Understanding viral shedding of severe acute respiratory coronavirus virus 2 (SARS-CoV-2): Review of current literature

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Abstract

Objective: Transmission of SARS-CoV-2 has significant implications for hospital infection prevention and control, discharge management, and public health. We reviewed available literature to reach an evidenced-based consensus on the expected duration of viral shedding.

Design: We queried 4 scholarly repositories and search engines for studies reporting SARS-CoV-2 viral shedding dynamics by PCR and/or culture available through September 8, 2020. We calculated the pooled median duration of viral RNA shedding from respiratory and fecal sources.

Results: The review included 77 studies on SARS-CoV-2. All studies reported PCR-based testing and 12 also included viral culture data. Among 28 studies, the overall pooled median duration of RNA shedding from respiratory sources was 18.4 days (95% CI, 15.5–21.3; I² = 98.87%; P < .01). When stratified by disease severity, the pooled median duration of viral RNA shedding from respiratory sources was 19.8 days (95% CI, 16.2–23.5; I² = 96.42%; P < .01) among severely ill patients and 17.2 days (95% CI, 14.0–20.5; I² = 95.64%; P < .01) in mild-to-moderate illness. Viral RNA was detected up to 92 days after symptom onset. Viable virus was isolated by culture from –6 to 20 days relative to symptom onset.

Conclusions: SARS-CoV-2 RNA shedding can be prolonged, yet high heterogeneity exists. Detection of viral RNA may not correlate with infectivity since available viral culture data suggests shorter durations of shedding of viable virus. Additional data are needed to determine the duration of shedding of viable virus and the implications for risk of transmission.

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Knowledge of transmission dynamics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has significant implications for hospital infection prevention and control interventions, timely discharge management, and public health policies. Due to variability in the emerging data, policies on the duration of inpatient and outpatient isolation for people with coronavirus disease 2019 (COVID-19) have been controversial. Uncertainty continues regarding the significance of prolonged PCR positivity and the clinical importance of various routes of viral shedding. Understanding the duration and sources of viable viral shedding is critical to inform guidance around transmission-based isolation precautions.

We reviewed SARS-CoV-2 viral shedding data to help inform practical decisions related to infection control and public health policies. We reviewed available literature and summarized data on expected duration of viral RNA shedding, longevity of presumed infectivity as detected by viral culture, and factors that may influence shedding duration.

Methods

Search method and data extraction

We queried PubMed, LitCoVID, the World Health Organization COVID-19 literature repository, and Google Scholar for studies and reports available through September 8, 2020. Search terms included of “SARS shedding,” “COVID and viral shedding,” “COVID RNA and culture,” and “COVID culture.” In queries of SARS-CoV-2–specific databases, the words “SARS” and “COVID” were omitted from search terms. Additional studies were identified through review of reference lists of included studies. All authors participated in study identification, screening, and data extraction; all included studies were reviewed by at least 2 authors. Articles reporting duration of SARS-CoV-2 shedding based upon PCR testing or culture directly from human specimens were included. Day 0 was defined as either the day of the first positive test or the day of symptom onset, according to the original study. Studies reporting on exclusively pediatric patients were excluded. For each study, we reviewed the design, objective, population, healthcare system setting, diagnostic testing method, timing of tests, sample source, patient symptoms, and severity of illness. Predictors of prolonged shedding were also considered.

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Statistical analysis

We constructed random-effects models using the restricted maximum likelihood estimator for $\tau^2$ to calculate pooled median durations of viral RNA shedding. All studies providing sample size and sufficient data on measures of central tendency and spread were included in our analysis. We grouped nasopharyngeal (NP), oropharyngeal (OP), saliva, and sputum samples together as "respiratory" samples. Fecal samples included both stool and rectal swabs. We calculated pooled medians among PCR respiratory samples for all available, mild-to-moderate illness, severe-to-critical illness, and for all fecal samples. Insufficient data were available to warrant calculation of pooled medians for culture data. Analysis was performed using R version 4.0.0 software using the metadana package.

Results

Included studies

In total, 77 studies and reports were eligible for inclusion: prospective case series (N = 35), retrospective case series (N = 28), case reports (N = 11), point prevalence survey (N = 2), and position statements (N = 1) (Table 1). Overall, 59 of these studies were peer reviewed, 6 were from preprint servers, and 13 were research letters or letters to the editor. Moreover, 70 studies described hospitalized patients. All studies reported PCR-based assessments of viral shedding; 12 studies reviewed reported viral culture data. Also, 30 studies reported PCR testing of nonrespiratory specimens.

Duration of Viral RNA Shedding

Overall, 77 reports included data on viral RNA shedding by PCR. Box 1 summarizes the key points of viral shedding duration. The duration of viral RNA shedding ranged from a minimum of 1 day to a maximum of 83 days. Intermittent PCR positivity did occur through day 92 from symptom onset in 1 case report — that patient had previously tested negative at day 72 followed by repeat positive PCR. In a study of 56 serially tested hospitalized patients with mild-to-moderate disease, 66.1% of NP and OP swabs were still positive at 3 weeks. Positivity rates then declined weekly and all PCR tests were negative by week 6. Based on the 28 studies that provided sufficient data (Appendix Table 1 online), the pooled median duration of RNA shedding from respiratory samples was 18.4 days (95% CI, 15.5–21.3). High heterogeneity was observed among these studies ($I^2 = 98.87%$; $P < .01$).

We reviewed shedding data for patients with mild-to-moderate illness. Based on parametric regression modeling, Sun et al concluded that detection of viral RNA in throat swabs beyond 50 days post symptom onset in patients with mild illness would be a low probability event occurring beyond the 95th percentile. Despite this calculation, there are case reports of patients with viral RNA shedding ≥45 days from symptom onset. Among studies we reviewed, the longest duration of PCR positivity from a NP swab of a patient with mild illness was 92 days after symptom onset. The pooled median duration of viral RNA shedding from respiratory sources among patients with mild-to-moderate illness, based upon 10 studies that reported sufficient data (Appendix Table 1 online), was 17.2 days (95% CI, 14.0–20.5). Again, there was high heterogeneity among these studies ($I^2 = 95.64%$; $P < .01$).

There were multiple reports of patients with intermittently positive PCR results from respiratory specimens. Although not consistently defined, cessation of shedding was most often described as 2 consecutive negative PCR results ≥24–48 hours apart. Tests were frequently done in anticipation of discharge from the hospital. One report estimated that 26%–49% of patients were positive again after a negative test, but in other studies re-positivity varied between 3% and 35% (Wang et al). A patient that was discharged 75 days after illness onset following 3 consecutive negative tests. The patient then tested positive on days 82 and 92, followed by negative PCR tests on days 101 and 105. Another case report described a woman with mild COVID-19 who intermittently tested positive by NP PCR swabs for 72 days from disease onset despite developing IgM and IgG antibodies on day 38.

Wölfel et al observed that the pharyngeal rate of detection was highest in the first 5 days of symptom onset and then decreased. NP swabs may have a higher rate of detection than OP swabs, but they were only compared in 2 of the studies included in this review. Negative upper-tract specimens may not correlate with lower-tract specimens, though the significance of these findings is not well understood. In a postmortem analysis of a patient whose NP sample tested PCR negative, lung tissue was PCR positive and histology revealed coronavirus particles in bronchiolar epithelial cells.

Some studies included data for presymptomatic or asymptomatic patients and observed that PCR positivity can occur as early as 5 days prior to symptom onset. Multiple case series reported that the viral load of asymptomatic patients are as high as those with symptoms. In one case series, the asymptomatic individual in a family cluster had similar viral RNA loads in nasal and throat swabs to those of symptomatic family members. The majority of the subjects in this case series converted to a negative PCR by day 18. In addition, 5 studies included saliva samples. In a series of 13 patients with mild disease, viral RNA load was highest in saliva in the first week of illness, but 3 of the patients still had detectable viral load in their saliva at day 20 of illness. In another series, PCR turned negative in the saliva of 13 mildly ill patients before nasal swab PCR: an average (±SD) of 13.33 ± 5.27 days and 15.67 ± 6.68 days, respectively. In the same study, the average duration of positive PCR in sputum was shorter in non-ICU patients than ICU patients, who were positive for an average (SD) of 16.5 ± 6.19 days.

Predictors of extended duration of viral RNA shedding in respiratory samples

The most frequently identified predictor of prolonged viral RNA shedding was disease severity. Patients with severe disease have been observed to shed RNA for longer and have higher viral RNA loads at symptom onset followed by a gradual decline in viral RNA 3 weeks after symptom onset. Based on 10 studies, the pooled median duration of viral RNA shedding from respiratory samples in patients with severe illness was 19.8 days (95% CI, 16.2–23.5) (Appendix Table 1 online). Again, significant high heterogeneity exists ($I^2 = 96.42%$; $P < .01$). In one cohort of patients, the median duration (SD) of positive NP PCRs was 22.25 (±3.62) days in patients admitted to the ICU, compared to 15.67 (±6.68) days in non-ICU patients. Sun et al also observed prolonged duration of RNA shedding from NP swabs in those with severe illness compared to those with mild disease, with median durations of 33.5 days and 22.7 days, respectively.

Predictors of severe disease and duration of shedding ≥15 days in hospitalized patients included older age, hypertension, coronary artery disease, and diabetes mellitus. Gender was not
| Study                          | Country       | Design                                | Patient Population                     | No. of Patients | Severity of Illness       | Specimen Sources | Testing Methods                      |
|-------------------------------|---------------|---------------------------------------|----------------------------------------|-----------------|---------------------------|------------------|--------------------------------------|
| Andersson M et al [16]        | United Kingdom| Prospective case series               | Hospitalized, outpatient, recovered    | 278             | Not defined               | Serum            | PCR, Viral culture                   |
| Arashiro T et al [17]         | Japan         | Case report                           | Hospitalized                           | 2               | Mild                      | Not specified    | PCR                                  |
| Arons MM et al [17]           | United States | Point prevalence                      | Skilled nursing facility residents     | 76              | Not defined               | NP, OP           | PCR, Viral culture if PCR +           |
| Bullard J et al [18]          | Canada        | Retrospective cross-sectional         | Not specified                          | 90              | Not defined               | NP, ET tube      | PCR, Viral culture                   |
| Campioli C et al [19]         | United States | Retrospective case series             | Hospitalized, outpatient               | 251             | Not defined               | NP               | PCR                                  |
| Chang M et al [20]            | China         | Prospective case series               | Hospitalized                           | 16              | Not defined               | Throat           | PCR                                  |
| Chau NW et al [21]            | Vietnam       | Prospective case series               | Quarantine center                      | 30              | Asymptomatic, mild        | Saliva, NP       | PCR                                  |
| Chen Y et al [22]             | China         | Retrospective cohort study            | Hospitalized                           | 42              | Uncomplicated, mild, severe | NP Urine Stool | PCR                                  |
| COVID-19 Investigation Team [23] | United States | Retrospective case series             | Mixed – hospitalized and home isolation | 12              | Not defined               | OP, NP Serum Stool Urine | PCR, Viral culture Whole genome sequencing |
| Danzetta ML et al [24]        | Italy         | Retrospective case series             | Hospitalized and outpatient            | 14,200 tested; 605 positives | Not defined       | NP, OP                         | PCR                                  |
| Di Tian LW et al [25]         | China         | Prospective case series               | Hospitalized                           | 75              | Mild, moderate, severe, critical | Not specified    | PCR                                  |
| Fang Z et al [26]             | China         | Prospective case series               | Hospitalized                           | 32              | ICU or non-ICU            | NP Saliva Tears Blood Urine Stool | PCR                                  |
| Fu S et al [27]               | China         | Retrospective case series             | Hospitalized                           | 50              | Severe                    | NP, Throat Rectal | PCR                                  |
| Fu Y et al [28]               | China         | Retrospective case series             | Hospitalized                           | 410             | Not defined               | Throat           | PCR                                  |
| Gombar S et al [29]           | United States | Retrospective case series             | Not specified, but primarily outpatient | 150             | Not defined               | NP               | PCR                                  |
| Han J et al [30]              | China         | Retrospective case series             | Hospitalized                           | 185             | Mild, moderate, severe, critical | Respiratory      | PCR                                  |
| He X et al [31]               | China         | Prospective case series               | Hospitalized                           | 94              | Moderate                  | Throat           | PCR                                  |
| Huang J et al [32]            | China         | Retrospective case series             | Hospitalized                           | 33              | Moderate and severe       | Throat Sputum Stool | PCR                                  |
| Huang JT et al [33]           | China         | Retrospective case series             | Hospitalized                           | 308             | General, severe, critically ill | Nasal Pharyngeal | PCR                                  |
| Hung IF et al [34]            | Hong Kong     | Prospective case series               | Hospitalized                           | 9               | Symptomatic and asymptomatic | NP Throat        | PCR                                  |
| Ikegami S et al [35]          | United States | Prospective case series               | Outpatient                             | 272             | Recovered                 | NP               | PCR                                  |

(Continued)
Table 1 (Continued)

| Study                  | Country      | Design                   | Patient Population   | No. of Patients | Severity of Illness | Specimen Sources          | Testing Methods |
|------------------------|--------------|--------------------------|----------------------|-----------------|---------------------|---------------------------|-----------------|
| Jiang X et al[14]      | China        | Case report              | Home isolation       | 1               | Asymptomatic        | NP                        | PCR             |
| Kim ES et al[22]       | Korea        | Retrospective case series| Hospitalized         | 28              | From 1 (no limit of activity) to 8 (death) | NP OP Sputum             | PCR             |
| Lan L et al[33]        | China        | Prospective case series  | Hospitalized         | 4               | Asymptomatic        | Symptomatic               | Throat PCR      |
| La Scola B et al[31]   | France       | Prospective case series  | Hospitalized         | 155             | Not defined         | NP Sputum                 | PCR Viral culture|
| Le TQM et al[37]       | Vietnam      | Prospective case series  | Hospitalized         | 12              | 1 asymptomatic, rest not specified | Throat PCR         | PCR Viral culture|
| Lee S et al[34]        | Korea        | Retrospective case series| Community treatment center | 303             | Symptomatic and asymptomatic | NP OP Sputum | PCR             |
| Li N et al[38]         | China        | Retrospective case series| Hospitalized         | 36              | Mild or severe      | Respiratory Saliva        | PCR             |
| Li J et al[39]         | China        | Case report              | Hospitalized         | 1               | Mild/moderate       | NP OP                     | PCR             |
| Li W et al[47]         | China        | Retrospective case series| Hospitalized         | 18              | Asymptomatic or mild | NP Nasal Sputum Throat Anal | PCR             |
| Lin A et al[44]        | China        | Prospective case series  | Hospitalized         | 137             | Mild or severe      | Not specified             | PCR             |
| Ling Y et al[45]       | China        | Prospective case series  | Hospitalized         | 66              | Not defined         | OP Blood Urine Stool      | PCR             |
| Liu WD et al[12]       | Taiwan       | Case report              | Hospitalized         | 1               | Not defined         | Sputum Stool              | PCR Viral culture |
| Liu Y et al[46]        | China        | Case report              | Hospitalized         | 1               | Severe              | OP                        | PCR             |
| Liu F et al[40]        | China        | Case report              | Hospitalized         | 1               | Moderate            | NP                        | PCR             |
| Lo IL et al[54]        | China        | Prospective case series  | Hospitalized         | 10              | Mild, moderate, or severe | NP Urine Stool | PCR             |
| Long QX et al[55]      | China        | Point prevalence         | Hospitalized         | 178             | Asymptomatic, mild  | NP                        | PCR             |
| Min C et al[56]        | Singapore    | Retrospective case series and position statement | Not specified | 766             | Not specified       | NP                        | PCR Viral culture |
| Miyamae Y et al[57]    | Japan        | Prospective case series  | Hospitalized         | 23              | Asymptomatic, mild  | NP OP                     | PCR             |
| Noh JY et al[58]       | Korea        | Retrospective case series| Residential treatment center | 199             | Asymptomatic or atypical symptoms | Not defined | PCR             |
| Park SY et al[59]      | Korea        | Prospective case series  | Hospitalized         | 6               | Not defined         | NP OP Sputum Saliva       | PCR             |
| Park SK et al[62]      | Korea        | Prospective case series  | Outpatient           | 46              | Asymptomatic and mild | Respiratory Stool | PCR             |
| Pongpirul WA et al[63] | Thailand     | Prospective case series  | Hospitalized         | 11              | Asymptomatic, mild, moderate | Upper respiratory | PCR             |
| Study            | Country  | Design               | Patient Population | No. of Patients | Severity of Illness | Specimen Sources | Testing Methods |
|------------------|----------|----------------------|--------------------|-----------------|---------------------|------------------|-----------------|
| Qi L et al       | China    | Retrospective case series | Hospitalized      | 147             | Mild, moderate, or severe | Respiratory      | PCR             |
| Qian GQ et al    | China    | Retrospective case series | Hospitalized      | 24              | Not defined         | Throat Rectal    | PCR             |
| Ridgway JP et al | United States | Retrospective case series | Hospitalized and outpatient | 555          | Not defined         | NP              | PCR             |
| Sakurai A et al  | Japan    | Retrospective case series | Cruise ship       | 90              | Asymptomatic        | NP              | PCR             |
| Seah IYJ et al   | Singapore| Prospective case series | Hospitalized       | 17              | Not defined         | Tears NP         | PCR             |
| Sun J et al      | China    | Prospective case series | Hospitalized      | 49              | Mild or severe      | NP Sputum Throat Stool | PCR             |
| Talmy T et al    | Israel   | Retrospective case series | Hospitalized      | 219             | Mild                | NP OP           | PCR             |
| Tan W et al      | China    | Prospective case series | Hospitalized      | 67              | Mild, moderate, severe | NP Sputum Blood Urine Stool | PCR             |
| To KK et al      | Hong Kong| Prospective case series | Hospitalized      | 23              | Mild or severe      | OP Saliva       | PCR             |
| Van Kampen JJA et al | Netherlands | Prospective case series | Hospitalized      | 129             | Mechanically ventilated, ICU with oxygen therapy, ward with oxygen therapy, ward without oxygen therapy | NP Sputum | PCR Viral culture |
| Wang W et al     | China    | Prospective case series | Hospitalized      | 205             | Severe Nonsevere    | Nasal Blood Sputum Stool Urine | PCR             |
| Wang J et al     | China    | Case report           | Hospitalized      | 1               | Mild                | NP              | PCR             |
| Wang K et al     | China    | Prospective case series | Hospitalized      | 68              | CURB-65 scores 1–3 | NP Sputum | PCR             |
| Wang C et al     | China    | Case report           | Hospitalized      | 1               | Mild                | NP OP           | PCR             |
| Wang Y et al     | China    | Prospective case series | Hospitalized      | 23              | Mild and severe     | NP Sputum Throat Fecal Urine Blood | PCR             |
| Wölfel R et al   | Germany  | Prospective case series | Hospitalized      | 9               | Mild                | Sputum NP Throat Stool | PCR Viral culture Whole-genome sequencing |
| Wu Y et al       | China    | Prospective case series | Hospitalized      | 98              | Not defined         | Throat Stool    | PCR             |
| Xiao F et al     | China    | Prospective case series | Hospitalized      | 28              | Not defined         | NP OP Stool     | PCR Viral culture |
| Xiao AT et al    | China    | Prospective case series | Hospitalized      | 56              | Mild to moderate    | NP Throat       | PCR             |
| Xu K et al       | China    | Retrospective case series | Hospitalized      | 113             | Mild, pneumonia, severe pneumonia, ARDS, septic shock | Sputum NP Throat BAL | PCR             |
consistently identified as a risk factor for severe disease or prolonged shedding but comparisons were limited by small sample sizes. 

47,49,50,51,62

Viral RNA shedding in nonrespiratory samples

A subset of studies presented PCR data from both respiratory and fecal samples. 

10-14,16,20,24,25,33,36,37,45,47,50,51,55,65,66,70-75,78 Rectal/stool PCR pooled median duration of positivity based on 5 studies was 22.1 days (95% CI, 14.4–29.8; I² = 95.86%; P < .01). Stool PCR positivity has been observed to lag behind both PCR positivity of pharyngeal specimens and symptom improvement and even may become positive after the OP PCR has become negative. 

16 RNA replication in the stool was observed ≥2 weeks after symptom onset. 

10,20,50,51,73 In one study, the number of PCR-positive stool samples increased between the first and third weeks of illness, with a median time to detection in the stool of 19–22 days. 

50,70 Based on the limited data available thus far, illness severity does not seem to impact stool RNA detection, as similar durations of RNA shedding in the stool have been observed in mild and severe illness. 

16 Park et al detected SARS-CoV-2 RNA in stool 50–55 days after initial diagnosis of asymptomatic or mild SARS-CoV-2 illness. In this study, people with higher viral loads were more likely to have viral RNA in the stool. 

72 However, stool shedding was not consistently observed, and some studies showed that virus was detectable in only 35%–59% of patients screened. 

50,75 Data for serum and blood are limited but are evolving. Among studies reporting serum or blood testing, viral RNA was detected in 30%–87.5% of patients with COVID-19, though a smaller study did not detect viral RNA in any of the 14 patients tested. 

47,50,55,75,82 The ability to detect RNA in blood and serum may be reflective of disease severity. 

55,82 Virus was detected by PCR for longer in blood samples

| Study | Country | Design | Patient Population | No. of Patients | Severity of Illness | Specimen Sources | Testing Methods |
|-------|---------|--------|--------------------|-----------------|---------------------|-----------------|----------------|
| Young BE et al | Singapore | Prospective case series | Hospitalized | 18 | Not defined | NP Urine Stool Blood | PCR |
| Zhang L et al | China | Case report | Hospitalized | 1 | Mild | Throat | PCR |
| Zhang J et al | China | Retrospective case series | Hospitalized | 14 | Not defined | OP Stool | PCR |
| Zhang WY et al | China | Case report | Hospitalized | 1 | Mild | Pharyngeal | PCR |
| Zhang W et al | China | Prospective case series | Hospitalized | 39 | Severe Nonsevere Clinical condition unknown | Oral Rectal | PCR |
| Zhang N et al | China | Prospective case series | Hospitalized | 23 | Mild, moderate, critical | Upper respiratory Urine Stool Blood | PCR Viral Culture |
| Zhao F et al | China | Retrospective case series | Hospitalized | 401 | Mild, moderate, severe | Respiratory Fecal | PCR |
| Zheng S et al | China | Retrospective case series | Hospitalized | 96 | Mild, severe | Respiratory Blood Urine Stool | PCR |
| Zheng X et al | China | Retrospective case series | Hospitalized | 80 | Common, severe | Throat Stool | PCR |
| Zhou B et al | China | Prospective case series | Hospitalized | 41 | Severe | Throat | PCR |
| Zhou F et al | China | Retrospective case series | Hospitalized | 191 | Mild, moderate, severe, critical | Respiratory | PCR |
| Zhou R et al | China | Retrospective case series | Hospitalized | 31 | Asymptomatic | NP | PCR |
| Yao XH et al | China | Case report | Hospitalized | 1 | Severe | NP Lung Liver Heart Intestine Skin | PCR Histopathology |
| Zou L et al | China | Prospective case series | Hospitalized | 18 | Asymptomatic, mild-to-moderate, severe | NP | PCR |

Note. NP, nasopharyngeal; OP, oropharyngeal; PCR, polymerase chain reaction; ET, endotracheal.
of ICU patients [14.63 days (±5.88 SD)] compared to non-ICU patients [10.17 days (±6.13 SD)].

**Correlation between viral culture and PCR**

In total, 12 studies also included both PCR and viral culture information. Sequential viral cultures were not performed in all studies, which is a key limitation. Growth of SARS-CoV-2 on viral respiratory culture was reported ranging from 6 days before symptom onset through day 20 after symptom onset. A position statement published in Singapore reported that viable cultured virus was not isolated after day 11. Culture data suggest that the duration of shedding of viable virus may vary according to illness severity. In a study of patients with moderate-to-severe illness, Van Kampen et al found the median duration of shedding viable virus was 8 days (IQR, 5–11 days; range, 0–20 days) with the probability of detecting virus <5% after 15.2 days. In contrast, 4 studies of mildly ill patients did not find viable virus past day 8 or 9 of illness, but viral culture was not consistently reattempted. Liu et al described a patient with mild disease whose sputum viral culture was positive on day 18, but continued to have viral RNA detection until day 63, 45 days longer than detection of viable virus.

The correlation of SAR-CoV-2 viral loads and PCR cycle thresholds (Ct) values with isolation of viable virus is a topic of interest. The Ct value upper bound cutoff that determined a positive PCR was inconsistent among studies reporting this threshold, though most reported positive values at ≤23 or ≤24. Bullard et al compared PCR Ct value with culture positivity and found that the ability to isolate virus in culture was reduced when Ct value was ≥24. They reported that the odds ratio for infectivity decreased by 32% for every 1 point increase in the Ct value. La Scola et al report significant correlation between Ct value and culture positivity rates. Positive cultures occurred in all samples with Ct values 13–17 but culture positivity decreased to 12% at a Ct value of 33. Isolating virus in culture with positive PCR samples containing viral loads ≤10⁶ copies per milliliter is less likely to be successful.

Limited data exist regarding SARS-CoV-2 cultures in nonrespiratory specimens. Viral culture was attempted in serum samples of PCR-positive patients without growth. Viral stool cultures have yielded mixed results. Wöllfle et al performed viral culture of 13 stool samples from 4 different patients with mild disease on days 6–12 without growth, despite RNA detected in the stool through day 21. Viable virus was detected in the stool of a critically ill patient on day 19 with negative cultures beyond this despite a positive NP/OP PCR through day 28. Of 7 studies that processed urine samples, 2 reported detecting viable virus by culture. Also, 2 studies of patients with positive respiratory PCR samples attempted to culture virus from tears, but they yielded no growth.

**Discussion**

We summarized available data on duration of SARS-CoV-2 viral RNA shedding, isolation of viable virus, and the impact of infection severity on shedding duration. The pooled median duration of RNA shedding from respiratory samples of subjects was 18.4 days (95% CI, 15.54–21.3). In general, the highest viral loads occur within 1–2 weeks of illness onset, regardless of symptoms, with a subsequent gradual decline. However, several studies described PCR positivity beyond 2 weeks. Patients with more severe illness shed viral RNA for a longer period of time, with a pooled median duration of 19.8 days (95% CI, 16.2–23.5), compared to 17.2 days (95% CI, 14.0–20.5) for mild illness. Although these pooled medians should be interpreted with caution given the high heterogeneity of the studies and overlapping confidence intervals, viral culture data appear to support this conclusion. In reviewed studies, viable virus from respiratory cultures was not recovered past day 9 of illness for mildly ill patients but was cultured from severely ill patients through day 20.

Interpreting positive PCR samples beyond 2–3 weeks of illness is complex. Potential explanations for these intermittently negative PCR tests include a viral load below the detection limit of the assay, specimen source, quality of specimen collection, timing of specimen collection or reinfecion. Although viral culture positivity may also not correlate perfectly with transmissibility, the correlation between culture data and Ct thresholds may help predict infectiousness. Further data are needed to understand the correlation between transmission risk, culture positivity and Ct thresholds. The studies that examined viral culture were limited by small size, inclusion of patients with mostly mild illness, and lack of serial cultures on all patients. Isolation of viable virus in respiratory samples correlates with the timing of peak viral loads which occur within 1–2 weeks of illness onset. Only 1 study reported culturing viable virus from a respiratory sample beyond the second week of illness. Based on this information, it seems more likely that a positive PCR past 2–3 weeks of illness represents shedding of nonviable virus. Although the pooled median viral RNA shedding duration from patients with mild-to-moderate and severe disease do not differ greatly, reports of positive viral cultures through day 20 in severely ill patients support the potential for a prolonged infectious period for sicker patients. In addition, viable virus has been recovered from stool cultures, but further studies are needed to determine the implications for person-to-person spread.

Our review supports the US Centers for Disease Control and Prevention (CDC) interim guidance, which recommends maintaining transmission-based precautions for 10 days after symptom
onset in asymptomatic or mildly ill patients and for 20 days in severely ill patients. The decision to extend the duration of transmission-based precautions is complicated given the potentially profound impact on patients and their families, hospital systems, and public health. Prolonged home isolation may lead to longer periods of unemployment, social separation, and feelings of isolation. In the hospital, the supply of personal protective equipment, staff allocation, availability of patient beds, and the health system budget are impacted by the duration of isolation for patients with COVID-19. That said, aggressive infection control measures are required in the setting of an outbreak to control the virus and to avoid overwhelming healthcare systems.

In calculating the pooled median duration of shedding, we identified a significantly high degree of heterogeneity between studies. In a standard meta-analysis, we would not report a pooled measure of association when heterogeneity was high. However, the pooled median is not intended to inform our knowledge of causality or effect size but, rather, to better inform the policy decisions that currently must be made on the very limited data available at this time in the SARS-CoV-2 pandemic. Factors contributing heterogeneity may include the variable timing of sample collection for PCR or viral culture, Ct threshold, sample types, SARS-CoV-2 genotype, and host factors such as pharmacotherapy, comorbidities, and disease severity. We noted broad variability in the definitions of disease severity applied. Although no formal definitions existed initially, the National Commission of China developed a classification scheme for mild, moderate, and severe illness that include specific clinical variables. The National Institutes of Health and World Health Organization have since developed similar severity scales also. Going forward, these definitions will facilitate the conduct of generalizable studies of viral dynamics.

This comprehensive review details the evidence available to date pertaining to SARS-CoV-2 viral dynamics. Although PCR positivity can be prolonged, culture data suggest that virus viability is typically shorter in duration. Continued reporting of viral shedding data via PCR and viral culture with improved standardization in methods and definitions, in coordination with transmission data, will facilitate evidence-based decision making for the infection control and public health measures necessary to control the pandemic.

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