Optimising the swab test regimen of contacts to minimise the risk of releasing falsely negative SARS-CoV-2 individuals from traveller quarantine or isolation following tracing

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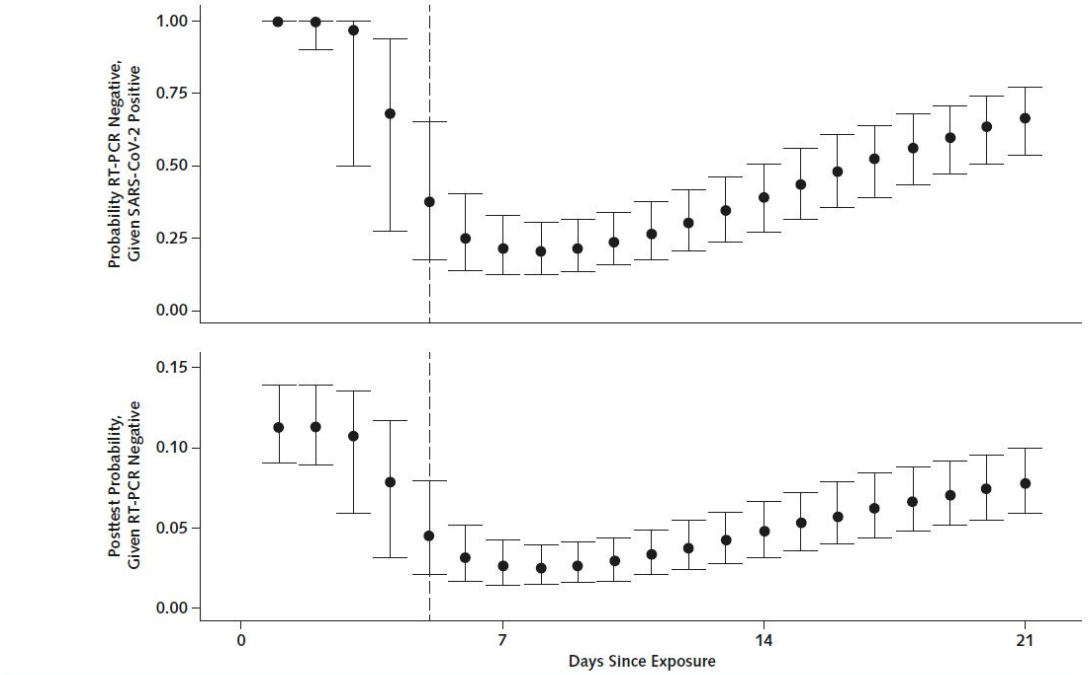
Brief: We were asked to consider the impact of time-varying sensitivity of swab testing in deciding the early release of individuals from isolation (or quarantine). The concern is that tests returning false negatives may lead to erroneous release of infected individuals. How may sequential testing help reduce early release of occult infections? While the intended scenario was that of quarantined passengers arriving into the UK, we also considered the scenario of contacts traced from an index case and instructed to isolate.

Summary: A testing regimen requiring 3 successive negative tests on days 5, 6 and 7 following exposure (day 0) is necessary to reduce the risk of releasing an infected individual from isolation to below 5%. Identifying when best to commence this regime following arrival into the UK for passengers, or notification for contacts, requires further work.

Time-varying sensitivity of swab tests

Negative results from the testing of a person in quarantine or isolation could be used to release them early from isolation, with potential economic and welfare benefits. However, the sensitivity of the swab test (rt-PCR) is not 100%, and the probability of a false negative result changes over the time since exposure (infection); **Figure 1**. The question then arises, when and how often should the quarantined/isolated person be tested for SARS-CoV-2 to minimise the risk of releasing infected individuals from isolation? To address this, we first need to identify how far into an infection (days since exposure) individuals may be when testing can practically commence.



RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Figure 1. taken directly from Kucirka *et al.* 2020. Probability of having a negative RT-PCR test result given SARS-CoV-2 infection (top) and of being infected with SARS-CoV-2 after a negative RT-PCR test result (bottom), by days since exposure. Both graphs assume a 5 day incubation period.

For passengers arriving into the UK, individuals cannot be tested until arrival, yet they may have been infected several days prior to travel, or could have been infected en route. Thus we could reasonably expect a distribution of days since exposure when testing could commence, assuming testing could commence on the day of arrival.

Likewise, in the case of a contact self-isolating, the contact cannot be identified until their infectee (index case) develops symptoms and notifies the Test and Trace system (T&T). However, there are likely to be additional systemic delays that extend this period. These include the delay in person A notifying T&T since their symptom onset, and the delay in T&T taking contact history and notifying person B.

To identify what testing regimen to impose on passengers or contacts to minimise the risk of early release we therefore need to identify:

1. the distribution of days since exposure when the passenger arrives into the UK, or a contact is notified by the T&T system;
2. the probability of releasing the passenger from quarantine or contact from isolation, given that they are infected, and given a regimen of testing since their exposure and notification.

We consider these in turn, and identify the ‘best’ testing strategy in light of possible further systemic and logistical delays.

Estimating the timing of (initial) testing relative to time since exposure

Scenario 1 – quarantine and testing of arriving travellers to the UK

Here, we consider infected passengers arriving into the UK, and who would undergo a 14 day quarantine following arrival; **Figure 2**. We assume passengers are infected up to 14 days prior to their arrival, and individuals with symptom onset prior to travel do not depart. We simulated 10 million instances of infected passengers, assuming they are infected in the 14 days prior to arrival, sampling from a uniform distribution (between 0 and 14 days). We assign an incubation period to each individual, drawn randomly from a observed incubation period (log-normal distribution, log(mean)=1.621, log(sd)=0.418, from Lauer *et al.* 2020); **Figure 3A**. We assume a uniform journey time of 12 hours for all passengers, though the results are not particularly sensitive to this assumption.

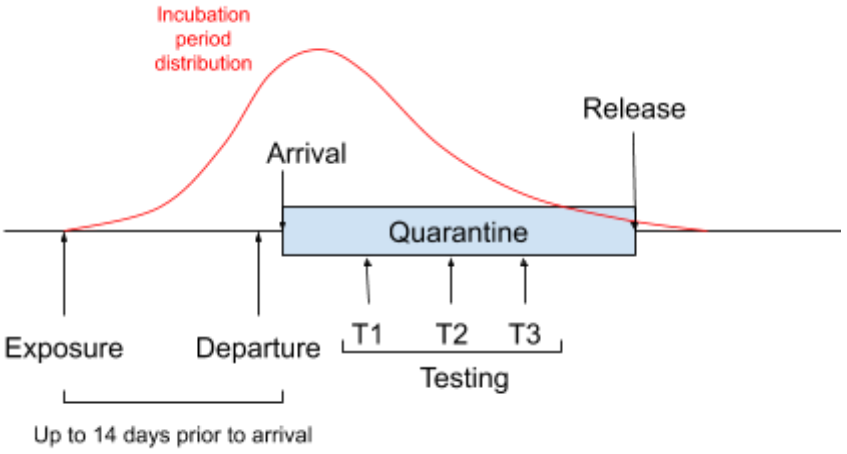


Figure 2. Schematic of disease, travel and intervention events for passengers arriving into UK

Individuals with onset prior to departure are excluded (55.6%); **Figure 3B**., The resulting distribution of the interval between exposure and day of arrival calculated; **Figure 3C**. This represents how far into their infection individuals may be upon arrival into the UK, and informs the efficacy of testing commencing upon arrival. This distribution has a mean of 3.4 days, median 3.0 days and IQR 1.5–4.9. Thus, the first day on which testing could commence on infected passengers (assuming it could begin on the day of their arrival) would, on average, be on day 3 of their infection. Due to the long tail of the incubation period distribution, 0.3% of infected arriving passengers could make it to the end of the 14 days quarantine period without developing symptoms.

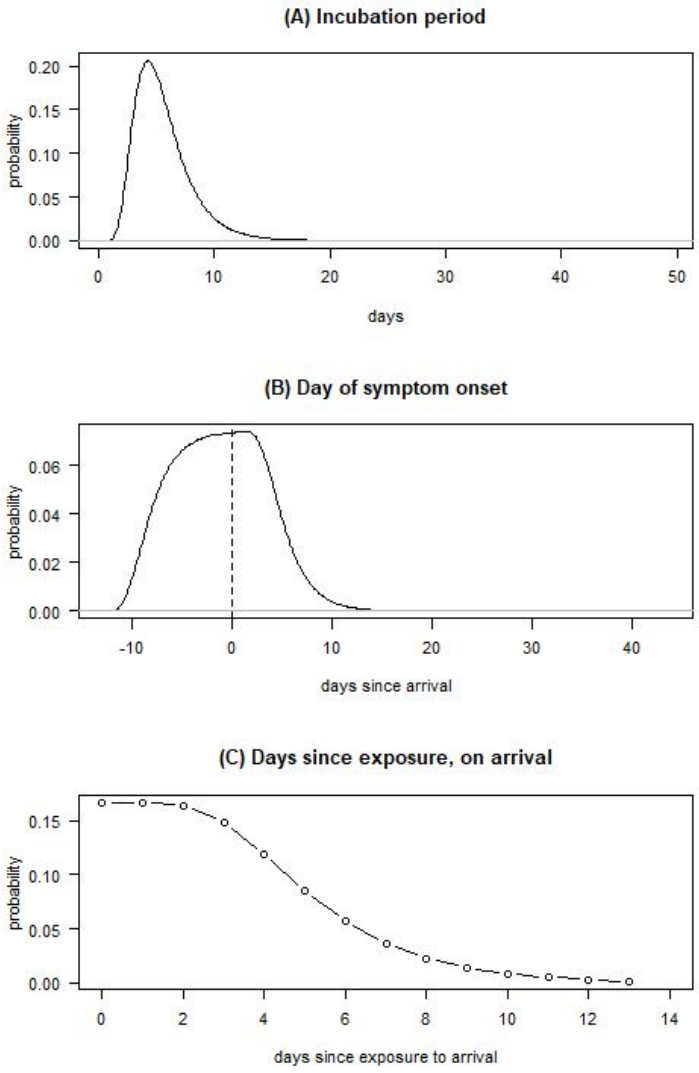


Figure 3. (A) Incubation period distribution. (B) Distribution of the timing of symptom onset relative to arrival day.Those with symptom onset prior to departure/arrival have negative values. (C) 'Floored' distribution of the days since exposure, upon arrival into the UK.

Scenario 2 – notification of an exposed (infected) contact

Here, we consider the scenario of two individuals, person A and person B, where person B is a contact of person A, a suspected case; **Figure 4**. Person A is not traced: they are identified as an index case, and so they are dependent on becoming symptomatic and alerting the Test and Trace (T&T) service. Once notified that they are a contact, person B will be instructed to self-isolate and begin a swab testing regimen.

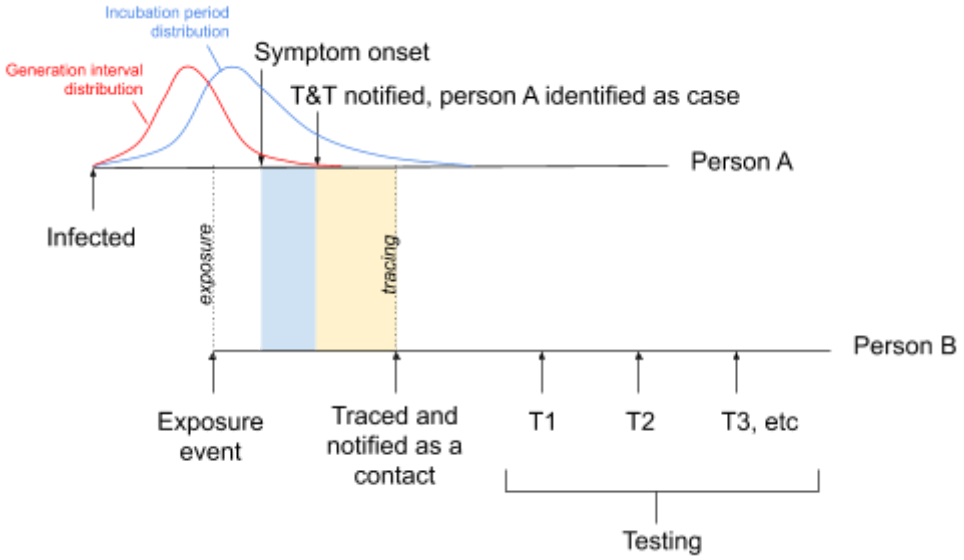


Figure 4. Chronology of disease natural history, tracing and testing events for persons A and B. The blue and yellow areas, combined, represent the delay between symptom onset in person A and person B being traced.

We simulated 10 million instances of person A and person B, where the timing of the exposure event (relative to the time person A was infected) was drawn from a observed generation interval (Gamma distribution, mean 5.2 days, sd 1.72, from Ganyani *et al.* 2020), and the interval from person A being infected and person B being notified was drawn from a observed incubation period (log-normal distribution, log(mean)=1.621, log(sd)=0.418, from Lauer *et al.* 2020) with an additional Poisson distribution (mean 24 hours) to represent the systemic delay in the process. We assume full awareness and compliance with self-isolation advice, and therefore person A self-isolates upon symptom onset. As such, we only consider instances where person B is infected prior to symptom onset of person A. For all realisations we calculated the interval between infection of person B and symptom onset in person A, and added Poisson noise (mean 1 day) to represent systemic delay in notification and contact tracing. This resulted in a right-skewed distribution with mean 3.5 days, median 2.9, and IQR 1.8-2.5; **Figure 5**. Thus, we expect the majority of infected contacts to be notified between 1 and 4 days since their exposure.

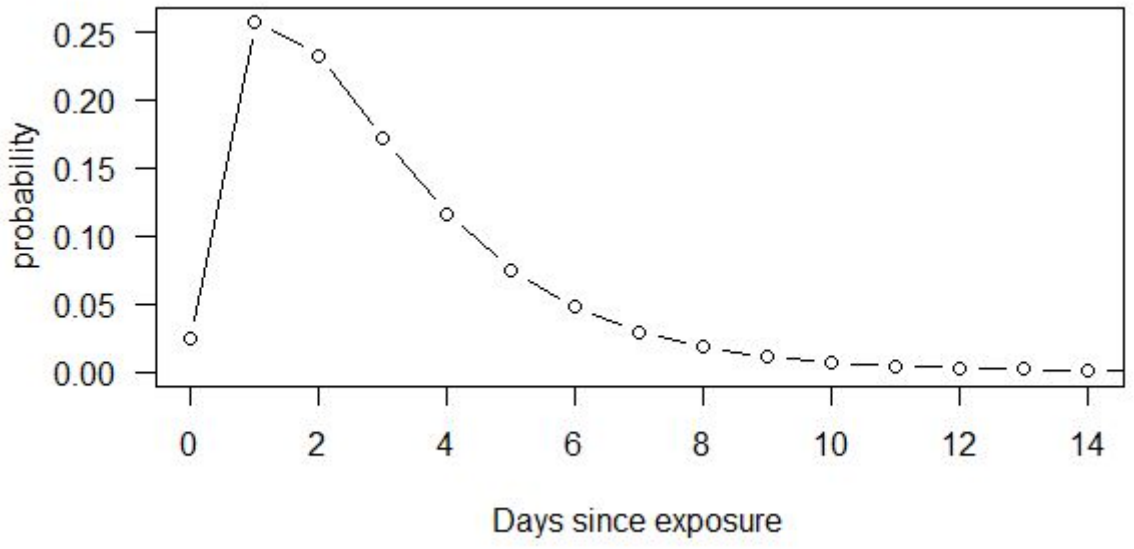


Figure 5. The distribution of the interval from exposure to notification in person B; simulated intervals are floored to whole days.

Number of tests required for disease free status

In this section, we study the design of a serial testing regimen for contact-traced individuals. We assume that having been contact-traced, individuals self-isolate. They then begin a sequence of daily tests, beginning on a specified day since exposure to the index case. We wish to optimise both the starting day and the number of tests performed, subject to changing test sensitivity over time (Kucirka *et al.*, 2020, predicated on a 5-day incubation period). Specifically, we ask the question of how many negative tests are required before we can be 95% certain that the individual is disease free. This cutoff is arbitrary, and should be chosen in line with a desired level of acceptable risk.

Method

We wish to know the probability that an individual is infected given a sequence of n negative tests $T^{-}_{1}, \cdots, T^{-}n$.

$$Pr(D^{+}|T^{-}_{1}, \cdots, T^{-}n) \qquad (1)$$

We have known sensitivity data from Kucirka *et al.* (2020) which gives us the probability that an individual tests positive given that they have the disease on day *t* post-exposure, $Pr(T^{+}_{t}|D^{+})$. Therefore, the probability that someone tests *negative* given that they have the disease is $Pr(T^{-}_{t}|D^{+}) = 1 - Pr(T^{+}_{t}|D^{+})$.

We assume that given an individual's true disease status, all sequentially-applied tests are independent (i.e. knowing the result of a test at time *t*, doesn't alter *how* we apply it at time

t+1). Therefore, the joint probability of a sequence of negative tests given the person is infected is

$$Pr(T^{-}_{1}, \cdots, T^{-}n|D^{+}) = \prod_{t=1}^{n} Pr(T^{-}_{t}|D^{+}) \quad (2)$$

In order to obtain our required quantity in Expression 1, we use Bayes' Theorem to invert the probability in Equation 2 to give our required answer

$$Pr(D^{+}|T^{-}_{1}, \cdots, T^{-}n) = \frac{Pr(T^{-}_{1},\cdots,T^{-}n|D^{+})Pr(D+)}{Pr(T^{-}_{1},\cdots,T^{-}_{n}|D^{+})Pr(D+)+Pr(T^{-}_{1},\cdots,T^{-}_{n}|D^{-})Pr(D^{-})} \quad (3)$$

In Equation 3, we must postulate the *a priori* probability of an individual being infected. We also need to know the *specificity* of the diagnostic test which we assume to be 100%, i.e. $Pr(T^{-}|D^{-}) = 1$.

Results

We use our method to study the effect on the probability of being infected given a sequence of daily negative tests, starting the daily testing regimen on days 1-5 *post* exposure to the index case. For each start day, we also explore the effect of different assumptions about the *a priori* disease status of the individual of interest. Primarily we are interested in minimising the number of negative tests required before we can be 95% certain that an individual is disease free.

Our results, shown in **Figure 6**, indicate that given the sensitivity profile of the test over time, testing on the first 3 days post-exposure provides negligible information gain over the *a priori* estimate of the probability of being infected. Thereafter, sequential negative tests give successive gains in information and therefore successively smaller *a posteriori* infection probabilities.

Starting testing 5 days post-exposure requires 3 negative tests to give an *a posteriori* probability of infection of less than 5%. Starting testing earlier than 5 days post-exposure requires more tests to reach the same level of certainty, whereas starting testing later than 5 days indicates no further reduction in the number of tests required. Importantly, these results are robust to a wide range of *a priori* assumptions about the infection status of the individual of interest.

We note that our 5% cutoff is an arbitrary choice, based on the need for a straw man exposition of our method. In practice, the actual *a posteriori* infection probability is 3% for all *a priori* infection probabilities tested. We leave the choice of cutoff as a policy choice, respecting a desired level of risk acceptance.

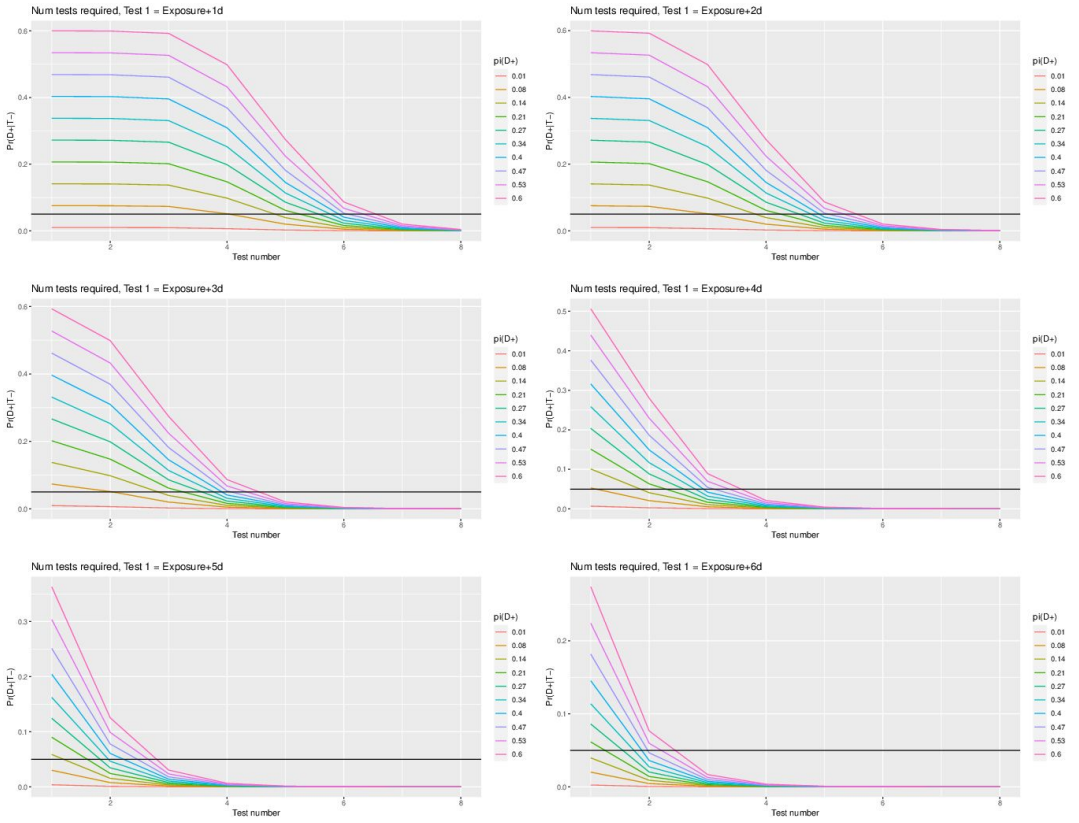


Figure 6. Posterior probabilities of infection given number of sequential tests starting on days 1, 2, 3, 4, 5, and 6 post exposure. The horizontal black line represents an *a posteriori* infection probability of 5%.

Overall conclusions and points of discussion

A testing regimen requiring 3 successive negative tests on days 5, 6 and 7 following exposure (day 0) is necessary to reduce the risk of releasing an infected individual from isolation to below 5%. Should any test prove positive, or the individual develop symptoms, they should be considered infected, and isolation continued for the prescribed duration.

For arriving infected passengers, it may be beneficial to delay testing by 1 or 2 days with the aim of optimising the delay to ensure testing begins on day 5 following exposure for the majority of infected passengers. Practically this may be difficult to achieve.

For the contact tracing scenario, given the time-since-exposure sensitivity of the swab test, it makes little sense in testing a contact immediately following their notification, should there be no delay in tracing them; ideally testing should start 5 days following exposure. However, the probable delay in tracing and notifying them is likely to eat into these 5 days, and so it may be worthwhile commencing testing upon notification. As for arriving passengers, we recommend that testing begins relative to exposure event time rather than notification time *per se*. However this may be difficult to implement accurately, and so a rule of thumb, such as “start testing *n* days after notification”, may be easier. We note different delays between

testing based on postal swab kits and attendance at testing sites would need to be incorporated.

Key limitations: The scenarios modelled here are critically dependent upon the assumed shapes of the incubation period distribution and the generation interval distribution, and the time-varying sensitivity of the test. We have not incorporated empirical uncertainty in the observed distributions into this analysis, relying on the point estimates.

We suggest several points of discussion:

1. We welcome a discussion around a desired "safe" level of certainty in an individual's disease status required on which to base the number of tests. 5% is an arbitrary choice for exemplification, though we note in practice a lower posterior probability of infection is attained after the 3rd test with the 5-day post-exposure strategy.
2. We welcome a discussion around what an optimal test design should be targeted towards. For example, do we want to minimise the number of tests given an acceptable level of infection risk (as we have done above)?
3. Currently, the delay between an individual being exposed and notified that they have been in contact with an infected individual is not clear. We need to develop the work above to incorporate uncertainty on the initial test day (post exposure), drawing together the two sections above. The time interval between exposure and notification should be monitored closely by the NHS Track and Trace system, as it impacts on the testing regimen described above.
4. The prior probability of infection $Pr(D^{+})$ should be re-evaluated as we gain more data from the contact tracing programme. Evidence supporting a lower prior probability of infection may allow a further decrease in the number of tests required, allowing an individual to return from self-isolation earlier.
5. How is it envisaged that serial testing for contacts be rolled out? The design of a serial testng programme depends heavily on logistic constraints. For example, if reliant on postal delivery and return (and self swabbing) then turnaround time for the return of the result to the patient is likely to be 24hrs minimum (depending on when they put swab in post). Attending a testing center (for example on day 5 if no symptoms developed) also presents difficulty, in that they may present at the point at (or just before) symptom onset when they may be most infectious.
6. A health economic analysis of the relative costs of prolonged case isolation (personal and wider economic impact) versus the cost of the testing regimen itself could be performed.

References

Ganyani, T., Kremer, C., Chen, D., Torneri, A., Faes, C., Wallinga, J., & Hens, N. (2020). Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Eurosurveillance*, 25(17), 2000257.

Lauer, S. A., Grantz, K. H., Bi, Q., Jones, F. K., Zheng, Q., Meredith, H. R., ... & Lessler, J. (2020). The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Annals of internal medicine*, 172(9), 577-582.

Kucirka, L. M., Lauer, S. A., Laeyendecker, O., Boon, D., & Lessler, J. (2020). Variation in false-negative rate of reverse transcriptase polymerase chain reaction–based SARS-CoV-2 tests by time since exposure. *Annals of Internal Medicine*.