SARS-CoV-2 detection, viral load and infectivity over the course of an infection.

AUTHOR(S)

Kieran A Walsh, Karen Jordan, Barbara Clyne, Daniela Rohde, Linda Drummond, Paula Byrne, Susannah Ahern, Paul G Carty, Kirsty K O'Brien, Eaomon O'Murchu, Michelle O'Neill, Susan Smith, Mairin Ryan, Patricia Harrington

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Kieran A. Walsh, PhD;[a†] Karen Jordan, BSc;[a] Barbara Clyne, PhD;[a,b] Daniela Rohde, PhD;[a] Linda Drummond, PhD;[a] Paula Byrne, PhD;[a] Susan Ahern, MSc;[a] Paul G. Carty, MSc;[a] Kirsty K. O'Brien, PhD;[a] Eamon O'Murchu, MB, BCh, BAO, MPH;[a] Michelle O'Neill, MSc;[a] Susan M. Smith, MD, MSc;[b] Máirín Ryan, PhD;[*a,c] Patricia Harrington, PhD.[*a]

*** Both authors are co-senior authors**

[a]Health Information and Quality Authority, Smithfield, Dublin 7, Ireland

[b]Health Research Board Centre for Primary Care Research, Department of General Practice, Royal College of Surgeons in Ireland, 123 St Stephens Green, Dublin 2, Ireland

[c] Department of Pharmacology & Therapeutics, Trinity College Dublin, Trinity Health Sciences, James Street, Dublin 8, Ireland.

† Corresponding author

Dr Kieran A Walsh. **Address:** Health Information and Quality Authority, Unit 1301, City Gate, Mahon, Cork, Ireland. T12 Y2XT; **Email:** kiwalsh@hiqa.ie; **Phone:** + 353 21 - 240 9300

Abstract

Objectives: To summarise the evidence on the detection pattern and viral load of SARSCoV-2 over the course of an infection (including any asymptomatic or pre-symptomatic phase), and the duration of infectivity.

Methods: A systematic literature search was undertaken in PubMed, Europe PubMed Central and EMBASE from 30 December 2019 to 12 May 2020.

Results: We identified 113 studies conducted in 17 countries. The evidence from upper respiratory tract samples suggests that the viral load of SARS-CoV-2 peaks around symptom onset or a few days thereafter, and becomes undetectable about two weeks after symptom onset; however, viral loads from sputum samples may be higher, peak later and persist for longer. There is evidence of prolonged virus detection in stool samples, with unclear clinical significance.

No study was found that definitively measured the duration of infectivity; however, patients may not be infectious for the entire duration of virus detection, as the presence of viral ribonucleic acid may not represent transmissible live virus.

Conclusion: There is a relatively consistent trajectory of SARS-CoV-2 viral load over the course of COVID-19 from respiratory tract samples, however the duration of infectivity remains uncertain.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, Viral load, Infectivity, RNA, review

Highlights

- SARS-CoV-2 viral loads peak from upper respiratory tract samples around symptom onset
- Viral loads from sputum samples may be higher than upper respiratory tract samples

- Viral loads appear to be similar between asymptomatic and symptomatic patients
- The prolonged virus detection in stool samples has unclear clinical significance
- Patients may not be infectious for the entire duration of virus detection

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Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic is a public health emergency of international concern causing a substantial number of cases and deaths globally.[1, 2] COVID-19 presents an unprecedented challenge to governments worldwide due to the transmissibility of the virus, the scale of its impact on morbidity and mortality, the uncertainty regarding the development of long-term immunity in those infected, the current lack of vaccine or treatment options, and the impact on healthcare systems, economies and society.[3, 4] Much remains unknown about COVID-19; however, evidence is emerging at a fast pace.[5] Our team at the Health Information and Quality Authority (HIQA) of Ireland has conducted a series of rapid reviews on various public health topics relating to COVID-19. The rapid reviews arose directly from questions posed by policy makers and expert clinicians supporting the Irish National Public Health Emergency Team (NPHET). Hence, the findings of these reviews have informed the national response to the COVID-19 pandemic in Ireland,[6] and have implications for international health policy as well as clinical and public health guidance.

Understanding the trajectory of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the duration of infectivity is of critical importance to controlling the pandemic.[7] As SARS-CoV-2 is a novel virus in the human population, there is substantial uncertainty regarding virological levels (i.e. detection and viral load) in patients and how this relates to infectivity and disease severity. Information relating to SARS-CoV-2 detection and viral load at different time points of an infection, including in those without any symptoms, will aid with the clinical interpretation of real-time reverse transcriptase polymerase chain reaction (rRT-PCR) test results. Furthermore, information pertaining to the duration of infectivity will help inform public health protocols for quarantine, isolation and contact tracing.

We defined detection as the presence (i.e. detectability) or absence (i.e. undetectability) of the virus in a sample at a given time. We defined viral load as the quantity (or titre) of virus in a volume of fluid at a given time. For this current article, we summarise the available evidence to address the following two research questions:

1. What is the detection pattern and viral load of SARS-CoV-2 over the course of an infection (including any asymptomatic or pre-symptomatic phase)? Patients who remain symptomless throughout the duration of disease are referred to as 'asymptomatic', and those who are in the early stages of disease, after transmission has occurred, but in whom symptoms have not yet developed are referred to as 'presymptomatic'.[8]
2. What is the duration of infectivity of SARS-CoV-2? Duration of infectivity is defined as the time interval during which an infectious agent may be transferred from an infected person to another person.[8]

Materials and Methods

We conducted rapid reviews for a broad range of public health topics related to COVID-19 following a standardised protocol,[8] in keeping with Cochrane rapid review methodology guidance.[9] Initially, we conducted a systematic literature search of electronic databases (PubMed, EMBASE, Science Direct, Cochrane, National Health Service [NHS] Evidence, and Infectious Diseases Society of America search of infectious disease journals) and pre-print servers (medRxiv, bioRxiv and Health Research Board [HRB] Open) using COVID-19 search terms. The purpose of the initial broad search was to identify all COVID-19 scientific and medical literature to answer a range of research questions. Due to the proliferation of COVID-19 literature, the vast majority of which were not relevant to our research question, we employed a more specific search strategy from 27 March 2020 onwards. Hence, we conducted a systematic literature search of PubMed, Europe PubMed Central and EMBASE

from 30 December 2019. The search combined terms for COVID-19 with terms for viral load, detection and infectivity. Only articles including human subjects were included. No language restrictions were applied. The last update for this rapid review was conducted on 12 May 2020. The protocol, which is available online, contains the detailed search strategies.[8]

All potentially eligible papers, including non-peer-reviewed pre-prints, were exported to Endnote X8.2 and screened for relevance. Any study (regardless of design) that addressed the research question and met the inclusion criteria (Table 1) was included. For each included study, data on the study design, participant demographics and clinically relevant data were extracted. Various validated risk of bias tools were used for quality appraisal of included studies, where appropriate (e.g. Cochrane Risk of Bias (RoB) tool for Randomized Controlled Trials [RCTs][10] and Risk Of Bias In Non-randomized studies of Interventions tool (ROBINS-I)).[11] For study designs where no universally accepted quality appraisal tool existed (e.g. case series, modelling studies), a de-novo tool, adapted from related tools, was used.[8] The findings of the research question were synthesised narratively due to the heterogeneity of study designs and data.

Results

Summary of included studies

A total of 113 studies were included[12-124] (Table 2 and Appendix Table 1). Seventy-four studies were conducted in China.[12, 14-21, 26-28, 32, 35, 36, 39, 40, 52, 53, 56, 57, 59-62, 64, 66, 68, 70-72, 76-78, 80, 82, 84, 85, 89-94, 96, 97, 99-111, 113-125] Five studies each were conducted in Taiwan[22-24, 49, 58] and the United States (US).[13, 34, 44, 74, 75] Four studies each were conducted in Singapore[31, 42, 95, 112] and Italy,[46, 65, 67, 79] three studies each were conducted in Germany,[25, 41, 98] France[30, 45, 50] and Vietnam,[47, 48, 83] two studies each were conducted in Hong Kong,[87, 88] the United Kingdom (UK)[33, 54] and South Korea,[43, 55] with one study conducted in each of the

following: Bangladesh,[38] Switzerland,[51] Thailand,[69] Japan,[73] Australia,[86] and Canada.[63] One hundred-and-eleven studies were observational in nature,[12-15, 17-29, 31-80, 82-125] one study was a randomised controlled trial (RCT)[16] and one was a non-randomised controlled trial (NRCT).[30] The majority of included observational studies (n=95) were case reports or series.[12, 14, 15, 17-22, 24-29, 31, 33, 34, 36-39, 42-44, 47-70, 72-76, 78-80, 82-86, 88-90, 93-102, 104-119, 121, 123-125] The sample size of included studies ranged from one patient (26 case reports)[18, 24, 26, 31, 33, 34, 38, 39, 42, 47, 49, 55, 58, 61, 63, 65, 67, 70, 72-75, 83, 86, 94, 108] to 3,712 patients,[41] with a median sample size across all studies of 15 patients.

Viral load of SARS-CoV-2

Viral load in different sample sites

Fifty studies reported the viral load of SARS-CoV-2 over the course of the infection using rRT-PCR testing.[13, 16, 20, 22, 25, 30-34, 37, 41-46, 48, 50, 51, 55, 58, 59, 61, 63, 64, 66, 68, 74, 76, 77, 79, 82, 83, 86-88, 90, 98, 102, 104, 106, 108, 112-114, 118, 120, 124, 125] In general, the highest viral loads from upper respiratory tract samples were observed at the time of symptom onset and for a few days after (generally within one week), with levels slowly decreasing over the next one to three weeks.

Some studies have observed clear differences between the viral loads detected in upper respiratory tract and stool specimens. In general, viral loads from upper respiratory tract samples were observed to peak within a week of symptom onset and followed a relatively consistent downward trajectory, whereas viral loads from stool samples were found to peak later in the disease (generally two to three weeks after symptom onset)[120] and followed a more erratic pattern (Table 2).[21, 39, 42, 43, 53, 58, 60, 65, 80, 83-85, 91, 96, 98, 102, 106, 111, 116, 118-120]

Eight studies reported that viral ribonucleic acid (RNA) from sputum samples peaked at a later stage (generally two weeks after symptom onset)[58, 74, 91, 120] and contained higher viral

loads than upper respiratory tract samples.[21, 58, 66, 113] Data on the differences in viral load dynamics between different upper respiratory sample sites are inconsistent, with some studies reporting higher viral loads in nasal samples,[124] and others reporting higher viral loads in throat samples.[113]

Association between disease severity and viral load

Nine studies reported an association between higher viral loads and more severe symptoms.[50, 59, 66, 77, 87, 113, 114, 120, 125] One of these studies (n=76 patients) found that the mean viral load of severe cases was around 60 times higher than that of mild cases (using nasopharyngeal samples), and this relationship was maintained from early to later stages of the infection.[59] Although another study (n=23 patients) found higher viral loads (about 10 times higher) in those with severe disease (using posterior oropharyngeal saliva or endotracheal aspirate) compared with mild disease, this relationship was not found to be statistically significant.[87]

Seven studies observed increases in viral loads prior to clinical deterioration (particularly those based on lower respiratory tract specimens) with decreases in viral load observed prior to improvement of symptoms.[43, 66, 98, 113, 114, 120, 125] One of these studies analysed sputum samples from 92 patients collected at hospital admission, and found a significant positive association between higher sputum viral load at baseline and risk of disease progression.[114]

Viral load in asymptomatic or pre-symptomatic patients

Seven studies measured viral load in pre-symptomatic or asymptomatic patients, and generally found little to no difference in viral load between pre-symptomatic, asymptomatic and symptomatic patients.[13, 25, 30, 42, 46, 48, 90] A study was conducted in the municipality of Vo in Italy, where rRT-PCR testing was undertaken in 85.9% (n=2,812) and 71.5% (n=2,343) of the total population (n=3,275) at two consecutive time points less than two weeks

apart.[46] At the first time point, 73 people (2.6%) tested positive and at the second time point, 29 (1.2%) tested positive. Notably, 43.2% (95% CI 32.2-54.7%) of the confirmed SARS-CoV-2 infections detected across the two time points were asymptomatic. The authors found no statistically significant difference in the viral load between symptomatic and asymptomatic patient samples.[46] Arons et al. conducted a study in a nursing facility in Washington State, US, where residents in the facility were offered rRT-PCR testing on two separate occasions, seven days apart. Of the 76 residents tested, 48 (63%) tested positive. Of these 48 positive residents, 27 (56%) had no symptoms at the time of testing; 24 of these 27 patients (88%) subsequently developed symptoms (i.e. they were presymptomatic) and 3 (12%) remained asymptomatic.[13] The authors found that the viral loads were similar between asymptomatic, pre-symptomatic and symptomatic patients. Symptomatic patients were sub-divided into those displaying typical symptoms (i.e. fever, cough and shortness of breath) and those displaying atypical symptoms (i.e. chills, malaise, increased confusion, rhinorrhoea/nasal congestion, myalgia, dizziness, headache, nausea, and diarrhoea). The median cycle threshold (Ct) values for asymptomatic residents, presymptomatic residents, residents with atypical symptoms and residents with typical symptoms, were 25.5, 23.1, 24.2, and 24.8, respectively (note that lower Ct values infer higher viral loads.[13]

A case report of a 6-month old noted no symptoms on admission to hospital, but a relatively high viral load (nasopharyngeal sample targeting ORF1ab-gene, peak viral load Ct value = 13.73). The viral load decreased over the next nine days, although it raised slightly when the child experienced a fever on day two of admission, before falling again once the fever resolved.[42]

Duration of SARS-CoV-2 detection

Duration of virus detection in different sample sites

Eighty-eight studies reported the duration of virus detection, with the end point being the first day of two consecutive negative tests taken 24 hours apart, using rRT-PCR.[12, 14, 15, 17-19, 21, 22, 24, 26, 27, 29, 30, 32, 33, 35-38, 43-50, 52-63, 65-76, 78, 79, 82, 83, 85-87, 89-94, 96-102, 105-107, 109-112, 115-123, 125]

Additionally, two recent studies required three consecutive negative tests taken 24 hours apart prior to establishment of virus clearance.[28, 103] Of these 90 studies, 66 reported the duration of virus detection from onset of symptoms using upper respiratory tract specimens,[12, 14, 15, 17-19, 22, 24, 26, 27, 30, 32, 33, 38, 43, 46-50, 52, 54, 56, 58, 60-63, 65-70, 72, 73, 75, 76, 79, 82, 83, 85, 86, 91, 93, 94, 96-101, 106, 107, 110-112, 117-123] and ten reported the duration of virus detection from onset of symptoms using lower respiratory tract specimens.[22, 24, 43, 44, 55, 58, 66, 91, 98, 103] The longest duration observed was 83 days in one patient from upper respiratory tract samples.[52] At the aggregate study-level, the median duration of virus detection from symptom onset using upper respiratory tract samples was 14.5 days (range of study-level medians: 1-53.5 days).[52, 75] In lower respiratory tract samples, the median duration of virus detection from symptom onset at the aggregate study-level was 15.5 days (range of study-level medians: 10-44 days).[58, 66] Four studies reported that viral RNA in lower respiratory tract samples may persist for longer periods than upper respiratory tract samples.[37, 58, 91, 120]

Thirty-two studies, reported detectable levels of viral RNA in stool samples for a prolonged period of time (often greater than three to four weeks after symptom onset),[12, 15, 21, 24, 26, 34, 37, 39, 42, 44, 50, 53, 56, 58, 60, 62, 65, 80, 83-85, 91, 96, 98, 99, 102, 106, 111, 116, 118-120] and possibly longer in children.[15, 26, 39, 42, 62, 80, 84, 85, 102, 106, 119] However, there are concerns regarding truncated data for the duration of virus detection in stool samples, as the data appear to reflect the maximum duration of follow-up, rather than the true duration of virus detection.[21, 24, 26, 37, 44,

50, 53, 56, 62, 83, 98, 99, 111, 118, 120)

In general, studies that tested blood samples in populations with mild-to-moderate severity disease did not detect viral RNA or reported weakly positive or inconsistent results.(14, 33, 42, 43, 56, 58, 84, 85, 87, 98, 112) Other sample sites such as urine,(14, 21, 24, 27, 33, 34, 42-44, 50, 53, 56, 65-67, 83, 86, 87, 98, 108, 112, 113, 118, 120) conjunctival fluid (50, 65) and semen(65, 67) were used less frequently and produced inconsistent findings.

Association between duration of virus detection and severity of disease or older age

There are inconsistent findings for the association between disease severity (and/or ICU admission), and the duration of virus detection, with studies reporting either a positive association,(12, 15, 19, 21, 27, 28, 36, 50, 59, 76, 113, 120, 125) or no association.(60, 71, 87, 107, 111, 121) There are also inconsistent findings for the association between older age (generally defined as >65 years) and the duration of virus detection, with studies reporting either a positive(12, 15, 35, 50, 100, 107, 120) or no association.(121) Four studies observed that detection of viral RNA in blood samples was associated with severe disease,(20, 25, 44, 50) however, one case report of a patient with severe pneumonia did not detect viral RNA in the blood.(34)

Duration of virus detection in asymptomatic or pre-symptomatic patients

Eight studies measured the duration of virus detection in asymptomatic or pre-symptomatic patients(36, 48, 60, 71, 85, 90, 105, 111) with estimates found to vary widely. One study included 24 cases with asymptomatic and pre-symptomatic COVID-19 infections screened from close contacts.(36) The estimated median duration from the first positive test to the first of two consecutive negative tests was 9.5 days (range: 1-21 days). The authors reported that the virus was detected for a longer period of time in those who subsequently developed symptoms (pre-symptomatic: n=5, median 12 days) compared with those who remained

asymptomatic (n=19, median 6 days). Of the five pre-symptomatic cases, the earliest positive rRT-PCR test occurred two days before symptom onset (n=1). Two of the five presymptomatic cases had previously tested negative seven and eight days prior to first symptoms, respectively (but after suspected exposure).[36]

A case series conducted by Xu et al. investigated the epidemiological and clinical features of 15 asymptomatic hospitalised COVID-19 patients in China.[105] All 15 patients remained asymptomatic for the duration of hospitalisation (median: 11 days). The authors reported a median time of 7 days (IQR 4-9 days) from the first positive test to the first of two consecutive negative tests.

In a study by Yongchen et al., five asymptomatic patients had a longer median duration of virus detection (18 days) compared with five patients with severe disease (14 days) and 11 patients with non-severe, but symptomatic disease (10 days).[111] Other case series reported detection of virus in hospitalised asymptomatic adults ranging from 7 to 23 days [48, 60, 90].

In terms of paediatric cases, a study involving 36 children (age range: 1-16 years) reported 10 cases (28%) who remained asymptomatic for the duration of hospitalisation (ranging from 10 to 20 days) and for a further two weeks of post-discharge quarantine.[71] Though individual rRT-PCR results were not provided for each of these 10 cases, for one of these asymptomatic cases, it took 10 days to become rRT-PCR-negative.[71] In a case series study by Tan et al., one asymptomatic child had detectable virus for 17 days.[85]

Duration of SARS-CoV-2 infectivity

Virus culture studies

No study was found that definitively measured the duration of infectivity. Four studies were found that correlated serial rRT-PCR test results with virus cultures.[13, 45, 58, 98] Arons et al. conducted virus culture in 46 of the 48 residents of a nursing facility in the US who tested

positive for SARS-CoV-2.[13] Positive culture growth was recorded in 31 (67.4%) of these upper respiratory tract samples. Viable virus was isolated from asymptomatic, presymptomatic and symptomatic residents. The lowest viral load (Ct value) for which there was positive culture growth was 34.3. Viable virus was isolated from specimens collected between six days before, to nine days after, the first evidence of typical symptoms. When atypical symptoms are also considered, viable virus was isolated from samples collected six days before to 13 days after first evidence of any symptoms. However, as samples were only collected up to a maximum of 13 days after symptom onset, it is not known if samples collected at later dates would have resulted in positive culture growth.

Woelfel et al. found that no infectious isolates were obtained from any sample (n=9 patients) taken after day eight of symptom onset in spite of ongoing high viral loads. The authors suggested that early discharge followed by home isolation could be chosen for patients with less than 10^5 RNA copies per ml of sputum who are beyond day 10 of symptom onset.[98] The detection of infectious isolates was noted to differ by sample site, being readily isolated from throat and lung-derived samples, but not stool samples. This was despite prolonged detection of SARS-CoV-2 viral RNA in stool samples.[98]

A study by La Scola et al. conducted serial rRT-PCR testing and virus culture of 183 nasopharyngeal samples from 155 patients.[45] They found that the virus could not be isolated from samples collected after day eight of symptom onset, in spite of ongoing high viral loads of approximately 10^5 RNA copies/mL of sample. Additionally, they found that positive culture growth decreased progressively according to the viral load. No culture was obtained from samples with Ct values ≥34 targeting the E gene. The authors inferred that patients with Ct values ≥34 were no longer contagious and could be considered suitable for discharge.[45]

Liu et al. reported virus isolation in cell cultures from throat swabs collected upon admission, and from all sputum specimens collected within 18 days of symptom onset in a 50-year old woman in Taiwan. SARS-CoV-2 continued to be detectable from sputum samples using rRTPCR for 62 days from symptom onset.[58] However there is very limited information relating to the virus culture results reported in this study, hence these findings should be interpreted with caution.[58]

Epidemiological and modelling data

Five studies that used epidemiological (n=3) or modelling (n=2) approaches to address the duration of infectivity were found.[23, 32, 40, 74, 95] A prospective case-ascertained study found that all 22 secondary cases, identified from 2,761 close contacts of 100 index cases, had their first day of exposure within five days of the index case's symptom onset and up to five days before symptom onset, suggesting high transmissibility near, or even before symptom onset. No contacts were infected when first exposure occurred five days after the index case's symptom onset.[23] A study conducted in Singapore evaluating seven clusters of COVID-19 found that pre-symptomatic transmission likely occurred between 1-3 days before symptom onset in the pre-symptomatic source patient in four of these clusters.[95] An epidemiological investigation of an individual with mild disease in the US, found no onward transmission to 16 close contacts (defined as persons exposed to the case, from one day before diagnosis) including one intimate partner.[74]

One modelling study based primarily on epidemiological data estimated that 44% of transmission could occur before first symptoms present (starting from 2.3 days before symptom onset [95% CI, 3.0 to 0.8 days before symptom onset] and reaching its peak at 0.7 days before symptom onset [95% CI, 2.0 days before to 0.2 days after symptom onset]). The authors also estimated that infectivity declines relatively quickly within seven days of symptom onset.[32] A modelling study conducted in Guangzhou, China applied a

statistical transmission model to contact-tracing data of 349 lab-confirmed COVID-19 cases in that region.[40] The authors found that a mean incubation period of four days and a maximum infectious period (including the incubation period) of 13 days provided the best fit of the observed data. The model suggested that COVID-19 cases were at least as infectious during their incubation period as from symptom onset.[40]

Differences between adults and children

Thirty-six studies included children (18 years or younger) either exclusively,[14, 26, 39, 42, 47, 51, 71, 84, 85, 102, 106, 119] or in combination with adults.[12, 17, 23, 30, 36, 37, 40, 41, 46, 48, 56, 60, 62, 68, 77, 78, 80, 92, 93, 105, 109, 111, 113, 115] No discernible differences with regards to viral load or duration of virus detection were apparent between adults and children. Two included studies compared findings between children and adults, either directly[41] or indirectly (through reference to published findings).[51]

L'Huillier et al. conducted rRT-PCR testing and virus culture in 23 symptomatic children (age range, 7 days - 15.9 years).[51] The median viral load at time of diagnosis was 3×10^6 copies/ml (IQR 6.9×10^3 - 4.4×10^8 copies/ml), which the authors comment, is comparable to peak viral load levels typically reported in adults in the literature. Virus isolation was successful in 12/23 (52%) of the children. The youngest patient that SARS-CoV-2 was successfully isolated from was a seven-day old neonate. The authors concluded that infectious virus isolation success was largely comparable to that of adults, and two samples yielded an isolate at a lower viral load (1.2×10^4 and 1.4×10^5 copies/ml) than is typically reported in adults in the literature.[51] Another study by Jones et al. analysed viral loads from 3,712 patients (of all ages) with confirmed COVID-19 identified from routine testing at a laboratory testing centre in Germany.[41] The authors found no significant differences in viral load across age groups, although the relative sample size of children aged ten years or younger (n=49, 1.3%) was small compared with older age groups.[41] There has been

criticism of the statistical analysis undertaken in the study by Jones at al.,[126] with a secondary re-analysis of these data suggesting there is moderate, but not overwhelming evidence for increasing viral load with increasing age based on a test for trend. The commentator also points to the unbalanced sample sizes between children and adults, and suggests that the study is inconclusive.[126] Hence, caution is warranted when interpreting the findings by Jones et al.[41]

Methodological quality of studies

Overall, the studies were of low-to-moderate quality. Given that the majority of the included studies (n=95 studies, 84.1%) comprised case series and case reports, the findings should be viewed with caution and will require confirmation using larger more robust study designs. There are also concerns relating to the pre-print status of 17 studies (15%), which had not been peer-reviewed at time of writing.[12, 28, 37, 40, 41, 46, 51, 75, 79, 83, 89, 91, 92, 94, 109, 115, 118]

As the majority of included studies (n=74 studies, 65.5%) were conducted in China, the findings may not be generalisable to other populations given differences in demographics and healthcare practices. Furthermore, given the volume of studies published from China, particularly those comprising single case reports and small case series at the early stages of the pandemic, there is a strong possibility of overlapping data with later publications of larger studies.

Discussion

The evidence to date suggest that the viral load in respiratory tract samples peaks around symptom onset and decreases within one to three weeks. Although the duration of detection and the size of the viral load differs between patients, viral RNA generally becomes undetectable (from upper respiratory tract specimens) about two weeks after symptom onset (median 14.5 days). For lower respiratory tract samples, there is conflicting evidence

regarding the timing of peak viral loads and duration of virus detection, with some evidence suggesting that the peak occurs later and the duration of detection is longer compared with upper respiratory tract samples (median 15.5 days).[37, 74, 113, 120] However, it is unclear whether the lower respiratory tract findings are influenced by the fact that not all COVID-19 patients experience productive coughs (particularly those without symptoms),[127] and hence certain patients are unable to have their lower respiratory tract sampled (without induction which is not recommended for safety reasons).[128]

Viral shedding in stool samples is prolonged and sometimes erratic. The clinical significance of virus detection in stool samples is unclear as there was no evidence of successful virus isolation from stool samples in any of the 113 studies included in this review. However, a study published on 18 May 2020 has reported the successful isolation of SARS-CoV-2 virus from stool samples in two of the three patients tested.[129] Hence, it is possible that faecaloral transmission may occur. Moreover, a systematic review and meta-analysis published by Parasa et al. found that SARS-CoV-2 RNA was detected in the stool samples of 41% of patients, and that 12% of all COVID-19 patients reported gastrointestinal symptoms.[130] The authors similarly concluded that faecal-oral transmission is possible and warrants ongoing monitoring of the evidence.

The relationship between SARS-CoV-2 detection, viral load and infectivity is not fully understood, as the presence of viral RNA may not represent transmissible live virus. There is evidence that COVID-19 patients are infectious from one to three days before symptom onset, although viable virus has been successfully isolated from upper respiratory tract samples up to six days before onset of symptoms.[13] Two separate epidemiological investigations concluded that there was high transmissibility near, and even before symptom onset.[23, 95] Furthermore, no statistically significant difference in the viral load between symptomatic and asymptomatic patient samples was found in two included studies.[13, 46] The evidence regarding pre-symptomatic and asymptomatic transmission has been reported

separately by our research group.[131] Based on the totality of the evidence, it was concluded that pre-symptomatic transmission is likely occurring. A secondary analysis of published data by Casey et al. estimated the proportion of pre-symptomatic transmission to be approximately 56%.[132] Evidence of transmission in asymptomatic patients is, however, more limited (perhaps due to difficulties in identifying truly asymptomatic cases, as it would appear that a large proportion are actually pre-symptomatic).[46] While asymptomatic transmission is plausible, it may not be a driver of overall transmission.[131] Important questions remain regarding the timing and duration of infectivity in asymptomatic patients.

In symptomatic patients, there is evidence of a reduction in infectivity 7-10 days after onset of symptoms. Two virus culture studies obtained no infectious isolates from any sample taken eight days after symptom onset in spite of ongoing high viral loads.[45, 98] One of these studies found that patients with Ct values ≥34 were no longer contagious.[45] These findings appear to support early epidemiological and modelling studies,[23, 32, 40] with one study suggesting that transmission may be limited to five days after symptom onset.[23] The findings of this review appear to broadly support the recommendation by the World Health Organization (WHO) to discontinue transmission-based precautions, including isolation, and release a patient from COVID-19 care pathways, if it has been 10 days since symptom onset and the patient has been symptom-free for at least three days (or 10 days after first testing positive if asymptomatic).[133] The duration of infectivity, however, remains uncertain as two recent studies have reported isolation of viable virus from upper and lower respiratory samples 13 days (maximum follow-up)[13] and 18 days[58] respectively after symptom onset. Therefore, clinicians should be careful before discontinuing transmission-based precautions for all COVID-19 patients at 10 days post symptom onset, even if symptom-free for three days.[133]

A limited number of studies that compared findings between children and adults report no differences in terms of viral load and duration of virus detection. However, there are concerns regarding the statistical analysis undertaken in the largest of these studies, with re-analysis suggesting a non-significant trend between increasing age and increasing viral load.[41, 126] Even if children have comparable viral loads to adults,[41, 51] the relationship between viral load and infectivity is not well understood as viral load is a proxy measurement of infectivity and may not translate to transmissibility. In our companion rapid review examining the role of children in the transmission of SARS-CoV-2, we concluded that, based on the limited number of studies to-date, children do not appear to contribute substantially to the spread of the virus.[134] Children have generally been under-represented in COVID-19 studies to-date, although this may be a function of testing practices which have typically prioritised those with more severe symptoms, healthcare workers and those residing in long term care settings. Given reports of milder symptoms in children, they would be less likely to be tested and diagnosed.[135] The reduced severity of symptoms as a potential explanation for this under-representation of children in COVID-19 studies appears to be supported by provisional results from the UK Office of National Statistics based on home, self-sampling of nasopharyngeal swabs of over 10,000 individuals.[136] This study found no evidence of differences between age groups in the proportions of those testing positive in the community (excluding infections reported in hospitals, care homes or other institutional settings). This would suggest that symptomatic children are potentially as likely to test positive as other age groups.[136] There is still, however, substantial uncertainty as to how children become infected, how the virus manifests in children and how it transmits from children to others.

The early peak of viral load in COVID-19 patients, and the detection of virus in asymptomatic and pre-symptomatic patients underlines the critical importance of ongoing widespread public health and social measures and the rapid detection, diagnosis, isolation

and contact tracing of suspected COVID-19 cases.[137] In particular, the evidence suggests that due to the potentially high viral load in the early stages of the infection, often prior to symptom onset, contact tracing should include a period of at least 48 hours prior to symptom onset in the index case.[137, 138] Our review highlights a key virological difference between the current SARS-CoV-2 virus and the SARS-CoV-1 virus that caused severe acute respiratory syndrome (SARS) in 2002/2003. That is, SARS-CoV-1 viral load peaked later in the disease trajectory (usually seven to 10 days after symptom onset);[139, 140] hence, different public health strategies were more successful in containing this infection. However, recent findings of later viral load peaking and prolonged virus detection from lower respiratory tract samples of SARS-CoV-2, as well as evidence of virus isolation from stool samples, warrants further investigation as these findings may have important public health implications.[37, 120, 129]

This review summarises the evidence relating to the detection, viral load and infectivity of SARS-CoV-2 over the course of an infection, and provides important information to support the clinical interpretation of rRT-PCR test results, and to inform public health and social measures in the context of COVID-19. Further research examining the relationship between viral load and infectivity, particularly in children, is required, as this knowledge is key to informing public health policy. A recently published review by Byrne et al. reported similar challenges in determining the period of infectivity due to substantial variations in how this is estimated in the literature.[141] Research that combines virological and epidemiological data, using robust study designs and larger patient numbers, is required to determine the true duration of infectivity.

Conclusion

The evidence suggests that the viral load of SARS-CoV-2 peaks from upper respiratory tract samples around the time of symptom onset or a few days after, and becomes undetectable

within about two weeks. However, some studies report that for lower respiratory tract samples, this peak may occur at a slightly later stage and that the virus may persist for longer. Viral load in stool samples tend to peak at a later stage and follow a more erratic pattern, however the clinical significance of this finding is uncertain. There is some evidence that patients may not be infectious for the entire period that they are SARS-CoV-2 positive

and that infectivity may be related to the viral load and time since symptom onset. Further research is required to establish the duration of infectivity of SARS-CoV-2, which is key to informing public health policy in managing the pandemic.

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Table 1: Population, Outcomes and Study types (POS) framework for study inclusion

Population	Patients (of any age) infected with COVID-19 with information on either viral load or detection during infection (including in the pre-symptomatic phase) and/or duration of infectivity. ▪ Subgroups of interest adults vs children
Outcomes	**Primary outcomes:** ▪ Ribonucleic Acid (viral load or detection) during infection (the test used [including cut-off if reported], sample site [e.g. upper/lower respiratory, faecal, urine], test timing [number of days symptomatic pre-testing (if relevant)], clinical characteristics of the population (age, comorbidity) and clinical syndrome associated with COVID-19 (asymptomatic, mild illness, pneumonia, severe pneumonia, ARDS, sepsis, septic shock) ▪ Duration of virus detection (define start as: first confirmed positive test (or symptom onset); use WHO criteria (where reported) for end of detection, that is, two consecutive negative PCR tests 24 hours apart). ▪ Period of infectiousness/infectivity (defined as the time interval during which SARS-CoV-2 may be transferred directly or indirectly from an infected person to another person).
Types of Studies	**Include:** ▪ any study that reports on the viral load or duration of viral detection or infectivity of COVID-19. **Exclude:** ▪ studies where COVID-19 was not confirmed with a laboratory test.

Key: ARDS - acute respiratory distress syndrome; COVID-19 - coronavirus disease 2019; SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2; WHO - World Health Organization

Table 2: Characteristics of Included Studies

First Author	Country	Study design	Population	Aggregate study-level duration of virus detection since symptom onset from URT samples*	Aggregate study-level duration of virus detection since symptom onset from LRT samples*	Aggregate study-level duration of virus detection since symptom onset from stool sample*	Timing of Peak viral load in relation to symptom onset and day of testing (sample site)
An[12]	China	Case series	262 adults and children	Median between 15 and 20 days. Range, 5-47 days †	-	Median between 15 and 20 days. Range, 5-47 days †	-
Arons[13]	US	Cross-sectional	76 residents	-	-	-	4 of 12 patients had VL peaking prior to symptom onset
Cai[14]	China	Case series	10 children	Median (IQR), 12 (8-15) days. Range, 6-22	-	Range, 10 to >30 days (and still testing positive)	-
Cai[15]	China	Case series	298 adults	Median (IQR), 14 (10-20) days	-	-	-
Cao[16]	China	RCT	199 adults	-	-	-	Day of randomisation, which took place a median of 13 (IQR 11–16) days after symptom onset, 1st test (URT)
Chang[17]	China	Case series	16 adults and children	Median (IQR): 10.5 (6-12) days	-	-	-
Chen[18]	China	Case report	1 adult	11 days	-	-	-
Chen[19]	China	Case series	249 adults	Median (95% CI), 11 (10-12) days	-	-	-
Chen[20]	China	Case series	57 patients (unknown age)	-	-	-	Days 10-12 of symptoms – 1st to 4th test (URT)
Chen[21]	China	Case series	42 adults	Median (IQR), 8 (5-12) days		Median, 9 days in uncomplicated, 8 (IQR 4.5-14) days in mild, and 14 (IQR 9.5- 18) days in severe cases	-
Cheng[22]	Taiwan	Case series	5 adults	15 days	15 days	-	Days 1-8 of symptoms -1st–3rd day of testing (URT). Days 1-6 of symptoms – 1st to 2nd test (LRT)
Cheng[23]	Taiwan	Case-ascertained study	2,761 adults and children	-	-	-	-
Cheng[24]	Taiwan	Case report	1 adult	20 days	16 days	24 days	-
Corman[25]	Germany	Case series	18 adults	-	-	-	Peak VL measured, but timing not reported (URT)

***Fan*[26]**	China	Case report	1 child	14 days	-	Still positive at 28 days	-
***Fang*[27]**	China	Case series	32 adults	Mean ± SD, 17.3 ± 6.6 days	-	-	-
***Fu*[28]**	China	Case series	50 adults	-	-	Median (IQR) 31 (IQR, 27–34 days)†	-
***Gao*[29]**	China	Case series	2 adults	-	-	-	-
***Gautret*[30]**	France	NRCT	36 adults and children	Median (IQR), 7 days (4.5-9.5) (however limited follow-up)	-	-	Day of randomisation, which took place an average of 4 (±2.6 SD) days after symptom onset, 1st test (URT)
***Goh*[31]**	Singapore	Case report	1 adult	-	-	-	Day 10 of symptoms, 1st test (ETT)
***He*[32]**	China	Epidemiological modelling study	94 adults	Approx. 21 days (using spline analysis)	-	-	Soon after symptom onset, 1st test (URT)
***Hill*[33]**	Scotland	Case report	1 adult	7.5 days	-	ND	Day 3 of symptoms, 1st test (URT)
***Holshue*[34]**	US	Case report	1 adult	-	-	-	Day 4 of symptoms, 1st test (URT)
***Hu*[35]**	China	Cohort study	59 adults	-	-	-	-
***Hu*[36]**	China	Case series	24 adults and children	Median (IQR): 20.5 (16-26.25) days *(from day of suspected exposure*)	-	-	-
***Huang*[37]**	China	Case series	33 adults and children	Median (IQR), 18.5 (13.25-22) days *(from day of diagnosis)*	Median (IQR), 22 (18.5-27.5) days *(from day of diagnosis)*	Median (IQR), 17 (11.5-32) days *(from day of diagnosis)*	1st test (URT), 1st test (LRT), erratic peaking pattern (stool)
***Jahan*[38]**	Bangladesh	Case report	1 adult	10 days	-	-	-
***Jiang*[39]**	China	Case report	1 child	-	-	41 days (until first negative test)	-
***Jing*[40]**	China	Statistical transmission model	349 adults and children	-	-	-	-
***Jones*[41]**	Germany	Cross-sectional	3,712 adults and children	-	-	-	Peak VL measured, but timing not reported (URT)
***Kam*[42]**	Singapore	Case report	1 child	-	-	-	Day 1 of hospitalization, 1st test (URT); Day 8 of hospitalisation, 2nd test (stool)
***Kim*[43]**	South Korea	Case series	2 adults	14.5 days	11.5 days	9 days	Day 2 of symptoms, 1st test (URT); Day 5 of symptoms, 2nd test (LRT); Day 10 of symptoms, 6th test (stool)
***Kujawski*[44]**	US	Case series	12 adults	25 days (maximum)	28 days (maximum)	26 days (maximum)	VLs were lower in the first week of illness than the second in most patients (URT)
***La Scola*[45]**	France	Cross-sectional	155 patients	20 days (maximum) †		-	-

***Lavezzo*[46]**	Italy	Cross-sectional	2,812 adults and children	Mean ± SD: 9.3 ±2 days	-	-	-
***Le*[47]**	Vietnam	Case report	1 child	12 days	-	-	-
***Le*[48]**	Vietnam	Case series	12 adults and children	Median (range): 8.5 (6-12) days	-	-	Peaked earlier in the disease trajectory (~ 7 days after potential exposure) (URT)
***Lee*[49]**	Taiwan	Case report	1 adult	19 days	-	-	-
***Lescure*[50]**	France	Case series	5 adults	11 days	-	-	Days 2-9 of symptoms. 1st or 3rd tests, (URT). 1st or 2nd tests (Stool)
***L'Huillier*[51]**	Switzerland	Case series	23 children	-	-	-	Peak VL measured, but timing not reported (URT)
***Li*[52]**	China	Case series	36 adults	Median (IQR): 53.5 days (47.75-60.5) days	-	-	-
***Li*[53]**	China	Case series	13 adults	Mean ± SD: 25 ± 6 days	4 patients positive between 5 – 14 days after discharge	2 patients tested positive 14 or 15 days after sputum tested negative.	-
***Lillie*[54]**	UK	Case series	2 adults	7.5 days	-	-	-
***Lim*[55]**	South Korea	Case report	1 adult	-	10 days	-	Day 9 of symptoms, 1st test (LRT)
***Ling*[56]**	China	Case series	66 adults and children	Median (IQR) 9.5 (6.0-11.0) days. Range 2-22 days	-	Median (IQR): 11 (9.0-16.0) days	-
***Liu*[57]**	China	Case series	10 adults	Median (IQR): 10 days (9-12) Range: 6-17 days (*from first day of hospitalisation*)	-	-	-
***Liu*[58]**	Taiwan	Case report	1 adult	6 days	44 days	Only detected in 1 sample before repeatedly testing negative thereafter	Day 1 of symptoms, 1st test (LRT) Day 2 of symptoms, 2nd test (URT)
***Liu*[59]**	China	Case series	76 adults	-	-	-	Highest viral load detected on 1st test for majority of patients (URT).
***Lo*[60]**	China	Case series	10 adults and children	Mean ± SD, 18.2 ± 4.6 days	-	Mean ± SD, 19.3 ± 3.4 days	-
***Lv*[61]**	China	Case report	1 adult	25 days	ND	ND	Day 16 of symptoms, 4th test (URT)
***Ma*[62]**	China	Case series	8 adults and children	2-3 weeks	-	Turned positive in weeks 3-5 and remained positive until end of follow up in 7 of 8 patients.	-
***Marchand-Senécal*[63]**	Canada	Case report	1 adult	7 days	-	-	Day 3 of symptoms, 2nd test (URT)

***Meng*[64]**	China	Case series	42 adults	-	-	-	Day of peak VL not reported
***Nicastri*[65]**	Italy	Case report	1 adult	7 days *(from first day of hospitalisation)*	-	9 days *(from first day of hospitalisation)*	-
***Pan*[66]**	China	Case series	2 patients of unknown age (plus samples from 80 other patients)	9 days	10 days	ND	Days 5-6 of symptoms, 2nd or 3rd test (URT)
***Paoli*[67]**	Italy	Case report	1 adult	16 days	-	-	-
***Peng*[68]**	China	Case report	2 adults and children	15 days	-	ND	Day 6 of symptoms, 1st test (URT)
***Pongpirul*[69]**	Thailand	Case series	11 adults	14 days	-	-	-
***Qian*[70]**	China	Case report	1 adult	42 days	-	Only detected once	-
***Qiu*[71]**	China	Cohort study	36 children	Mean ± SD, 10 ± 2 days, range 7-22 days (*from first day of hospitalization*)	-	-	-
***Qu*[72]**	China	Case report	1 adult	22 days	-	-	-
***Saito*[73]**	Japan	Case report	1 adult	15 days	-	-	-
***Scott*[74]**	US	Case report	1 adult	20 days *(from day of diagnosis)*	-	-	Day 1 and 6 of diagnosis, 1st and 2nd test (different URT samples) Day 8 of diagnosis, 2nd test (LRT)
***Segar*[75]**	US	Case report	1 adult	1 day	Positive on days 10 and 11 of symptoms	-	-
***Shen*[76]**	China	Case series	5 adults	24.5 days	-	-	Days 2-21 days of symptoms, 1st test for 2 patients, unknown number for others (URT)
***Shi*[77]**	China	Cross-sectional	114 adults and children	-	-	-	-
***Song*[78]**	China	Case series	24 adults and children	15 days *(from day of diagnosis)*	-	-	-
***Stebbing*[79]**	Italy	Case series	4 adults	15 days	-	-	Days 1-16 of symptoms, 1st or 7th test (URT)
***Su*[80]**	China	Case series	23 adults and children	11.5 days *(from day of hospitalisation for children)* NR for adults	ND in children NR for adults	Turned positive for 5 discharged children NR for adults	-
***Tan*[81]**	China	Case series	142 adults	-	-	-	-
***Tan*[82]**	China	Case series	2 adults	38 days (range 24-52)	-	-	Day 27 of symptoms, 4th test (URT)
***Tan*[83]**	Vietnam	Case report	1 adult	15 days	-	22 days	Day 6 of symptoms, 1st test (URT) Day 21 of symptoms, 12th (stool)

***Tan*[84]**	China	Case series	13 children	13 days *(from day of diagnosis)*	-	Only detected for unknown duration in 1 child	-
***Tan*[85]**	China	Case series	10 children	14 days	-	Detected inconsistently in 3 children	-
***Thevarajan*[86]**	Australia	Case report	1 adult	6 days	-	ND	Day 4 of symptoms, 1st test (URT) Day 6 of illness, 1st test (LRT and stool)
***To*[87]**	Hong Kong	Cohort study	23 adults	-	-	-	Salivary VL was highest during the first week after symptom onset.
***To*[88]**	Hong Kong	Case series	12 adults	-	-	-	1st test (median of 2 days hospitalized) for all patients (except one where the VL was higher on 2nd test) (URT)
***Tu*[89]**	China	Case series	40 adults	-	-	-	-
***Wan*[90]**	China	Case series	2 adults	15 days	-	-	1st test for both asymptomatic patients (URT)
***Wang*[91]**	China	Cohort study	4 adults	19 days	39 days	1 patient was still testing positive after 35 days	-
***Wang*[92]**	China	Cohort study	182 adults and children	21 days *(only provided for one patient)*	-	Patient fluctuated between positive and negative anal swab results for 4 weeks after URT tested negative	-
***Wang*[93]**	China	Case series	18 adults and children	19.5 days	-	-	-
***Wang*[94]**	China	Case report	1 adult	32 days	-	-	-
***Wei*[95]**	Singapore	Case series	18 adults	-	-	-	-
***Wei*[96]**	China	Case series	84 adults	Mean ± SD, 12.5 ± 4 days, (*for patients with diarrhoea).* 9.2 ± 3.9 days (*for patients without diarrhoea)*	-	Elimination from stool took longer than elimination from the nose and throat	-
***Wei*[97]**	China	Case series	14 adults	12 days *(from day of diagnosis)*	-	-	-
***Woelfel*[98]**	Germany	Case series	9 adults	9.5 days	11.5 days	Persistently positive	Days 3-10 of symptoms, generally 1st test (URT) Days 2-11 of symptoms, generally 1st – 3rd test (LRT) Days 3-18 of symptoms, generally 1st – 3rd test (stool)

***Wu*[99]**	China	Case series	74 adults	Mean ± SD, 16.1 ± 6.7 days	-	Mean *± SD,* 27.9 *± 10.7* days	-
***Xiao*[100]**	China	Case series	301 adults	20 days	-	-	-
***Xing*[101]**	China	Case series	2 adults	17.5 days	-	-	-
***Xing*[102]**	China	Case series	3 children	Median, 13 days (*from first day of hospitalization*)	-	Median, 30 days (from first day of hospitalization)	Day of admission,1st test (URT) Day 4 of hospitalisation, 2nd test (stool)
***Xu*[103]**	China	Cohort	113 adults	-	17 days†	-	-
***Xu*[104]**	China	Case series	51 adults	-	-	-	Mostly highest in 1st tests
***Xu*[105]**	China	Case series	15 adults and children	7 days (*from day of diagnosis)* †	-	-	-
***Xu*[106]**	China	Case series	10 children	Median (IQR), 5 (3.5-13.0) days	-	Median (IQR), 22 (7-23) days	Day of admission, 1st test (URT) Day 18 of hospitalisation, 18th test (stool)
***Yan*[107]**	China	Case series	120 adults	Median (IQR), 23 (18-23) days	-	-	-
***Yang*[108]**	China	Case report	1 adult	Still testing positive after 74 days since symptom onset	-	-	Day 36 of symptoms, 5th test (URT)
***Yang*[109]**	China	Case series	55 adults and children	Mean (95% CI), 9.71 (8.21-11.22) days *(since day of diagnosis)* †	-	-	-
***Yang*[110]**	China	Case series	82 adults	Median between 13 and 17 days	-	-	-
***Yongchen*[111]**	China	Case series	21 adults and children	14 days	-	3 of 15 anal swabs remained positive after respiratory swab samples turned negative	-
***Young*[112]**	Singapore	Case series	18 adults	Median, 11.5 days	-	-	Days 3-5 of symptoms, generally between 1st and 3rd test (URT)
***Yu*[113]**	China	Case series	76 adults and children	-	-	-	VL higher in 'early and progressive stages' than 'recovery stages' (LRT)
***Yu*[114]**	China	Case series	92 adults	-	-	-	VL highest at admission for patients admitted with severe disease. VL peaked at a later stage for patients admitted with mild-moderate disease who deteriorated (LRT)
***Yuan*[115]**	China	Case series	25 adults and children	Median (IQR), 6 (4-10) days *(time from initial negative result to testing positive again*)	-	-	-

***Yuan*[116]**	China	Case series	6 adults	Median (range), 9.5 (6-17) days *(after the onset of treatment)*	-	Stool samples were persistently positive in some patients	-
***Zha*[117]**	China	Case series	31 adults	Median (IQR), 14 (11.5–16) days	-	-	-
***Zhang*[118]**	China	Case series	23 adults	Median (IQR),10 (8 to 17) days	-	Median (IQR), 22 (15.5 - 23.5) days	Days 6-9 of symptoms, 1st or 2nd test (URT) Days 14-18 days of symptom onset, unclear number of tests (stool)
***Zhang*[119]**	China	Case series	3 children	Median (range), 15 (14-25) days	-	Persistently positive	-
***Zheng*[120]**	China	Cohort study	96 adults	Median (IQR), 18.5 (13-29) days†	-	Median (IQR), 22 (17-31) days *(from day of diagnosis)*	After week 2 of symptoms (LRT) During weeks 2-3 of symptoms (stool)
***Zhou*[121]**	China	Case series	41 adults	Median (IQR), 31 (24–40) days	-	-	-
***Zhou*[122]**	China	Cohort study	191 adults	Median (IQR) 20 (16 – 23) days	-	-	-
***Zhu*[123]**	China	Case series	20 adults	Mean ± SD, 19.4 ± 10.7 days	-	-	-
***Zou*[124]**	China	Case series	18 adults	-	-	-	Day 1 to 3 of symptoms, 1st or 2nd test (URT)

Key: ETT - Endotracheal tube aspirate; Ct – cycle threshold; IQR – interquartile range; LRT – lower respiratory tract; ND – not detected; NRCT – non-randomized controlled trial; RCT – randomized controlled trial; URT – upper respiratory tract; VL – viral load.

* Viral clearance defined as two consecutive negative results with PCR detection at an interval of 24 hours (counting the first day of negative results as the final day)

- Not measured by the study authors (site not tested, viral load not measured, or only tested on a single occasion)

† Site of sampling not distinguishable in this study