I}$    | 0.799     |

The $\rho$ are factors by which isolation reduces contributions to the force of infection; the other parameters are per-capita rates.

**Table 2**

| Parameter (ii) | Estimates |
|---------------|-----------|
| $\beta_{I}$   | 0.024     |
| $\beta_{R}$   | 0.152     |
| $\beta_{E}$   | 0.582     |
| Two epochs    | $t < 3/14$| $t > 3/2$|
| $\gamma$      | 0        |
| Four epochs   | $t < 3/2$| $t > 3/2$| $t_{1} < t < t_{2}$| $t > t_{2}$|
| $\rho_{E}$    | 0.049     |
| $\rho_{R}$    | 0.157     |
| $\rho_{I}$    | 0.162     |
| $\phi_{I}$    | 0.165     |
| $\phi_{E}$    | 0.245     |

Times correspond to 14 and 24 March, and 8 April, when control efforts changed (e.g., began or intensified). $\chi$ represents the per capita rate at which exposed individuals are quarantined.
corresponding author. Version 6 or higher of this software or its player, available from http://www.wolfram.com/products/player/, also is required.

Empirical results for SARS include parameter estimates from hospital admissions during the first 30 days and entire outbreak in Singapore by epoch; assessment of the reproduction number \( R_0 \), and impact of control measures via sensitivity analyses and final outbreak sizes under hypothetical scenarios.

Trial periods in Table 1 correspond to before 14 March, when the second generation of cases began being reported, and between 14 and 24 March, when home quarantine began. In addition to these, Table 2’s trial periods correspond to between 24 March and 8 April, when cumulative cases abruptly increased by about 10%, and after 8 April. Fig. 2 illustrates model fits to hospital admissions with these two parameter sets.

3.1. Parameter estimates

The infection rates, \( \beta_i \), differ quantitatively (e.g., those during the acute phase are two to three times those during the prodrome and 21–25 times those during the incubation period, respectively subscripted \( R, P, \) and \( E \)) when estimated from admissions during the first 30 days or entire outbreak (Tables 2 and 3, respectively); but not qualitatively (i.e., infectiousness is negligible until patients are acutely ill). Isolation efficiency \( \rho \) among those hospitalized during the prodrome increased from 0.16 to 0.7 during the first epoch to 0.76 during the last. Among those hospitalized while acutely ill, efficiency increased from 0.16 to almost 1. Similarly, the hospitalization rate \( \phi \) increased from 0.16 to 0.7 during the prodrome, while that during acute illness increased from 0.25 to 0.88. Both isolation efficiencies and hospitalization rates are respectively subscripted \( P \) and \( R \). Estimates for intervening periods are intermediate (Table 2).

3.2. Reproduction numbers

Our estimates of \( R_0 \) and contributions of each infectious state before and after control measures were introduced, given the assumed distributions and ranges described in Table 3, are shown with their associated uncertainties in Table 4 and Fig. 3. Our estimates of \( R_0 \), 3.16 and 0.86 before and after 24 March are comparable to Wallinga’s and Teunis’ (2004) 3.1 and 0.7 before and after 12 March, respectively.

![Fig. 2. Cumulative probable cases by date of symptom onset in Singapore (symbols) and fits to the first 30 days (dashed line) and entire outbreak (solid line). Parameter estimates differ quantitatively (i.e., they are higher initially), but are similarly qualitatively (Tables 1 and 3), particularly the ratio of infection rates during successive clinical phases.](image)

### Table 4

Results of uncertainty analysis.

| Parameter | Before 3/24 | After 3/24 |
|-----------|-------------|------------|
| \( R_0 \) | Mean | Std. Dev. | \( P (R_0 > 1) \) | Mean | Std. Dev. | \( P (R_0 > 1) \) |
| \( 0.147 \) | 0.147 | 0.002 | 0.114 | 0.103 | 0.0002 |
| \( 0 \) | | | 0.017 | 0.024 | 0 |
| \( 0.259 \) | 0.2 | 0.007 | 0.175 | 0.137 | 0.0007 |
| \( 0.382 \) | 0.318 | 0.05 | 0.203 | 0.187 | 0.007 |
| \( 0 \) | | | 0.052 | 0.061 | 0 |
| \( 0.217 \) | 0.265 | 0.02 | 0.109 | 0.131 | 0.002 |
| \( 0.644 \) | 0.806 | 0.19 | 0.036 | 0.049 | 0 |
| \( 1.511 \) | 1.475 | 0.528 | 0.155 | 0.135 | 0.003 |
| \( 3.159 \) | 2.25 | 0.922 | 0.861 | 0.413 | 0.295 |

These \( R_0 \) are contributions to \( R_0 \), their sum, by infectious individuals in transit (see Appendix A for definitions).

![Fig. 3. a and b. Histograms of \( \delta_i \) (i = 1, ..., 8) and \( \delta_0 \) before and after 24 March, when quarantine began and hospital infection control measures were more stringently enforced, from which the statistics in Table 4 were calculated.](image)

### Table 5

Sensitivity of \( R_0 \) to uncertain parameters.

| Parameter | Before 3/24 | After 3/24 |
|-----------|-------------|------------|
| \( f \) | PRCC | p-Value | PRCC | p-Value |
| \( 0.164 \) | <0.0001 | 0.162 | <0.0001 |
| \( 0.309 \) | <0.0001 | 0.192 | <0.0001 |
| \( 0.906 \) | <0.0001 | 0.581 | <0.0001 |
| \( 0.19 \) | <0.0001 | 0.459 | <0.0001 |
| \( 0.552 \) | <0.0001 | 0.786 | <0.0001 |
| \( 0.919 \) | <0.0001 | 0.783 | <0.0001 |
| \( \lambda \) | -0.029 | 0.004 |
| \( \phi_P \) | -0.032 | 0.002 | -0.061 | 0.0001 |
| \( \phi_E \) | -0.004 | 0.0004 | -0.051 | 0.0001 |
| \( \phi_f \) | -0.005 | 0.062 | -0.051 | 0.0001 |
| \( \phi_r \) | -0.124 | <0.0001 | -0.255 | 0.0001 |

Sensitivity to control parameters is shown in Table 5. Isolation efficiency during the incubation period hardly affects \( R_0 \), as infectiousness is negligible then. Because people did not seek care until acutely ill prior to 24 March, \( R_0 \) is also relatively insensitive to isolation efficiency during the prodrome or, by virtue of nosocomial transmission during that epoch (Leo et al., 2003), hospitalization while acutely ill.

3.3. Experiments

Final outbreak sizes (when birth and death are ignored, i.e., \( \mu = 0 \)) would have been larger had interventions been delayed
symptom onset (Lipsitch et al., 2003) and observed viral loads (Peiris et al., 2003)—infectiousness of patients with SARS was negligible until symptom onset and only one third during their prodrome as while acutely ill (Tables 2 and 3). Estimates based on the entire outbreak indicate temporal variation in the rates at which ill people sought care, probabilities of diagnosis and efficacy of isolation (Table 2).

Identifying infected people before they become ill is so difficult that quarantine is exceedingly inefficient. Consequently, unless infected people could infect many susceptible ones before becoming symptomatic—by virtue of being very infectious or infectious long before symptomatic—public health authorities should focus on identifying people with symptoms that may herald disease, encouraging them to seek care, especially if they might have been exposed to someone since diagnosed. Similarly, they should assist clinicians in diagnosing, and hospital infection control personnel in isolating effectively, those people before they become acutely ill.

To evaluate actual or hypothetical control measures, one must compare otherwise identical scenarios. Community intervention trials approach this ideal, but only modeling attains it. Not using all available measures that could be effective as expeditiously as possible during actual outbreaks of potentially lethal diseases would be unthinkable, but model outbreaks can be compared with and without interventions, alone or in various combinations, or with interventions at different times, to assess their impacts.

Our final size calculations with and without quarantine, but all else equal (i.e., experiments), indicate its impact would have been comparable to hospitalization during the prodrome (cf. Figs. 4c and d). But this assumes authorities could identify infected people during their incubation period. Reassuringly, our independent estimate of the rate at which exposed people were quarantined, \( \chi \) (Table 2) resembles the proportion of probable SARS patients actually quarantined, \( \frac{1}{2} \) (Tan, 2005). In Taiwan, where this proportion was strikingly similar, \( \frac{1}{2} \) (Hsieh et al., 2005), quarantined individuals were suspected of having SARS earlier than others (within 1.2 versus 2.89 days, respectively), but not reclassified any sooner (Hsieh et al., 2005). Our final size calculations illustrate the importance of timely interventions, but as only probable cases had priority for limited isolation facilities, evidently these shorter onset-diagnosis intervals contributed little.

In contrast, the rate at which probable cases were hospitalized during the prodrome, \( \phi_p \), increased from about 0.16 to 0.7 during the outbreak in Singapore (Table 2), contributing much more to control. The potential impact of quarantine has been so regularly confused with its actual contribution to SARS’ control that one wonders if this longstanding staple of public health (McNeill, 1977; Rosner, 1995) has been rigorously evaluated before. Day et al. (2006) refine Fraser et al.’s (2004) conditions for quarantine to be effective: the number of asymptomatic infections and fraction preventable—essentially the number of pre-symptomatic infections—must be large and the probability of infected individuals being quarantined high. Short of everyone staying home after a household member becomes ill, the last condition will be difficult to meet for respiratory diseases.

5. Conclusions

As the temporal distribution of infectiousness largely determines the optimal public health response (Fraser et al., 2004; Day et al., 2006), this is among the most important epidemiological unknowns early in outbreaks of new human diseases. If patients could be infectious before developing symptoms, quarantine must be considered. But identifying people whose contacts were...
sufficiently intimate for infection is extremely difficult, especially given uncertainty about the mode of transmission. The gain in efficiency—by ensuring instead that people with early signs and symptoms seek medical care, clinicians diagnose, and infection-control personnel isolate them effectively—may more than compensate for any loss of efficacy due to infections during the prodrome. Modeling can help to determine this distribution and, conditional on that essential information, to evaluate the relative impact of various possible public health interventions.

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Appendix A

Here we present the system of equations corresponding to Fig. A1; an expression for \( n_t \), the realized reproduction number, derived via the approach of Feng et al. (2007); take its partial derivatives with respect to control parameters, and describe the intrinsic number, \( \gamma_0 \), as a special case. A Mathematica™ notebook available from the corresponding author evaluates these expressions for user-supplied parameter values.

A.1. Mathematical model

Let \( S = S(t) \), \( E = E(t) \), \( Q = Q(t) \), \( I_{PP} = I_{PP}(t) \), \( H_{PP} = H_{PP}(t) \) and \( R = R(t) \) denote numbers susceptible, exposed (infected, but not yet symptomatic), quarantined, symptomatic, hospitalized (isolated), and recovered (or immune) individuals at time \( t \), respectively. Primed denotes lettered subscripts, the prodrome and acute respiratory stages and numbered ones subscripts, of which there are \( m, n \) and \( l \) respectively (Fig. A1):

\[
S = \mu N - \lambda(t)S - \mu S, \\
E_j = \lambda(t)S - (\chi + mx + \mu)E_j, \quad j = 2, \ldots, m, \\
Q_j = \chi E_j - (mx + \mu)Q_j, \quad j = 2, \ldots, m, \\
Pm_j = mxS - (\phi r + n\delta r + \mu)Pm_j, \quad j = 2, \ldots, n, \\
Pn_j = n\delta rPm_j - (\phi r + n\delta r + \mu)Pn_j, \quad j = 2, \ldots, n, \\
Hp_j = \phi rPm_j - n\delta rHp_j - (n\delta r + \mu)Hp_j, \quad j = 2, \ldots, n, \\
Hr = \phi rPm + n\delta rHp + (n\delta r + \mu)Hr, \\
L_T = n\delta rPm - (\phi r + n\delta r + \mu)L_T, \\
L_j = n\delta rHp_{j-1} - (\phi r + n\delta r + \mu)L_j, \quad j = 2, \ldots, l, \\
H_T = n\delta rHr + \phi rL_T - (n\delta r + \mu)H_T, \\
H_j = \phi rL_j + n\delta rHp_{j-1} - (n\delta r + \mu)H_j, \quad j = 2, \ldots, l, \\
R = \phi rL + n\delta rHp - n\delta rHr - \mu R, \\
\]

and \( N = S + E + P + H + R \) is the total population, whose size is constant by virtue of equal per capita rates of birth and death, \( \mu \). Other rates, reciprocals of mean sojourns, are: \( \gamma \), quarantine; \( \phi \), hospitalization; and progression during the incubation, \( \alpha \) and successive stages of acute illness denoted by subscripts, \( \delta \).

\[
\begin{align*}
\dot{L}_T &= \frac{1}{\mu} \left[ \frac{\beta_F [E + (1 - \rho)Q] + \beta_H [P + (1 - \rho)H]}{Q} \right] \\
&\quad + \beta_H [H_e + (1 - \rho)H], \quad E = \sum_{j=1}^{m} E_j, \quad Q = \sum_{j=1}^{m} Q_j, \\
\dot{I}_T &= \sum_{j=1}^{l} I_j, \quad H_p = \sum_{j=1}^{l} H_p_j, \quad I_R = \sum_{j=1}^{l} I_R_j, \quad H_R = \sum_{j=1}^{l} H_R_j.
\end{align*}
\]

In \( \lambda(t) \), the force of infection, the \( \beta_{EF,FR} \) transmission coefficients and \( \rho_{EF,FR} \) fractional reductions due to quarantine at home or other suitable facilities and isolation in hospitals.

A.2. Realized reproduction number

Given the transition probabilities, \( T_i \) and \( T_r \) and sojourns, \( D_i \) and \( D_r \) defined in Table A1, \( n_t \) is given by \( n_t = n_E + n_Q + n_t + n_{Qhr} + n_{Ihr} + n_{th} + n_{eth} \), where

\[
\begin{align*}
n_E &= \beta_T D_E, \\
n_Q &= (1 - \rho_E) \beta_T (D_E - D_E), \\
n_h &= \beta_T T_r D_r, \\
n_{Qhr} &= (1 - \rho_F) \beta_T (D_E - D_E), \\
n_{Ihr} &= (1 - \rho_F) \beta_T (D_E - D_E), \\
n_{th} &= \beta_T T_r D_r, \\
n_{eth} &= (1 - \rho_F) \beta_T (D_E - D_E).
\end{align*}
\]

Table A1

| Variable | Definition |
|----------|------------|
| \( T_E \) = \( \frac{mx}{mx + \mu} \) | Probability of surviving exposure to enter the prodrome |
| \( T_r \) = \( \frac{mx}{mx + \mu} \) | Probability of surviving the prodrome to become acutely ill |
| \( D_E \) = \( \frac{1}{mx + \mu} \) | Quarantine adjusted probability of surviving exposure |
| \( D_r \) = \( \frac{1}{mx + \mu} \) | Quarantine adjusted probability of surviving the prodrome |
| \( D_{th} \) = \( \frac{1}{mx + \mu} \) | Probability of acutely ill surviving and becoming clinically ill |

Fig. A1. Markov model diagram with sub-stages denoted by lettered and numbered subscripts, e.g., the incubation period is partitioned into \( E_r, E_s < E_s < E_r, \) and \( E_{rs} \), the prodrome into \( I_{rs}, I_{rn} < I_{rn} < I_{rs} \), and \( I_{rs} \), and the acute respiratory phase into \( I_{rs}, I_{rn} < I_{rn} < I_{rs} \), and \( I_{rs} \).
A.3. Impact of control measures

The derivatives of $R_0$ with respect to quarantine, hospitalization during the prodrome and acute illness and the efficacy of isolation during the prodrome and acute illness and the efficacy of isolation during these stages are

$$\frac{\partial R_0}{\partial q} = \beta_R \rho_T D_k + \beta_R \rho_T D_{k_T} T_D,$$

$$= -\beta_R \rho_T \left( \frac{1}{(mz + \chi + \mu)^i} \sum_{i=0}^{m-1} \left( \frac{mz}{mz + \chi + \mu} \right)^i \right),$$

$$- \left\{ \beta_R \rho_T \left( \frac{1}{h_D + \phi + \mu} \right) ^{n} \sum_{i=0}^{n-1} \left( \frac{h_D + \phi + \mu}{h_D + \phi + \mu} \right)^i \right\} \left( \frac{mz}{mz + \chi + \mu} \right)^i \leq 0,$$

$$\frac{\partial R_0}{\partial d} = \beta_R \rho_T \left( \frac{mz}{mz + \chi + \mu} \right)^m \left( \frac{n\phi}{n\phi + \phi + \mu} \right)^n \sum_{i=0}^{n-1} \left( \frac{\phi}{\phi + \phi + \mu} \right)^i \leq 0,$$

$$\frac{\partial R_0}{\partial l} = -\beta \left( \frac{1}{(mz + \chi + \mu)^i} \sum_{i=0}^{m-1} \left( \frac{mz}{mz + \chi + \mu} \right)^i \right) \leq 0,$$

$$\frac{\partial R_0}{\partial p} = \beta_R \left( \frac{mz}{mz + \chi + \mu} \right)^m \left( \frac{n\phi}{n\phi + \phi + \mu} \right)^n \sum_{i=0}^{n-1} \left( \frac{\phi}{\phi + \phi + \mu} \right)^i \leq 0,$$

$$\frac{\partial R_0}{\partial k} = \beta_R \left( \frac{mz}{mz + \chi + \mu} \right)^m \left( \frac{n\phi}{n\phi + \phi + \mu} \right)^n \sum_{i=0}^{n-1} \left( \frac{\phi}{\phi + \phi + \mu} \right)^i \leq 0.$$

A.4. Intrinsic reproduction number

Absent control, the realized reproduction number reduces to the basic reproduction number, $R_0 = \beta_R D_k + \beta_R T_D + \beta_R T_{k_D} D_{k_D}$. Their relationship is given by

$$R_0 = \begin{cases} \left[ \beta_R D_k + \beta_R T_D - \Gamma_k D_k \right] \\ + \beta_R T_{k_D} D_{k_D} \end{cases}.$$

Clearly, $R_0$ when all control parameter values are zero, as $D_k = D_D$ and $T_D = T_{k_D}$, making the three terms in brackets all equal to zero. Also, $R_0 < R_0$ since $D_k > D_D$ and $T_D > T_{k_D}$, which implies that the quantity inside the brackets is positive if some control parameters are not zero.

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