Know-C19
A policy, health and implementation response to COVID-19

COVID-19 Mathematical Modelling of Diagnostics and Screening: report 1 | 6 May 2020

A model providing guidance on community testing of COVID-19
Key Findings and Recommendations

COVID-19 Diagnostics and Testing Mathematical Modelling

In the absence of a vaccine or effective treatment, increased testing and surveillance has been identified as a mechanism to ease current social distancing measures. **However, the likely effect of a test and quarantine approach on COVID-19 transmission has not been quantified.** We used a deterministic compartmental epidemic model to estimate the effect of testing and surveillance on the spread of COVID-19 in Australia.

Key Findings

1) Early detection of cases is important.

Targeted testing of people with symptoms helps detect future epidemic waves. This is done by increasing the rate of testing among those with respiratory- and other potentially COVID-related symptoms.

2) Random asymptomatic testing is not effective

Random testing of asymptomatic individuals is not effective for early detection of a second wave.

3) A fast turn around of the test results is important.

Maintaining a 1-day return of test results is the second key strategy for early detection of cases.

4) Timely testing combined with quarantine are effective in slowing the epidemic

Test and quarantine alone cannot avert another wave of infection, but they can slow the growth of the epidemic. The time taken for an individual with respiratory symptoms to seek testing, adherence to quarantine among those diagnosed, and the relative adherence to quarantine among those awaiting results all play a role in maximizing the effectiveness of a test and quarantine approach.

5) RT-PCR was the best test currently available for screening

The test sensitivity in the infectious period and the late symptomatic period and test specificity were the most important factors predicting early detection of a second wave. The only test with adequate sensitivity and specificity at this time period is the nasal pharyngeal swab RT-PCR.

Recommendations

1) Having a test one day earlier, even if symptoms are mild, has a big impact

Encourage early testing among anyone with respiratory symptoms, however mild. A clear message to the population is if you have symptoms then get a tests needs to be conveyed to the community. Also key is to ensure that testing facilities are easy-to-access, don't have long wait times and are not perceived to increase risk of acquisition of COVID-19.

2) Fast return of results

Continue to scale-up capacity to return positive test results in a timely fashion: Time to provision of test results is also key for timely detection of a second wave.

3) Quarantine adherence is important

Continue to support people in their efforts to quarantine. Moderate-high adherence to quarantine among people who are awaiting test results or diagnosed with COVID-19 (70% or higher) reduces the rate of growth of a new epidemic in the initial phases. A reduction in adherence from 100%-70% has the equivalent epidemic impact of increasing the time from symptom onset to test from 1 day to 4 days. Once adherence to quarantine falls below 70%, test and quarantine becomes far less effective, and the epidemic growth rate increases substantially.

4) RT-PCR is the only currently available test with utility for screening:

Currently available antibody based tests would either result in high false-positive rates making it impossible to detect small increases in cases (such as at the beginning of a second wave of infection), or lack sensitivity in the infectious phase of the disease so detect cases too late for effective quarantine. Therefore, the nasal pharyngeal swab RT-PCR should be the only test used for public health surveillance at this stage.

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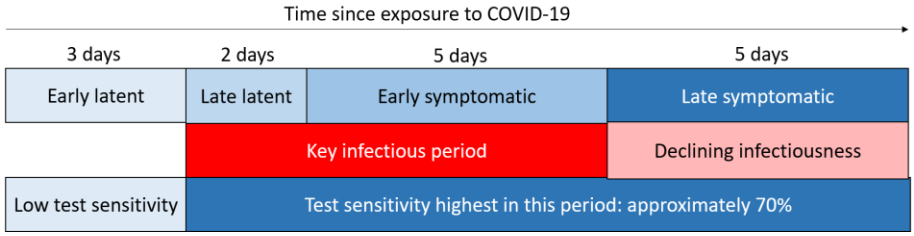
The findings and recommendations outlined above are derived from a mathematical model developed by the Burnet Institute.

Mathematical model

We developed a deterministic SARS-CoV-2 transmission model based on the following schema of the COVID-19 infection course:



The model incorporates SARS-CoV-2 importation to Australia, and transmission given age-dependent mixing patterns, diagnostic testing and quarantine. The transmission probability per social contact was calibrated to reproduce the diagnosed COVID-19 cases and deaths observed in Australia from February 19-April 25 2020. We simulated current social distancing measures continuing until the 11th of May and then being removed. We then simulated the first 80 days after releasing social distancing under variations in test characteristics (sensitivity in the latent, infectious, and late symptomatic periods), test specificity, and time from onset of symptoms until testing. Initial findings reported here do not take quarantine due to contact tracing into account. Further work accounting for quarantine of contacts is currently underway.

Note: Targeted testing of people with symptoms remained a key finding even when the pre-symptomatic infectious period was assumed to be longer than two days (we tested a period of five days).

Detailed information to inform Findings 1,2 and 3.

Early detection of cases is important; Random testing is not effective; A fast turn-around of the test results is important.

Early detection of a second wave after relaxing social distancing

We simulated the first 80 days of the epidemic after releasing social distancing restrictions. We measured the time until 1000 new infections, which we defined as an early sign of a new wave of infections. In order to measure early detection of the second wave, we measured the delay from the first 1000 infections until 1000 cases were detected (diagnosed).

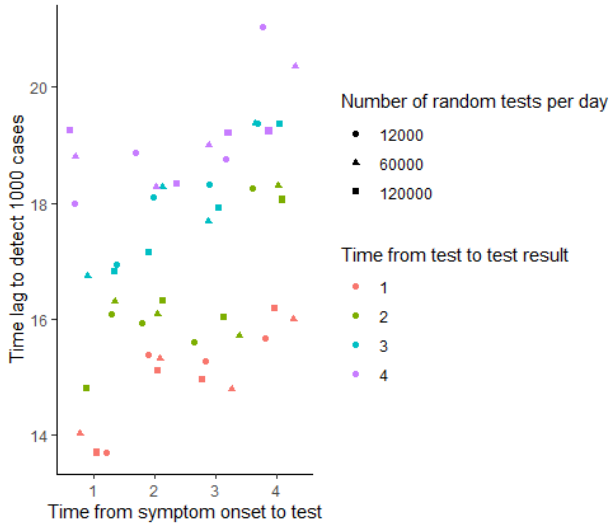
We assumed:

- Test properties (sensitivity and specificity) of the nasal pharyngeal swab RT-PCR (current standard test)
- Optimistic adherence to quarantine (90% among diagnosed, and 80% among those waiting for results)

We tested the following scenarios:

- Number of random tests per day: 12K, 60K, 120K
- Number of days from symptom onset to testing among those with symptoms: 1 day, 2 days, 3 days, 4 days
- Time from test to test result: 1 day, 2 days, 3 days, 4 days

We measured the delay to detecting the first 1000 cases in each of these scenarios. Different rates of testing in people with symptoms and different turnaround times for test results resulted in delays to detect the first 1000 cases ranging from 14 to 21 days as shown:



Currently, in the Flu-tracker online cohort in which approximately 75000 Australians complete an online survey each week, respiratory symptoms are at a seasonally historic low due to social distancing measures. In the week ending 26 April, 0.2% of respondents reported fever and cough compared to approximately 1.4% at the same time of year in 2019. Nonetheless, this is still a large group relative to those with COVID-19 (0.2% of Australians/week would be the equivalent of approximately 7500 people per day) and testing everyone with even milder symptoms would entail a scale-up of testing capacity. In order to maintain high rates of testing in this group after social distancing is relaxed and other respiratory infections increase in prevalence, further scale-up will be required.

Recommendations:

- Encourage people with respiratory and other COVID-related symptoms to seek testing, and to do so early (ideally in the first day of symptoms).
- Facilitate easy-to-access community testing, where the risk of exposure to infected cases is minimized such that people are not afraid to seek testing.
- Continue to scale-up testing capacity in order to process tests in a timely manner.

Detailed information to inform Finding 4.

Timely testing combined with quarantine are effective in slowing the epidemic

In addition to assessing early detection of a potential second wave of infections, we also assessed the number of infections and number of deaths in the first 80 days after releasing social distancing restrictions under a broader range of scenarios.

We assumed:

- Test properties (sensitivity and specificity) of the nasal pharyngeal swab RT-PCR (current standard test)
- Test strategies focusing on symptomatic rather than random testing

We tested the following scenarios:

- Number of days from symptom onset to testing among those with symptoms: 1 day, 2 days, 3 days, 4 days
- Time from test to test result: 1 day, 2 days, 3 days, 4 days
- Adherence to quarantine among diagnosed: 100%, 90%, 70%, 50%
- Relative adherence to quarantine among those tested and awaiting results compared to those diagnosed: 100%, 75%, 50% as adherent as those diagnosed

The number of deaths in the first 80 days of a new wave assuming no social distancing interventions had been introduced ranged from 69-859. The number of infections (including asymptomatic infections), ranged from 70K-1354K. Testing and quarantine alone cannot prevent a second wave of COVID-19, but they can result in reduced rate of growth of a second wave.

The key factors associated with reduced infections and deaths in order of importance were:

- Adherence to quarantine among those diagnosed
- The rate of testing among those with symptoms
- Adherence to quarantine among those awaiting results
- Turnaround time for test results

Adherence to quarantine and reducing the time from symptom onset to testing among those with symptoms were the two most important factors determining the effect of test and quarantine on the epidemic. A reduction in time to test from 4 days to 1 day was a little more effective than increasing adherence to quarantine from 70% to 100% keeping other variables equal. Once adherence to quarantine fell below 70%, the test and quarantine strategy became far less effective.

If the adherence to quarantine among those waiting for test results was low relative to the adherence among those diagnosed, then the time to test results also impacted on epidemic growth.

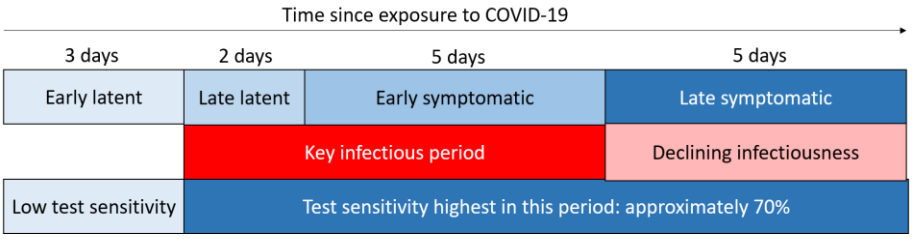
Similar to the factors associated with timely case detection, targeted testing of people with symptoms was much more effective than random screening of asymptomatic people. Random screening did not impact on these public health objectives, even when high volumes of asymptomatic people were tested (120,000 per day).

Recommendations

- Continue to support people in their efforts to quarantine. Moderate-high adherence to quarantine among people who are awaiting test results or diagnosed with COVID-19 (70% or higher) reduces the rate of growth of a new epidemic in the initial phases. A reduction in adherence from 100%-70% has the equivalent epidemic impact of increasing the time from symptom onset to test from 1 day to 4 days. Once adherence to quarantine falls below 70%, test and quarantine becomes far less effective and the epidemic growth rate increases substantially.

Finding 3
Ideal test characteristics

Our model was based on the following disease stages:



Notably, infectiousness was assumed to begin before symptom onset and the highest test sensitivity coincides mainly with the infectious period.

We tested several possible characteristics of an ideal test for COVID-19 including:

- Test specificity (the proportion of true negatives that test negative): 95%, 100%
- Test sensitivity (the proportion of true positives that test positive) at the following stages:
    - *Early latent period:* not at all sensitive, half sensitivity compared to infectious period, same sensitivity as infectious period
    - *Infectious period (including late latent and late symptomatic):* 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%
    - *Late symptomatic period:* 0%, 70%, 90%

We found that test sensitivity in the infectious period and the late symptomatic period and test specificity were the most important factors predicting early detection of a second wave, and reductions in number of infections and deaths in the first 80 days of a new epidemic.

Currently available tests can roughly be divided into three groups

- The current standard of care nasal pharyngeal swab RT-PCR test
- Antibody tests with specificity between 90-98%
- Antibody tests with 100% specificity

The current standard of care test has very high specificity (100%), moderate sensitivity in the infectious stage (70%), reducing with time from symptom onset. While these characteristics are not perfect, they are far better than the available antibody tests for public health surveillance.

The antibody tests with specificity between 90-98% are not appropriate for public health surveillance because the number of false-positives will far outweigh the number of true-positives and make it impossible to detect a second wave of infections.

The antibody tests with 100% specificity have sensitivity ranging from 20-40% in the first week after symptom onset, and around 50% in the second week after symptom onset. Although sensitivity increases after that, this is (a) too late for early detection of a new wave of infections, (b) too late to avert transmissions through test and quarantine, and (c) does not coincide with the main time period where people seek testing (the first two weeks of symptoms).

Recommendations:

- Continue to use nasal pharyngeal swab RT-PCR tests
- Educate the public to ensure that they understand that other tests are not effective for detecting COVID-19

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