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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Kiang MV, Chin ET, Huynh BQ, et al. Routine asymptomatic testing strategies for airline travel during the COVID-19 pandemic: a simulation study. *Lancet Infect Dis* 2021; published online March 22. https://doi.org/10.1016/S1473-3099(21)00134.

Supplemental Materials

Kiang MV, Chin ET, Huynh BQ, Chapman LAC, Rodríguez-Barraquer I, Greenhouse B, Rutherford GW, Bibbins-Domingo K, Havlir D, Basu S, and Lo NC. Routine asymptomatic testing strategies for airline travel during the COVID-19 pandemic: a simulation study. Lancet Infectious Diseases. 2021.

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Section 1: Technical appendix

In this supplement, we provide additional methodological details on the mathematical transmission model for SARS-CoV-2 and the simulation of test-and-travel strategies.

Additional modeling details

We developed a microsimulation model of SARS-CoV-2 transmission that simulates individual people. Each person was assigned a single health state for a given time point. The health states were mutually exclusive and collectively exhaustive, and included:

- susceptible to infection (non-immune; S);
- latent period;
- early infectious period (the pre-symptomatic infectious period) with eventual clinical disease (C,1);
- early infectious period with sub-clinical infection (S,1);
- late infectious period with clinical disease (C,2);
- late infectious period with sub-clinical infection (S,2);
- recovered with immunity (R).

This is depicted in the Figure A1. We did not include waning of recovered individuals back to susceptible.

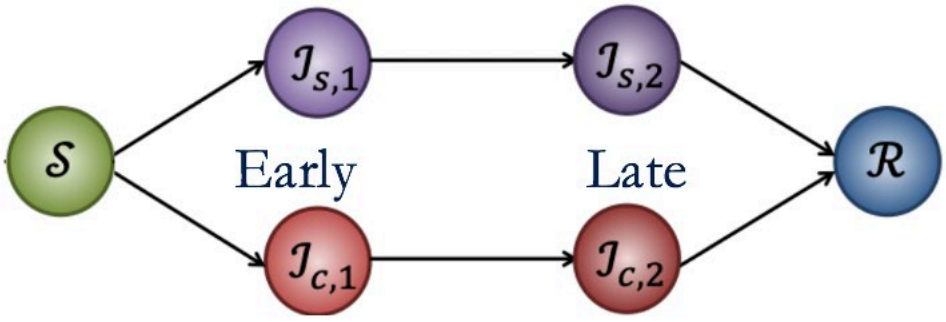

Figure A1: Model schematic

The model simulated 100,000 travelers. Key model parameters and inputs are shown in Table S1. The study simulation ran over period of 18 days, including three days prior to travel (when the earliest testing would take place), the day of travel, and two weeks after arrival at their final destination. We simulated new infections occurring during the first week of the simulation (those attributable around the travel period), but counted infections over the entire travel period as defined in the main text (to include those exposed on the day of travel). We used a 2 month burn in period to ensure travelers were distributed amongst the health states, including a modest percentage in the seroconverted state (see Table S2).

The fixed model inputs on natural history and transmission were sourced from literature (Table S1). The distributions on model inputs can be found in Table 1 and the analytic code.[1] For each traveler in a health state, we randomly sampled from a defined distribution for the average duration of time (days) in each state to introduce random variation We fixed the risk of daily infection for SARS-CoV-2 with a base case of 150 new infections per 100,000 persons, which is

representative of the current incidence observed in many US states as of January 29, 2021 (Figure S1). The daily risk of infection was varied in sensitivity analysis from 5 to 500 daily infections per 100,000 persons. The model was static and did not include transmission dynamics. We did include a sensitivity analysis where the risk of infection on the day of travel depended upon whether pre-travel testing had occurred (effectively reducing the number of infectious persons in the airport), which provides a sensitivity analysis for transmission dynamics in this context.

We evaluated five viral testing strategies of airline travelers around the time of travel, including: i) anterior nasal PCR within 3 days of departure, meaning passengers were tested 2-3 days prior to the day of travel; ii) PCR within 3 days of departure and PCR on day 5 after arrival with 5 days of quarantine upon arrival; iii) rapid antigen test on the day of travel; iv) rapid antigen test on the day of travel and PCR on day 5 after arrival with 5 days of quarantine upon arrival; and v) PCR within 5 days of arrival, meaning passengers were tested on the fifth day after arrival. In the quarantine strategies, we assumed no new infections occurred during the quarantine period, although accounted for imperfect adherence. PCR 3 days prior to travel was assumed to be split evenly over day 2 and 3 prior to travel. The rapid antigen test was assumed to have a sensitivity of 90% relative to PCR (during periods of high viral loads compatible with infectiousness, meaning only during the early and late infectious state in the model) and specificity of 99.5-100% (mean 99.8%).[2]

We measured two main study outcomes. First, we measured the cumulative infectious days in the cohort of 100,000 passengers over the travel period. To do this, we summed the number of days each traveler spent in the early infectious or late infectious states over the travel period for each strategy. Second, we measured the number of infectious travelers with SARS-CoV-2 detected on the day of travel. This was defined as the number of persons on the day of travel in the early infectious or late infectious states that tested positive by the pre-travel testing strategy.

Further details on the model structure and technical specifications can be found in the analytic code.[1] The code is available in R with in-line commenting on the function of assumptions in the analysis.

Table S1: Cohort characteristics and COVID-19 natural history and transmission parameters.

Parameter	Base case value	Range	Distribution	References
Cohort characteristics				
Population size	100,000		Fixed	
Natural history				
Latent period[a]	3 days	2-5 days	Rounded triangle distribution (median 3, lower 1.5, upper 5.5)	3-5
Mean duration of infectiousness	5 days	2-8 days	Truncated normal (mean 5, SD 1, bounds 1 and infinity)	3,4
Sub-clinical fraction	30%	30-40%	Fixed	6,7
Proportion of transmission during pre-symptomatic period[b]	50%		Fixed	6,8
Daily SARS-CoV-2 infection incidence	150 infection per 100,000 persons	5 to 500 infections per 100,000 persons	Binomial	
Relative risk of COVID-19 infection during day of travel	2.0	1.0-10.0	Fixed at 1, 2, 4, 10	9,10
Test performance				
PCR sensitivity	Time-varying, approximately 80-95% during infectious period	+/- 10%	Figure S2	11,12
PCR specificity	99.8%	99.5-100%	Truncated normal (mean 0.998, SD 0.001, bounds 0.995 and 1.0)	11,12
Rapid antigen test sensitivity (e.g., Abbott BinaxNOW)	90% relative to PCR	Variable relative to PCR		2,13,14
Rapid antigen test specificity (e.g., Abbott BinaxNOW)	99.8%	99.5-100%		2,13,14
Adherence with testing	100%		Fixed	
Non-adherence to symptom screening[c]	20%		Fixed	15
Non-adherence to quarantine	20%		Fixed	15

Note: Population was assumed to be initially fully susceptible.
[a]The latent period is defined as duration from exposure to infectiousness. References include estimation based on onset of symptoms (incubation period), which was adjusted given onset of infectiousness prior to symptom onset.
[b]The pre-symptomatic period is defined as the proportion of infectious days prior to onset of symptoms.
[c]The non-adherence to symptom screening is defined as the proportion of people that experience new symptoms compatible with COVID-19 that did not follow public health guidance and attempted to travel.

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Section 2: Supplemental tables and figures

Table S2. Number of active SARS-CoV-2 infections and the number of initial recovered persons for different daily probabilities of infection.

Daily incidence of infection per 100,000 persons	Average number of active infections	Number of recovered persons after burn-in (baseline number of seroconverted)
5 per 100,000 persons	115 (95% UI: 91, 140)	220 (95% UI: 189, 253)
10 per 100,000 persons	229 (95% UI: 193, 269)	439 (95% UI: 392, 485)
20 per 100,000 persons	456 (95% UI: 396, 522)	874 (95% UI: 800, 949)
50 per 100,000 persons	1,123 (95% UI: 1001, 1271)	2,174 (95% UI: 2,020, 2,317)
100 per 100,000 persons	2,187 (95% UI: 1958, 2458)	4,296 (95% UI: 4,017, 4,541)
150 per 100,000 persons	3,186 (95% UI: 2870, 3571)	6,383 (95% UI: 5,970, 6,722)
250 per 100,000 persons	5,030 (95% UI: 4531, 5615)	10,411 (95% UI: 9,818, 10,934)
500 per 100,000 persons	8,773 (95% UI: 7870, 9918)	19,748 (95% UI: 18,583, 20,662)

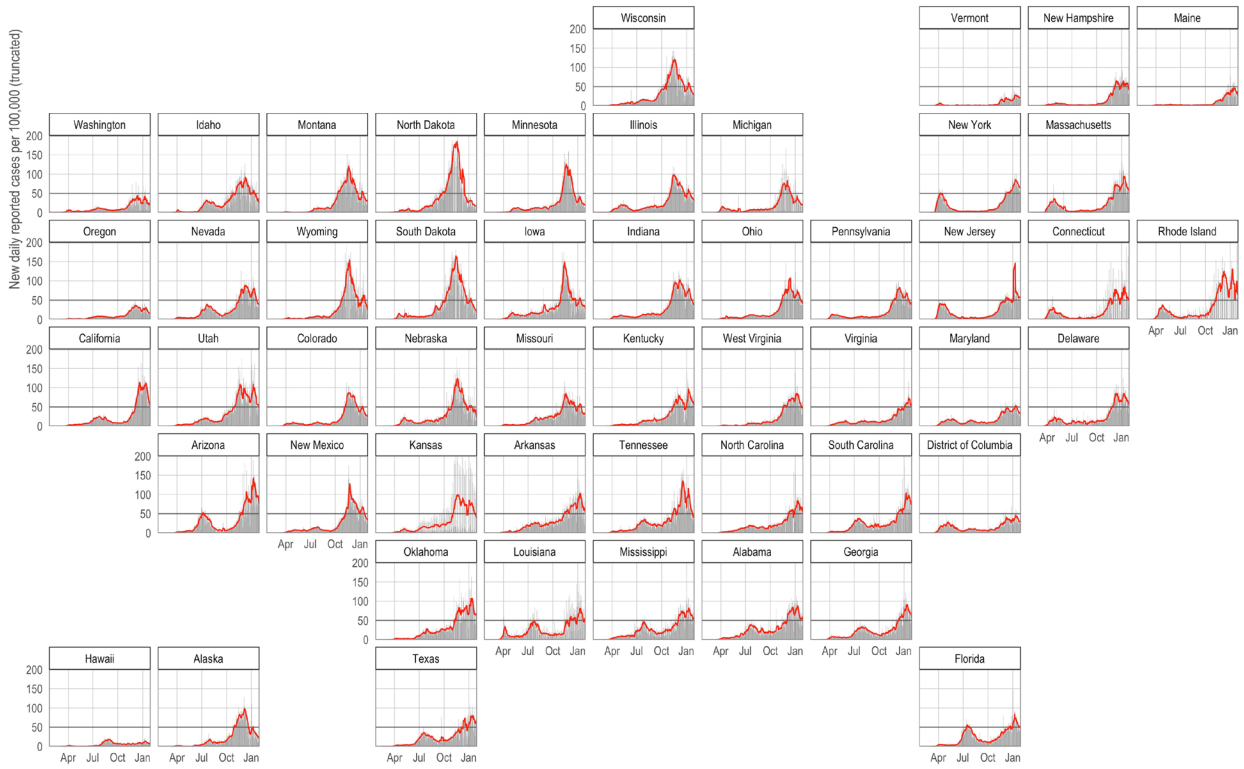

Figure S1. Number of COVID-19 cases per 100,000 population in the United States. We plotted the number of COVID-19 clinical cases (y-axis) by day (grey bar) and 7-day rolling average (red line) between January 21, 2020 and January 31, 2021 (x-axis). Each panel is a state in approximately geographic location. The number of infections is likely multi-fold greater due to sub-clinical cases and lack of universal testing. The grey reference line at 50 daily infections per 100,000 population.

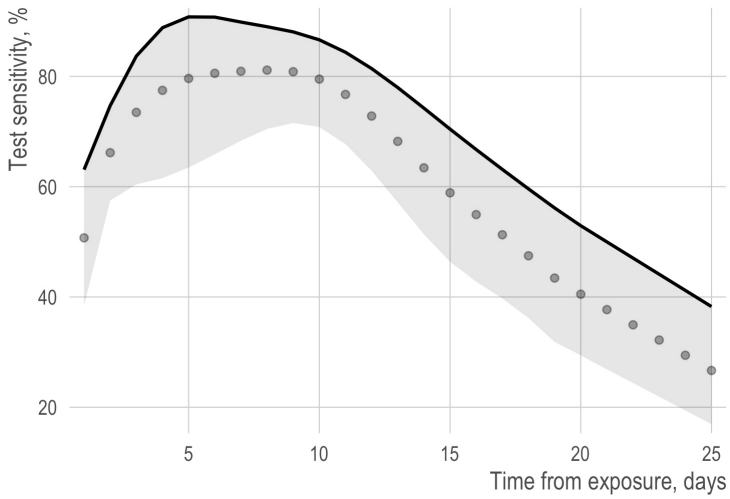

Figure S2. PCR sensitivity since day of exposure to person with COVID-19. We used published data on the PCR test sensitivity for SARS-CoV-2 based on the day since exposure to SARS-CoV-2. The base case estimate is shown in the black line. This estimate was based on the average of two published studies[11,12] and ultimately was adapted from the upper 95% confidence interval of Kucirka LM et al (2020 Annals IM) that was the average of published literature. Sensitivity analyses using the median values are provided in Section 3 (Figure S7).

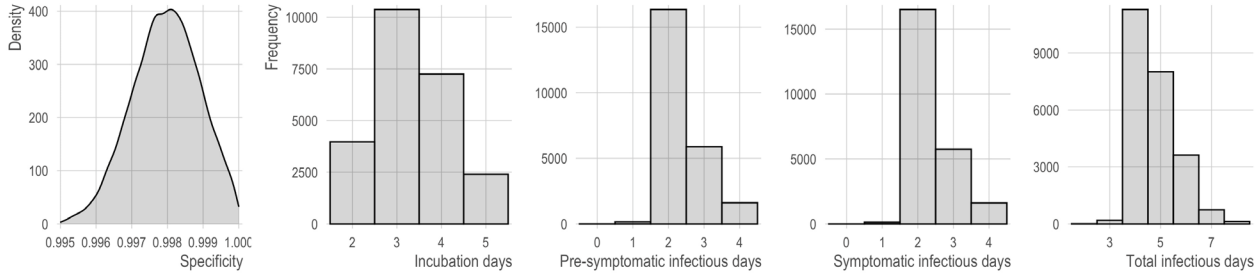

Figure S3. Distribution of parameters in the microsimulation. The following plots provide a distribution of model inputs for test specificity (PCR and rapid antigen tests), incubation period, pre-symptomatic infectious days, symptomatic infectious days, and total infectious days.

Section 3: Sensitivity analyses

This section presents the sensitivity analyses in the study. Numerical results can be viewed in the online repository.

Tables:

Table S2: Number of infectious persons on day of flight days varying test sensitivity of PCR.

Table S3: Number of infectious persons on day of flight days by testing strategy varying subclinical fraction.

Table S4: Number and reduction of actively infectious persons on day of flight days by timing of pre-travel PCR testing.

Figures:

Figure S4. Cumulative SARS-CoV-2 infectious days over time varying incidence of SARS-CoV-2.

Figure S5. Cumulative infectious days over time varying day-of-travel risk multiplier.

Figure S6. Cumulative infectious days over time varying test sensitivity of rapid antigen tests.

Figure S7. Cumulative infectious days over time varying test sensitivity of PCR.

Figure S8. Cumulative infectious days over time varying adherence to symptomatic self-isolation.

Figure S9. Number of actively infectious passengers on day of flight by adherence to symptomatic self-isolation and testing strategies.

Figure S10. Cumulative infectious days over time by testing strategy and adherence to post-travel quarantine.

Figure S11. Cumulative infectious days over time by testing strategy and percent of infections that are subclinical.

Figure S12. Cumulative infectious days over time by timing of pre-travel PCR testing.

Figure S13. Cumulative infectious days over time by testing strategy and duration of post-travel quarantine.

Figure S14. Sensitivity analysis for reduced risk of infection on day of travel for strategies with pre-travel testing.

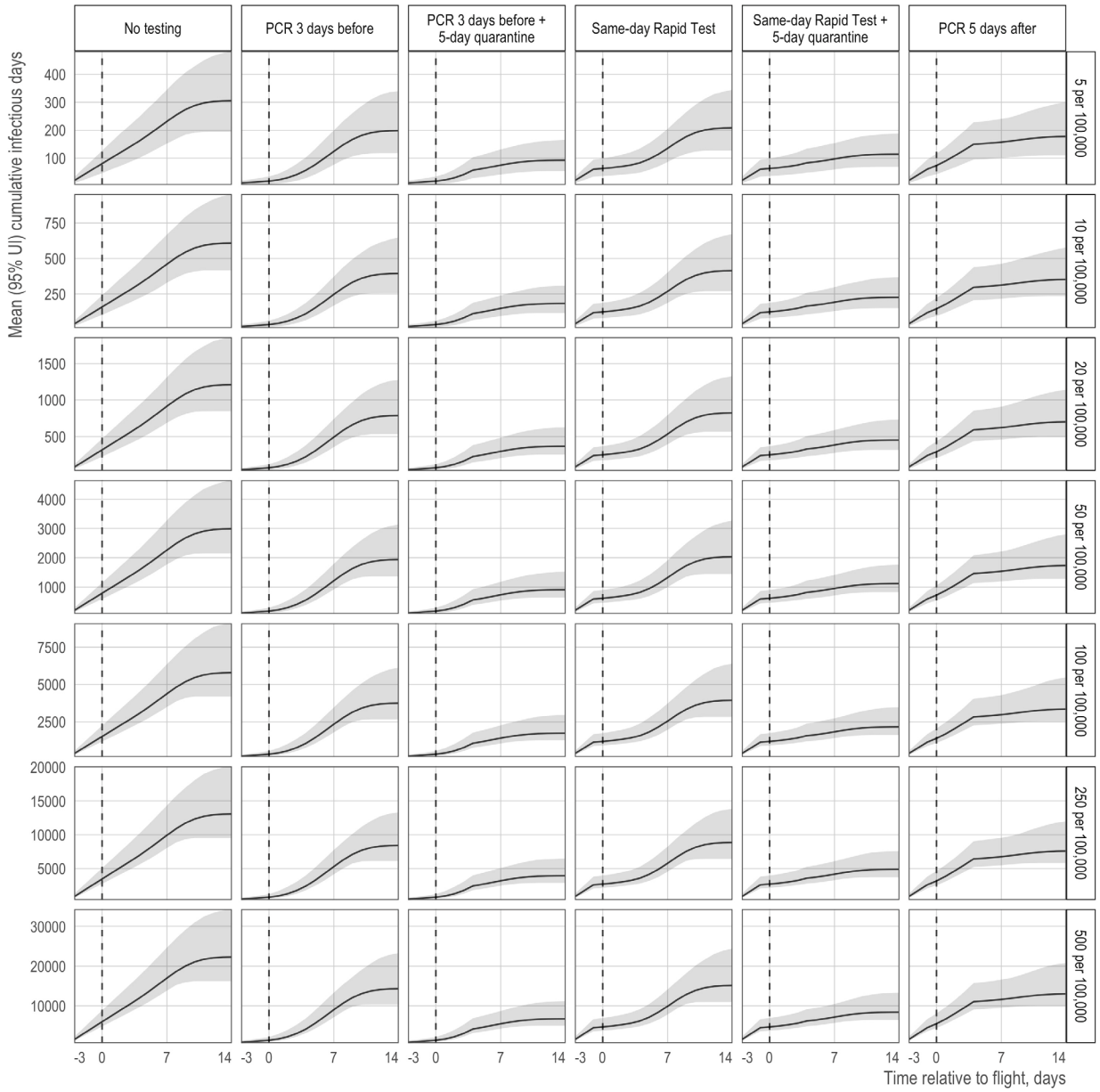

Figure S4. Cumulative SARS-CoV-2 infectious days over time varying incidence of SARS-CoV-2. We vary incidence of SARS-CoV-2 from 5 to 500 daily infections per 100,000 persons (rows). We conduct this sensitivity analysis for all testing strategies (columns).

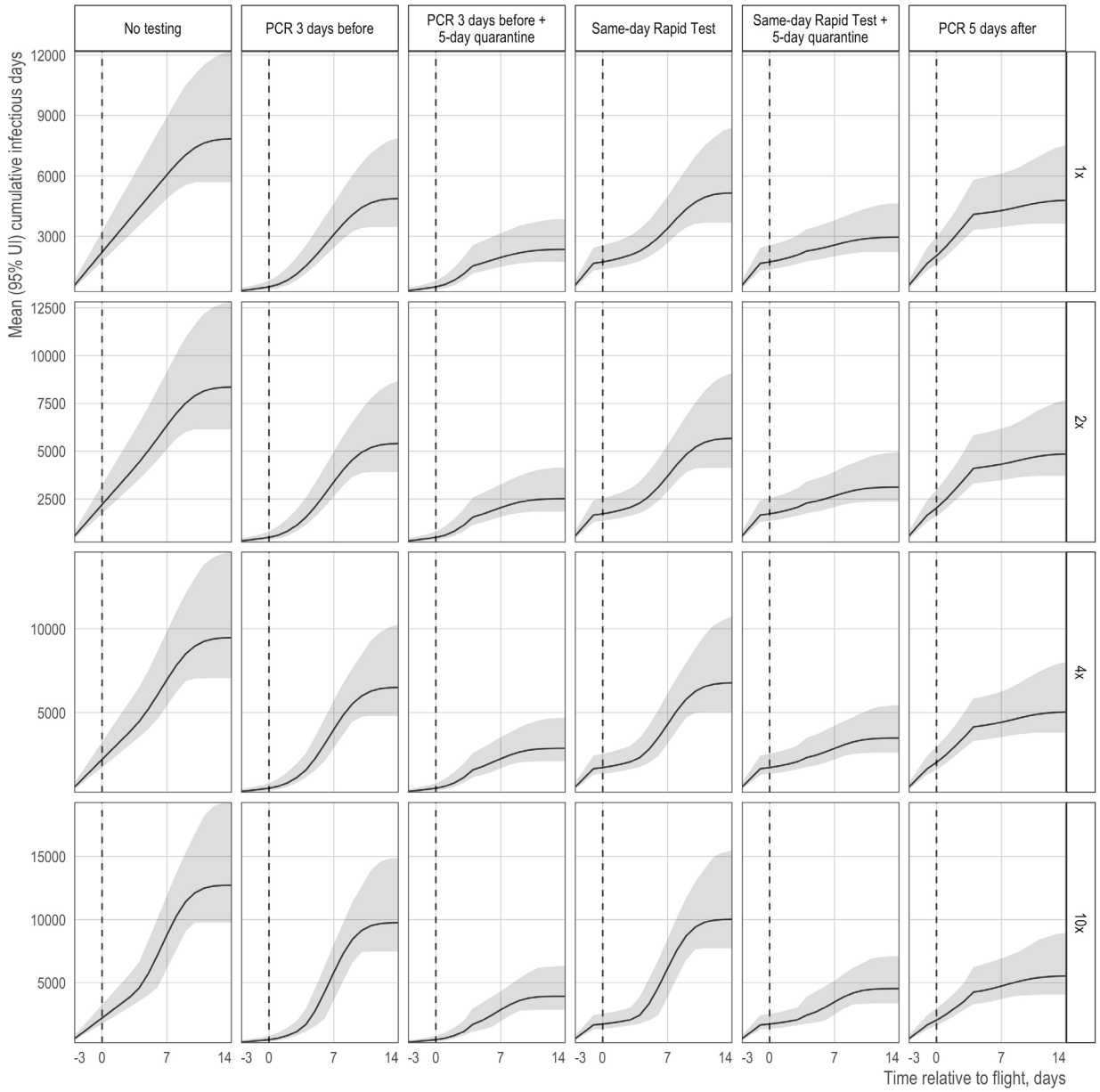

Figure S5. Cumulative infectious days over time varying day-of-travel risk multiplier. We vary the day of travel multiplier for daily risk of infection from 1x (assumes no additional risk from airline travel) to 10x (assumes 1,000% increased daily probability of infection on the day of travel) as shown in the rows. We conduct this sensitivity analysis for all testing strategies (columns).

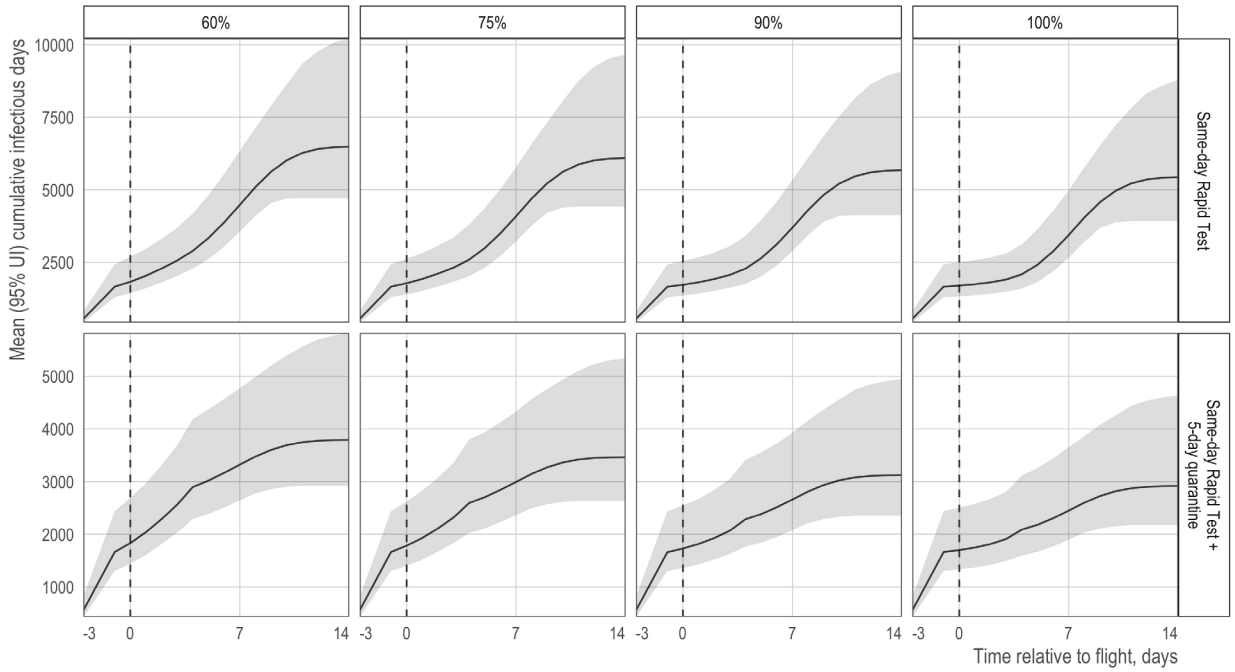

Figure S6. Cumulative infectious days over time varying test sensitivity of rapid antigen tests. We evaluated alternative test sensitivity for rapid antigen tests from equivalent to PCR (100% column) to 60% the sensitivity of PCR (meaning the rapid test is 40% less sensitive than PCR). The test sensitivity of the rapid antigen tests is varied relative to PCR (columns). This analysis is conducted for the primary study outcome of cumulative infectious days without isolation or quarantine.

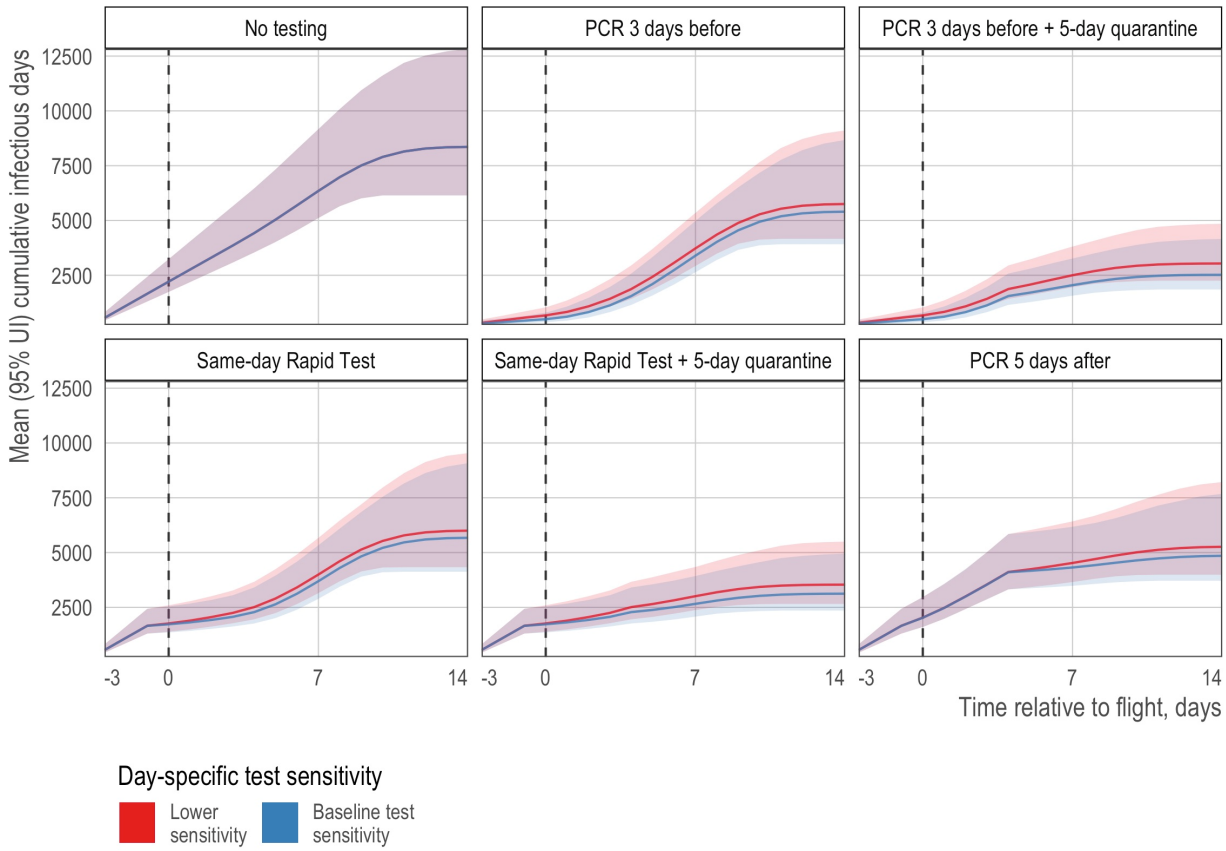

Figure S7. Cumulative infectious days over time varying test sensitivity of PCR. We evaluated alternative test sensitivity PCR using the base case (blue) and more pessimistic assumption for test sensitivity for PCR (red). This data is incorporated from Kucirka et al. (Figure S2). This analysis is conducted for the primary study outcome of cumulative infectious days without isolation or quarantine.

Table S2: Number of infectious persons on day of flight days varying test sensitivity of PCR.

	Mean (95% UI) number of active infections on day of flight	
Testing Strategy	**Lower PCR test sensitivity**	**Baseline PCR test sensitivity**
No testing	649 (95% UI: 505, 950)	649 (95% UI: 505, 950)
Same-day Rapid Test	131 (95% UI: 94, 208)	89 (95% UI: 61, 144)
PCR 3 days before	128 (95% UI: 83, 269)	80 (95% UI: 46, 201)
PCR 5 days after	468 (95% UI: 362, 691)	467 (95% UI: 360, 695)

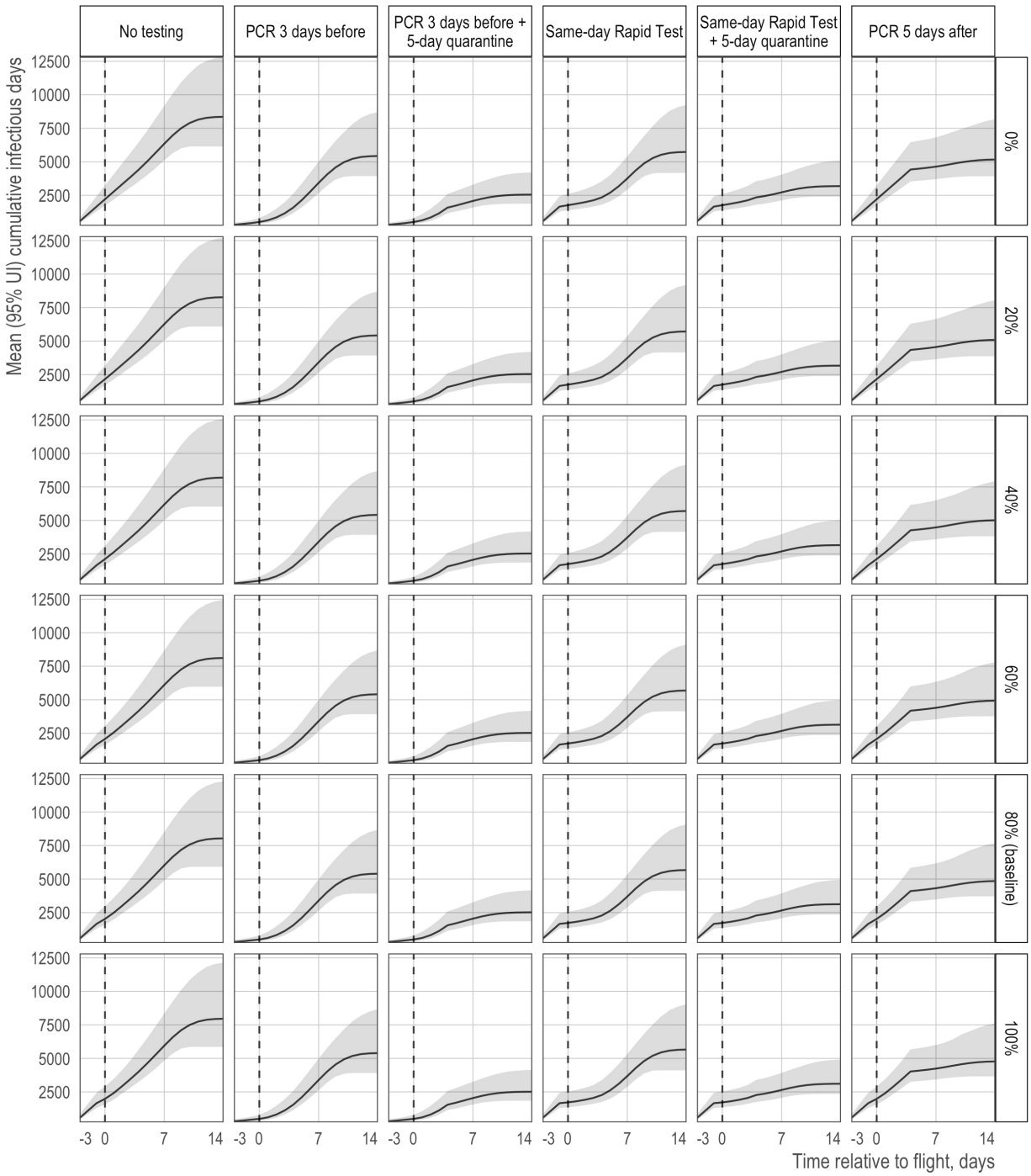

Figure S8. Cumulative infectious days over time varying adherence to symptomatic self-isolation. We vary the proportion of symptomatic passengers who self-isolate as shown in the rows from 0% to 100% (perfect self-isolation). We conduct this sensitivity analysis for all testing strategies (columns). Our base models assumed 80% (fifth row down) of symptomatic passengers will self-isolate and not travel. This analysis is conducted for the primary study outcome of cumulative infectious days without isolation or quarantine.

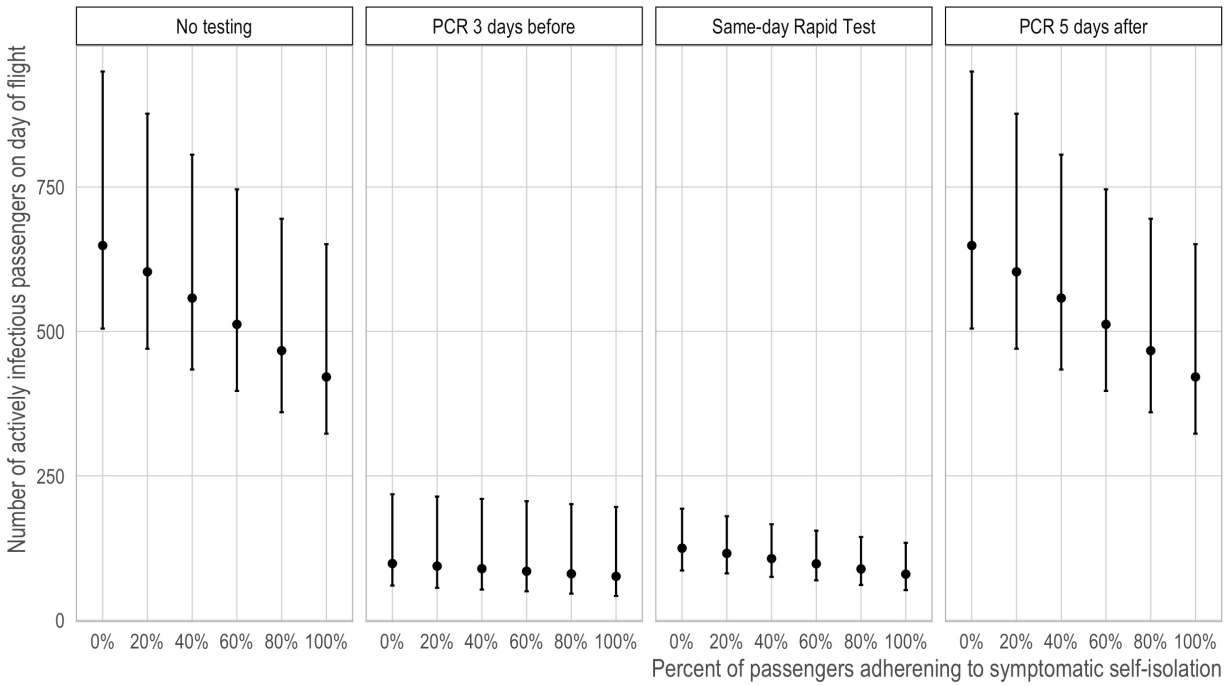

Figure S9. Number of actively infectious passengers on day of flight by adherence to symptomatic self-isolation and testing strategies. We vary the proportion of symptomatic passengers who self-isolate as shown in the rows from 0% to 100% (perfect self-isolation). We conduct this sensitivity analysis for all testing strategies (panels). Our base models assumed 80% of symptomatic passengers will self-isolate and not travel. This analysis is conducted for the secondary study outcome of number of actively infectious passengers on the day of travel.

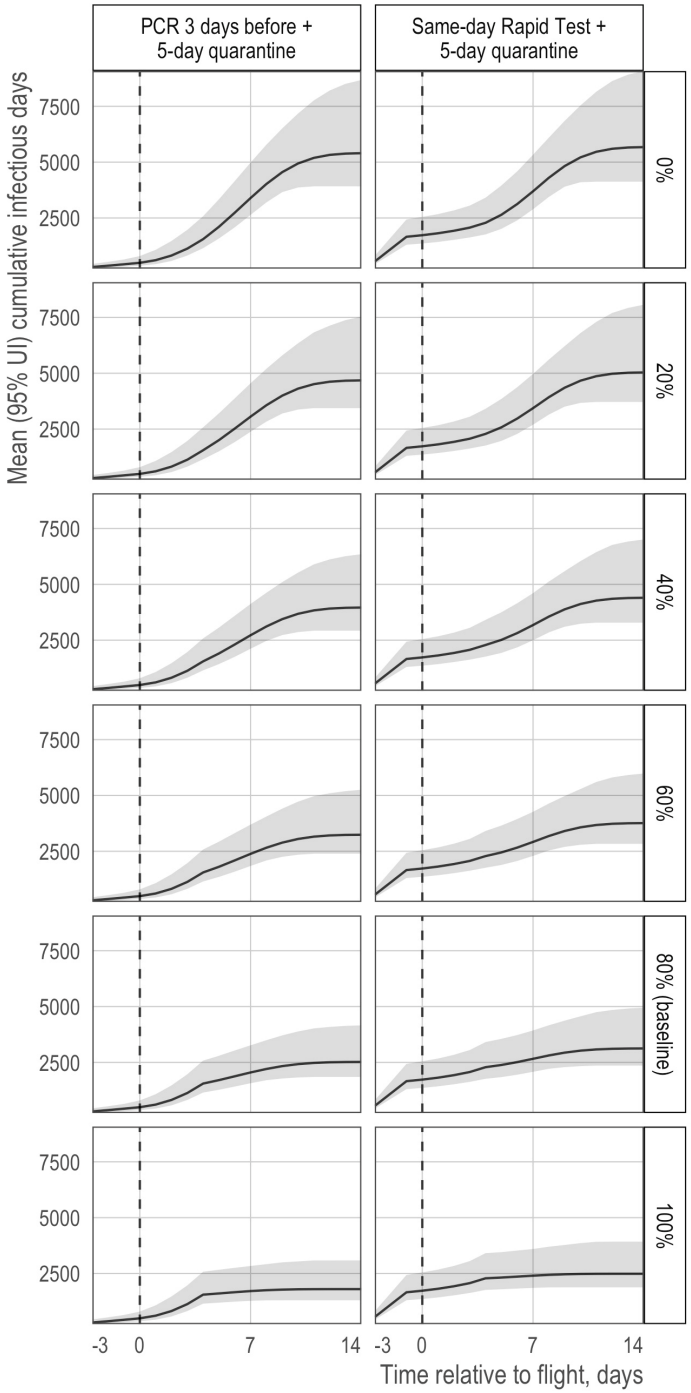

Figure S10. Cumulative infectious days over time by testing strategy and adherence to post-travel quarantine. Our base models assume 80% (fifth row down) of passengers will quarantine for five days upon arrival; here, we show the change in results by proportion of passengers who adhere to quarantine upon arrival varying from 0% (top row) to perfect adherence or 100% (bottom row).

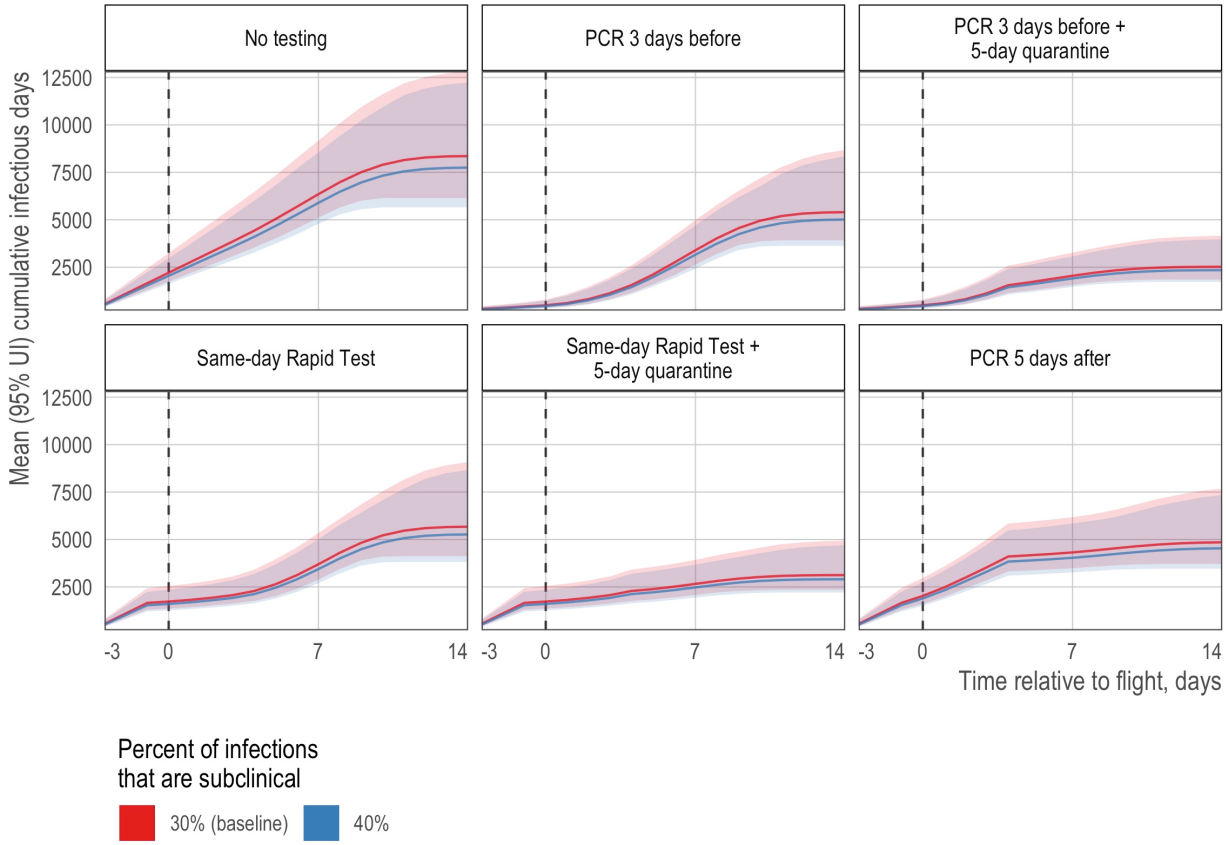

Figure S11. Cumulative infectious days over time by testing strategy and percent of infections that are subclinical. In our primary analyses, we show the cumulative infectious days (y-axis) over time (x-axis) when assuming 30% of infections are subclinical (red); here, we test the sensitivity of this assumption by changing the percent of subclinical infections to 40% (blue).

Table S3: Number of infectious persons on day of flight days by testing strategy varying subclinical fraction.

	Mean (95% UI) number of active infections on day of flight	
Testing Strategy	**30% subclinical (base case)**	**40% subclinical**
No testing	649 (95% UI: 505, 950)	639 (95% UI: 499, 927)
PCR 3 days before	80 (95% UI: 46, 201)	80 (95% UI: 46, 199)
Same-day Rapid Test	89 (95% UI: 61, 144)	93 (95% UI: 64, 147)
PCR 5 days after	467 (95% UI: 360, 695)	486 (95% UI: 370, 725)

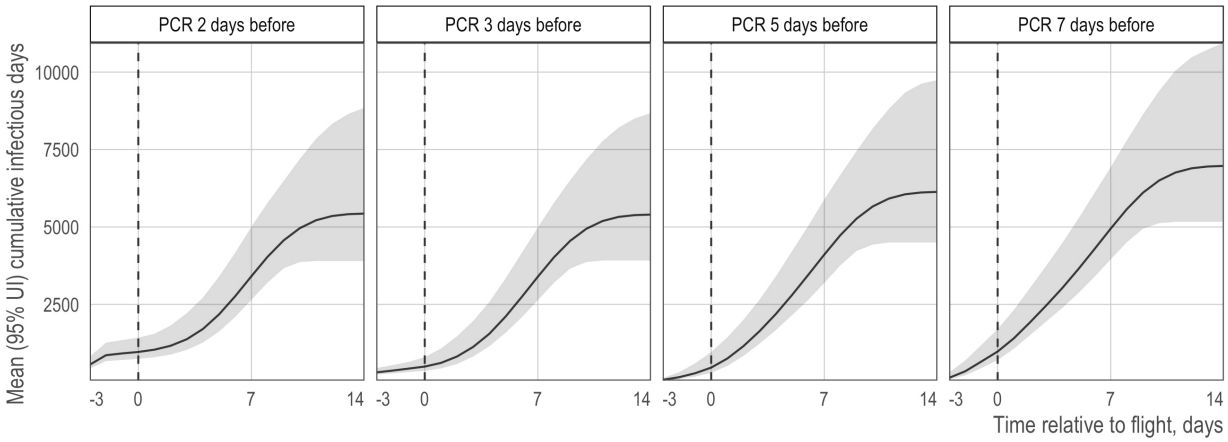

Figure S12. Cumulative infectious days over time by timing of pre-travel PCR testing. In our primary analyses, we assume a PCR test is required within 3 days of travel with a 1 day turn around for results; here, we test the sensitivity of pre-travel PCR testing timed at 2, 5, and 7 days before travel.

Table S4: Number and reduction of actively infectious persons on day of flight days by timing of pre-travel PCR testing.

Testing Strategy	Mean (95% UI)	Relative reduction
No testing	649 (95% UI: 505, 950)	—
Same Day Rapid Test	89 (95% UI: 61, 144)	0.86 (95% UI: 0.83, 0.89)
PCR 2 days before	58 (95% UI: 33, 120)	0.91 (95% UI: 0.86, 0.94)
PCR 3 days before	80 (95% UI: 46, 201)	0.88 (95% UI: 0.76, 0.92)
PCR 5 days before	220 (95% UI: 136, 430)	0.67 (95% UI: 0.48, 0.80)
PCR 7 days before	393 (95% UI: 303, 611)	0.39 (95% UI: 0.26, 0.57)

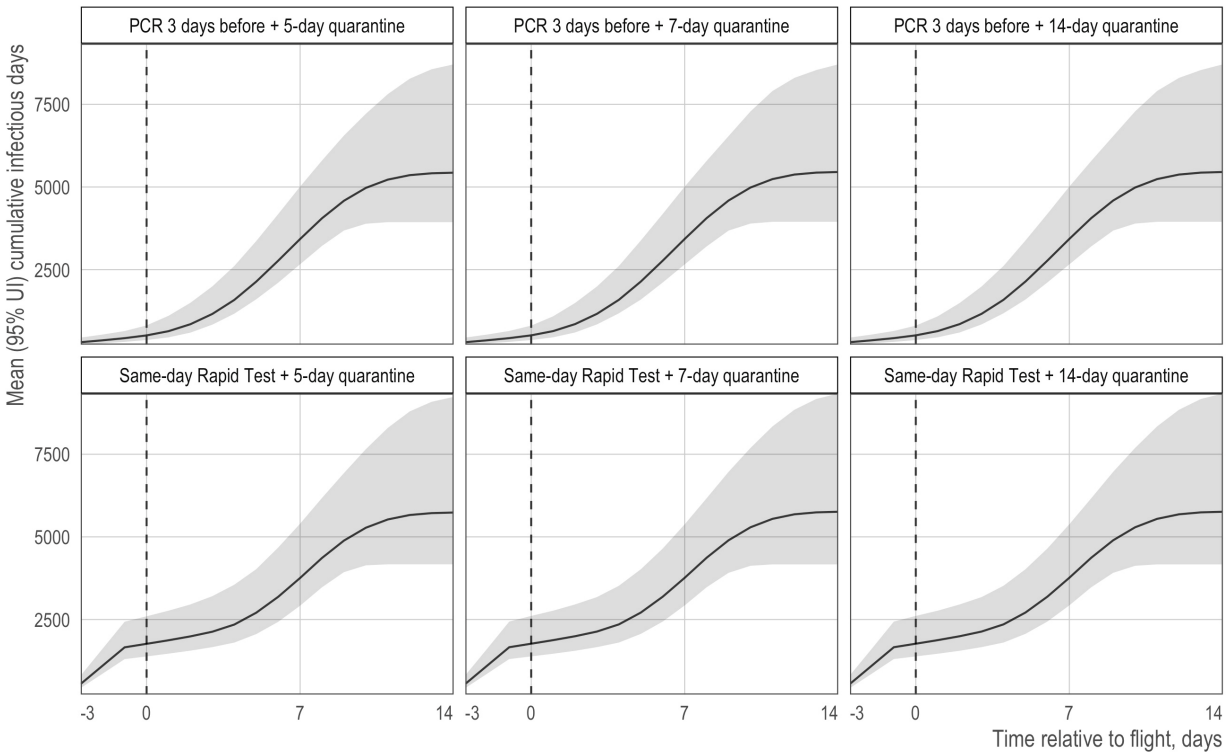

Figure S13. Cumulative infectious days over time by testing strategy and duration of post-travel quarantine. We evaluated alternative duration of post-travel quarantine for strategy 2 and 4 (rows) that include both pre- and post-travel testing. The base case analysis assumed a 5-day quarantine period. In sensitivity analysis, we extend the post-travel quarantine to 7- and 14-day quarantine (columns). This analysis is conducted for the primary study outcome of cumulative infectious days without isolation or quarantine.

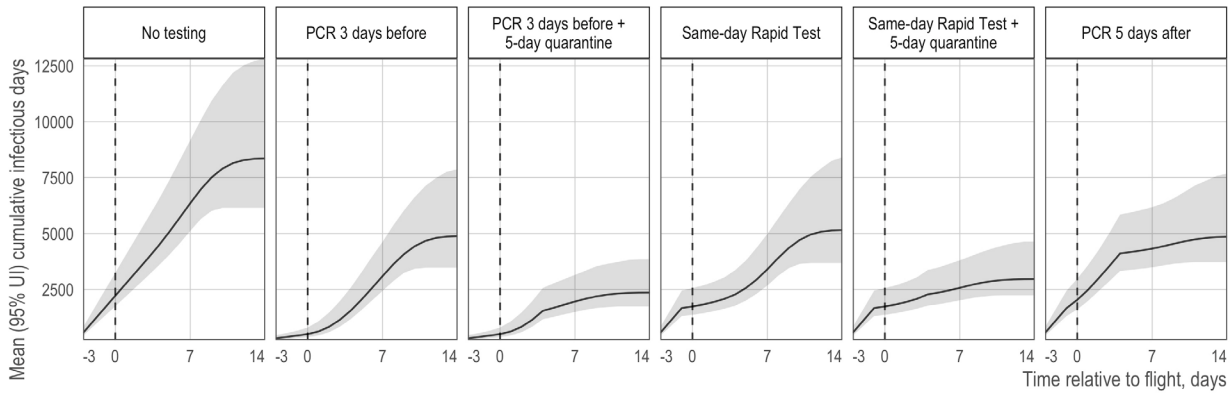

Figure S14. Sensitivity analysis for reduced risk of infection on day of travel for strategies with pre-travel testing. We modeled risk of infection on the day of travel that depended upon whether there was pre-departure testing in sensitivity analysis by reducing the risk of infection on the day of travel for strategies with pre-travel testing, which would reduce the number of infectious persons in the airport and impact transmission dynamics**.** We assumed a 2-fold increased risk on the day of travel for all scenarios; however, it is reasonable that pre-flight testing and same-day rapid testing scenarios would not experience increased risk of infection on the day of travel since passengers would not go inside of the airport. Here, we show the standard, 2-fold increased risk on day of travel, for the "No testing" and "PCR 5 days after" scenarios compared to no increased risk on day of travel for the pre-travel testing and same-day testing scenarios.