Frequency of routine testing for COVID-19 in high-risk healthcare environments to reduce outbreaks

Technical Appendix

Methods

We developed a microsimulation model of SARS-CoV-2 transmission to estimate the impact of variable frequency of routine asymptomatic PCR testing on the mean control reproduction number, R_c, in a high-risk healthcare environment. We developed a susceptible-exposed-infectious-recovered (SEIR)-like model in which individuals interact with an age-structured community population as well as within a high-risk healthcare environment (e.g. nursing home, hospital). We simulated PCR-based testing for each individual in a healthcare environment and varied the time intervals for routine PCR testing from daily to monthly. We assumed persons self-isolate when receiving a positive test or when symptoms occur, so that transmission within the healthcare environment occurs only from sub-clinical or early-clinical infected persons. We also assumed individuals take one day to receive results after testing, although we varied this is in a sensitivity analysis. We probabilistically varied the following parameters: incubation time, early infectious period, late infectious period, test sensitivity, and test specificity (see Table A2).

The model tracked three features of each simulated person: (i) the person's true state of infection (susceptible, early sub-clinical infection, late sub-clinical infection, early clinical infection, late clinical infection, or recovered) (Figure A1, Table A1); (ii) the observed state of infection based on test results (uninfected, currently infected based on positive PCR, or immune based on positive PCR followed by completion of a 14 day self-isolation period); and (iii) whether the person was present in the healthcare environment.

A susceptible individual can be exposed to infectious individuals in both the community and other members of the healthcare environment. We applied a constant probability of infection from the community, where incidence was assumed to be 0.5%. We chose a high daily incidence to ensure sufficient number of new infections for the simulation; this choice should not affect the study results (mean control reproduction number), and was also tested in sensitivity analysis to verify this (Figure A5). Simulations using a lower incidence (0.1%, 0.01%, and 0.001%) affected the precision of the estimate, but the mean remained stable.

We assume a healthcare setting where the majority (75%) of contacts occur between a person in the healthcare environment and the community. We assume that 100% of symptomatic individuals in the healthcare environment and 75% of the community will self-isolate. The force of infection, $\lambda_i(t)$, on each individual i on day t is proportional to the prevalence of infectious individuals within the community and healthcare environment they are exposed to on day t and their infectiousness:

$$\lambda_i(t) = \mathbb{I}_i(t)\left(\beta^w \frac{h\left(\sum_{j \in \mathcal{I}_s^w} f(j,t)\right) + \sum_{j \in \mathcal{I}_{c,1}^w} f(j,t)}{N_w} + \beta^c\left(h\,(1-p_c)\bar{f} + p_c\,\overline{f_c}\right)\right) \quad (1)$$

Here, β is the transmission rate coefficient derived from the basic reproductive number – healthcare environment and community transmission rate coefficients being denoted by superscripts w and c respectively. $\mathbb{I}_i(t)$ is an indicator function for whether the individual is present in the healthcare environment on day t. $\mathcal{I}(t)$ represents the infectious individuals on day t in different states of infection – subclinical and clinical, denoted by subscripts s and c

respectively, early and late stage, denoted by subscripts 1 and 2 respectively. h is the infectiousness of subclinically infected individuals relative to those with clinical symptoms. f is a function for the daily infectiousness of an individual j on day t (Figure A2). $\bar{f}$ is the mean daily infectiousness across all days of infection and $\overline{f_c}$ is the mean daily infectiousness for clinical infections in the community, where we assume that 75% of symptomatic individuals self-isolate. See Table A2 for parameter values used in the simulations.

Each individual believed to be uninfected in the population is tested at varying intervals. We simulated transmission among 100 healthcare workers for 300 days across 1000 simulations for each parameter setting. We model three risk groups – low: $R_0 = 1.5$, medium: $R_0 = 2$, and high: $R_0 = 2.5$ – under time-varying PCR sensitivities (Figure A3) with a test result delay of one day. To model the ideal case, we assume 100% sensitivity and no delay in test results in a low-risk group. To calculate the reduction in transmission to estimate R_c, we take the mean total number of infectious days, weighted by infectiousness (Table A3), under a specific testing frequency and divide it by the counterfactual, which we define as the mean total number of weighted infectious days under no testing.

To estimate R_c, we multiplied the R_0 for the workplace under no testing by the reduction in transmission at a given testing frequency. The bands in Figure 1 represent the interquartile range of the distribution of the effective reproduction number over uncertainty in the parameter values and stochasticity. The model assumes a constant population and that individuals gain immunity in the short-term after recovery.

We additionally modeled lower sensitivity rapid tests, such as antigen tests, by estimating the reduction in infectiousness and cumulative number of infections under lower test sensitivity, using a discount factor of 0.8, and zero and one-day delays in test results. For further sensitivity analysis, we also modeled test result delays of 3 and 5 days to assess the effect of test turnaround times on testing impact (Figure A4).

Data and code available at: https://github.com/etchin/covid-testing

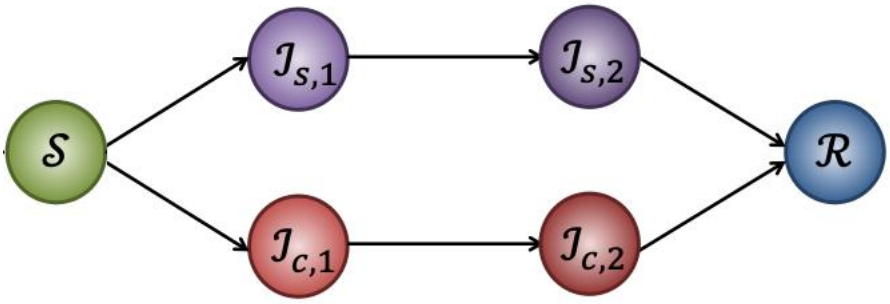


Figure A1. Structure of stochastic individual-level model of COVID-19 transmission. The labels of each state correspond with definitions in Table A1.

Frequency of routine testing for COVID-19 in high-risk healthcare environments to reduce outbreaks

Table A1: Definition of states in the transmission model

State	Symbol	Infectious	Symptomatic	Detectable viral load	Immune
Susceptible	$\mathcal{S}(t)$	×	×	×	×
Early subclinical infection	$\mathcal{I}_{s,1}(t)$	✓	×	✓	×
Late subclinical infection	$\mathcal{I}_{s,2}(t)$	✓	×	✓	×
Early clinical infection	$\mathcal{I}_{c,1}(t)$	✓	×	✓	×
Late clinical infection	$\mathcal{I}_{c,2}(t)$	✓	✓	✓	×
Recovered*	$\mathcal{R}(t)$	×	×	×	✓

* Because we estimate a low level of infectiousness for the right-tail of the late infectious state and assume a late infectious period length of 20 days, we assume that individuals do not test positive in the Recovered state.

Table A2: Model parameters and distributions in model

Parameter	Distribution/Value	References
Sensitivity of PCR	Time-varying* estimates fit to a truncated normal distribution by day of infection (Figure A3)	1
Specificity of PCR	98-100% fit to a truncated normal distribution	2-5
Infectiousness	Time-varying estimates by day of infection. Fit to a gamma distribution Infectiousness is assumed to peak at the start of the late infectious period fit to a truncated normal distribution (Figure A2)	6
Early infectious period	5.2 days (95% CI, 4.1-6.4) fit to a log-normal distribution	6
Late infectious period	Up to 20 days, infectiousness decreases after symptom onset (Figure A2)	6
Proportion sub-clinical	40%	7
Discount factor for sub-clinical infectiousness	50% as infectious as symptomatic infection	8,9

* Sensitivity estimates by day of infection were obtained from Kucirka et al. [1]. Sensitivity estimates during the incubation period were excluded because sensitivity was fit using the data of only one individual from the Danis et al study (PMID: 32277759). This patient tested negative for SARS-CoV-2 when obtained using nasopharyngeal swabs during the pre-symptomatic phase. Upon symptom onset, the patient had an endotracheal aspirate (ETA) sample test positive; however, the nasopharyngeal swabs of the same day and the following days remained negative. Thus, we assume exponential growth of test sensitivity during the early infectious period.

Frequency of routine testing for COVID-19 in high-risk healthcare environments to reduce outbreaks

Table A3: Ranges of mean percent reduction of infectiousness in a healthcare environment.

Testing frequency	Low Risk (R_0 = 1.5)	Medium Risk (R_0 = 2)	High Risk (R_0 = 2.5)	Ideal Case
1	85.3% (85.1,85.6)	83% (82.8,83.2)	82.2% (82,82.5)	98.9% (98.6,99.1)
2	73.9% (73.6,74.2)	71.5% (71.3,71.8)	69.5% (69.2,69.7)	94.8% (94.6,95.1)
3	64.5% (64.2,64.8)	62.3% (62,62.6)	61.4% (61.2,61.7)	89.6% (89.4,89.9)
4	56.6% (56.2,56.9)	53.2% (53,53.5)	52.1% (51.8,52.4)	85.1% (84.8,85.3)
5	49.7% (49.4,50.1)	47.4% (47.1,47.7)	45.4% (45.1,45.7)	78.3% (78.1,78.6)
7	38.1% (37.8,38.5)	35.9% (35.6,36.3)	36.9% (36.5,37.2)	69.5% (69.2,69.8)
10	30.5% (30.2,30.9)	27.8% (27.5,28.1)	27.4% (27.1,27.7)	61.5% (61.2,61.8)
15	15.6% (15.2,15.9)	17.9% (17.6,18.2)	16.8% (16.5,17.1)	40.6% (40.3,41)
20	12% (11.7,12.4)	12.7% (12.4,12.9)	12.6% (12.3,12.9)	44.2% (43.9,44.5)
25	9.4% (9,9.7)	9.3% (9.1,9.6)	12.3% (12,12.6)	40.4% (40,40.7)
30	8.8% (8.5,9.1)	8.2% (7.9,8.5)	8.9% (8.7,9.2)	31% (30.7,31.4)

Simulations were stratified for various risk groups (low: R_0 = 1.5, medium: R_0 = 2, high: R_0 = 2.5) under time-varying PCR test sensitivities with a test result delay of 1 day. The percent reduction under the ideal case was simulated with 100% sensitivity and no test result delay in a low-risk population.

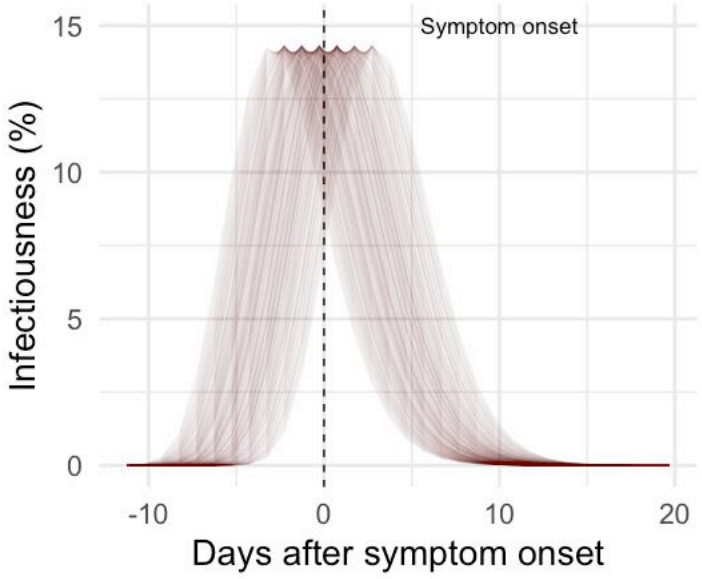


Figure A2: Infectiousness by day of infection

Frequency of routine testing for COVID-19 in high-risk healthcare environments to reduce outbreaks

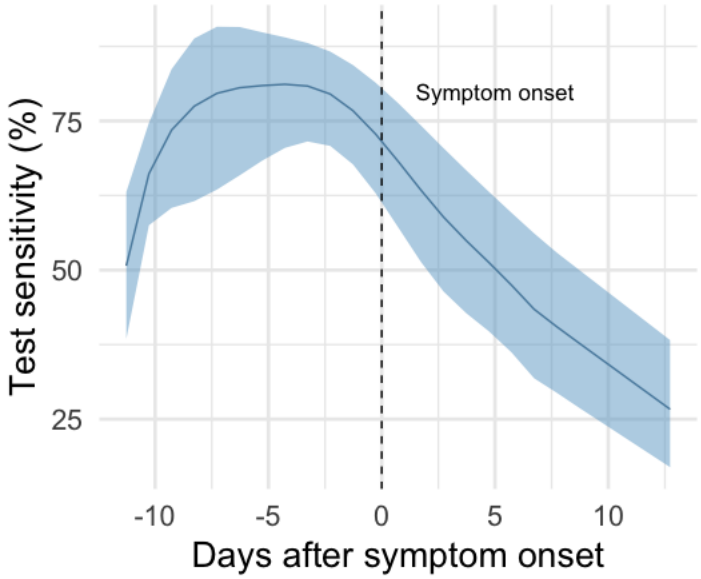


Figure A3. PCR sensitivity by day of infection

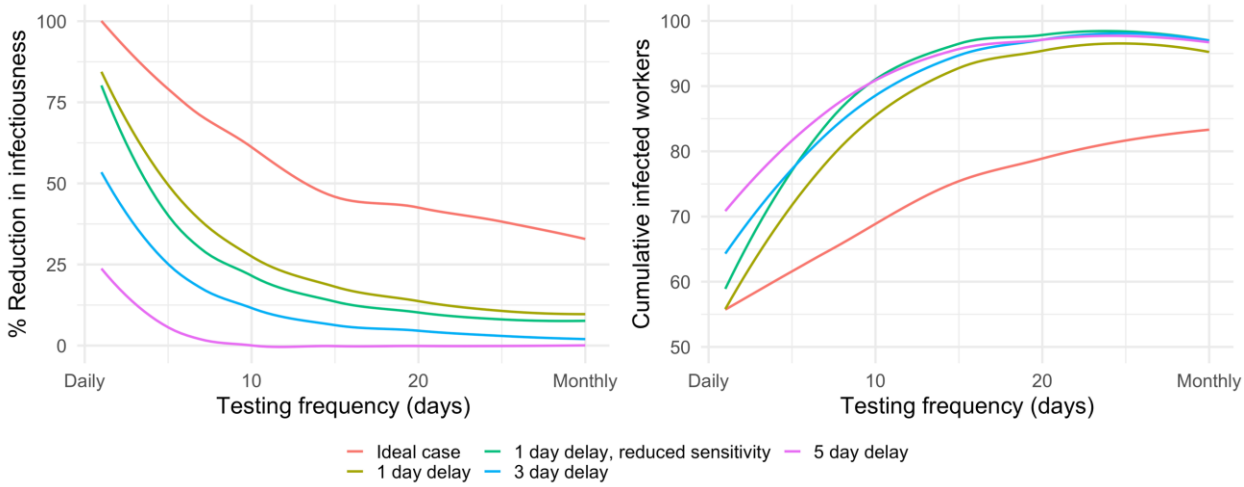
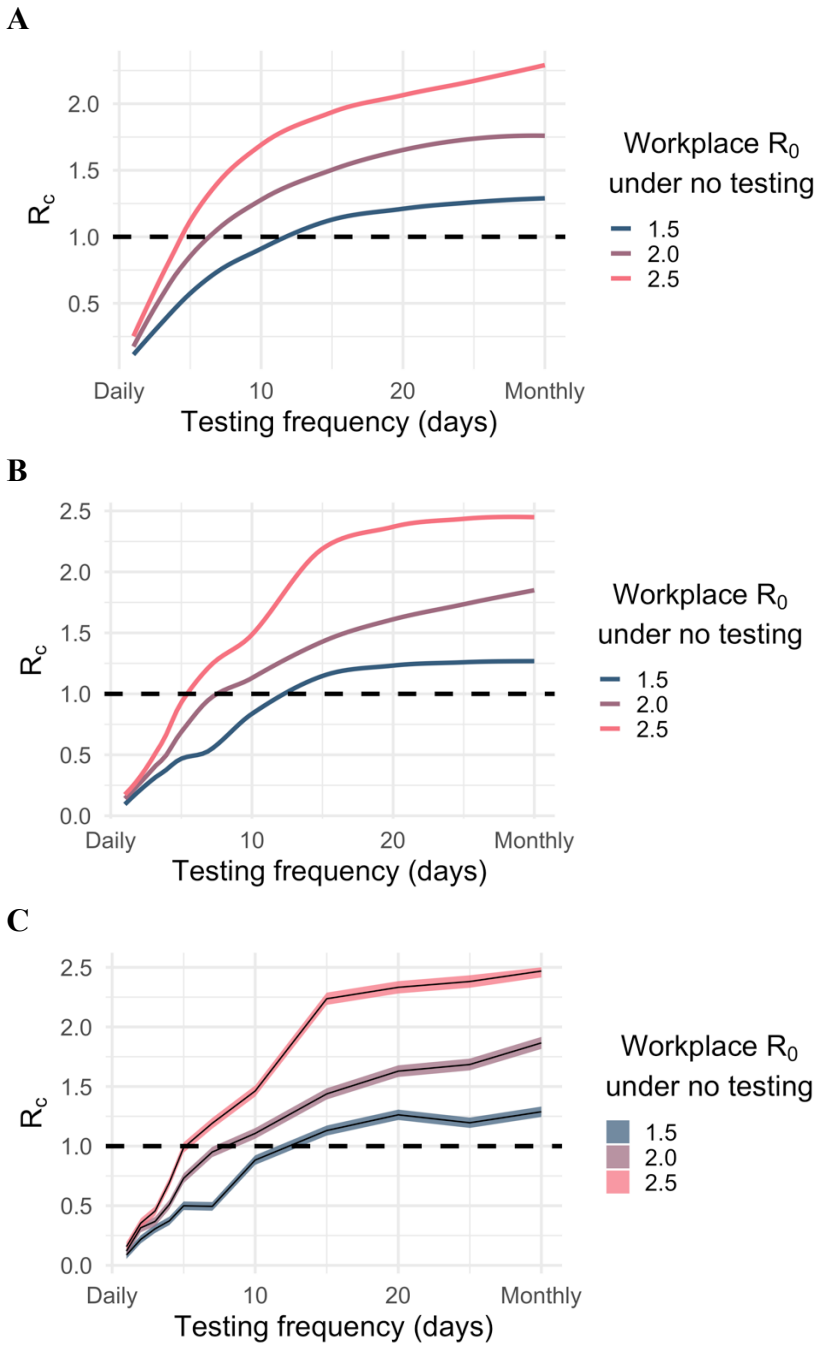


Figure A4: Reduction in infectiousness and cumulative infected workers under various testing strategies

Frequency of routine testing for COVID-19 in high-risk healthcare environments to reduce outbreaks



Simulations using a lower incidence (0.1%, 0.01%, and 0.001%)

Figure A5: Projected impact of routine PCR testing frequency on the mean control reproduction number under different daily incidence. We repeated the base case simulation while testing alternate daily incidence estimates including: (A) 0.1%; (B) 0.01%; and (C) 0.001%.

Frequency of routine testing for COVID-19 in high-risk healthcare environments to reduce outbreaks

Appendix References

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