Figure 5
Sensitivity of the number of secondary transmissions caused by released infectious individuals to the different lengths of quarantine and prevalence levels at the source. A. Quarantine alone. **B.** Quarantine combined with rapid diagnostic testing. Sensitivity of the number of secondary transmissions caused by released infectious individuals is examined for different lengths of quarantine (2.8, 4.8, 5.7 and 8.7 days) and prevalence levels at the source (1%, 5% and 10%). Each dot represents median estimate of 100 simulation runs. The whiskers extend out to 5th and 95th percentiles of the simulations.

theoretical distribution [16-21]. For instance, 95th percentiles of the incubation period for severe acute respiratory syndrome (SARS) and smallpox were suggested to be 11–13 days [19,21] and 16–17 days [16] since exposure, respectively. Direct application of this concept to pandemic influenza suggests that the optimal quarantine period for pandemic influenza is only 2.73 days since exposure, which is far shorter than those for SARS and smallpox. However, since influenza involves a non-negligible fraction of asymptomatic infections [12,22], we also undertook the additional step of incorporating this feature into our assessment of quarantine effectiveness. This refinement permitted further elaboration of effectiveness estimates, which we believe contributes to theoretical considerations around the control of other infectious diseases. In addition, we reasonably showed the preventive performance of quarantine, expressed as the number of released infectious individuals and the ripple benefit expressed as number of secondary transmissions caused by them. Using further information on the contact structure in the island nation, our framework could be further extended to estimate the probability of extinction and the delay effect of epidemic spread imposed by quarantine, the latter of which was discussed by a recent study [35]. Although the recent study theoretically emphasises the

difficulty of effective border control (including quarantine) [35], we stress that the epidemiologic characteristics of influenza (e.g., short incubation period and generation time) permit anticipating large ripple benefits from quarantine (given that importation may continue for only a short period of time before full border closure occurs).

Access to a highly sensitive test for pandemic influenza infection may increase the effectiveness of quarantine and shorten the quarantine period routinely required for incoming travellers. Preventive performance in finding true positives (i.e., PPV of quarantine combined with rapid diagnostic testing) appeared not to be very sensitive to the length of quarantine (for $t > 2$ days). This result suggests that if diagnostic test kit supplies are plentiful, then testing should be done early in quarantine. But if a test kit sparing approach is used (i.e., avoiding testing of those who become symptomatic) then there is not much benefit in delaying testing until after day 2 in quarantine. A test with both high sensitivity and high specificity would also allow for better use of resources if the travellers who tested negative are released into the community. Since PPV is mainly determined by prevalence at the source, it should be noted that an exit screening process at the source lowers the prevalence as well as PPV. Nevertheless, the effectiveness of
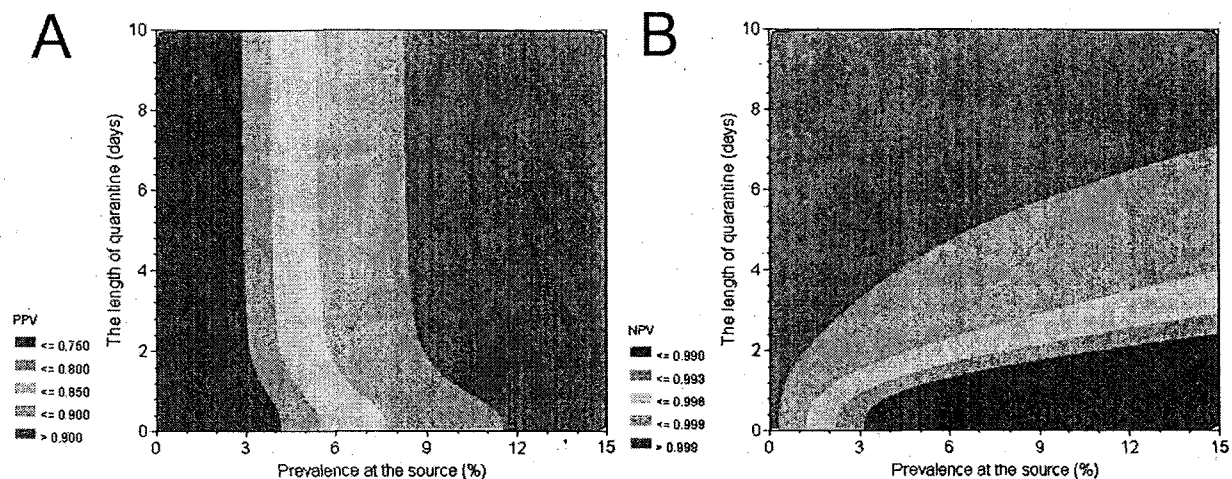
Figure 6
Diagnostic performance of quarantine with use of rapid diagnostic testing. A. Positive predictive values (PPV) and **B.** Negative predictive values (NPV) of quarantine combined with rapid diagnostic testing as functions of the length of quarantine and prevalence at the source. For the quarantine of 3 days or longer, PPV is less sensitive to the length of quarantine and depends almost only on the prevalence. NPV is sensitive to both the length of quarantine and prevalence at the source, achieving extremely high estimates to correctly release true negative individuals into the community.

quarantine itself is independent of the prevalence, and moreover, lower prevalence among incoming individuals yields a higher chance of extinction (or greater ripple effect of quarantine (Figures 4 and 5)). NPV of quarantine combined with diagnostic testing would be extremely high with quarantine periods for lengths of 3 days or longer, supporting our suggestion to release quarantined individuals testing negative to the rapid diagnostic test into the community (if there was high confidence in test performance parameters for the emergent pandemic strain). In light of our findings, island countries may consider including influenza testing capacity and test kit stockpiles in their pandemic plans. The use of rapid diagnostic tests, if available through stockpiling in advance or rapid delivery after pandemic emergence, may permit more effective border control, with more efficient use of isolation facilities and shortening of the quarantine period.

The operation of quarantine would be most feasible for islands with low traveller numbers and with pre-existing facilities that could be used for quarantine (e.g., hotels). Our study was indeed motivated by the consideration of protecting small island nations (e.g., in the South Pacific and Caribbean), because use of border control at usually just one or two international airports would be the major way in which the introduction of pandemic influenza could be prevented in these islands. Yet the analysis could potentially hold for larger island nations such as Australia, whose pandemic plan also includes border quarantine [40]. The logistics of quarantine might be far more demanding in Australia with its multiple international air-

ports, but which nonetheless used strict maritime quarantine to successfully delay the entry of the 1918 pandemic [41]. Evidence about the geographic spread of influenza highlights the importance of quarantine in multiple locations [42-44]. Small countries with land borders and limited entry points could also use these approaches to delay entry of pandemic influenza as occurred for Israel in the 1957 influenza pandemic [5]. Facility-based quarantine could also be supplemented with ongoing surveillance in the community of those released from quarantine.

Our analysis employed a number of simplifying assumptions, among which we should emphasise the most important one. The detailed natural history parameters for seasonal influenza are not well documented and, moreover, we of course do not know if the incubation period and generation time of an emergent pandemic strain would be close to those of seasonal influenza documented in the limited number of publications to date. It should be noted that our analysis is solely based on the available published evidence and that the effectiveness of quarantine would be overestimated if the emergent strain of pandemic influenza had a longer incubation period or a longer generation time than we have assumed. However, the incubation period for human infection with H5N1 appears to be similar to other sub-types infecting humans [45]. This issue applies not only to the incubation period but also to other parameters, the role of which for each can be inspected using equations (4) and (5). For example, a historical analysis suggests that only 9% of infections resulted in an asymptomatic infection [46], which

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would contribute to improved quarantine effectiveness (compared to our results). Given that our exercise indicates the critical importance of the incubation period and generation time, epidemiological investigations should be performed to better quantify these parameters and further inform evidence-based pandemic planning.

Extrinsic factors should also be more precisely quantified in future. As an indirect extrinsic effect, when infected individuals are released into the community and become infectious to others, recently quarantined individuals may be detected and isolated earlier than those who have not been quarantined [47]. Another issue of detection is that some island states may have access to laboratory-based PCR influenza tests which are far more sensitive and specific than rapid tests [48], which could offer the test results in a few hours and greatly shorten the length of quarantine.

To more appropriately quantify the effectiveness of quarantine, two other technical issues have to be discussed. The first is concerned with skewness of the offspring distribution (i.e. the distribution of the number of secondary transmissions caused by a single primary case). Although our study reasonably showed the absence of secondary transmissions for quarantine of certain lengths, we ignored the skewness (i.e., the presence of potential super-spreaders [49]), and thus, the uncertainty bounds might have been smaller than in reality. Although the mean and median of the predicted number of secondary transmissions are still valid, and even though the skewed offspring distribution was partly incorporated in the model with the right-skewed generation time distribution, super-spreading events played a key role in triggering the international spread during the epidemic of SARS, and in light of this, quantification of the dispersion parameter (of the offspring distribution) is needed in future studies. Another issue is related to our conservative assumption that all incoming individuals experienced infection upon arrival. Since it is impractical to know the time of infection for all incoming infected individuals (which should ideally be known when the quarantine is started at time $t = 0$), we adopted a worst case scenario where all infected individuals experience infection at $t = 0$ (see Appendix). This assumption could have overestimated the optimal length of quarantine. If further research demonstrates that influenza transmission on board flights is very rare, then it would be possible to set the quarantine period to begin at the start of the flight and therefore reduce its duration correspondingly following arrival. However, then we have to take into account the possible secondary transmissions during the quarantine period. Estimation of the effectiveness of imperfect quarantine (i.e., quarantine which allows secondary transmissions within the quarantine facility) would be far more complicated than our simpler model, and clarification on this point is a task for future research.

In addition to the present study, it should be noted that quarantine may be combined with reduction of travel volumes (e.g., even mandatory restrictions on non-essential travel) which would have a large effect if it occurred rapidly [35,50,51]. Substantial reductions of travel volumes could make the logistics of quarantine far more feasible for island nations and increase the probability of ensuring the absence of secondary transmissions (given the same prevalence level to that of a larger travel volume). Moreover, there is the potential usefulness of antiviral prophylaxis during the quarantine period which could theoretically reduce the number of infectious individuals. Despite the plausible reduction of infectiousness under antiviral prophylaxis, the probability of symptomatic infection will also likely be reduced, and thus, the detection of cases might be reduced. Unless the efficacy of antiviral prophylaxis and detection under this measure are well documented and promisingly high, it is difficult to determine if this countermeasure is likely to offer an overall positive impact on the success of quarantine, and this point should be clarified in future research. Another topic area to be clarified further is concerned with cost-effectiveness. Although we implicitly assumed that the governments of island nations may be willing to allocate quarantine facilities and spend sufficient money for diagnostic testing, these measures are economically demanding, especially for developing island nations. Extension of our method would permit estimating the required cost to achieve a specific ripple benefit (e.g., zero secondary cases for a certain period of time). Use of home-based quarantine (with health agency surveillance and support) is another cost-saving option that could be considered for islands with limited capacity for using facility-based quarantine (e.g., those with few hotels that could be requisitioned), but it should be noted that home-based quarantine might violate our assumption of ignoring secondary transmissions during the quarantine period. In practice, there may also be scenarios where it is not practical to separate all incoming travellers into separate quarters within a quarantine facility (e.g. parents with small children). In such cases, health workers may need to monitor such individuals especially closely and isolation may need to include a parent and infant when only one is symptomatic (all of which would increase costs).

Despite our simplifying assumptions, the present study reasonably suggests that use of quarantine has the potential to substantially reduce the risk of pandemic influenza arriving or at least significantly delay arrival, in small island nations. To ensure the absence of secondary transmissions for plausible ranges of prevalence at the source and a modest number of incoming travellers, we recommend quarantining the incoming individuals for 9 days if quarantine alone is implemented and 6 days if quarantine is combined with rapid diagnostic testing.

Conclusion

To inform border control for pandemic influenza in small island nations we examined the potential effectiveness of quarantine using several parameters which describe the epidemiologic characteristics of influenza. In particular, our modelling approach accounted for asymptomatic infection which is deemed a key requirement for successful influenza control [52,53]. The effectiveness was modelled as a relative reduction of the risk of introducing infectious individuals into the community as a function of time since arrival. We recommend a quarantine period of 9 days to reduce by more than 99% the risk of introducing infectious individuals and to ensure the absence of secondary transmissions. When rapid diagnostic testing is combined with quarantine, we recommend quarantine for 6 days to similarly prevent secondary transmissions.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NW and MGB conceived of the study and participated in its design and coordination. HN developed methodological ideas and performed statistical analyses. HN and NW did most of the work on drafting the manuscript. All authors read and approved the final manuscript.

Appendix

Earlier infection before quarantine

For simplicity, we consider the impact of earlier exposure to infection on the effectiveness of quarantine in terms of the frequency of onset during the quarantine period, which is relevant to the determination of the incubation period conducted by Anderson Grey McKendrick [15,29]. Let the length of quarantine be t. To account for earlier infections before starting quarantine at $t = 0$, we consider infection-age (i.e. the time since infection) for infected individuals, denoted by τ. Let $i(t, \tau)$ and $j(\tau)$, respectively, be the number of incubating infected individuals at quarantine period t and infection-age τ and the number of incubating infected individuals at infection-age τ at the beginning of quarantine $t = 0$ (i.e. $i(0, \tau) = j(\tau)$). $i(t, \tau)$ is written as

$$i(t,\tau) = j(\tau - t)\frac{\Gamma(\tau)}{\Gamma(\tau-t)} \qquad (A1)$$

for $\tau - t > 0$ where $\Gamma(\tau)$ informs the survivorship function of incubating individuals at infection-age τ, i.e.,

$$\Gamma(\tau) = \exp\left(-\int_0^\tau \gamma(\sigma)d\sigma\right) \qquad (A2)$$

where $\gamma(\tau)$ is the rate (or force) of onset at infection-age τ. Consequently, the density function of the incubation period, $f(\tau)$, is given by

$$f(\tau) = \gamma(\tau)\Gamma(\tau) \qquad (A3)$$

Since we assume that there is no secondary transmission during quarantine period, $i(t, \tau) = 0$ for $t-\tau > 0$. The number of new symptomatic cases at quarantine of length t, $n(t)$, is

$$n(t) = \int_t^\infty \gamma(\tau)i(t,\tau)d\tau \qquad (A4)$$

Replacing the right-hand side of (A4) by that of (A1), we get

$$n(t) = \int_t^\infty \gamma(\tau)j(\tau - t)\frac{\Gamma(\tau)}{\Gamma(\tau-t)}d\tau = \int_0^\infty f(t + \sigma)\frac{j(\sigma)}{\Gamma(\sigma)}d\sigma \qquad (A5)$$

In our setting, all quarantined individuals have not experienced symptom onset before quarantine starts at $t = 0$. Assuming that all infected individuals eventually experience symptom onset (just for now), the total number of infected individuals satisfies

$$\int_0^\infty n(t)dt = \int_0^\infty j(\tau)d\tau \qquad (A6)$$

Using (A5) and (A6), the density of symptom onset at quarantine period t (i.e. the frequency of symptom onset relative to the quarantine period t), $h(t)$, is

$$h(t) = \frac{n(t)}{\int_0^\infty n(t)dt} = \int_0^\infty \frac{f(t+\sigma)}{\Gamma(\sigma)}\frac{j(\sigma)}{\int_0^\infty j(s)ds}d\sigma \qquad (A7)$$

Equation (A7) indicates the critical importance in understanding the earlier exposure in order to determine the optimal length of quarantine. That is, the density of symptom onset $h(t)$ always depends on the infection-age distribution (which is informed by $j(\tau)$) at the starting time point of quarantine $(t = 0)$.

If the epidemic at the source country becomes endemic and reaches a stationary state with constant incidence Q, and if the infected travellers result from random sampling of infected individuals at the source country, we have $j(\tau) = Q\Gamma(\tau)$, leading to

$$h(t) = \frac{\Gamma(t)}{\int_0^\infty \Gamma(\tau)d\tau} \qquad (A8)$$

which is equivalent to the survivorship of the incubating infected individuals (written as $1-F(t)$ in the main text using the cumulative distribution function of the incubation period $F(t)$). The simplification in (A8) holds only when a stationary state is the case at the source country, which is not likely to be observed in the event of an influenza pandemic.
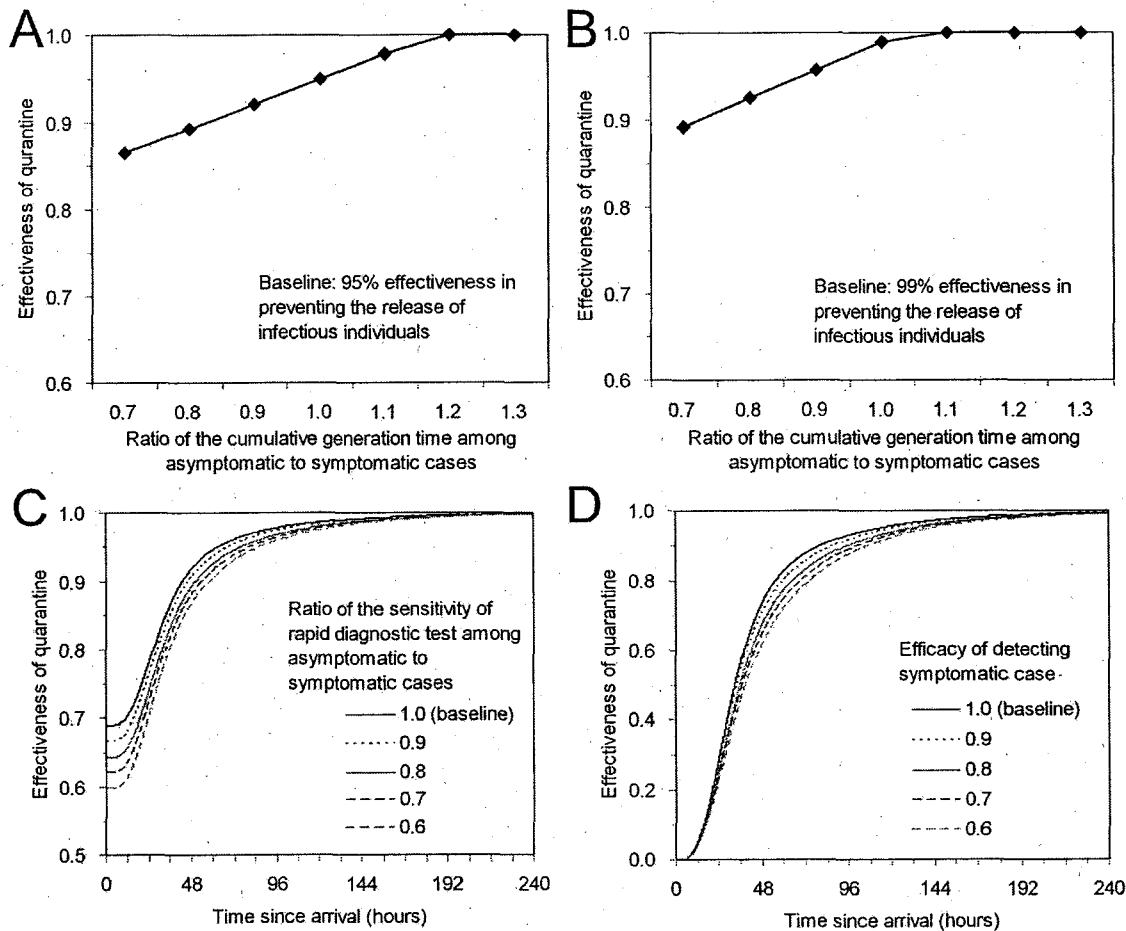
Figure 7
Sensitivity of the effectiveness of quarantine to uncertain epidemiologic variables. A & B. Effectiveness of quarantine as a function of the ratio of the cumulative generation time among asymptomatic to symptomatic cases. Sensitivity of the point estimates of the effectiveness with baseline values of 95% and 99% are examined in A and B, respectively. C. Sensitivity of the effectiveness of quarantine in the presence of rapid diagnostic testing to the diagnostic sensitivity among asymptomatic infected individuals. D. Effectiveness of quarantine with imperfect efficacy of case detection of symptomatic cases.

Thus, we need to use (A7) with some prior information of $j(\tau)$. Nevertheless, since the infection event is unobservable, we seldom know $j(\tau)$. Therefore, we recommend assuming that the start of quarantine $t = 0$ as the time of infection, which is the worst case scenario. Although the above mentioned arguments apply to symptomatic cases alone, we find exactly the same issue in the survivorship of infectiousness.

Differing parameters between symptomatic and asymptomatic cases
First, we consider the impact of differing generation times between symptomatic and asymptomatic cases on the effectiveness of quarantine. Although the generation time distribution of asymptomatic influenza infection has yet to be clarified, we at least theoretically separate the cumu-

lative distributions $G_s(t)$ and $G_a(t)$, respectively, for symptomatic and asymptomatic cases. The equation (4) in the main text is replaced by

$$\varepsilon(t) = 1 - [\alpha(1 - F(t))(1 - G_s(t)) + (1 - \alpha)(1 - G_a(t))]$$
(A9)

Since $G_a(t)$ is unknown, we examine the sensitivity of ε (t_β), where the effectiveness is calculated as $100\beta\%$ (i.e. β = 0.95 and 0.99), to different ratios of $G_a(t_\beta)$ to $G_s(t_\beta)$. Let c be $G_a(t_\beta)/G_s(t_\beta)$. $G_s(t)$ is assumed to be equivalent to $G(t)$ in the main text.

Figures 7A and 7B show the sensitivity of ε (t_β) to different values of the ratio c with t_β= 4.74 and 8.62 days. When c

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is smaller than 1 (i.e. when there are more asymptomatic infected individuals with extremely long generation times compared to symptomatic cases), the effectiveness measure (A9) becomes smaller than the baseline which we get from (4) in the main text. On the contrary, if the generation time of asymptomatic infected individuals is shorter than that of symptomatic infected individuals, the effectiveness rises up close to 100% with the assumed lengths of quarantine, suggesting the need to accumulate epidemiological evidence of the generation time.

Second, we investigate the impact of differing sensitivity of rapid diagnostic testing between symptomatic and asymptomatic cases on the effectiveness of quarantine. We theoretically separate the sensitivity S_e into $S_{e,s}$ and $S_{e,a}$ for symptomatic and asymptomatic cases, respectively. Since asymptomatic cases may shed lower titres of virus, we suspect that the ratio $S_{e,a}$ to $S_{e,s}$ ($r := S_{e,a}/S_{e,s}$) is smaller than 1. The equation (5) in the main text is replaced by

$$\varepsilon_d(t) = 1 - [(1 - S_{e,s})\ \alpha(1 - F(t))(1 - G(t)) + (1 - S_{e,a})\ (1 - \alpha)(1 - G(t))] \qquad (A10)$$

Figure 7C shows the sensitivity of $\varepsilon_d(t)$ to different values of the ratio r assuming that $S_{e,s} = 0.69$. As the ratio r becomes smaller (i.e. as the diagnosis of asymptomatic infected individuals becomes more difficult than that of symptomatic cases), the effectiveness also becomes smaller. Although the difference in $\varepsilon_d(t)$ is greater for short quarantine periods, the effectiveness becomes less sensitive to r as the length of quarantine becomes longer. We estimated that 99.0% effectiveness in reducing the risk of introducing infectious individuals into the community is achieved with $t = 5.71$ days using the rapid diagnostic test of $r = 1.0$ in the main text. The effectiveness estimate with the same length of quarantine and $r = 0.6$ is still as large as 98.1%.

Imperfect case detection
Although we considered perfect detection of symptomatic cases upon symptom onset during quarantine in the main text, here we examine the sensitivity of the effectiveness of quarantine to differing efficacy of case detection. Let the efficacy of case finding be k which we assumed as 1 in the main text. In reality, it might be difficult to detect all flu-like symptoms (i.e. $k < 1$). The equation (4) in the main text is replaced by

$$\varepsilon(t) = 1 - [\alpha(1 - kF(t))\ (1 - G(t)) + (1 - \alpha)\ (1 - G(t))] \qquad (A11)$$

It should be noted that k influences symptomatic cases alone, because the detection of symptoms does not apply to asymptomatic infected individuals. Figure 7D shows the sensitivity of $\varepsilon(t)$ to different values of the ratio k

which was assumed to lie in the range of 0.6 – 1.0. As the ratio k becomes smaller (i.e. as the detection becomes less efficient), the effectiveness becomes smaller. The difference in $\varepsilon(t)$ between different ratios k is particularly highlighted when the quarantine period is between 2 and 5 days. Nevertheless, for the shorter and longer quarantine periods, difference in $\varepsilon(t)$ is almost negligible. In the main text, we estimated that quarantine for 8.62 days achieves 99.0% effectiveness of reducing the risk of releasing infectious individuals into the community with $k = 1.0$. The effectiveness estimate with the same length of quarantine and $k = 0.6$ is still as large as 98.2%.

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