Title: **Interventions targeting air travellers early in the pandemic may delay local outbreaks of SARS-CoV-2**

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High level summary

Aim: To determine if interventions aimed at air travellers can delay establishment of a SARS-CoV-2 outbreak in a previously unaffected country with no shared border with China.
Methods Summary: Determining how many imported cases are needed to trigger an outbreak in a new location is critical to quantifying if SARS-CoV-2 outbreaks can be delayed. Here we rely on the "outbreak threshold", which is a function of the average number of secondary cases produced by each infected case, plus the variation from person-to-person in how many secondary cases they generate (often referred to as "the dispersion parameter, k").
We define a traveller intervention as either: a) screening for symptoms at either departure or arrival, b) sensitisation of arrivals to signs of illness, or c) a combination of both. We assume that sensitisation will result in a lower individual reproduction number for the traveller (e.g. by self-isolation and more rapid reporting which triggers contact tracing) and that syndromic screening reduces the number of infected travellers who can seed an outbreak.
We then calculate the delay in reaching the outbreak threshold according to the number of infected travellers arriving each week, and the effectiveness of interventions a, b, and c, assuming the basic reproduction number to be gamma distributed with CIs ranging from 1.4 to 3.9. Because of the considerable uncertainty in the estimate we report no central estimates but rather 50% and 95% quantiles, focusing specifically on the lower bounds as a measure of likely minimal impact.
Results Summary: We evaluated sensitisation effectiveness of 30, 50 and 70%, assuming either 1, 10, or 100 infected travellers per week. We found that early in the outbreak when only few infected travellers arrive, traveller sensitisation can delay a major outbreak in a previously unaffected region. For 50% effectiveness, and assuming 1 infected traveller per week, we find that in 75% of simulations the outbreak is delayed by at least 11 days (97.5% of simulations: at least 7 days). The possible delay decreases rapidly for more travellers, lower effectiveness of sensitisation, higher R_0 or lower heterogeneity thereof. However, syndromic traveller screening at departure and/or arrival can further enhance impact. In combination with sensitisation, syndromic screening can delay an outbreak substantially longer. In 75% of simulations we find

an outbreak delay of at least 111 days (97.5% of simulations: at least 23 days) for 1 infected traveller per week and at least 9 days (97.5% of simulations: at least 4 days) for 10 infected travellers per week.

Limitations include:

- We assume a constant rate of infected travellers. However, this may increase rapidly as the epidemic continues to spread exponentially in China and potentially elsewhere. There is currently little evidence for an exponential increase in infected travellers to Europe as airports in the highest risk regions have shut. If indeed infected traveller numbers were to increase exponentially numbers would increase from 1 to 10 and 100 per week within about 19 and 38 days respectively (assuming R=2.5 and serial interval of 7.5) and estimated delays would decrease accordingly.
- The only estimate from the current outbreak for the variation between individuals in the number of secondary cases (*k*) is including large confidence intervals that span estimates for SARS and seasonal influenza. The estimated delay of an outbreak was highly sensitive to k.
- We assume that syndromic surveillance at entry leads to immediate case isolation and hence no onward transmission. This is ignoring that during the flight the index case may have infected other travellers.
- We assume that only sensitised travellers would pick up quickly on relevant symptoms and self-isolate and report to trigger contact tracing. Non sensitised travellers are assumed to not pay attention to early influenza-like symptoms during the winter season and hence only report with severe symptoms, i.e. when most of secondary cases have been infected and themselves have potentially further spread the virus. This may overestimate the estimated impact of sensitisation.
- We don't explicitly account for potential asymptomatic transmission. However, we implicitly do so as both the syndromic screening as well as the contact tracing work that infomed our estimates accounted for a small proportion of asymptomatic transmitters.

Abstract

Objectives: To determine if interventions aimed at air travellers can delay establishment of a SARS-CoV-2 outbreak in a previously unaffected country.

Design: Simulation study

Setting: Countries with no sustained SARS-CoV-2 transmission and with no shared border with affected regions

Participants: Infected air travellers

Interventions: Syndromic screening at departure and/or arrival & traveller sensitisation to the COVID-2019-like symptoms with the aim to trigger rapid self-isolation and reporting on symptom onset.

Main outcome measures: The achievable delay until a major local outbreak is likely to occur

Results: We evaluated traveller sensitisation effectiveness in reducing the number of secondary cases of 30, 50 and 70%, and assumed either 1, 10, or 100 infected travellers per week. Early in the outbreak when only few infected travellers arrive, traveller sensitisation can delay a major outbreak in a previously unaffected region. For 50% sensitisation effectiveness, and assuming 1 infected traveller per week, we find that in 75% of simulations the outbreak is delayed by at least 11 days (97.5% of simulations: at least 7 days). The possible delay decreases rapidly for more travellers, lower effectiveness of sensitisation, higher R_0 or lower heterogeneity thereof. Syndromic traveller screening at departure and/or arrival can further enhance outbreak delays. In combination with sensitisation, syndromic screening can delay an outbreak substantially longer. In 75% of simulations we find an outbreak delay of at least 111 days (97.5% of simulations: at least 23 days) for 1 infected traveller per week and at least 9 days (97.5% of simulations: at least 4 days) for 10 infected travellers per week.

Conclusion: Air-traveller targeted interventions, particularly in combination, can delay local SARS-CoV-2 outbreaks in the magnitude of a few weeks to potentially even months if the number of infected travellers remains low.

Background

Similar to outbreaks of other respiratory pathogens (1–4), syndromic airport screening at arrival of travellers from regions with high risk of human-to-human transmission of SARS-CoV-2 is unlikely to prevent a sufficient proportion of infected travellers to prevent global spread (5,6). However, sensitising potentially affected travellers to the symptoms and risk of SARS-CoV-2 and to encourage self isolation as well as seeking for medical assistance via telephone, may have a more pronounced effect and is currently used in many transport hubs. Although, with increasing numbers of infected travellers contact tracing is unlikely to be sustainable for long because of the immensely resource intensive nature of contact tracing and hence unlikely to completely prevent local transmission (7).

We aim to estimate the effectiveness of syndromic screening and traveller sensitisation for delaying the onset of sustained SARS-CoV-2 spread in previously unaffected regions.

Methods

Model of symptom screening and sensitisation

To simulate a variety of scenarios of global SARS-CoV-2 spread we assumed that a number of infected travellers per week, λ, who do not have severe symptoms at boarding, would attempt to travel to a specific previously unaffected region (Table 1). We have previously estimated the probability of SARS-CoV-2 infected travellers not being detected at either exit or entry

screening, θ, as 46% for long-haul flights (6). We use similar base case assumptions of a 12 hour travel period with 86% sensitivity for syndromic screening at both exit and entry, and average times from infection to onset of symptoms, and from onset to severe symptoms/hospitalisation of 5.2 and 9.2 days, respectively (8). We assume that traveller sensitisation via posters and handouts to arrivals from high risk regions will lead to their increased awareness and, on onset of symptoms, to self isolation and care seeking which will result in SARS-CoV-2 identification and subsequent contact tracing. In line with Hellewell et al (7) we assume that these self-isolation measures in combination with intensive contact tracing in the early stages of the SARS-CoV-2 pandemic can reduce the average number of onward transmitting secondary infections by about 50%. The effectiveness of an intervention in delaying a coronavirus outbreak in a previously unaffected region is then estimated as the delay in reaching the outbreak threshold, T_0 , which is the number of infected individuals needed to make it almost certain that an outbreak will occur (9). We tested when this time was reached under different air traveller intervention scenarios: (a) no interventions; (b) syndromic exit and entry screening, (c) traveller sensitisation on arrival, or (d) the combination of (b) and (c).

Effect of interventions on outbreak threshold

The outbreak threshold, T_0, is a function of both R_0 and the dispersion parameter, k, which describes how heterogeneous R_0 is between individuals in a population (9). Here we consider an outbreak threshold such that the probability of an outbreak given R_0 and k is at least 50%. The effective reproduction number (R_{eff}) is R_0 reduced by the impact of interventions, and in this case, $R_{eff} = (1-\rho)R_0$, where ρ is the effectiveness of traveller sensitisation to Covid-19. We sample the number of undetected infected travellers arriving in one week, I , by bootstrapping from a $Binomial(p = \theta, n = \lambda)$ to represent the variation in arrival rates. We approximate the probability of the occurrence of a major outbreak by time t in days as $1 - R_0^{-\lambda(t/7)}$ (10), where R_0 is sampled from a $\Gamma(\alpha = 15.1, \beta = 6.06)$ - having a 95% interval of $(1.4, 3.9)$ (11). The delay in reaching T_0 due to traveller sensitisation and/or syndromic entry screening then is then t', such that, $R_0^{-\lambda(t_0/7)} = R_{eff}^{-\lambda\theta(t_0+t')/7}$, where $t_0 = T_0/I$ is the time, in days, at which the local outbreak threshold T_0 is reached. The delay can be calculated as $t' = t_0(logR_0/(\theta \log((1-\rho)R_0) - 1)$ and summarised with interval statistics.

Scenarios considered

We assumed that either 1, 10 or 100 infected travellers per week would arrive (Table 1). In addition the base case of 50% reduction in secondary cases as a result of traveller sensitisation we also investigated for sensitivity analyses 30% and 70% effectiveness of sensitisation. To incorporate uncertainty around the reproduction number of SARS-CoV-2 we sample R_0 from a gamma distribution whose 95% quantiles are 1.40 and 3.90 and whose 50% quantiles are 2.04 and 2.89 (11). The dispersion parameter for the number of secondary cases with mean R was

assumed to be similar to SARS (k=0.16), with sensitivity analyses assuming influenza-like dispersion of R (k=2) (7). Because of considerable uncertainty around point estimates, results are presented as the 50% quantiles and 95% quantiles. If the upper confidence interval (CI) estimate is an infinite delay, i.e. no outbreak, we report as a delay of at least the lower bound.

All analyses were done with R 3.6.2 (12) and can be found on github at https://github.com/samclifford/screening_outbreak_delay.

Table 1: Overview of parameter assumptions for the model.

Parameter	**Value**	**Source**
R_0, basic reproduction number	Central 95% range is 1.4 to 3.9 Log-normally distributed	(11)
λ, infected travellers per week	1, 10 or 100	assumption
θ, probability that infected traveller is not detected by screening	Exit screening only: 46% Entry and exit screening: 42%	(6)
I, sampled number of infected arrivals in a week	$I \sim Binomial(p = \theta, n = \lambda)$. $E(I) = \theta\lambda$	Derived
ρ, effectiveness of traveller sensitisation	50%, Sensitivity analyses: 30%, 70%	(7)
T_0, outbreak threshold	Derived from R_0, k	(9)
t_0, time until outbreak	Expected time for number of infected arrivals to reach T_0. $t_0 = 7T_0/I$.	Derived.
k, dispersion parameter for R_0	0.54 Sensitivity analyses: 0.16 (SARS-like) & 2.00 (Influenza-like)	(13,14)

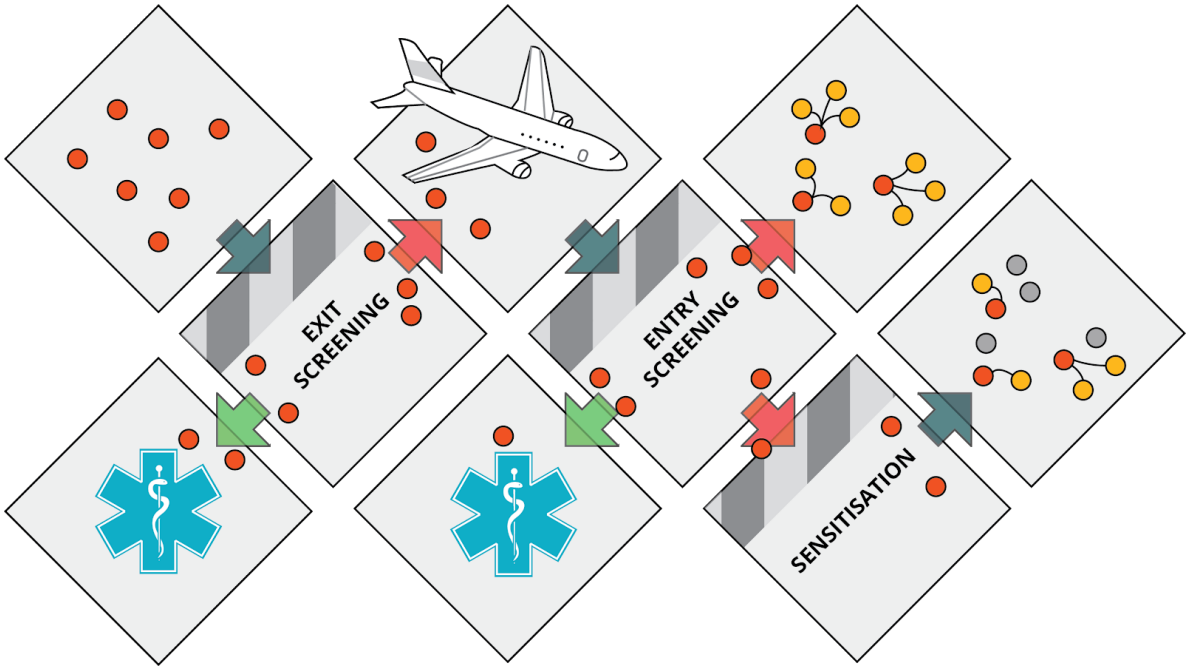

Figure 1: Schematic of the air traveller intervention process. A proportion of infected travellers will be detected through syndromic exit or entry screening and will immediately be isolated and not cause secondary cases in the yet unaffected destination. Sensitised travellers will enter the destination but cause fewer secondary cases because of an increased likelihood of self-isolation and rapid care seeking.

Results

We estimate that with no traveller sensitisation and under baseline assumptions for the effectiveness of syndromic screening at exit and entry, in the early stages of the SARS-CoV-2 outbreak with 1 infected traveller per week, an outbreak may be delayed by more than 11 days (95%CI: more than 7) (Figure 2). However, this is largely due to exit screening at departure, which on its own is estimated to delay the outbreak by more than 9 days (95%CI: more than 6) (Figure S1). As the number of infected travellers increases during the oversea's outbreak, the delay in onset of a local outbreak through screening declines rapidly; specifically, if infected traveller numbers approach 10 and 100 per week, syndromic screening can only delay the outbreak by 2 - 4 days (95%CI: 1 - 13) and by 0 - 1 days (95%CI: 0 - 1), respectively.

Similarly, we estimate that in the absence of syndromic air traveller screening, a 50% effective traveller sensitisation can delay the outbreak by 12 - 288 days (95%CI: more than 5) early in the epidemic with 1 infected traveller per week but delays reduce to 1 - 29 days (95%CI: potentially less than 1 day) once 10 infected travellers per week arrive.

Combining syndromic screening with traveller sensitisation has the potential to substantially delay an outbreak even with moderate levels of international spread. If 10 infected travellers per week arrive we estimate an outbreak delay of 9 - 207 days (95%CI: more than 4) under baseline

assumptions. Again, the incremental benefit of syndromic entry screening in this scenario is highly dependent on the effectiveness of the exit screening. With 10 infected travellers per week arriving and under baseline assumptions of effective exit screening, exit screening combined with traveller sensitisation and in the absence of syndromic entry screening can already delay the outbreak by 7 - 167 days (95%CI: more than 3).

For sensitivity analyses we varied the effectiveness of traveller sensitisation and the heterogeneity in the number of secondary infections. A 70% reduction in the effective reproduction number through traveller sensitisation followed by case isolation and contact tracing can potentially prevent a local outbreak independent of the number of infected arrivals if the basic reproduction number is smaller than 3.3 (i.e., $R_0(1-\varrho) < 1$ when R_0 is 3.3 and traveller sensitisation is 70%). If traveller sensitisation is assumed to be only 30% effective in reducing R_0 then the associated outbreak delay is only 3 - 10 days (95%CI: more than 1) if 1 infected traveller per week arrives. However, in combination with syndromic screening substantial outbreak delays may still be possible in the early stages of the outbreak. If the number of secondary infections is substantially less disperse, e.g. influenza-like, outbreak delays decrease by about 50%, as the outbreak becomes less reliant on occasional super-spreading events (Figure S1). If, however, the number of secondary infections is slightly more disperse, e.g. SARS-like, then outbreak delays almost triple.

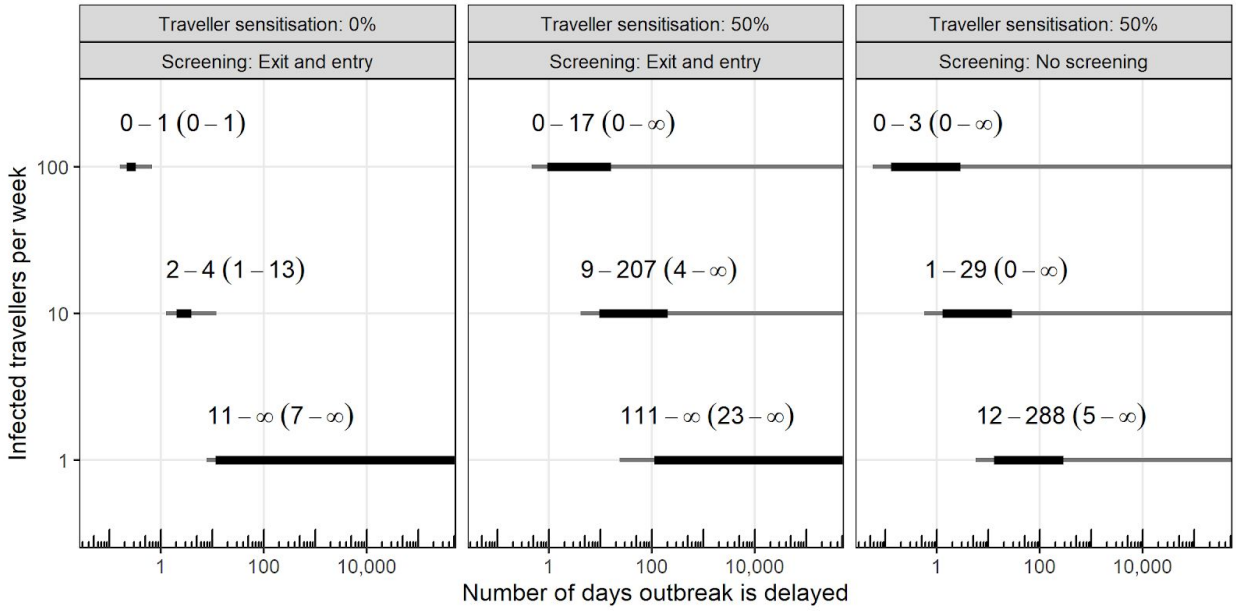

Figure 2: Estimated number of days an outbreak is delayed given an intervention consisting of a combination of traveller screening and sensitization and contact tracing. Thick black lines show 50% bootstrapped confidence intervals (with thin grey lines showing 95% bootstrapped confidence intervals) Comparisons are made to no contact tracing and no screening.

Discussion

Syndromic screening of air travellers at departure and/or arrival is unlikely to prevent a sufficient proportion of SARS-CoV-2 infected travellers from entering a yet unaffected country and thereby prevent a local outbreak. Similarly, sensitisation of travellers from high risk countries to encourage self isolation and enable rapid case detection and contact tracing if indeed infected will likely not be able to halt an outbreak indefinitely, particularly when many infected travellers arrive undetected. We investigate here how syndromic screening and traveller sensitisation as well as their combination may delay an outbreak of SARS-CoV-2. We find that while there is only about 1 infected traveller per week, either syndromic airport screening or traveller sensitisation has the potential to slightly delay an outbreak (about 75% probability to delay more than 2 weeks). The incremental effect of syndromic entry screening, however, is only notable if exit screening is poor. As soon as 10 infected passengers per week arrive the delay reduces substantially, although if both interventions are used in combination a 75% probability for at least about a one and a half week delay remains. Our results, however, are sensitive to a number of key assumptions: with increasing R_0, less heterogeneous R_0, less effect of traveller sensitisation on R_0 and increasing numbers of infected travellers the estimated achievable delay quickly becomes negligible, on the order of a few days.

We find a potential role for interventions targeting air-passengers to delay major outbreaks of SARS-CoV-2 in previously unaffected regions as long as implemented when there are only few infected travellers per week. We find that syndromic screening on arrival can add to the effect of traveller sensitisation in these early stages of a pandemic. Syndromic screening can also aid to reduce the number of passengers that would eventually self-report and then require resource intensive follow up, including contact tracing. Therefore, syndromic screening may help to sustain control efforts for longer. Of note, however, is that syndromic screening at arrival only substantially adds to control efforts if syndromic screening at departure is absent or largely ineffective.

While our findings may encourage implementation of both syndromic screening on entry and traveller sensitisation in the early stages of the SARS-CoV-2 pandemic, it is important to note that these findings are highly sensitive to the underlying base-case assumptions and do not consider the economical implications of large scale air passenger screening and contact tracing. With increasing numbers of infected travellers, a higher number of secondary infections or a lower heterogeneity thereof, or less effective interventions, the achievable delay quickly drops down to a few days of delay. While all of our assumptions include the best knowledge on SARS-CoV-2 to date, there is considerable uncertainty associated with all of these assumptions. E.g. we have assumed recently reported heterogeneity in the individual R_0 , however the reported range of uncertainty includes SARS-like and influenza-like which can drastically alter the results. Some recent, yet not peer reviewed estimates would suggest more SARS like or even more overdispersed k which would imply that longer outbreak delays are possible (15). Further, we have assumed constant importation rates for infected cases. While

the proportion of infected travellers may increase exponentially during the early phase of an outbreak, closure of airports in highly affected regions during the outbreak so far may have helped to keep the number of infected travellers at a level where control is still possible. We also don't explicitly account for potential asymptomatic transmission. However, we implicitly do so as both the syndromic screening as well as the contact tracing work that infomed our estimates accounted for a small proportion of asymptomatic transmitters. Notably, we assume a constant rate of infected travellers. However, this may increase rapidly as the epidemic continues to spread exponentially in China and potentially elsewhere. There is currently little evidence for an exponential increase in infected travellers to Europe as airports in the highest risk regions in China have shut. If indeed infected traveller numbers were to increase exponentially numbers would increase from 1 to 10 and 100 per week within about 19 and 38 days respectively (assuming R=2.5 and serial interval of 7.5) and estimated delays would decrease accordingly.

All major airlines have currently suspended flights from mainland China. In the last two weeks three SARS-CoV-2 infected travellers reported with symptoms within a few days after arrival (16). This may suggested that indeed the UK and similarly other parts of Europe are currently in a situation where air-traveller targeted interventions may substantially delay major local outbreaks, however, under-reporting of cases is likely and with quickly rising case numbers in Hong Kong, Singapore, Japan and Korea this situation may change rapidly in the coming weeks.

Despite limited evidence that supports its effectiveness (17), the US has recently banned entry to the US by most foreigners who have recently visited China (18). In our work we did not investigate such a drastic interruption of air travel. While a travel ban for entry with history of travel to all high-risk regions would indeed likely further limit the number of infected travellers entering to those who enter by different means, it would also come with substantial economical implications. It does also run the risk that travellers arriving in the US despite their travel history would likely not be reached by targeted sensitisation and/or that they would avoid self-reporting if symptomatic, with potentially dire implications for local spread.

In summary, we find that targeting air-travellers with syndromic screening at exit or entry and sensitisation for signs of symptoms following their arrival may delay a major outbreak in the early stages of the SARS-CoV-2 outbreak. In most countries air-traveller sensitisation and rapid contact tracing protocols are already in place in response to the SARS-CoV-2 outbreak. We find that syndromic screening at arrival may further enhance such control efforts while the number of infected passengers is less than about 10 per week, but only in the absence of syndromic screening at departure.

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Competing interests

We declare no competing interests.

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Neither patients nor the public were involved with the design, conduct, reporting, or dissemination plans of our research. As this work is a simulation study, there are no participants to which we can disseminate the results of this research.

Appendix

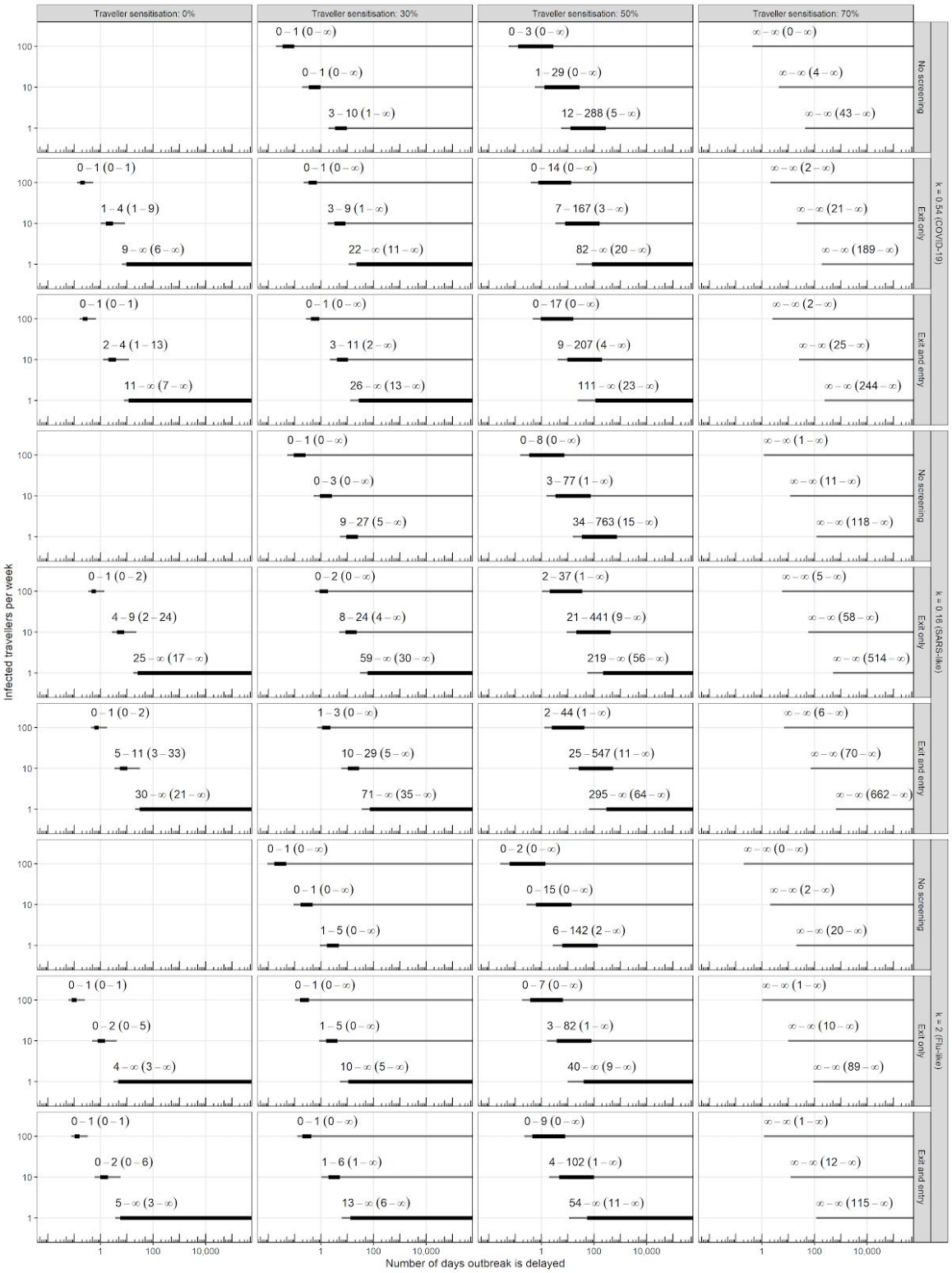
Traveller sensitisation: 0%
Traveller sensitisation: 30%
Traveller sensitisation: 50%
Traveller sensitisation: 70%
No screening
Exit only
Exit and entry
k = 0.54 (COVID-19)
k = 0.16 (SARS-like)
k = 2 (Flu-like)
Infected travellers per week
Number of days outbreak is delayed
0 – 1 (0 – ∞)
0 – 3 (0 – ∞)
∞ – ∞ (0 – ∞)
0 – 1 (0 – ∞)
1 – 29 (0 – ∞)
∞ – ∞ (4 – ∞)
3 – 10 (1 – ∞)
12 – 288 (5 – ∞)
∞ – ∞ (43 – ∞)
0 – 1 (0 – 1)
0 – 1 (0 – ∞)
0 – 14 (0 – ∞)
∞ – ∞ (2 – ∞)
1 – 4 (1 – 9)
3 – 9 (1 – ∞)
7 – 167 (3 – ∞)
∞ – ∞ (21 – ∞)
9 – ∞ (6 – ∞)
22 – ∞ (11 – ∞)
82 – ∞ (20 – ∞)
∞ – ∞ (189 – ∞)
0 – 1 (0 – 1)
0 – 1 (0 – ∞)
0 – 17 (0 – ∞)
∞ – ∞ (2 – ∞)
2 – 4 (1 – 13)
3 – 11 (2 – ∞)
9 – 207 (4 – ∞)
∞ – ∞ (25 – ∞)
11 – ∞ (7 – ∞)
26 – ∞ (13 – ∞)
111 – ∞ (23 – ∞)
∞ – ∞ (244 – ∞)
0 – 1 (0 – ∞)
0 – 8 (0 – ∞)
∞ – ∞ (1 – ∞)
0 – 3 (0 – ∞)
3 – 77 (1 – ∞)
∞ – ∞ (11 – ∞)
9 – 27 (5 – ∞)
34 – 763 (15 – ∞)
∞ – ∞ (118 – ∞)
0 – 1 (0 – 2)
0 – 2 (0 – ∞)
2 – 37 (1 – ∞)
∞ – ∞ (5 – ∞)
4 – 9 (2 – 24)
8 – 24 (4 – ∞)
21 – 441 (9 – ∞)
∞ – ∞ (58 – ∞)
25 – ∞ (17 – ∞)
59 – ∞ (30 – ∞)
219 – ∞ (56 – ∞)
∞ – ∞ (514 – ∞)
0 – 1 (0 – 2)
1 – 3 (0 – ∞)
2 – 44 (1 – ∞)
∞ – ∞ (6 – ∞)
5 – 11 (3 – 33)
10 – 29 (5 – ∞)
25 – 547 (11 – ∞)
∞ – ∞ (70 – ∞)
30 – ∞ (21 – ∞)
71 – ∞ (35 – ∞)
295 – ∞ (64 – ∞)
∞ – ∞ (662 – ∞)
0 – 1 (0 – ∞)
0 – 2 (0 – ∞)
∞ – ∞ (0 – ∞)
0 – 1 (0 – ∞)
0 – 15 (0 – ∞)
∞ – ∞ (2 – ∞)
1 – 5 (0 – ∞)
6 – 142 (2 – ∞)
∞ – ∞ (20 – ∞)
0 – 1 (0 – 1)
0 – 1 (0 – ∞)
0 – 7 (0 – ∞)
∞ – ∞ (1 – ∞)
0 – 2 (0 – 5)
1 – 5 (0 – ∞)
3 – 82 (1 – ∞)
∞ – ∞ (10 – ∞)
4 – ∞ (3 – ∞)
10 – ∞ (5 – ∞)
40 – ∞ (9 – ∞)
∞ – ∞ (89 – ∞)
0 – 1 (0 – 1)
0 – 1 (0 – ∞)
0 – 9 (0 – ∞)
∞ – ∞ (1 – ∞)
0 – 2 (0 – 6)
1 – 6 (1 – ∞)
4 – 102 (1 – ∞)
∞ – ∞ (12 – ∞)
5 – ∞ (3 – ∞)
13 – ∞ (6 – ∞)
54 – ∞ (11 – ∞)
∞ – ∞ (115 – ∞)
100
10
1
1
100
10,000

Figure S1: All scenarios for Figure 1 - the estimated number of days an outbreak is delayed given an intervention consisting of a combination of traveller screening and sensitization and contact tracing. Thick black lines show 50% bootstrapped confidence intervals (with thin grey lines showing 95% bootstrapped confidence intervals) Comparisons are made to no contact tracing and no screening.

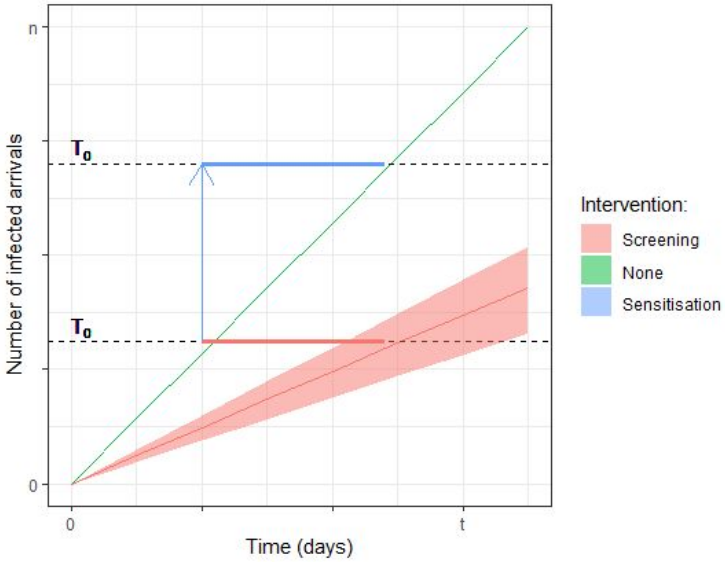

Figure S2: Schematic of delay (solid bold lines) in expected onset of an outbreak with either syndromic screening (red) or traveller sensitisation (blue). The dashed line represents the outbreak threshold. The effect of syndromic screening is to delay the time until the outbreak threshold is reached by reducing the number of infected travellers entering the region. The effect of traveller sensitisation is to reduce the number of secondary infections and thereby increase the outbreak threshold.