(ARCHIVED) COVID-19 – What We Know So Far About…Viral Detection

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Introduction

PHO is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents are intended to provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

The development of these documents includes a systematic search of the published literature as well as scientific grey literature (e.g., ProMed, CIDRAP, Johns Hopkins Situation Reports) and media reports, where appropriate. Relevant results are reviewed and data extracted for synthesis. All "What We Know So Far" documents are reviewed by PHO subject-matter experts before posting.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in these documents is only current as of the date of posting.

Key Points

- The ability to detect SARS-CoV-2, the virus that causes COVID-19, may vary by specimen type collected, quality of specimen collection, and timing of collection with respect to symptom onset. In general, nasal swabs are more sensitive compared to throat swabs for collection of upper respiratory tract specimens.

- Viral load is highest in the first week after symptom onset followed by a gradual decrease. SARS-CoV-2 RNA has been detected in specimens collected 3-4 weeks after onset; however, it is not clear how this correlates with infectiousness.

- SARS-CoV-2 RNA has been detected in specimens collected from asymptomatic individuals.

- At this time, limited data are available regarding the association between detection of viral RNA and infectious virus; however, live virus has been recovered from a variety of respiratory specimens and stool samples.

Background

The purpose of this document is to outline what is known about detection of SARS-CoV-2 based on a review of the scientific literature. Viral RNA detection is in reference to the use of real-time reverse transcription polymerase chain reaction (rRT-PCR) for specific detection of SARS-CoV-2 RNA, with or without viral culture. rRT-PCR results are often reported as cycle threshold (Ct) values, where Ct is inversely proportional to viral load (i.e. low Ct value indicates a higher load). It is important to note that the presence of RNA does not always correlate with infectiousness, as the presence of nucleic acid does not always indicate live virus.

Viral Detection and Clinical Specimen Type

The sensitivity of rRT-PCR may vary by clinical specimen type. Understanding the optimal specimen to collect is important for sensitive diagnosis of SARS-CoV-2.

- COVID-19 has been detected in upper respiratory (nasopharyngeal swabs, nasopharyngeal wash/aspirate, oropharyngeal swabs, saliva) (Pan et al.) and lower respiratory specimens (sputum, bronchoalveolar lavage, lung tissue), as well as stool, rectal swabs and blood (Wang et al.).

- Discordant results between rRT-PCR results have been reported when multiple specimen types were collected (Wang et al., Xiao et al.). In a study of patients from China, 37 paired specimens (throat and nasal swab) were collected at the same time, and found discordant results for 14 pairs (37.8%) with positive nasal swabs and negative throat swabs for 12 pairs (32.4%), and positive throat swabs and negative nasal swabs for 2 pairs (5.4%).

- Higher viral loads have been detected in respiratory specimens over non-respiratory specimens (Chan et al.). With respect to upper respiratory specimens, nasal swabs have been reported to have higher viral loads than throat swabs (Zou et al.). Comparing upper respiratory specimens to lower, generally a higher viral load has been detected in sputum compared to throat swabs but the difference is not always statistically significant (Pan et al.).

- Viral culture has been more successful in respiratory specimens than other specimen types. Viable SARS-CoV-2 has been cultured from sputum, nasopharyngeal and oropharyngeal specimens (Kim et al., Wölfel et al.), and in a small number of cases SARS-CoV-2 has been cultured from stool (Wang et al., Zhang et al.).

Viral Detection and Patient Demographics

At the present time there is limited information regarding the association between patient demographics, detection of SARS-CoV-2, and the level of viral load.

- Several studies with conflicting evidence for the relationship between age and viral load have been published. In one study, researchers found no obvious difference in viral loads across sex, age groups and disease severity. Note, these findings were determined through a descriptive

analysis of Ct values with each variable, without a statistical analysis controlling for multiple variables. In contrast, a study of SARS-CoV-2 in Hong Kong patients found that increased age was positively associated with higher viral loads (Spearman's p=0.48, 95% CI 0.074–0.75; *p*=0.020). This was a small study of 23 SARS-CoV-2 cases and similar to the other two studies, did not control for other variables such as sex, disease severity, or comorbidities.

- A study of pregnant women in China found that only 16 of 41 (39%) had positive rRT-PCR testing. The remaining women were diagnosed through clinical symptoms and computerized tomography (CT) scans.

- Children may be more likely to have persistently positive specimens. A case study of a household cluster including a 6-month-old infant showed that nasopharyngeal swabs were consistently positive (up to 16 days following hospital admission) for the infant, whereas the mother was intermittently positive. Furthermore, stool specimens in particular may remain positive in children for a longer period. In a study comparing adults and children, SARS-CoV-2 RNA was detected in stool specimens longer for children and after clearance in their respiratory specimens.

Disease Severity and Viral Detection

SARS-CoV-2 has been detected in cases with a range of disease severity, including prior to symptom onset and in asymptomatic cases. At present, there is only a single study regarding the viability of the virus in presymptomatic and asymptomatic cases. Additionally, reports of transmission linked to asymptomatic individuals with SARS-CoV-2 RNA detected in respiratory specimens provides support to the presence of live virus in asymptomatic individuals.

- Testing of respiratory specimens collected from individuals on the Diamond Princess cruise ship found that 320/634 (51%) of all confirmed cases were reported to be asymptomatic at the time of collection. However, to account for patients that later developed symptoms, modelling estimated the total number of true asymptomatic cases as 113.3 (95% credible interval (CrI): 98.2-128.3) with a proportion of 17.9% (95% CrI: 15.5-20.2%).

- Several studies of SARS-CoV-2 infected individuals have demonstrated detection of viral RNA prior to symptom onset (up to 3 days prior), or in those that are asymptomatic or have only minor clinical symptoms (Chan et al., Hoehl et al., Hu et al.). This is in line with epidemiological data analysis based on symptom onset timing and transmission pairs, which suggests that viral shedding may begin 2 to 3 days before the appearance of the first symptoms.

- A single study using viral culture showed that viable virus was isolated from respiratory specimens from 17/24 (70.8%) presymptomatic and 1/3 (33.3%) asymptomatic individuals. Further, viable virus was isolated from specimens collected 6 days before the onset of symptoms.

- In a small cohort of 18 individuals in China, the viral load detected in respiratory specimens (nasal and throat swabs) collected from a single asymptomatic individual were similar to that seen in the symptomatic patients. Another study in Washington that included three asymptomatic individuals had similar findings.

- A study examining 76 hospitalized patients in Nanchang, China with laboratory-confirmed SARS-CoV-2, found that severe cases had a mean viral load ~60x higher than that of mild cases. The authors suggest that a higher viral load may be associated with more severe illness.

Viral Detection and Course of Illness

Viral load can change over the course of illness. Understanding the optimal timing to collect specimens is important for diagnostic accuracy.

- A number of studies have indicated that viral loads from respiratory specimens are highest early in the course of illness, peaking within the first week of symptom onset (Pan et al., Zou et al., Wölfel et al., To et al., Kim et al.).

- Viral loads for specimens collected in the first week after symptom onset have been reported in the range of 10^2 to 10^9 copies per mL from respiratory specimens (Pan et al., Wölfel et al.).

- Serial specimen collection and testing using rRT-PCR has demonstrated that viral load gradually decreases after the first week following symptom onset (Pan et al., Zou et al., He et al.), although patients with severe COVID-19 tend to have a high viral load and a longer virus-shedding period (Liu et al.).

- A retrospective study of 191 hospitalized patients in Wuhan, China with SARS-CoV-2 found the median duration of viral shedding for survivors was 20 days (interquartile range 17–24 days) with the longest detected at 37 days. Detection of SARS-CoV-2 continued until death for non-survivors.

- Conversion of respiratory specimens from positive to negative for SARS-CoV-2 RNA appears to occur earlier than for stool specimens, indicating prolonged shedding from the gastrointestinal tract. In a cohort of 74 cases with continuous monitoring through collection of respiratory and stool specimens, over half of patients' stool samples remained positive for SARS-CoV-2 RNA for a mean of 11.2 days after respiratory specimens converted to test negative (overall mean duration of positivity of stool samples was 27.9 days after symptom onset).

- Another study similarly found a prolonged positivity of stool specimens, with the median duration in stool (22 days, interquartile range (IQR) 17-31 days) significantly longer than in respiratory specimens (18 days, IQR 13-29 days). When comparing severe to mild cases the median duration in respiratory specimens was 21 days (IQR 14-30 days) and 14 days (IQR 10-21 days), respectively.

- To understand infectivity over the course of COVID-19 illness, a study using viral culture to assess virus viability showed that SARS-CoV-2 could not be grown from throat or sputum specimens after day 8 of illness from individuals with mild infections, despite high levels of viral RNA. Further, virus could not be isolated from 13 stool samples taken between days 6-12. Another study found that viable virus could be isolated from respiratory specimens up to 9 days post symptom onset.

Detection of SARS-CoV-2 RNA in Recently Recovered Patients

Although not commonly reported in the literature, there have been a small number of cases where SARS-CoV-2 RNA was detected by rRT-PCR in the days after patients were considered cleared of COVID-19. Clearance is generally defined as two consecutive negative rRT-PCR results from specimens collected at least 24-hours apart. It is unclear if viral RNA detection post-recovery represents infectious virus as viral culture was not done in these studies. It is possible that this represents intermittent low-level shedding of viral RNA that is close to the limit of detection of the assays.

- A case study from China of a confirmed patient with serial sampling, reported two consecutive SARS-CoV-2 negative tests from oropharyngeal swabs taken two days apart which were then followed by a positive test 3 days later. Two subsequent tests were negative.

- Similarly, a study of four medical staff exposed to SARS-CoV-2 through their work and diagnosed by positive rRT-PCR were considered "cleared" after two consecutive negative rRT-PCR test results, resolved symptoms and clear CT scans. Follow-up repeat rRT-PCR tests 5 to 13 days later were found to be positive for SARS-CoV-2 in all cases. All patients remained asymptomatic.

- Two case series reports involving two and six confirmed patients with serial specimens collected over the course of illness were found to have positive results on follow-up surveillance testing 6 to 10 days after being discharged from hospital. Patients had been discharged upon meeting clinical and testing criteria (two consecutive negative RT-PCR results 24-hours apart).

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