MANATŪ HAUORA
MINISTRY OF HEALTH

133 Molesworth Street
PO Box 5013
Wellington 6140
New Zealand
T+64 4 496 2000

14 December 2022

James

By email: fyi-request-21306-d9c90673@requests.fyi.org.nz
Ref: H2022018035

Tēnā koe James

Response to your request for official information

Thank you for your request under the Official Information Act 1982 (the Act) transferred to Manatū Hauora (the Ministry of Health) from Te Whatu Ora- Health New Zealand (Te Whatu Ora) on 2 December 2022 for information regarding COVID-19 infectious period calculations and processes. You requested:

> *"I am seeking the information and directives given to the National Contact Tracing Service and any other COVID-19 officials around infectious period calculations and processes. Specifically, I am looking for the directives that relate to when a person's day 0 and infectious period begins when they have tested positive more than 7 days after symptom onset. I am also looking for the health advice that supports such directives."*

One document titled *Efficacy of Test to Release* has been identified within scope of your request. This document is attached to this letter as Appendix 1 and is released to you in full.

I trust this information fulfils your request. Under section 28(3) of the Act, you have the right to ask the Ombudsman to review any decisions made under this request. The Ombudsman may be contacted by email at: info@ombudsman.parliament.nz or by calling 0800 802 602.

Please note that this response, with your personal details removed, may be published on the Manatū Hauora website at: www.health.govt.nz/about-ministry/information-releases/responses-official-information-act-requests.

Nāku noa, nā

Dave Henderson
Interim Group Manager, Intelligence, Surveillance and Knowledge
Public Health Agency | Te Pou Hauora Tūmatanui

Efficacy of Test to Release

The purpose of this document is to provide evidence for the efficacy of Rapid Antigen Tests (RATs) in a "Test to Release" schedule.

The current period of isolation is a fixed period of 7 days from the date of onset of symptoms, or diagnosis, whichever is earlier. A test to release schedule uses a combination of a lower and upper fixed period of time for isolation combined with release form isolation if an individual tests negative between these dates. The rationale is that RATs are able to predict infectiousness with sufficient accuracy to ensure infectious individuals are isolated, while non-infectious individuals are released from isolation.

The ability of RATs to identify infectious individuals in a "Test to Release Schedule" does not need to be 100% accurate for this method to be used to determine the period of isolation. Instead, the evidence should provide sufficient basis to conclude that a "Test to Release Schedule" is superior to a "Fixed Isolation Period" of 7 (or some other number of) days. In this setting, superiority would be inferred, if there was evidence that a "Test to Release" schedule resulted in fewer infectious individuals being released into the community without a significant increase in non-infectious individuals being isolated or a similar proportion of individuals being released with a significantly deceased period of isolation in non-infectious individuals.

Summary.

- The performance of test to release strategy primarily depends upon the ability of rapid antigen tests to differentiate between those who are infectious and those who are not infectious. As the cohort of individuals isolating have already been diagnosed using RATs, the subsequent test performance is expected to be high, as those who have a false negative RAT will not be captured by either strategy.
- Infectiousness is not directly measurable. The current most reliable measure of infectiousness is the ability to culture live virus. Culture of virus is not possible to use in a clinical setting as the tests are too expensive and time consuming to use on a large scale. An individual who is "culture negative" is very unlikely to be infectious. An individual who is "culture positive" is potentially infectious.
- It is well recognised that infectiousness is not evenly distributed throughout those individuals who test positive. Both biological and behavioural factors will influence this variation in infectiousness. Some individuals are substantially more infectious than others. It has been estimated that the majority of transmission occurs from a minority of individuals. This observation indicates that individuals who are highly infectious are also highly likely to return a positive RAT test.
- It is well recognised that infectiousness varies markedly over time. As RATs measure viral antigens, not intact virions, it is likely that the relationship between a positive RAT and infectiousness will also decrease over time.
- **The current evidence would support the assumption that within the first week of infection, a positive RAT is strongly correlated with culturable virus and that the individual is infectious. However, a negative RAT early in the course of disease (before day 5) does not guarantee an individual will not be infectious.**
- **The current evidence would support the assumption that after the first week of infection, a negative RAT is strongly correlated with non-culturable virus and that the individual is**

unlikely to be infectious. A positive RAT is correlated with infectiousness, but not as strongly as within the first week. At more than 14 days either a positive RAT or culturable virus are uncommon.

- The transmissibility of Omicron variant is markedly increased compared to the original Wuhan or later Delta variants. Much of this is due to immune evasion, but there is also an element of increased infectiousness. Data regarding the rates or risks of infectiousness from previous variants must be interpreted with caution for the current outbreak.

The relationship between PCR Ct value and culture positivity

There is a clear relationship between the Ct value and Culture positivity. Culture positivity decreases as the Ct value rises, which is assumed to be due to a decreasing viral load. Virus is almost always culturable at a Ct value of 25 or less, decreasing to less than 10% at a Ct value of 35 or more (Figs 1&2) (1) (2). However, there is a stronger relationship between culture positivity and time since the beginning of infection, indicating that the relationship between CT value and culture positivity will vary over the course of an infection.

Fig 1. Relationship between RT-PCR Ct value time since infection and culture positivity.

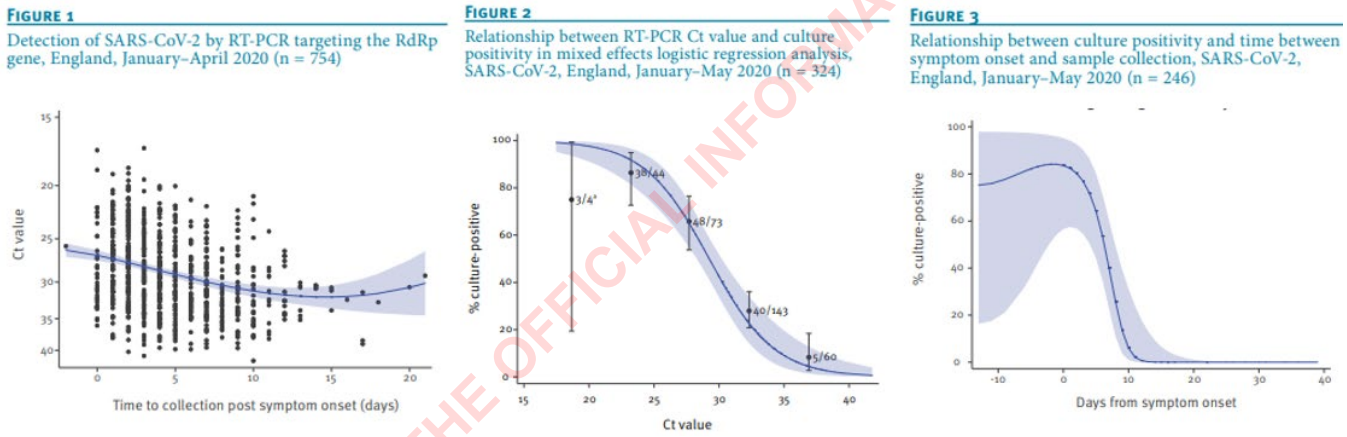


Fig 2 Relationship between culture and PCR Ct values

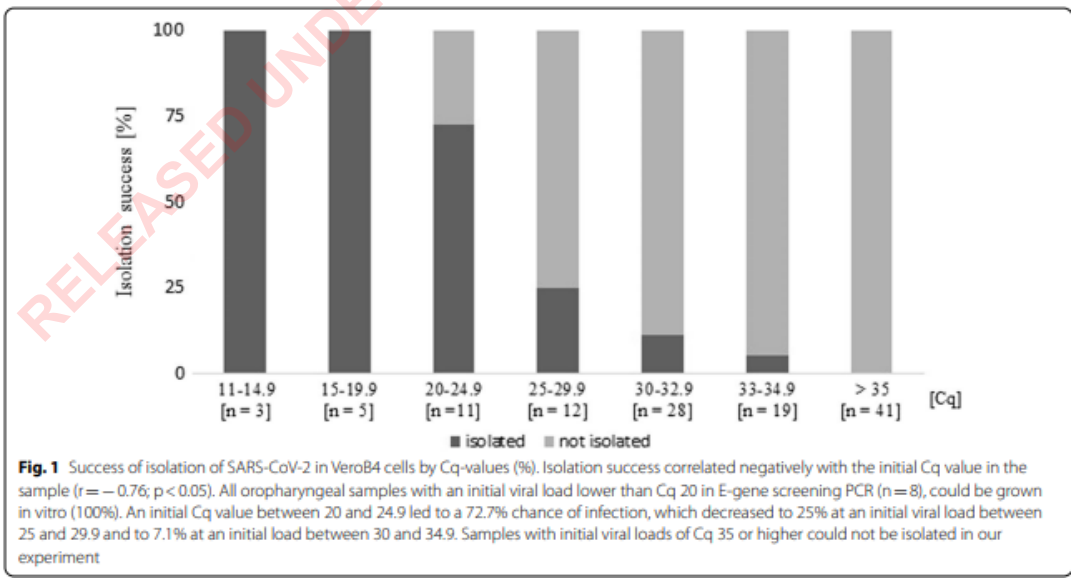
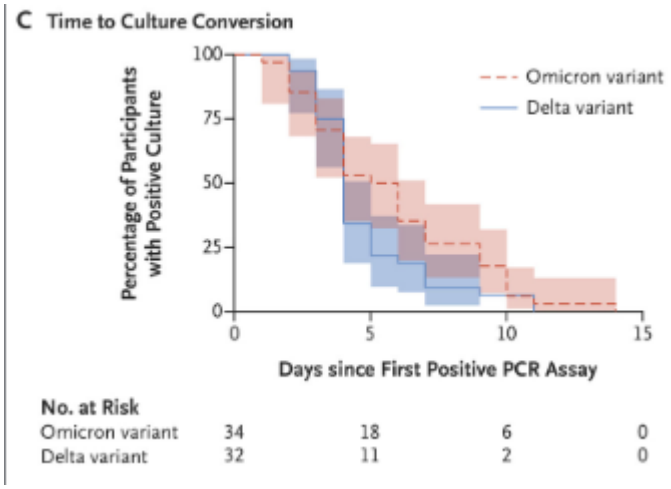


Fig. 1 Success of isolation of SARS-CoV-2 in VeroB4 cells by Cq-values (%). Isolation success correlated negatively with the initial Cq value in the sample ($r = -0.76$; $p < 0.05$). All oropharyngeal samples with an initial viral load lower than Cq 20 in E-gene screening PCR ($n = 8$), could be grown in vitro (100%). An initial Cq value between 20 and 24.9 led to a 72.7% chance of infection, which decreased to 25% at an initial viral load between 25 and 29.9 and to 7.1% at an initial load between 30 and 34.9. Samples with initial viral loads of Cq 35 or higher could not be isolated in our experiment

Omicron

Are more recent study analysing differences in the duration of shedding of the Omicron and Delta variants reported that the time to culture conversion was greater for Omicron than Delta (3). For Omicron, the proportion that are still shedding culturable virus at day 10 was 25%, while for Delta, the proportion was 6%. Culturable virus was not recovered after day 14.



The relationship between RATs, PCR Ct and positive cultures

The Human Challenge Trial assessed the relationship between infection and culturable virus and reported that the RAT sensitivity for culturable virus exceeded 80%, once a positive PCR test had been obtained. The study also reported that a negative RAT was a reliable indicator of a negative viral culture (4).

A systematic review of the performance of Rapid Antigen Tests (RATs) reported that assays shown to meet appropriate criteria, such as WHO's priority target product profiles for COVID-19 diagnostics ('acceptable' sensitivity ≥ 80% and specificity ≥ 97%), can be considered as a replacement for laboratory-based RT-PCR when immediate decisions about patient care must be made, or where RT-PCR cannot be delivered in a timely manner (5). However, this review also states that "Test accuracy studies cannot adequately assess the ability of antigen tests to differentiate those who are infectious and require isolation from those who pose no risk, as there is no reference standard for infectiousness". A review of the performance of 14 RATs reported substantial variability in the limit of detection measured against the Ct value of paired samples, from 26.8 to 34.7. This encompasses the range of results which occur for many individuals over the entire course of an illness. However, the most effective RATs demonstrated a true positive rate compared to paired samples from PCR for values of 99.1% for a Ct value of ≤30 and 90.9% for a Ct value of ≤33 (6).

All RATs used in New Zealand have undergone a rigorous assessment to ensure that the test has a sensitivity of at least 80% overall and >90% for CT values <25. RATs are also assessed for usability which has been uniformly high.

Similar results have been reported by other studies (3, 7, 8).

The relationship between Culture and Infectiousness

The ability to culture virus does not automatically indicate infectiousness. The minimum infectious dose for Omicron, or any other variant is still unknown, but the higher the viral load of intact virus, the greater the risk of infection. The relationship between dose and infection will be sigmoid, with a

very low rate of infection at low doses, rising to a very high rate of infection as the dose increases. It has been estimated that a sample with 10^8 RNA copies per ml, a positive culture rate of approximately 50% will be achieved (9).

Therefore, it is clear that not all individuals from whom culturable virus can be obtained will produce enough virus to infect other in the majority of exposure events. Indeed an argument can be made that as the majority of infections are caused by a minority of highly infectious individuals. Two epidemiological parameters often characterise the transmissibility of infectious diseases: the basic reproductive number (R0) and the dispersion parameter (k). R0 describes, on average, how many individuals in a susceptible population will be infected by someone with that disease, and k details the variation in individual infectiousness. The smaller the k value, the greater the variation. That is, fewer cases cause the majority of infections, and a greater proportion of infections tend to be linked to large clusters via superspreading events. (10) During the COVID-19 pandemic, transmission of SARS-CoV-2 has been highly overdispersed, as 60–75% of cases infect no one and, propelled by superspreading events, 10–20% of cases cause 80% of secondary infections (11-13)

Modelling studies have reported that the number of super-emitters of SARS-CoV-2 has increased progressively so that for the WT, one in 1,000 infected persons was a super-emitter; for Delta one in 30; and for Omicron one in 20 or one in 10, depending on the viral load estimate used [1] . The infectivity-strengthening mutations N440K, T478K, and N501Y enhance infectiousness. Among them, T478K is one of two RBD mutations in the Delta variant, while N501Y is presented on many prevailing variants (14).

The conclusion is that it is not necessary to identify all of the individuals who are infectious to have an impact on the rate of transmission, but to identify those who are superspreaders, who are most likely to have the highest viral load and be RAT positive.

Real world studies of test to release

Although several countries or States have implemented test to release policies, there is no reliable analysis of the success of these policies. Changes in regulations have often comprised a package of alterations to interventions, which, in addition to the natural variation in case numbers, results in difficulty in ascribing a causal relationship to changes in the duration of isolation.

Modelling studies of test to release

Modelling of test to release have been published. Two of the key components of the model include the sensitivity of the RAT test in predicting infectiousness and the distribution of infectious cases over time (3). For a RAT sensitivity of between 0.7 and 0.8 and a model which predicts a 16% risk of infectiousness at day 7, an isolation schedule of at least 7 days would result in 15.8% of released individuals being infectious for a mean excess isolation per person of 76.8 hours. A test to release schedule would reduce the proportion of infectious cases released to 9.2% for no significant change in the mean excess isolation per person of 79.2 hours.

A model assessing the ability of two consecutive day negative RATs reported that the number of infectious days in the community can be reduced to almost zero (15). The model was based on data relating viral load to test positivity over time so maybe less dependent on assumptions about test performance at different points in time. Testing was just as efficient if commenced on day 3 or day 5.

[1]DOI: https://doi.org/10.4414/smw.2022.w30133
Publication Date: 06.01.2022
Swiss Med Wkly. 2022;152:w30133

This model assumed that the infection kinetics for Omicron are similar to those for pre-Omicron variants.

Conclusion

The aim of isolation is to decrease the risk of individuals who are infectious, being released from isolation. However, infectiousness is not a binary (yes or no) state and there is ample evidence to support the observations that individuals who are highly infectious, are the primary drivers of community spread. Therefore the identification of infectiousness does not need to be perfect but to identify those who are the most infectious. These individuals are likely to within the cohort identified by a positive RAT and to remain positive until the viral load has substantially reduced. This time will be variable and for the most infectious likely to be more than 7 days. RATs may be unreliable at less than 5 days after infection, and be unnecessary more than 10 days after diagnosis or symptom onset.

References

1. Singanayagam A, Patel M, Charlett A, Lopez Bernal J, Saliba V, Ellis J, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill. 2020;25(32).
2. Jefferson T, Spencer EA, Brassey J, Heneghan C. Viral Cultures for Coronavirus Disease 2019 Infectivity Assessment: A Systematic Review. Clinical Infectious Diseases. 2020;73(11):e3884-e99.
3. Bays D, Whiteley T, Pindar M, Taylor J, Walker B, Williams H, et al. Mitigating isolation: The use of rapid antigen testing to reduce the impact of self-isolation periods. medRxiv. 2021:2021.12.23.21268326.
4. Killingley B, Mann AJ, Kalinova M, Boyers A, Goonawardane N, Zhou J, et al. Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults. Nature Medicine. 2022.
5. Dinnes J, Deeks JJ, Berhane S, Taylor M, Adriano A, Davenport C, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database of Systematic Reviews. 2021(3).
6. Routsias JG, Mavrouli M, Tsoplou P, Dioikitopoulou K, Tsakris A. Diagnostic performance of rapid antigen tests (RATs) for SARS-CoV-2 and their efficacy in monitoring the infectiousness of COVID-19 patients. Scientific Reports. 2021;11(1):22863.
7. Boucau J, Marino C, Regan J, Uddin R, Choudhary MC, Flynn JP, et al. Duration of viable virus shedding in SARS-CoV-2 omicron variant infection. medRxiv. 2022:2022.03.01.22271582.
8. National Institute of Infectious Disease. Active epidemiological investigation on SARS-CoV-2 infection caused by Omicron variant (Pango lineage B.1.1.529) in Japan: preliminary report on infectious period. National Institute of Infectious Disease,; 2022 5 Jan 2022.

9. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-9.
10. Chen PZ, Koopmans M, Fisman DN, Gu FX. Understanding why superspreading drives the COVID-19 pandemic but not the H1N1 pandemic. The Lancet Infectious Diseases. 2021;21(9):1203-4.
11. Sun K, Wang W, Gao L, Wang Y, Luo K, Ren L, et al. Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2. Science. 2021;371(6526).
12. Lau MS, Grenfell B, Thomas M, Bryan M, Nelson K, Lopman B. Characterizing superspreading events and age-specific infectiousness of SARS-CoV-2 transmission in Georgia, USA. Proceedings of the National Academy of Sciences. 2020;117(36):22430-5.
13. Hasan A, Susanto H, Kasim MF, Nuraini N, Lestari B, Triany D, et al. Superspreading in early transmissions of COVID-19 in Indonesia. Scientific reports. 2020;10(1):1-4.
14. Chen J, Wang R, Gilby NB, Wei G-W. Omicron Variant (B.1.1.529): Infectivity, Vaccine Breakthrough, and Antibody Resistance. Journal of Chemical Information and Modeling. 2022;62(2):412-22.
15. Quilty BJ, Pulliam JRC, Pearson CAB. Test to release from isolation after testing positive for SARS-CoV-2. medRxiv. 2022:2022.01.04.21268372.