Public Health Ontario | Santé publique Ontario

SYNTHESIS

02/03/2021

Factors Affecting COVID-19 Period of Communicability – What We Know So Far

Introduction

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

Key Findings

- The primary literature agreed that the period of communicability was prolonged in patients with immune system compromise. This was the only factor examined in which respective studies used the detection of live virus to determine the period of communicability. There was not enough data to quantify how much longer communicability is in patients with immune system compromise; therefore, we can only conclude that in some instances communicability exceeded 20 days post symptom-onset.
- The remaining variables were only examined using the detection of viral RNA shedding. Treatment with corticosteroids, more severe disease, and delays in diagnosis potentially contributed to a relatively longer period of viral RNA shedding; sex was not associated with the duration of viral RNA shedding. A single systematic review and meta-analysis showed that increasing age was associated with prolonged viral RNA shedding, particularly in those older than 60 years. While several factors were associated with prolonged viral RNA shedding, we cannot correlate this with live virus and prolonged infectiousness.

Background

The period of communicability is when a patient is shedding virus at a sufficient quantity and viability to infect another person and many factors can lengthen or shorten the period of communicability. We examine the factors that affect the period of communicability by examining the literature on 1) live virus culture, and 2) viral RNA shedding. Live virus refers to the detection of a cytopathic effect (CPE) in cell cultures or the isolation of live virus from cell cultures inoculated with clinical samples from patients with COVID-19. In general, the presence of live virus in a sample from a patient with COVID-19 is an indication that the patient is infectious. However, specimen quality (e.g., deep frozen specimens) and different laboratory methods for assessing the presence of live virus may contribute to an underestimate of viability.

Epidemiological studies with contact tracing are another good indicator of the period of communicability, especially for the presymptomatic transmission period when there is accurate tracing of presymptomatic patients and their close contacts. However, assessment of transmission late in infection is challenged by the individual typically being aware of their infection by that point and employing measures to prevent transmission. Viral RNA shedding provides additional proxy evidence for the period of communicability, and refers to the detection of various targeted RNA sequences in patient samples through reverse transcription polymerase chain reaction (RT-PCR). A positive RT-PCR may or may not represent the presence of live or infectious virus, as the RNA detected potentially only represents the presence of fragmented or residual viral particles; however, detection of higher levels of virus is more likely to be correlated with live or infectious virus.

Here we synthesize the current literature investigating the factors affecting the period of communicability of COVID-19. Out-of-scope for this rapid review are viral factors (e.g., lineages or variants of concern) or host factors (e.g., genetics) that may impact the period of communicability.

Methods

In considering feasibility, scope, and a need for responsiveness, we chose a rapid review as an appropriate approach to determining the factors affecting the period of communicability of COVID-19. A rapid review is a knowledge synthesis where certain steps of the systematic review process are compromised in order to be timely (e.g., quality assessment).[1]

On December 2, 2020, PHO Library Services conducted a literature search in MEDLINE; searches in National Institutes of Health COVID-19 Portfolio (preprints), Embase and Scopus were performed on December 3, 2020 (Appendix A, search strategies available upon request). We searched PubMed and Google Scholar on December 31, 2020 for additional articles of interest.

English-language peer-reviewed and non-peer-reviewed records that described factors affecting the period of communicability of COVID-19 were included. We examined the research question by concentrating on evidence from systematic reviews and meta-analyses where possible. We restricted primary literature to studies with 100 or more patients. We reviewed citations from included systematic reviews and primary studies to identify additional research. The potential impact of COVID-19 variants of concern on the period of communicability is out-of-scope for this rapid review.

Prior to posting, PHO subject-matter experts review all “What We Know So Far” documents. As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in this document is only current as of the date of respective literature searches.

Factors Affecting the Period of Communicability

The evidence concerning factors associated with prolonging or shortening the duration of viral RNA or live virus shedding in COVID-19 patients is still evolving. We screened 371 reviews and 930 primary research articles for this rapid review (Appendix A). After screening the literature for relevant articles, we included eight systematic reviews (with or without meta-analyses) and 29 primary research articles. 8.1% (3/37) of studies were non-peer-reviewed preprint articles.

Only studies examining immune system compromise used live virus to determine communicability; therefore, most of the factors described in this synthesis are based on viral RNA shedding as determined by RT-PCR testing. Since viral RNA shedding is not indicative of transmissibility, we cannot state that

there is a specific period for the prolongation in communicability. We can assume that prolonged viral RNA shedding is related to a likewise, but undeterminable, increase in relative live virus shedding. Until more studies are performed where live virus culturing is attempted, it is not possible to determine the exact period of communicability based on viral RNA shedding.

We have attempted to report factors affecting the period of communicability according to the strength of the evidence; therefore, we start with immune system compromise studies that reported live virus culturing. The remaining factors are generally in order of those with more systematic reviews first, followed by factors with more primary literature.

Immune System Compromise

No systematic reviews or meta-analyses examined the period of communicability of COVID-19 according to immune system compromise. Live virus was detected in individual patients with immune system compromise 25–143 days post symptom-onset (PSO), with confirmation of ongoing initial infection.

- In a cohort study of 508 patients in Italy, Farina et al. reported that the probability of viral clearance in the upper respiratory track (URT) by 28 days PSO in patients with neoplasia was lower compared to patients without neoplasia (hazard ratio [HR]: 0.13; 95% confidence interval [CI]: 0.02–0.70; p=0.018; multivariable Cox model).[2] The median duration of viral RNA shedding in all patients was 25 days PSO (interquartile range [IQR]: 17–31).
- Aydillo et al. investigated the shedding of live SARS-CoV-2 in 20 patients with cancer and immune system compromise (median age: 61 years; range: 35–77) in New York City.[3] Three patients had live virus detected in nasopharyngeal (NP) and sputum samples collected later than 20 days PSO (i.e., 25, 26 and 61 days); whole genome sequencing (WGS) indicated a persistent infection. Two of these patients were undergoing allogeneic hematopoietic stem-cell transplants and one patient was undergoing chimeric antigen receptor T-cell therapy within the last six months. All three patients remained negative for SARS-CoV-2 IgG. Two of the three patients had severe disease (i.e., requiring supplemental oxygen via non-rebreather masks or mechanical ventilation).
- In a case report of a 45 year old patient with antiphospholipid syndrome in Boston, Massachusetts, Choi et al. reported that live virus was detected in cell cultures from NP swabs collected 75 and 143 days PSO.[4] The patient was undergoing chemotherapy, with additional treatment with glucocorticoids and monoclonal antibodies. WGS of viral samples during the course of infection indicated a persistent infection.
- In a case report of a 71 year old patient with chronic lymphocytic leukemia with immune system compromise in Washington, United States (US), Avanzato et al. reported that live virus was detected in cell cultures from NP swabs up to 70 days after initial positive RT-PCR.[5] NP swabs collected 49 and 70 days since the first positive RT-PCR were cultured and produced CPE; scanning and transmission microscopy showed presence of viral particles.
- In a case report of an 84 year old male in Milan, Italy undergoing treatment for prostate cancer, viral RNA persisted in NP samples for 71 days PSO, with positive viral cultures up to 30 days PSO.[6] The patient also had a history of chronic obstructive pulmonary disease, atrial fibrillation and valvulopathy.
- Baang et al. reported on a 60 year old patient in Michigan, US with lymphoma and B-cell immunodeficiency.[7] All 10 NP swabs collected from 7–119 days PSO produced CPE in cell cultures, except for day 81. Sequencing ruled out reinfection in this case.

Aside from detection of live virus, multiple case reports have demonstrated viral RNA shedding past 30 days PSO in patients undergoing immune system suppression for lymphoma,[7,8] kidney transplant,[9,10] X chromosome-linked agammaglobulinemia,[11] and heart transplant.[12]

Disease Severity

The systematic reviews and meta-analyses reviewed agreed that increasing disease severity was associated with prolonged viral RNA shedding. Three systematic reviews and meta-analyses demonstrated that more severe disease was associated with approximately 3–9 additional days of viral RNA shedding. An important caveat is that we cannot confirm that definitions for disease severity categories were comparable among these studies (e.g., variable definitions used in primary studies, definitions were poorly described).

- In a systematic review of 30 studies, Park et al. (preprint) reported that the median duration of viral RNA shedding in respiratory samples from patients with mild disease was 14.0 days PSO (IQR: 8.1), for moderate disease was 15.5 days PSO (IQR: 9.3), and for severe disease was 24.0 days PSO (IQR: 7.0).[13] The authors defined disease severity as: 1) mild: patient with no symptoms or non-serious symptoms that did not require healthcare intervention; 2) moderate: patients that required acute care and/or intervention; and 3) severe: patients that required admission to the intensive care unit, vemntilator support, and/or resulted in death. For IQR, we cannot determine range from data, as authors only provided a single value (Q3-Q1).
- In a systematic review and meta-analysis, Fontana et al. reported that the pooled median duration of viral RNA shedding in respiratory samples from patients with severe-to-critical disease was 19.8 days PSO (95% CI: 16.2–23.5; n=10 studies), which was longer than in patients with mild-to-moderate disease at 17.2 days PSO (95% CI: 14.0–20.5; n=10 studies).[14] The authors did not specifically define mild-to-moderate or severe-to-critical disease; however, they noted there was wide variability in disease severity definitions used among the included primary studies.
- In the systematic review by Morone et al., viral RNA shedding was significantly longer in patients with severe disease than those with non-severe disease, for both URT/lower respiratory tract (LRT) samples ($p<0.001$; n=309 patients) and fecal samples ($p=0.01$; n=184 patients) using a Mann-Whitney U-test.[15] The authors defined severe "community-acquired pneumonia" according to criteria published by the American Thoracic Society and Infectious Disease Society of America.[16]

Decreased levels of lymphocytes or lymphocytopenia on admission or during the course of infection was associated with prolonged viral RNA shedding in six studies, with no relationship reported in a single study.

- Ji et al., in a study of 684 patients all treated with glucocorticoids in Wuhan, China, reported that patients with lower B-cell ($p=0.03$) and CD4 T-cell ($p=0.048$) counts at admission were associated with prolonged viral RNA clearance (>28 days vs. ≤14 days PSO; n=574; analysis type not reported).[17]
- Spagnuolo et al., in a study of 280 patients in Milan, Italy, reported that lymphocyte counts below 1.0×10^9/L was independently associated with a longer duration of viral RNA shedding (adjusted hazard ratio [aHR]: 1.6; 95% CI: 1.12–2.15; $p=0.009$; stepwise Cox proportional hazard model).[18]

- In a study of 183 patients in Tianmen, China, Hu et al. reported that lymphocyte count was not independently associated with the duration of viral RNA shedding (aHR: 1.2; 95% CI: 0.84–1.79; p=0.30; multivariate analysis).[19]
- Liu et al., in a study of 144 patients in Wuhan, China, reported that lymphocyte counts below 1.1 × 10^9/L was independently associated with a longer duration of viral RNA shedding (β: 4.3; 95% CI: 0.32–8.21; p=0.035; multivariate linear regression).[20]
- In a study of 112 patients in Wuhan, China, Gao et al. reported that lower lymphocyte counts (<1.1 × 10^9/L) were independently associated with prolonged viral RNA shedding (≥28 days PSO) (HR: 0.5; 95% CI: 0.28–1.00; p=0.051; multivariate analysis).[21]
- In Wuhan, China, Lu et al. noted that low lymphocyte counts (<2.0 × 10^9/L) were associated with prolonged (not defined) viral RNA shedding in throat or NP swabs in symptomatic children (p=0.008; n=110; multivariate analysis).[22]
- In a study of 104 patients in Hangzhou, China, Hao et al. reported that those with decreased B-cell counts (<90/µL) upon admission had prolonged viral RNA shedding (16 days PSO; 95% CI: 12–20) compared to those with normal B-cell counts (11 days PSO; 95% CI: 9–13) (p=0.001; multivariate Cox regression).[23]

We included four primary research papers comparing viral RNA shedding in asymptomatic and symptomatic patients with COVID-19. An important caveat is that duration of viral RNA shedding in someone who is asymptomatic is difficult as it is not possible to know when their infection began.

- In a study of 396 patients in South Korea, Uhm et al. reported that the median duration of viral RNA shedding in NP swabs was longer in symptomatic patients (18.0 days PSO; IQR: 15.0–22.0; n=328), compared to asymptomatic patients (14.5 days since first positive test; IQR: 11.0–21.0; n=68) (p=0.001; univariate analysis).[24]
- In a study of 199 patients in South Korea, Noh et al. reported viral RNA shedding in symptomatic patients was prolonged (25.2 ± 4.9 days PSO; n=146), compared to asymptomatic patients (22.6 ± 4.0 days since first positive test; n=53) (p<0.01; Mann-Whitney U-test).[25]
- Han et al., in a study of 155 patients in Tianjin, China, reported that being symptomatic was independently associated with prolonged viral RNA shedding (HR: 0.34; 95% CI: 0.19–0.61; p<0.001; multivariate analysis).[26]
- In a study of 110 children with mild disease in Wuhan, China, Lu et al. reported that the median duration of viral RNA shedding in URT swabs was longer in symptomatic patients (17 days PSO; IQR: 12–23; n=81) than in asymptomatic patients (11 days since first positive test; IQR: 9–13; n=29) (p<0.001; multivariate analysis).[22]

Additional factors related to disease severity that were independently associated with prolonged viral RNA shedding included a higher temperature at admission,[22,27] length of hospitalization,[23,27] and abnormal blood chemistry (e.g., elevated interleukin-2R, albumin, D-dimer)[20,21,28].

Age

There was evidence in 1 out of 2 systematic reviews and meta-analyses and 6 out of 9 primary studies that the duration of viral RNA shedding was prolonged in older adults (e.g., >60 years) or as age increased. It should be noted that the second systematic review did not specifically examine older age as a variable, rather compared children and adults. These studies did not examine for virus viability to determine whether or how much longer (e.g., longer than 10 days PSO) older adult patients are infectious.

Two systematic reviews and meta-analyses examined the effect of age and duration of viral RNA shedding.

- In a systematic review and meta-analysis of 41 studies, Cevik et al. reported that the mean duration of viral RNA shedding in the URT samples increased (continuous variable) with increasing mean age of patients (slope = 0.30; 95% CI: 0.12–0.49; p=0.0016; random-effects model).[29] From the primary studies used in the review, 10 identified prolonged viral shedding in those older than 60 years and three identified increasing age as a risk factor for prolonged viral RNA shedding.
- Morone et al., in a systematic review and meta-analysis, did not find a difference (Wilcoxin test) in the median duration of viral RNA shedding in respiratory samples from those <18 years (8 days PSO; IQR: 9; n=38 patients) and those ≥18 years (10 days PSO; IQR: 11; n=48 patients) with mild disease (as defined by primary literature included) (p=0.12).[15] For IQR, we cannot determine range from data, authors only provided a single value (Q3-Q1).

Primary research studies either showed (n=6) or did not show (n=3) a relationship between age and duration of viral RNA shedding.

- Stehlik et al. (preprint) studied 958 patients in Queensland, Australia, where the median time to apparent viral clearance was longer in those 65 years and over (median: 43 days PSO), compared to those under 65 years (median: 29 days PSO) (HR 1.9; 95% CI: 1.17–2.93; p=0.006; multivariate analysis).[30]
- In Italy, Farina et al. did not find a difference in the duration of viral RNA shedding according to age (HR: 0.998; 95% CI: 0.99–1.01; p=0.53) in a cohort of 508 patients.[2]
- In a study of 384 patients in Wuhan, China, Zhou et al. reported that longer viral RNA shedding in URT samples was associated with being “elderly” (odds ratio [OR]: 1.0; 95% CI: 1.01–1.04; p=0.003; multivariate logistic regression).[31] The authors did not define the elderly age group and we can only assume it is the “older age groups”, which included those ≥61 years old. The median duration of viral RNA shedding was 23 days PSO (IQR: 22) in those ≤40 years, 30 days PSO (IQR: 18) for those 41–50 years, 33 days PSO (IQR: 21) for those 51–60 years, 34 days PSO (IQR: 17) for those 61–70 years, and 34 days PSO (IQR: 17) for those >70 years.
- Spagnuolo et al., in a study of 280 patients in Milan, Italy, reported that an age over 70 years was independently associated with a longer duration of viral RNA shedding (aHR: 1.6; 95% CI: 1.11–2.23; p=0.011; stepwise Cox proportional hazard model).[18]
- In a study of 267 patients in Guangzhou, China, Chen et al. (preprint) reported that increasing age was independently associated with a longer duration of viral RNA shedding (HR: 0.99; 95% CI: 0.98–1.0; p=0.007; multivariable Cox regression model).[32] For those <16 years, the duration of viral RNA shedding was 8.0 days PSO (IQR: 5.5–15.3), followed by those 16–49 years (11.0 days PSO; IQR: 7.0–15.0), 50–64 years (13.0 days PSO; IQR: 10.0–17.0), and those ≥65 years (13.0 days PSO; IQR: 10.0–19.0).
- In a study of 147 patients in Changsha, China, Qi et al. reported that the median age of patients with prolonged viral RNA shedding past 17 days PSO (45.0 years; 95% CI: 37.5–59.5) was not different from those with viral RNA shedding ≤17 days PSO (41.0 years; 95% CI: 32.5–50.0) (p=0.093; univariate analysis).[27]
- In a study of 120 patients in Wuhan, China, Yan et al. reported that those ≥50 years had prolonged (>23 days PSO) viral RNA shedding (adjusted odds ratio [aOR]: 2.3; 95% CI: 1.1–4.8; p=0.03; multivariate logistic regression).[33]

- Xu et al., in a study of 113 symptomatic patients from outside Wuhan, China, reported that age was not an independent risk factor for prolonged (≥15 days PSO) viral RNA shedding (OR: 1.0; 95% CI: 0.96–1.03; p=0.91; multivariable analysis).[34]
- Gao et al., in a study of 112 patients in Wuhan, China, found that those ≥65 years experienced prolonged (≥28 days PSO) viral RNA shedding (HR: 2.0; 95% CI: 1.02–3.95; p<0.01).[21]

Comorbidities

Primary research articles showed that hypertension (5 out of 6) and type 2 diabetes mellitus (5 out of 5) were not associated with the duration of viral RNA shedding.

Hypertension:

- In a study of 384 patients in Wuhan, China, Zhou et al. reported that the duration of viral RNA shedding in URT samples was not associated with hypertension (OR: 1.2; 95% CI: 0.76–1.93; p=0.41; multivariate logistic regression).[31]
- In a retrospective cohort study (n=267 patients) in Guangzhou, China, Chen et al. (preprint) reported that the duration of viral RNA shedding in patients with hypertension (12.0 days PSO; 95% CI: 10.0–16.0) was similar to those without hypertension (12.0 days PSO; 95% CI: 8.0–17.0) (p=0.80; univariate analysis).[32]
- In a study of 147 patients in Changsha, China, Qi et al. reported that viral RNA shedding past 17 days PSO was not associated with hypertension (p=0.57; univariate analysis).
- In a study of 120 patients in Wuhan, China, Yan et al. reported that hypertension was not independently associated with the duration of viral RNA shedding (OR: 0.63; 95% CI: 0.28–1.42; p=0.26; univariate analysis).[33]
- Xu et al., in a study of 113 symptomatic patients from outside Wuhan, China, reported that hypertension was not an independent risk factor for prolonged (≥15 days PSO) viral RNA shedding (OR: 3.9; 95% CI: 0.86–18.15; p=0.079; multivariable analysis).[34]
- Gao et al., in a study of 112 patients in Wuhan, China, found that those with hypertension experienced prolonged (≥28 days PSO) viral RNA shedding (HR: 4.1; 95% CI: 1.6–18.2; p<0.01; multivariate analysis).[21]

Type 2 diabetes mellitus:

- In a study of 384 patients in Wuhan, China, Zhou et al. reported that the duration of viral RNA shedding in URT samples was not associated with diabetes (OR: 0.61; 95% CI: 0.33–1.12; p=0.41; multivariate logistic regression).[31]
- In a retrospective cohort study (n=267 patients) in Guangzhou, China, Chen et al. (preprint) reported that the duration of viral RNA shedding in patients with diabetes (11.0 days PSO; 95% CI: 8.0–19.0) was similar to those without diabetes (12.0 days PSO; 95% CI: 8.3–16.0) (p=0.80; univariate analysis).[32]
- In a study of 251 patients in the US, Cano et al. reported that patients with diabetes did not show prolonged viral RNA shedding (p=0.49; univariate regression model).[35] The median duration of viral RNA shedding in diabetic patients was 24 days PSO (IQR: 11.8), compared to those without diabetes at 23 days PSO (IQR: 12). The authors did not provide a range for the IQR, just a single value (Q3-Q1).
- In a study of 147 patients in Changsha, China, Qi et al. reported that viral RNA shedding past 17 days PSO was not associated with diabetes (p=1.0; univariate analysis).[27]

- In a study of 120 patients in Wuhan, China, Yan et al. reported that diabetes was not idependently associatd with the duration of viral RNA shedding (OR: 2.6; 95% CI: 0.64–10.59; p=0.18; univariate analysis).[33]

Sex

The literature was generally in agreement that there was no association between sex and duration of viral RNA shedding. Five primary studies did not find a relationship between sex and viral RNA shedding duration; however, one study found that viral RNA shedding was longer in male patients.

- Stehlik et al. (preprint) studied 958 patients in Queensland, Australia, where the median time to viral RNA clearance did not vary by sex (HR: 0.93; 95% CI: 0.66–1.30; multivariate analysis).[30]
- Ji et al., in a study of 684 patients all treated with glucocorticoids in Wuhan, China, reported that there was no difference (p=0.84; univariate analysis) in the duration of viral RNA shedding by sex (>28 days vs. ≤14 days PSO; n=574).[17]
- In a study of 384 patients in Wuhan, China, Zhou et al. reported that longer viral RNA shedding in URT samples was not associated with sex (OR: 0.68; 95% CI: 0.45–1.03; p=0.072; multivariate logistic regression).[31]
- In a retrospective cohort study (n=267 patients) in Guangzhou, China, Chen et al. (preprint) reported that the median duration of viral RNA shedding was 12.0 days PSO (IQR: 8.0–16.0) in males, which was not different for females (12.0 days PSO; IQR: 9.0–17.0) (p=0.99; univariate analysis).[32]
- In a study of 147 patients in Changsha, China, Qi et al. reported that viral RNA shedding past 17 days PSO was not associated with sex (p=0.12; univariate analysis).[27]
- In a study of 120 patients in Wuhan, China, Yan et al. reported that sex was not independently associated with the duration of viral RNA shedding (aOR: 0.60; 95% CI: 0.28–1.28; p=0.19; multivariate logistic regression).[33]
- Xu et al., in a study of 113 symptomatic patients in China, reported that male sex was independently associated with prolonged (≥15 days PSO) viral RNA shedding (OR: 3.2; 95% CI: 1.31–8.02; p=0.011; multivariable analysis).[34]

Delay in Period from Symptom-onset to Diagnosis or Hospitalization

No systematic reviews and meta-analyses examined this topic; however, six primary research articles demonstrated that increasing the time from symptom-onset to hospitalization or diagnosis resulted in prolonged viral RNA shedding. In most instances, the reason for the prolonged viral RNA shedding is attributed to disease severity, which in turn is the result of delayed treatment.

- Spagnuolo et al., in a study of 280 patients in Milan, Italy, reported that a delay of 5 or more days was independently associated with a longer duration of viral RNA shedding (aHR: 0.76; 95% CI: 0.61–0.94; p=0.013; stepwise Cox proportional hazard model).[18]
- In a retrospective cohort study (n=267 patients) in Guangzhou, China, Chen et al. (preprint) reported that delays in hospitalization (≥4 days) were independently associated with prolonged viral RNA shedding (HR: 0.91; 95% CI: 0.88–0.94; p<0.001; multivariable Cox regression).[32] The duration of viral RNA shedding was longer when a patient was delayed in getting hospitalized (14.0 days PSO; 95% CI: 11.0–17.0), compared to when a patient was hospitalized relatively quicker (10.0 days PSO; 95% CI: 6.0–15.0).

- In a study of 183 patients in Tianmen, China, Hu et al. reported that increasing time from symptom-onset to hospitalization was independently associated with longer viral RNA shedding (aHR: 0.83; 95% CI: 0.78–0.88; p<0.001; multivariate analysis).[19]
- Han et al., in a study of 155 patients in Tianjin, China, reported that a time from symptom-onset to treatment >4 days was independently associated with prolonged viral RNA shedding (HR: 0.68; 95% CI: 0.50–0.93; p=0.014; multivariate analysis).[26]
- In Wuhan, China, Qi et al., using multivariable logistic regression, reported that delayed admission was independently associated with viral RNA shedding past 17 days PSO (OR: 1.7; 95% CI: 1.3–2.3; p<0.001; n=147; multivariate analysis).[27] The authors suggested that the reason for prolonged viral RNA shedding was due to delayed treatment.
- Xu et al., in a study of 113 symptomatic patients from outside Wuhan, China, reported that increasing time from symptom-onset to hospitalization was an independent risk factor for prolonged (≥15 days PSO) viral RNA shedding (OR: 1.3; 95% CI: 1.10–1.54; p=0.002; multivariable analysis).[34] The authors noted that delays in hospitalization were associated with patients with more severe disease in the absence of effective treatment.

Treatments for COVID-19: Corticosteroids and Antivirals

We did not identify any systematic reviews and meta-analyses on the impact of treatments on the duration of viral RNA shedding. There were two types of treatments described in the literature in relation to period of communicability: corticosteroids and antivirals. It is difficult to draw a conclusion from these studies, as timing, duration and dosing varied widely among patients and studies.

Four primary studies showed that treatment with corticosteroids prolonged viral shedding. However, 2 studies showed viral RNA shedding was not prolonged in those recieving corticosteroids.

- In a retrospective cohort study (n=267 patients) in Guangzhou, China, Chen et al. (preprint) reported that treatment with corticosteroids was independently associated with prolonged viral RNA shedding (HR: 0.55; 95% CI: 0.36–0.84; p=0.005; multivariable Cox regression).[32] The duration of viral RNA shedding was longer in treated patients (18.0 days PSO; 95% CI: 12.5–27.0), compared to untreated patients (12.0 days PSO; 95% CI: 8.0–16.0).
- In a study of 183 patients in Tianmen, China, Hu et al. reported that treatment with corticosteroids was independently associated with longer viral RNA shedding (aHR: 0.50; 95% CI: 0.32–0.77; p=0.02; multivariate analysis).[19]
- In a study of 147 patients in Changsha, China, Qi et al. reported that viral RNA shedding past 17 days was independently associated with glucocorticoid treatment (OR: 4.0; 95% CI: 0.43–37.0; p=0.020; multivariate analysis).[27]
- Liu et al., in a study of 144 patients in Wuhan, China, reported that treatment with corticosteroids was independently associated with longer duration of viral RNA shedding (β: 6.2; 95% CI: 2.77–9.61; p<0.001; multivariate linear regression).[20]
- In a study of 120 patients in Wuhan, China, Yan et al. reported that treatment with corticosteroids was not independently associated with the duration of viral RNA shedding (OR: 0.80; 95% CI: 0.38–1.70; p=0.57; univariate analysis).[33]
- Xu et al., in a study of 113 symptomatic patients from outside Wuhan, China, reported that treatment with corticosteroids was not an independent risk factor for prolonged (≥15 days PSO) viral RNA shedding (OR: 1.4; 95% CI: 0.52–3.65; p=0.52; multivariable analysis).[34]

Three of five studies reported that prolonged viral RNA shedding was associated with treatment with various antivirals.

- In a retrospective cohort study (n=267 patients) in Guangzhou, China, Chen et al. (preprint) reported that treatment with lopinavir/ritonavir was independently associated with prolonged viral RNA shedding (HR: 0.71; 95% CI: 0.54–0.95; p=0.021; multivariable Cox regression).[32] The duration of viral RNA shedding was longer in treated patients (14.0 days PSO; 95% CI: 10.0–19.0), compared to untreated patients (12.0 days PSO; 95% CI: 8.0–16.0). There was no difference in duration of viral RNA shedding when patients were treated with oseltamivir (p=0.15).
- In a study of 183 patients in Tianmen, China, Hu et al. reported that treatment oseltamivir was independently associated with longer viral RNA shedding (aHR: 0.42; 95% CI: 0.28–0.62; p<0.001; multivariate analysis).[19]
- Liu et al., in a study of 144 patients in Wuhan, China, reported that treatment with lopinavir/ritonavir was not independently associated with the duration of viral RNA shedding (β: -1.7; 95% CI: -4.7 to 1.3; p=0.261; multivariate linear regression).[20]
- In a study of 120 patients in Wuhan, China, Yan et al. reported that those not treated with lopinavir/ritonavir shed viral RNA for a longer time (aOR: 2.4; 95% CI: 1.10–5.36; p=0.03; multivariate logistic regression).[33]

Specimen Type

Specimen type does not have an impact on the period of communicability of COVID-19. Prolonged detection of virus in various specimen types may suggest prolonged viable virus from various sampling sites. Six systematic reviews and meta-analyses examined the duration of viral RNA shedding according to sample type. The duration of viral RNA shedding was longer in LRT and gastrointestinal samples, compared to URT samples.

- In a systematic review and meta-analysis of 43 studies and 3,229 patients, Cevik et al. reported that the pooled mean duration of viral RNA shedding in URT samples was 17.0 days PSO (95% CI: 15.5–18.6; random-effects model).[29] The pooled mean duration of viral RNA shedding in stool samples was 17.2 days PSO (95% CI: 14.4–20.1; 13 studies and 586 patients), followed by serum samples at 16.6 days PSO (95% CI: 3.6–29.7; 2 studies with 108 patients) and LRT samples at 14.6 days PSO (95% CI: 9.3–20.0; 7 studies and 260 patients). The maximum duration of PSO viral RNA shedding was highest in stool (126 days), followed by URT (83 days), serum (60 days) and LRT (59 days) samples.
- In a systematic review of 32 studies and 1,023 patients, Mallet et al. reported that the median duration of viral RNA shedding was shorter in URT samples (12 days PSO; 95% CI: 8–15) compared to LRT samples (28 days PSO; 95% CI: 20–not estimated).[36] For NP swabs, the probability of detecting viral RNA decreased over time: 0–4 days PSO (89%; 95% CI: 83–93; n=166 patients) and 10–14 days PSO (54%; 95% CI: 47–61; n=222 patients).
- In a systematic review and meta-analysis of 4 studies and 41 patients, Weiss et al. reported that the pooled mean difference in viral RNA shedding time (URT-LRT) in adults with moderate or severe COVID-19 was -5.9 days PSO (95% CI: -9.4 to 2.3).[37]
- In a systematic review and meta-analysis of 37 studies and 364 patients, Morone et al. reported that the median duration of viral RNA shedding was shorter from respiratory samples (14 days PSO; IQR: 12), compared to fecal samples (19 days PSO; IQR: 14) (p<0.001; Mantel-Cox log rank

test).[15] For IQR, we cannot determine range from data, as authors provided only a single value (Q3-Q1).

- In a systematic review of 17 studies and 69 children, Xu et al. reported that the mean duration of viral RNA shedding in respiratory samples was 11.1 ± 5.8 days PSO (n=53 patients).[38] For gastrointestinal samples, the mean duration of shedding was 23.6 ± 8.8 days PSO (n=7 patients).
- Walsh et al. reported a median duration of viral RNA shedding in URT samples (66 studies) was 14.5 days PSO (range: 1.0–53.5) and for LRT samples (10 studies) was 15.5 days PSO (range: 10.0–44.0).[39]

Limitations

It is important to note that a portion of the literature in this rapid review is non-peer-reviewed, pre-print articles (8%). In addition, most of the systematic reviews we included used preprint articles in meta-analyses. Considering the rapid emergence of the COVID-19 pandemic, the volume of pre-print research is expected given the need for rapid dissemination of data.

We did not check systematic reviews for overlap among reviews in the studies that they included. Further, we did not check if our included primary studies were included in the systematic reviews. Thus, there is duplication of findings. Not all studies performed serial testing for the explicit purpose of determining the duration of viral shedding, thus some studies could underestimate the average duration.

There was a high degree of heterogeneity among studies, mostly due to varying methodologies and relatively small sample sizes. Different studies assessed virus viability by culture using various periods of time (4 to over 7 days), different cell lines, and deep frozen specimens, all of which are factors that could affect the detection of live virus. The conditions and specific gene targets used in RT-PCR assays varied among studies, making it difficult to compare studies and when performing meta-analyses in systematic reviews.

Considerations for the Period from Symptom-onset to Viral Clearance

Currently, Ontario recommends a non-test based approach to deciding when to discharge patients from isolation:[40]

- For patients with mild to moderate illness and no immune compromise, isolation can be discontinued after 10 days since symptom onset date or from first RT-PCR-positive date (if initially asymptomatic). For both categories, patients must be afebrile without use of fever-reducing medications and have improvement of symptoms over the previous 24 hours.
- For patients with severe illness who required intensive care unit admittance or with severe immune compromise, isolation can be discontinued after 20 days since symptom-onset date or from first RT-PCR-positive date (if initially asymptomatic).

Based on this rapid review, there is some evidence to suggest that a test-based approach may be warranted in some cases of immune compromise due to viable virus detections >20 days, and as much as >140 days after infection. While there was no evidence on viable virus detection, based on prolonged shedding of virus, additional factors to consider for an extended isolation period for patients with

COVID-19 include: older age (e.g., >60 years); treatment with corticosteroids; delayed time from symptoms to hospitalization; and lymphocytopenia. Further studies in these populations on virus viability are required to assess risk of transmission from prolonged virus detection, and whether an extension of isolation is warranted at the population level. The decision to extend a patient's period of isolation should be made on a case-by-case basis, and take into account resource use in the context of existing preventative measures.

Conclusions

The primary literature in our rapid review agreed that the period of communicability may be prolonged in patients with immune system compromise. Among the factors examined, immune system compromise was the only one in which respective studies used the detection of live virus to determine the period of communicability. There was not enough data to quantify how much longer communicability is in patients with immune system compromise; therefore, we can only conclude that in some instances communicability exceeded 20 days post symptom-onset.

The remaining factors investigated in this rapid review were only examined using the detection of viral RNA shedding. Treatment with corticosteroids, more severe disease, and delays in diagnosis potentially contributed to a relatively longer period of viral RNA shedding. Sex was not associated with duration of viral RNA shedding. A single systematic review and meta-analysis showed that increasing age was associated with prolonged viral RNA shedding, particularly in those older than 60 years. While several factors were associated with prolonged viral RNA shedding, we cannot correlate this with live virus and infectiousness. Further research is needed to clarify whether sex and antiviral use has an impact on the period of communicability.

PHO will continue to monitor the scientific evidence on the period of communicability of COVID-19, updating this document as necessary.

References

1. Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. Syst Rev. 2012;1:10. Available from: https://doi.org/10.1186/2046-4053-1-10

2. Farina N, Ramirez GA, De Lorenzo R, Di Filippo L, Conte C, Ciceri F, et al. COVID-19: pharmacology and kinetics of viral clearance. Pharmacol Res. 2020;161:105114. Available from: https://doi.org/10.1016/j.phrs.2020.105114

3. Aydillo T, Gonzalez-Reiche AS, Aslam S, van de Guchte A, Khan Z, Obla A, et al. Shedding of viable SARS-CoV-2 after immunosuppressive therapy for cancer. N Engl J Med. 2020;383(26):2586-88. Available from: https://doi.org/10.1056/NEJMc2031670

4. Choi B, Choudhary MC, Regan J, Sparks JA, Padera RF, Qiu X, et al. Persistence and evolution of SARS-CoV-2 in an immunocompromised host. N Engl J Med. 2020;383(23):2291-3. Available from: https://doi.org/10.1056/NEJMc2031364

5. Avanzato VA, Matson MJ, Seifert SN, Pryce R, Williamson BN, Anzick SL, et al. Case study: prolonged infectious SARS-CoV-2 shedding from an asymptomatic immunocompromised individual with cancer. Cell. 2020;183(7):1901-12. Available from: https://doi.org/10.1016/j.cell.2020.10.049

6. Mileto D, Foschi A, Mancon A, Merli S, Staurenghi F, Pezzati L, et al. A case of extremely prolonged viral shedding: could cell cultures be a diagnostic tool to drive the COVID-19 patients discharge? Int J Infect Dis. 2020 Nov 20 [Epub ahead of print]. Available from: https://doi.org/10.1016/j.ijid.2020.11.161

7. Baang JH, Smith C, Mirabelli C, Valesano AL, Manthei DM, Bachman MA, et al. Prolonged severe acute respiratory syndrome coronavirus 2 replication in an immunocompromised patient. J Infect Dis. 2021;223(1):23-7. Available from: https://doi.org/10.1093/infdis/jiaa666

8. Karatas A, Inkaya AC, Demiroglu H, Aksu S, Haziyev T, Cinar OE, et al. Prolonged viral shedding in a lymphoma patient with COVID-19 infection receiving convalescent plasma. Transfus Apher Sci. 2020:59(5):102871. Available from: https://doi.org/10.1016/j.transci.2020.102871

9. Zhu L, Gong N, Liu B, Lu X, Chen D, Chen S, et al. Coronavirus disease 2019 pneumonia in immunosuppressed renal transplant recipients: a summary of 10 confirmed cases in Wuhan, China. Eur Urol. 2020;77(6):748-54. Available from: https://doi.org/10.1016/j.eururo.2020.03.039

10. Man Z, Jing Z, Huibo S, Bin L, Fanjun Z. Viral shedding prolongation in a kidney transplant patient with COVID-19 pneumonia. Am J Transplant. 2020;20(9):2626-7. Available from: https://doi.org/10.1111/ajt.15996

11. Guetl K, Moazedi-Fuerst F, Rosskopf K, Brodmann M, Krause R, Eller P, et al. SARS-CoV-2 positive virus culture 7 weeks after onset of COVID-19 in an immunocompromised patient suffering from X chromosome-linked agammaglobulinemia. J Infect. 2020 Oct 27 [Epub ahead of print]. Available from: https://doi.org/10.1016/j.jinf.2020.10.025

12. Decker A, Welzel M, Laubner K, Grundmann S, Kochs G, Panning M, et al. Prolonged SARS-CoV-2 shedding and mild course of COVID-19 in a patient after recent heart transplantation. Am J Transplant. 2020;20(11):3239-45. Available from: https://doi.org/10.1111/ajt.16133

13. Park M, Pawliuk C, Nguyen T, Griffitt A, Dix-Cooper L, Fourik N, et al. Determining the period of communicability of SARS-CoV-2: a rapid review of the literature. medRxiv 20163873 [Preprint]. 2020 Jul 30 [cited 2021 Jan 06]. Available from: https://doi.org/10.1101/2020.07.28.20163873

14. Fontana LM, Villamagna AH, Sikka MK, McGregor JC. Understanding viral shedding of severe acute respiratory coronavirus virus 2 (SARS-CoV-2): review of current literature. Infect Control Hosp Epidemiol. 2020 Oct 20 [Epub head of print]. Available from: https://doi.org/10.1017/ice.2020.1273

15. Morone G, Palomba A, Iosa M, Caporaso T, De Angelis D, Venturiero V, et al. Incidence and persistence of viral shedding in COVID-19 post-acute patients with negativized pharyngeal swab: a systematic review. Front Med (Lausanne). 2020;7:562. Available from: https://doi.org/10.3389/fmed.2020.00562

16. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45-67. Available from: https://doi.org/10.1164/rccm.201908-1581ST

17. Ji J, Zhang J, Shao Z, Xie Q, Zhong L, Liu Z. Glucocorticoid therapy does not delay viral clearance in COVID-19 patients. Criti Care. 2020;24(1):565. Available from: https://doi.org/10.1186/s13054-020-03287-6

18. Spagnuolo V, Guffanti M, Galli L, Poli A, Querini PR, Ripa M, et al. Viral clearance after early corticosteroid treatment in patients with moderate or severe COVID-19. Sci Rep. 2020;10(1):21291. Available from: https://doi.org/10.1038/s41598-020-78039-1

19. Hu F, Yin G, Chen Y, Song J, Ye M, Liu J, et al. Corticosteroid, oseltamivir and delayed admission are independent risk factors for prolonged viral shedding in patients with coronavirus disease 2019. Clin Respir J. 2020;14(11):1067-75. Available from: https://doi.org/10.1111/crj.13243

20. Liu W, Liu Y, Xu Z, Jiang T, Kang Y, Zhu G, et al. Clinical characteristics and predictors of the duration of SARS-CoV-2 viral shedding in 140 healthcare workers. J Intern Med. 2020;288(6):725-36. Available from: https://doi.org/10.1111/joim.13160

21. Gao C, Zhu L, Jin CC, Tong YX, Xiao AT, Zhang S. Proinflammatory cytokines are associated with prolonged viral RNA shedding in COVID-19 patients. Clin Immunol. 2020;221:108611. Available from: https://doi.org/10.1016/j.clim.2020.108611

22. Lu Y, Li Y, Deng W, Liu M, He Y, Huang L, et al. Symptomatic infection is associated with prolonged duration of viral shedding in mild coronavirus disease 2019: a retrospective study of 110 children in Wuhan. Pediatr Infect Dis J. 2020;39(7):e95-9. Available from: https://doi.org/10.1097/inf.0000000000002729

23. Hao S, Lian J, Jin X, Lu Y, Jia H, Zheng L, et al. Decreased B cells on admission was associated with prolonged virus shedding from respiratory tract in coronavirus disease 2019: a case control study. J Infect Dis. 2020;222(3):367-71. Available from: https://doi.org/10.1093/infdis/jiaa311

24. Uhm JS, Ahn JY, Hyun J, Sohn Y, Kim JH, Jeong SJ, et al. Patterns of viral clearance in the natural course of asymptomatic COVID-19: comparison with symptomatic non-severe COVID-19. Int J Infect Dis. 2020;99:279-85. Available from: https://doi.org/10.1016/j.ijid.2020.07.070

25. Noh JY, Yoon JG, Seong H, Choi WS, Sohn JW, Cheong HJ, et al. Asymptomatic infection and atypical manifestations of COVID-19: comparison of viral shedding duration. J Infect. 2020;81(5):816-46. Available from: https://doi.org/10.1016/j.jinf.2020.05.035

26. Han J, Shi LX, Xie Y, Zhang YJ, Huang SP, Li JG, et al. Analysis of factors affecting the prognosis of COVID-19 patients and viral shedding duration. Epidemiol Infect. 2020;148:e125. Available from: https://doi.org/10.1017/S0950268820001399

27. Qi L, Yang Y, Jiang D, Tu C, Wan L, Chen X, et al. Factors associated with the duration of viral shedding in adults with COVID-19 outside of Wuhan, China: a retrospective cohort study. Int J Infect Dis. 2020;96:531-7. Available from: https://doi.org/10.1016/j.ijid.2020.05.045

28. Fu Y, Han P, Zhu R, Bai T, Yi J, Zhao X, et al. Risk factors for viral RNA shedding in COVID-19 patients. Eur Respir J. 2020;56(1):2001190. Available from: https://doi.org/10.1183/13993003.01190-2020

29. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV-1 and MERS-CoV viral load dynamics, duration of viral shedding and infectiousness: a living systematic review and meta-analysis. Lancet Microbe. 2021;2(1):e13-22. Available from: https://doi.org/10.1016/s2666-5247(20)30172-5

30. Stehlik P, Alcorn K, Jones A, Schlebusch S, Wattiaux A, Henry D. Repeat testing for SARS-CoV-2: persistence of viral RNA is common, and clearance is slower in older age groups. medRxiv 20183483 [Preprint]. 2020 Nov 30 [cited 2021 Jan 08]. Available from: https://doi.org/10.1101/2020.08.27.20183483

31. Zhou C, Zhang T, Ren H, Sun S, Yu X, Sheng J, et al. Impact of age on duration of viral RNA shedding in patients with COVID-19. Aging (Albany NY). 2020;12(22):22399-404. Available from: https://doi.org/10.18632/aging.104114

32. Chen X, Zhang Y, Zhu B, Zeng J, Hong W, He X, et al. Associations of clinical characteristics and antiviral drugs with viral RNA clearance in patients with COVID-19 in Guangzhou, China: a retrospective cohort study. medRxiv 20058941 [Preprint]. 2020 Apr 14 [cited 2021 Jan 08]. Available from: https://doi.org/10.1101/2020.04.09.20058941

33. Yan D, Liu XY, Zhu YN, Huang L, Dan BT, Zhang GJ, et al. Factors associated with prolonged viral shedding and impact of lopinavir/ritonavir treatment in hospitalised non-critically ill patients with SARS-CoV-2 infection. Eur Respir J. 2020;56(1):2000799. Available from: https://doi.org/10.1183/13993003.00799-2020

34. Xu K, Chen Y, Yuan J, Yi P, Ding C, Wu W, et al. Factors associated with prolonged viral RNA shedding in patients with coronavirus disease 2019 (COVID-19). Clin Infect Dis. 2020;71(15):799-806. Available from: https://doi.org/10.1093/cid/ciaa351

35. Cano E, Corsini Campioli C, O'Horo JC. Nasopharyngeal SARS-CoV-2 viral RNA shedding in patients with diabetes mellitus. Endocrine. 2021;71(1):26-7. Available from: https://doi.org/10.1007/s12020-020-02516-w

36. Mallett S, Allen AJ, Graziadio S, Taylor SA, Sakai NS, Green K, et al. At what times during infection is SARS-CoV-2 detectable and no longer detectable using RT-PCR-based tests? A systematic review of

individual participant data. BMC Med. 2020;18(1):346. Available from: http://doi.org/10.1186/s12916-020-01810-8

37. Weiss A, Jellingsø M, Sommer MOA. Spatial and temporal dynamics of SARS-CoV-2 in COVID-19 patients: a systematic review and meta-analysis. EBioMedicine. 2020;58:102916. Available from: https://doi.org/10.1016/j.ebiom.2020.102916

38. Xu CLH, Raval M, Schnall JA, Kwong JC, Holmes NE. Duration of respiratory and gastrointestinal viral shedding in children with SARS-CoV-2: a systematic review and synthesis of data. Pediatr Infect Dis J. 2020;39(9):e249-56. Available from: https://doi.org/10.1097/inf.0000000000002814

39. Walsh KA, Jordan K, Clyne B, Rohde D, Drummond L, Byrne P, et al. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. J Infect. 2020;81(3):357-71. Available from: https://doi.org/10.1016/j.jinf.2020.06.067

40. Ontario. Ministry of Health. COVID-19 quick reference public health guidance on testing and clearance [Internet]. Version 11.0. Toronto, ON: Queen's Printer for Ontario; 2020 [modified 2020 Nov 20; cited 2021 Jan 08]. Available from: http://health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/2019_testing_clearing_cases_guidance.pdf

Appendix A. Search Results

Databases Searched

Database	Date searched	Remaining
MEDLINE	12/02/2020	716
Embase	12/03/2020	124
Scopus	12/03/2020	130
NIH COVID-19 Portfolio (Preprints)	12/03/2020	569

Records Totals

Records source	Records
Records identified through database searching	1,539
Duplicates removed by bibliographic management software	238
Total records after duplicates removed	1,301
Total reviews	371
Total primary studies	930

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Factors affecting COVID-19 period of communicability – what we know so far. Toronto, ON: Queen's Printer for Ontario; 2021.

Disclaimer

This document was developed by Public Health Ontario (PHO). PHO provides scientific and technical advice to Ontario's government, public health organizations and health care providers. PHO's work is guided by the current best available evidence at the time of publication.

The application and use of this document is the responsibility of the user. PHO assumes no liability resulting from any such application or use.

Public Health Ontario

Public Health Ontario is an agency of the Government of Ontario dedicated to protecting and promoting the health of all Ontarians and reducing inequities in health. Public Health Ontario links public health practitioners, front-line health workers and researchers to the best scientific intelligence and knowledge from around the world.

For more information about PHO, visit publichealthontario.ca.

Ontario