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Evidence summary of the infectiousness of individuals reinfected with SARS-CoV-2 or other human coronaviruses

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**Health
Information
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An tÚdarás Um Fhaisnéis
agus Cáilíocht Sláinte

Evidence summary of the infectiousness of individuals reinfected with SARS-CoV-2 or other human coronaviruses

13 May 2020

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Key points

- No study was found that directly addressed whether individuals reinfected with SARS-CoV-2 or other human coronaviruses are infectious.
- Four case series studies were identified that examined onward transmission in individuals who retested positive for SARS-CoV-2 despite having two previous negative reverse transcriptase polymerase chain reaction (RT-PCR) tests.
- Due to the relatively short period between the two consecutive negative test results and the subsequent positive test result, and the limited onset of new symptoms, the evidence to suggest that any of the patients in these studies were definitively reinfected, is limited.
- None of the studies reported onward transmission to any of the close contacts of those who re-tested positive for SARS-CoV-2, though only one of the four studies explicitly conducted contact follow-up or tracing. However, as the convalescent patients were undergoing quarantine or self-isolation during the post-discharge period in all four studies, it is not clear whether their contacts would have been in close enough contact to be infected.
- The methodological quality of included studies is very low given the type of study designs included, the small sample sizes and the pre-print status of three included papers.
- The evidence for whether individuals reinfected with SARS-CoV-2 or other human coronaviruses are infectious is currently inconclusive.

Evidence summary for the infectiousness of individuals reinfected with SARS-CoV-2 or other human coronaviruses

The Health Information and Quality Authority (HIQA) has developed a series of 'Evidence Summaries' to assist the Clinical Expert Advisory Group (EAG) in supporting the National Public Health Emergency Team (NPHET) in their response to COVID-19. These summaries are based on specific research questions. This evidence summary was developed to address the following research question:

Are individuals reinfected with SARS-CoV-2 or other human coronaviruses infectious?

The processes as outlined in HIQA's protocol (available on www.hiqa.ie) were followed. Relevant databases of published literature and pre-print servers were searched. Below is the summary of all relevant evidence from 1 January 2000 until 23 April 2020. Data published by national agencies are not included.

Results

The systematic search did not identify any study that directly addressed this research question. However, four studies were identified that partially addressed this research question as they examined onward transmission in individuals who retested positive for SARS-CoV-2, despite having two previous negative reverse transcriptase polymerase chain reaction (RT-PCR) tests. These tests presumably used upper respiratory tract samples to determine whether patients satisfied discharge criteria; however, the sample site is not clearly reported in all of these studies.⁽¹⁻⁴⁾ All four studies were case series studies conducted in China, examining the re-detection of SARS-CoV-2 in patients recovering from COVID-19.⁽¹⁻⁴⁾ Three of these studies were pre-prints and hence were not yet peer-reviewed.^(1, 2, 4) No study was found that examined whether patients reinfected (or re-detected) with another human coronavirus were infectious.

All four studies had limited sample sizes, ranging from four^(2, 3) to 38.⁽¹⁾ Two of the included studies sampled from larger populations of patients who were discharged from hospital after recovering from COVID-19.^(1, 4) In all studies, patients were discharged in accordance with the Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment: (1) normal temperature for three days or more, (2) significant improvement in respiratory symptoms, (3) chest radiology findings show substantial improvement of acute exudative lesions, (4) two consecutive negative nucleic acid tests using respiratory tract samples (taken at least 24 hours apart).⁽⁵⁾

Wang et al. reported that 20 of the 182 patients (11%) that met the discharge criteria, tested positive again for SARS-CoV-2 RNA within 14 days of discharge.⁽⁴⁾ Fourteen of the 20 (70%) re-detected patients tested positive from nasopharyngeal swabs and the other six patients (30%) tested positive from anal swabs. No patient tested positive from both samples.⁽⁴⁾ Similarly, An et al. reported that 38 of the 262 patients (14.5%) that met the discharge criteria, tested positive again for SARS-CoV-2 RNA following discharge.⁽¹⁾ Nasopharyngeal and anal swabs were both used to test patients for re-detection of SARS-CoV-2. However, it is unclear what proportion tested positive from each sample site, or whether detection in both samples was required to classify as positive re-detection.

Notably, across all four studies, patients were only mildly symptomatic or had no symptoms upon re-detection of SARS-CoV-2.⁽¹⁻⁴⁾ None of the cases where SARS-CoV-2 was re-detected related to a patient classified as having severe disease on their initial presentation. Wang et al. observed that patients that were re-detected for SARS-CoV-2 had significantly shorter lengths of stay during their initial admission than patients who were not re-detected.⁽⁴⁾ However, other studies did not observe any significant difference. It is possible that the duration of the initial admission differed by disease severity; however, insufficient data were reported to assess potential confounding.

Post-discharge follow-up for re-detection of SARS-CoV-2 occurred for at least two weeks in one study,⁽¹⁾ for up to two weeks in two studies,^(3, 4) and for three days in a fourth study,⁽²⁾ with some individual cases reporting extensive follow-up due to continuous positive results from anal swabs.^(2, 4) In the single study that followed patients beyond 14 days, it is not clear whether any patient re-tested positive for SARS-CoV-2 greater than 14 days after meeting the discharge criteria, due to unclear reporting of the methods.⁽¹⁾ Hence, it is likely that re-detection of the original virus occurred in these studies rather than reinfection. However, as genome sequencing or virus culturing was not conducted in any of the included studies, it is not possible to rule out the possibility that patients were reinfected with a second virus, though this appears unlikely. None of the included studies reported viral load.

None of the four included studies reported onward transmission to any close contacts of those who re-tested positive for SARS-CoV-2. However, there was very limited information on how contact tracing was conducted for those contacts, what testing was conducted and how long the contacts were followed up for. Only one of the four studies explicitly reported conducting contact tracing, but provided limited details.⁽¹⁾ The other three studies simply stated that there were no reports of onward transmission, without providing any information on how this was established.⁽²⁻⁴⁾ As the convalescent patients were undergoing quarantine or self-isolation at home or in a hotel during the post-discharge period, it is not clear whether their contacts would have been in close enough contact to be infected. One study stated that they followed all 21 close contacts (of the 38 re-detected patients) until 10 March 2020, which was a median of 40-46 days since symptom onset.⁽¹⁾ However, no information

is provided in this study regarding the timing and degree of exposure between the index case and their contacts.

Methodological quality

The quality of the included studies is very low, given the type of studies included, the small sample sizes and the pre-print status of three included papers.^(1, 2, 4) In addition, there were some concerns regarding the applicability of the study contexts,⁽¹⁻⁴⁾ the unclear statistical analysis undertaken,⁽¹⁻⁴⁾ the inconsistent measurement of outcomes⁽¹⁻³⁾ and the non-consecutive inclusion criteria for cases.^(3, 4)

Discussion

No evidence was found to determine whether patients definitively *reinfected* with SARS-CoV-2 or any other coronavirus are infectious. Additionally, only very limited evidence was found regarding whether patients *re-detected*, and hence "*potentially reinfected*" with SARS-CoV-2 are infectious. Due to the relatively short period between the two consecutive negative test results and the subsequent positive test result (< 14 days in three of the four studies), and the limited onset of new symptoms, it appears more likely that patients in these studies experienced *re-detection* of the virus rather than *reinfection* with a second virus. None of the included studies sequenced and compared the genomes of the first and second infections, or attempted culture of viable virus in addition to RT-PCR testing. Therefore re-detection could reflect detection of non-viable viral material (which is being inconsistently shed) rather than viable virus. Whole genome sequencing (WGS) has been conducted to differentiate reactivation from reinfection in tuberculosis (TB).⁽⁶⁾ However, TB has a much longer time scale from initial infection to reactivation or new infection so WGS findings for TB are likely to be more reliable.

Notably, we could not find an agreed definition for reinfection with SARS-CoV-2, possibly due to the limited number of such events described in the literature. We considered the following two definitions for "possible reinfection" that we developed internally, one was stringent and the other was less stringent.

For the stringent criterion, "possible reinfection" was defined as:

"A positive viral respiratory RT-PCR sample for SARS-CoV-2 following recovery (defined as at least two negative upper respiratory tract samples for SARS-CoV-2, collected at \geq 24-hour intervals at a minimum of 14 days after the initial positive test AND a minimum of 14 days between symptomatic recovery (e.g., symptom resolution, fever-free) and onset of new symptoms)."

For the less stringent criterion, "possible reinfection" was defined as:

"A positive viral respiratory RT-PCR sample for SARS-CoV-2 following recovery (defined as at least two negative upper respiratory tract samples for

SARS-CoV-2, collected at ≥ 24 -hour intervals. For symptomatic patients, samples to document virus clearance should be collected at least seven days after the initial onset or after three days without fever. For asymptomatic SARS-CoV-2-infected persons, the tests to document virus clearance should be taken at a minimum of 14 days after the initial positive test)."

Using the stringent criterion, few, if any, of the cases in these studies would be defined as "possibly" reinfected. However, using the less stringent criteria, the majority of the 66 patients in these four studies, with re-detected viral RNA would be defined as "possibly" reinfected. A better understanding of the pathogenesis of how patients might become reinfected is required in order to develop a more robust definition for reinfection.

It is possible that the confirmation of virus clearance in the initial infection was based on a false negative test result. There may be a number of explanations for this. Firstly, there is a potential for pre-analytical errors including issues such as insufficient sampling, contamination of specimens, and inappropriate storage and transport conditions. Secondly, the analytical process can effect results with the use of different sample preparations, the presence of PCR inhibitors and operator errors.⁽⁷⁾ Thirdly, the viral dynamics of SARS-CoV-2 across the time course of the infection are still not fully understood. Hence, false negative test results may occur if samples are tested during the late convalescent phase, when virus levels may be fluctuating.⁽⁸⁾ Molecular diagnostic tests (such as RT-PCR) detect viral RNA, but do not confirm presence of live virus. Intermittently positive test results may therefore reflect inconsistent shedding of non-viable virus, later in the course of an infection. A rapid review conducted by Alberta Health Services similarly concluded that *"reports of reinfection may relate to the reliability of the testing instead of these being cases of reinfection. In particular, clinical cases that test negative and then positive later by RT-PCR when followed post infection may have declining amounts of non-viable virus which is inconsistently detected by RT-PCR testing."*⁽⁹⁾

Another rapid research report led by the Australian Chief Scientist, similarly concluded that the evidence for reinfection with SARS-CoV-2 is thus far, not compelling.⁽¹⁰⁾ The authors of the review suggested that there are three key questions to ask when considering whether a patient is definitively reinfected with SARS-CoV-2:

1. Does the patient have symptoms?
2. Is the patient shedding live virus?
3. Does the patient have neutralising antibodies to SARS-CoV-2?

Importantly, previous evidence summaries conducted by our research team found substantial discordance between different sample sites used for SARS-CoV-2 testing,⁽¹¹⁾ along with differences in viral kinetics.⁽¹²⁾ In particular, viral RNA from faecal samples has been found to be detected for a prolonged period after symptom

resolution,⁽¹³⁾ and hence may not be the most appropriate sample for determining reinfection. It is not entirely clear what specimens were used to determine discharge criteria in these studies, so the potential for false negative test results upon discharge cannot be ruled out.⁽¹⁻⁴⁾ The World Health Organization (WHO) recommends that *"if a negative result is obtained from a patient with a high index of suspicion for COVID-19 virus infection, particularly when only upper respiratory tract specimens were collected, additional specimens, including from the lower respiratory tract if possible, should be collected and tested."*⁽¹⁴⁾

Though none of the four studies included in this evidence summary reported any evidence of onward transmission, these findings may have been biased by the fact that discharged patients were aware of their prior infection and were undergoing quarantine or self-isolation. Hence the potential for onward transmission via close contacts was limited. Viral dynamics are as yet uncertain for SARS-CoV-2, but in any case it is not possible to comment on the level of infectiousness as none of the studies reported the viral load, and this is a significant limitation of the included studies. A news article by Reuters (dated 16 April 2020) reported that *"South Korean health authorities still haven't found cases where the 'reactivated' patients spread the virus to third parties, but if such infectiousness is proven, that would be a huge problem."* Although this information does not come from a research article, and thereby should be interpreted cautiously, it does suggest that health authorities in South Korea are monitoring the situation and up until that point at least, had not identified any cases of onward transmission from re-detected SARS-CoV-2 patients.⁽¹⁵⁾

Larger epidemiological studies with longer follow-up periods are required to establish whether patients re-detected (or reinfected) with SARS-CoV-2 are infectious. The evidence is still emerging and as this virus is still very new in humans, it is not evident whether patients can become reinfected with SARS-CoV-2 once they successfully clear the virus. Large cohort studies are needed to follow recovered COVID-19 patients to establish whether long term immunity is developed, and to what degree it offers protection from various future strains of the virus.

Conclusion

No evidence was found to determine whether patients definitively reinfected with SARS-CoV-2 or any other coronavirus are infectious. Only very limited evidence was found examining transmission from patients re-detected, or "potentially" reinfected with SARS-CoV-2 and this evidence was inconclusive.

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Table 1 Summary of identified studies

Author Country Study design Study URL	Population setting	Primary outcome results	
An⁽¹⁾ China Case series https://www.medrxiv.org/content/10.1101/2020.03.26.20044222v1	<p>Population setting: 262 discharged COVID-19 patients (38 (14.5%) of whom had re-tested positive for SARS-CoV-2 after meeting the discharge criteria).</p> <p>Demographics: <i>Mix of adults and children</i> <i>Sex:</i> n=242 patients with mild or moderate initial disease presentation Male, 116 (47.9%) Female, 126 (52.1%)</p> <p>Severe disease: NR</p> <p><i>Age</i> Mild disease, Median (range) Re-detected patients (n=11), 20 (5-64) Not re-detected (n=19), 23 (2-63)</p> <p>Moderate disease, Median (range) Re-detected patients (n=27), 38 (2-60) Not re-detected (n=185), 48 (1-86)</p> <p>Severe disease: NR</p> <p>Initial Infection <i>Initial Presentation (n=242 mild and moderate patients):</i></p>	<p>Test parameters</p> <p>Virus: SARS-CoV-2</p> <p>Test: qRT-PCR (GeneoDX Co., Ltd., Shanghai, China) and Sherlock assay (hypersensitive test) (Feng Zhang lab) for SARS-CoV-2 RNA detection</p> <p>ELISA assay for anti-SARS-CoV-2 IgG and IgM antibody (Sangon Biotech)</p> <p>Thresholds: Ct value \leq 37 = positive</p> <p>Gene Targets: Sherlock assay: S, ORF, Commercial qRT-PCR kit: N, ORF1</p> <p>Sample site(s): NP and anal (RNA) Serum (antibodies)</p> <p>Discharge criteria: Temperature returned to normal for more than three days, respiratory symptoms significantly improved, and significant absorption of pulmonary lesions of chest CT imaging, and at least 2</p>	<p>Infectiousness outcomes</p> <p>Location of patients after discharge: Discharged from hospital (at home or under intensive isolation for 14 days).</p> <p>Post-discharge follow-up for re-detection of SARS-CoV-2: At least 14 days (however unclear exactly how long patients were followed up for in total). Patients who tested positive again (n=38) were re-admitted to hospital for observation.</p> <p>Number of people in close contact with re-detected patients: 21 close contacts identified from the 38 who re-tested positive.</p>

<p>Fever, 165 (68.1%) Upper respiratory symptoms, 45 (18.6%) Lower respiratory symptoms, 121 (50%) Digestive tract symptoms, 20 (8.3%)</p> <p>Severe patients: NR</p> <p>COVID-19 Clinical syndromes (National Health Commission of the People's Republic of China definition): All 262 patients: Mild, 30 (11.4%) Moderate, 212 (81%) Severe, 20 (7.6%)</p> <p>38 re-detected patients Mild, 11 (28.9%) Moderate, 27 (71.1%) Severe, 0 (0%)</p> <p>Length of stay: <i>Symptom onset to hospital discharge</i> <i>Mild disease (n=30),</i> median 15 days, range 14-22 (re-detected) median 16 days, range 10-23 (not re-detected) <i>Moderate disease (n=212),</i> median 17 days, range 9-29 (re-detected) median 18 days, range 7-35 (not re-detected) <i>Severe disease, NR</i></p> <p>Redetected Cases <i>Clinical characteristics (n=38 mild and moderate patients)</i> Fever, 0 (0%) Cough, 6 (15.7%) Chest tightness, 2 (5.3%) Other symptom, 3 (7.9%)</p>	<p>consecutive negative upper respiratory tract sample (plus anal swab from February 22) RNA test results at least 24 hours apart.</p> <p>Redetection: Within 14 days of discharge via NP and anal swabs (unclear whether positive detection in both sampled required for re-detection).</p> <p>Genome testing: Not conducted</p>	<p>Number of close contacts subsequently infected: None</p> <p>Method of contact tracing undertaken: NR</p> <p>Duration of follow-up of contacts: Authors report follow-up of close contacts until 10 March 2020, which is a median of 40-46 days since symptom onset for all patients.</p>
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Author Country Study design Study URL	Population setting	Primary outcome results	
<p>Deng⁽²⁾</p> <p>China</p> <p>Case series</p> <p>https://europepmc.org/article/PPR/PPR122436</p>	<p>Population setting: 4 discharged patients with re-detected SARS-Cov-2 RNA 3 days after discharge.</p> <p>Demographics: <i>Mix of adults and children</i> Case 1: 29-year old male Case 2: 49-year old female (mother of case 1) Case 3: 12-year old female Case 4: 38-year old male</p> <p>Initial Infection <i>Initial Presentation:</i> Case 1: Fever and cough Case 2: Cough Case 3: No symptoms Case 4: Fever, fatigue and cough</p> <p>COVID-19 Clinical syndromes (National Health Commission of the People's Republic of China definition): Case 1: Mild Case 2: Mild Case 3: Mild Case 4: Pneumonia</p> <p>Length of stay:</p>	<p>Test parameters</p> <p>Virus: SARS-CoV-2</p> <p>Test: RT-PCR (device NR)</p> <p>Thresholds: NR</p> <p>Gene Targets: NR</p> <p>Sample site(s): NP and anal swabs</p> <p>Discharge criteria: 2 negative RT-PCR test results at least 1 day apart (sample site not reported).</p> <p>Redetection 3 days after discharge via NP swabs for 3 patients and via anal swabs for 1 patient Viral RNA was not consistently detected in subsequent tests in 3 of 4 patients.</p> <p>Genome testing: Not conducted</p>	<p>Infectiousness outcomes</p> <p>Location of patients after discharge: NR</p> <p>Post-discharge follow-up for re-detection of SARS-CoV-2: 3 days (all 4 patients were returned to hospital for quarantine)</p> <p>Number of people in close contact with re-detected patients: NR</p> <p>Number of close contacts subsequently infected: None</p> <p>Method of contact tracing undertaken: NR</p> <p>Duration of follow-up of contacts: NR</p>

	<p>Case 1: 14 days Case 2: 14 days Case 3: 14 days Case 4: 23 days</p> <p>Redetection <i>Clinical characteristics</i> Case 1: No symptoms Case 2: No symptoms Case 3: No symptoms Case 4: No symptoms</p>		
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Author Country Study design Study URL	Population setting	Primary outcome results	
<p>Lan⁽³⁾</p> <p>China</p> <p>Case series</p> <p>https://jamanetwork.com/journals/jama/fullarticle/2762452</p>	<p>Population setting: 1 hospitalised and 3 quarantined (at home) healthcare professionals, with re-detected SARS-Cov-2 RNA.</p> <p>Demographics: <i>Adults</i> Sex Male, 2 (50%) Female, 2 (50%)</p> <p><i>Age</i> Range, 30-36</p> <p>Initial Infection Initial Presentation: Among 3 of the patients, fever, cough, or both occurred 1 patient had no symptoms.</p> <p>COVID-19 Clinical syndromes (Definition not reported): Mild to moderate, 4 (100%)</p> <p>Length of stay: NR</p> <p>Redetection <i>Clinical characteristics</i> No symptoms</p>	<p>Test parameters</p> <p>Virus: SARS-CoV-2</p> <p>Test: RT-PCR (BioGerm)</p> <p>Thresholds: NR</p> <p>Gene Targets: NR</p> <p>Sample site(s): Throat</p> <p>Discharge/end of quarantine criteria: 1. normal temperature lasting longer than 3 days, 2. resolved respiratory symptoms, 3. substantially improved acute exudative lesions on CT images, and 4. 2 consecutively negative RT-PCR test results separated by at least 1 day (sample site not reported).</p> <p>Redetection Throat sample RT-PCR tests were repeated 5 to 13 days post-discharge and all were positive. All patients had 3 repeat RT-PCR tests performed over the next 4 to 5 days and all were positive.</p> <p>Genome testing: Not conducted</p>	<p>Infectiousness outcomes</p> <p>Location of patients after discharge: Home quarantine for 5 days.</p> <p>Post-discharge follow-up for re-detection of SARS-CoV-2: Up to 13 days after discharge (not clear whether patients were re-admitted to hospitals).</p> <p>Number of people in close contact with re-detected patients: NR</p> <p>Number of close contacts subsequently infected: None</p> <p>Method of contact tracing undertaken: NR</p> <p>Duration of follow-up of contacts: NR</p>

Author Country Study design Study URL	Population setting	Primary outcome results	
<p>Wang⁽⁴⁾</p> <p>China</p> <p>Case series</p> <p>https://europepmc.org/article/PPR/PPR150648</p>	<p>Population setting: 182 post-discharge patients recovering from COVID-19 under medical isolation (20 of whom (11%) re-tested again for SARS-CoV-2 within 14 days of meeting discharge criteria).</p> <p>Demographics (n=20 re-detected patients): <i>Mix of children and adults</i> Sex: Male, 7 (35%) Female, 13 (65%)</p> <p>Age: Median, 41.5 (Range 1-72)</p> <p>Initial Infection: Initial presentation: NR</p> <p>COVID-19 Clinical syndromes (n=20 re-detected patients) (Definition not reported): Non-severe, 20 (100%)</p> <p>Length of stay: Re-detected (n=20): Average ± SD, 20.8 ± 7.1 days</p>	<p>Test parameters</p> <p>Virus: SARS-CoV-2</p> <p>Test: RT-PCR (BioGerm) Total Ig, IgA, IgG and IgM (WANTAI BioPharm)</p> <p>Thresholds: Ct-value < 37 = positive Ct-value ≥ 40 was defined as negative. A medium load, more than 37 and less than 40, was defined as weak positive and required re-testing.</p> <p>Gene Targets: ORF1ab and N genes</p> <p>Sample site(s): NP and anal Blood for antibody testing</p> <p>Discharge criteria: 1. Temperature below 37 degrees lasting at least 3 consecutive days; 2. Resolved respiratory symptoms; 3. Substantially improved in chest lesions CT images, and 4. 2 consecutively negative RT-PCR test results with at least 1 day interval (sample site not reported)</p> <p>Redetection</p>	<p>Infectiousness outcomes</p> <p>Location of patients after discharge: 14 days of medical isolation observation in a hotel or at home.</p> <p>Post-discharge follow-up for re-detection of SARS-CoV-2: 14 days (20 patients who tested positive were re-admitted to hospital for quarantine).</p> <p>Number of people in close contact with re-detected patients: NR</p> <p>Number of close contacts subsequently infected: None</p> <p>Method of contact tracing undertaken: NR</p> <p>Duration of follow-up of contacts: NR</p>

	<p>Not re-detected (n=162): Average \pm SD, 25.6 \pm 7.6 days</p> <p>Redetection <i>Clinical characteristics</i> No symptoms, 20 (100%)</p>	<p>NP and anal swabs taken on day 7 and 14 post-discharge medical isolation. 14 were tested as NP swabs positive, and 6 were anal swabs positive, none had both positive. 13 of 20 tests were positive on day 7 post-discharge. 7 of 20 tests were positive on day 14 post-discharge.</p> <p>Genome testing: Not conducted</p>	
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Key: COVID-19 – Coronavirus disease 2019; CT – computed tomography Ct – cycle threshold; IgG/IgM – immunoglobulinG/M; IQR – interquartile range; NA – not applicable; NP – nasopharyngeal; ND – not detected; NR – not reported; OP – oropharyngeal (q)(r)RT-PCR – (quantitative) (real-time) reverse transcriptase polymerase chain reaction; RNA - ribonucleic acid; SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2.

