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SYNTHESIS

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COVID-19 Overview of the 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.

Updates to Latest Version

This document replaces the previous version *COVID-19 – What We Know So Far About…The Period of Communicability* (March 30, 2020) and presents results of an updated rapid review. This updated rapid review draws primarily on systematic reviews and meta-analyses, and primary research where applicable, updating evidence on the period of communicability.

See PHO's rapid review *Factors Affecting COVID-19 Period of Communicability – What We Know So Far* for the latest evidence on how host factors (e.g., age, immune system compromise, disease severity) can alter the period of communicability.[1]

Key Findings

- The specific period of communicability estimates varied among the reviewed studies and study types. Epidemiology studies found transmission occurred in the 3–5 days before symptom-onset and epidemiology, virus culture and modelling studies found transmission occurred in the 8–10 days post symptom-onset in index cases.
- While specific period of communicability estimates varied among the reviewed studies, there was concurrence that the risk of communicability peaked shortly before and after the time of symptom-onset in index cases.

Background

The period of communicability is when a patient is shedding virus at a sufficient quantity and viability to infect another person. Currently, the infectious dose for humans is not known. In a ferret model, inoculations of 5×10^4 to 5×10^6 plaque-forming units (PFUs) caused mild clinical disease with viral shedding in the upper respiratory tract (URT) of all animals (12/12), while a dose of 5×10^2 PFUs reduced shedding to 1/6 animals.[2] Infectivity is also dependent upon exposure time and route of transmission. Based on experiments in mice and modelling studies, the infectious dose was about 6.4×10^4 to 9.8×10^5 virus copies and the risk of a single virus copy to infect after one-hour exposure through aerosol route

was 10^{-6} to 10^{-4} and through close contact was 10^{-1}.[3] The infectious dose is an important metric that requires further research, especially when attempting to define the period of communicability using viral isolation and viral loads as measures.

For this rapid review, we infer the period of communicability of COVID-19 from studies investigating:

- Live virus culture
- Epidemiology and contact tracing
- Modelling
- 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, this does not always equate to infectiousness, as infectiousness is dose-dependent. Epidemiological studies with contact tracing are another good indicator of the period of communicability, especially for the presymptomatic transmission period, if accurate tracing of presymptomatic patients and their close contacts was conducted. Modelling studies, using information from the other types of evidence, provide additional insights into the period of communicability. Specifically, modelling studies are important for estimating the period of presymptomatic transmission and the period when transmission risk is highest. Viral RNA shedding provides additional 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.

This review synthesizes the current literature investigating the period of communicability of COVID-19, while considering the sub-intervals of the period of communicability: 1) presymptomatic transmission period, 2) period of highest risk of transmission, and 3) timing of when infectiousness ends.

Methods

In considering feasibility, scope, and a need for responsiveness, we chose a rapid review as an appropriate approach to determining the period of communicability of COVID-19. A rapid review is a knowledge synthesis where certain steps of the systematic review process are truncated in order to be timely (e.g., quality assessment).[4]

On December 2, 2020, PHO Library Services conducted a literature search in MEDLINE, National Institutes of Health (NIH) COVID-19 Portfolio (pre-prints), Embase and Scopus 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 the period of communicability of COVID-19 were included. We restricted the search to articles published after January 1, 2020. This rapid review concentrated on evidence from systematic reviews and meta-analyses, supplemented by primary literature where appropriate and necessary. We reviewed citations from included articles to identify additional research.

Prior to posting, PHO subject-matter experts review all "What We Know So Far" documents.

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

The potential impact of COVID-19 variants of concern on the period of communicability is out-of-scope for this rapid review.

Findings

We screened 371 reviews and 930 primary research articles for this rapid review (Appendix A). After screening the literature for relevant articles, we included 14 systematic reviews (with or without meta-analyses), 2 rapid reviews, and 29 primary research articles. 24.4% (11/45) of studies were non-peer reviewed pre-print articles.

We organized evidence by type (systematic review, then primary research if applicable), then by sample size (number of studies or patients). Evidence pertaining to the URT was selected as a primary focus of this review, as the URT is the most likely source of infectious Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). If authors did not report the total number of patients in a systematic review, only the total number of studies was included.

Live SARS-CoV-2 Shedding (Viral Culture)

Live virus was detected from 13 days before symptom-onset (BSO) to 32 days post symptom-onset (PSO). Authors did not routinely report average periods for live virus detection or isolation, rather they reported ranges or time-specific probabilities of detection. Nonetheless, the probability of detecting live virus was highest in the 8 to 10 days PSO, with few studies examining communicability BSO (Figure 1).

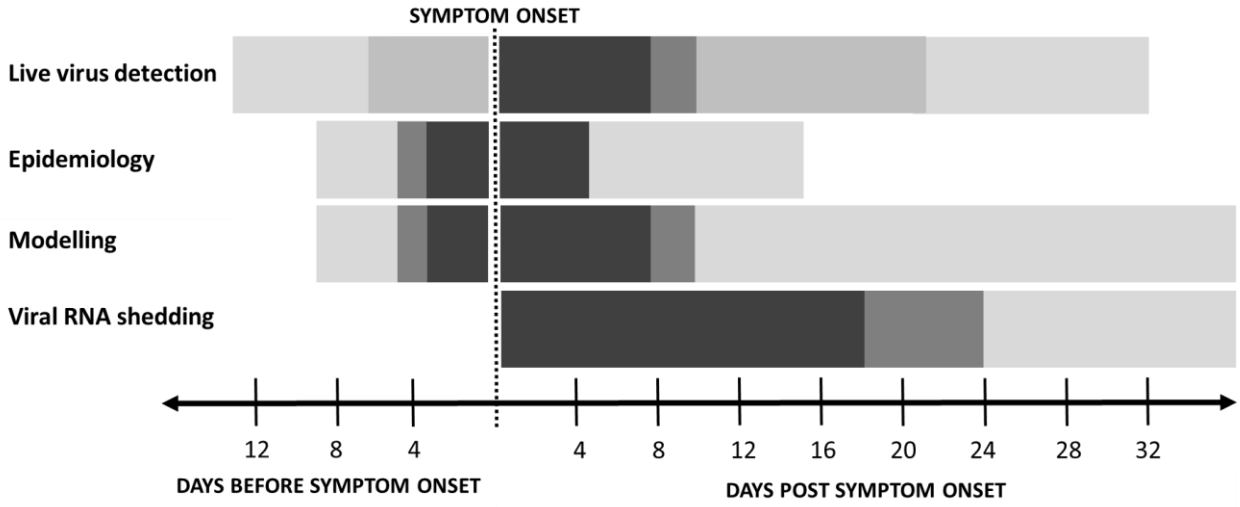
SYSTEMATIC AND RAPID REVIEWS

We examined five systematic reviews that reported on the detection of live SARS-CoV-2 from respiratory samples collected before (n=2 studies) and after (n=5 studies) symptom-onset (2 studies examined both periods). The detection of live virus was reported from 6 days BSO to 32 days PSO, with most studies reporting transmission within 10 days PSO.

- In a rapid review of 25 studies, the Public Health Agency of Canada (PHAC) reported that live SARS-CoV-2 was detected from respiratory samples collected from patients 1–6 days BSO and up to 8–10 days PSO.[5]
- In a systematic review, Walsh et al. adapted data from Singanayagam et al. to estimate viral culture positivity from respiratory samples (n=121 samples).[6,7] At 7 days PSO, the estimated culture positivity was 40.1% (95% confidence interval [CI]: 22.8–60.4), positivity decreased to 6.0% (95% CI: 0.9–31.2) at 10 days PSO and 0.03% (95% CI: 0.0–9.4) at 14 days PSO. Among the 13 studies included in the review, five reported the last day of positive culture occurred within 10 days PSO, another five studies reported that 3% of patients had positive cultures later than 10 days PSO.
- In a systematic review of 13 studies and 1,314 patients, Park et al. (pre-print) reported that the median duration of live virus shedding in respiratory samples was 9 days PSO (interquartile range [IQR]: 10), the mean ± standard deviation (SD) duration was 11.8 ± 8.47 days PSO (range: 2–32 days).[8]

- In a systematic review of 8 studies and 359 patients, Cevik et al. reported that no live virus was detectable in URT samples collected later than 9 days PSO.[9] The authors also noted that viral loads in URT samples peaked during the first week of illness.
- In a systematic review and meta-analysis of 4 studies and 304 patients, Fontana et al. reported that successful virus isolation from respiratory samples ranged from 6 days BSO to 20 days PSO.[10]

Figure 1. Summary of the period of communicability of COVID-19, for each type of study. The relative proportion of studies reporting a finding increases as the shading darkens (higher relative concordance among studies = black; lower relative concordance among studies = light grey).



PRIMARY RESEARCH

In 11 primary research articles, the detection of live SARS-CoV-2 from respiratory samples ranged from 13 days BSO to 32 days PSO. The majority of live virus detections were from respiratory samples collected within 10 days PSO (Figure 1).

- Singanayagam et al. examined 246 URT samples (RT-PCR positive) from 176 patients (mild to moderate disease in the United Kingdom) and found the median duration of live virus shedding was 4 days PSO (IQR: 1–8; range: -13 to 12).[7] The culture positivity rate was significantly higher during week 1 than week 2 (74% vs 20%; p=0.002).
- In a study of 195 patients in Australia, Basile et al. reported that the mean period from symptom-onset to positive viral culture was 4.5 days (range: 0–18).[11] Cultures were more likely to be positive from samples collected within the first week PSO, compared to the second week (80% vs. 45%; p=0·002), and between the second and third week (45% vs. 4%; p<0·001).
- In a study of 155 patients (174 nasopharyngeal [NP] swabs and 9 sputum samples) in Marseille, France, La Scola et al. did not detect live virus in respiratory samples collected after 8 days PSO, although viral RNA shedding occurred up to 20 days PSO.[12]
- In a study of 129 patients with severe disease in The Netherlands, van Kampen et al. reported that less than 5% of respiratory samples had viable virus when collected at 15.2 days PSO (95%

CI: 13.4–17.2) or more.[13] The median time of infectious virus shedding was 8 days PSO (IQR: 5–11; range: 0–20).

- In South Korea, researchers studied 285 patients that were repeat-positive by RT-PCR after being discharged from isolation after 14 days.[14] The average time from symptom-onset to re-positive test was 44.9 days (range: 8–82). No live virus was detected on respiratory samples from 108 patients; however, it is unclear when samples were collected for these patients.
- In a study of 105 patients in Spain, Folgueira et al. (pre-print) reported that the proportion of respiratory samples with positive cultures decreased as time from symptom-onset increased.[15] In hospitalized patients with severe disease (n=56 samples), 56.0% (14/25) of samples collected within 7 days PSO produced a positive viral culture, followed by 60.0% (9/15) of samples collected 8–14 days PSO, 60.0% (6/10) from 15–21 days PSO, and 33.3% (2/6) past 21 days (latest was 32 days PSO).
- Bullard et al., in a Manitoba study of 90 samples, reported that the probability of successful viral culture in NP swabs peaked at 80% at 3 days PSO (no growth occurred >8 days PSO).[16]
- In a Singapore study of 74 patients (152 samples), Young et al. reported that all NP swabs failed to grow in culture after 14 days PSO. In culture-positive NP samples, 57.1% (12/21) of positive samples were collected at 7 days PSO or less; 42.9% (9/21) were collected more than 7 days PSO (latest was 14 days PSO; 20/21 of positive samples were collected ≤10 days PSO).[17] Virus isolation decreased as PSO time increased (OR: 0.81; 95% CI: 0.70–0.92; p<0.0001).
- Perera et al. (pre-print), in a study of 35 patients (32 with mild disease; 68 samples) in Hong Kong, found that live SARS-CoV-2 were rarely detectable beyond 8 days PSO.[18] From 1–2 days PSO, 53% (8/15) of samples were successfully cultured, followed by 35% (8/23) at 3–8 days PSO, and 0% (0/30) at 9–30 days PSO.
- Sohn et al., in a study of 48 patients in South Korea with no symptoms or with mild disease in the late phase of disease, reported that no samples produced CPE in cell cultures when collected 20 days PSO or more.[19]
- In a skilled nursing facility in Washington, United States (US), Arons et al. reported that in 17 of 24 presymptomatic patients, live virus was detected from 6 days BSO to 9 days PSO.[20]

Epidemiological Studies

The period of communicability from epidemiological studies ranged approximately from 9 days BSO to 15 days PSO, with most transmission occurring approximately 3–5 days BSO to 5 days PSO (Figure 1).

It is important to note that definitions for asymptomatic, presymptomatic and symptomatic patients varied among studies. In addition, studies varied in their definitions of index cases (e.g., symptomatic or asymptomatic, or both included) and not all studies tested asymptomatic contacts of index patients.

SYSTEMATIC REVIEWS

No systematic reviews or meta-analyses examined the period of communicability of COVID-19 using epidemiological studies. However, five systematic reviews and meta-analyses reported that secondary attack rates were lower among contacts of presymptomatic patients, compared to symptomatic patients. These studies demonstrated that the risk of transmission from presymptomatic and asymptomatic index cases was relatively lower, compared to transmission from symptomatic cases, and that most transmission occurred after symptom-onset in index cases.

- In a systematic review of 19 studies, Madewell et al. reported that the household secondary attack rate in contacts of symptomatic cases (20%; 95% CI: 14.0–25.7) was significantly higher than that for asymptomatic cases (0.7%; 95% CI: 0.0–3.8) ($p<0.001$).[21] The authors noted that primary studies varied with respect to how they defined index cases and household contacts. In addition, the authors could not rule out transmission from outside households (which could lead to overestimation of secondary attack rates).
- In a systematic review and meta-analysis of five studies, Byambasuren et al. reported that the secondary attack rate was 42% lower among contacts of asymptomatic cases compared to symptomatic cases (pooled relative risk [RR]: 0.58; 95% CI: 0.34–0.99; p=0.047; fixed-effects model).[22] The authors defined exposure as contact with a confirmed case or potential contact with another pre-symptomatic person.
- In a living systematic review and meta-analysis of five empirical and modelling studies, Buitrago-Garcia et al. reported that the secondary attack rate was potentially lower in contacts of asymptomatic cases than symptomatic cases (pooled RR: 0.35; 95% CI: 0.10–1.27).[23] Similarly, the secondary attack rate was possibly lower for contacts of presymptomatic cases versus symptomatic cases (pooled RR: 0.63; 95% CI: 0.18–2.26).
- In a systematic review of three studies, Koh et al. reported that household secondary attack rates in contacts of symptomatic index cases (20.0%; 95% CI: 11.4–28.6) was higher than the secondary attack rates in contacts of asymptomatic index cases (4.7%; 95% CI: 1.1–8.3) (RR: 3.2; 95% CI: 1.5–7.1).[24] The authors noted that clinical definitions and follow-up periods varied among studies.
- Qiu et al. (pre-print) in a systematic review reported that the secondary attack rate in contacts of asymptomatic patients ranged from 0.0–2.8% (n=9 studies), which was lower than the secondary attack rates from presymptomatic patients that ranged from 0.7–31.8% (n=10 studies).[25]

PRIMARY STUDIES

We reviewed 11 epidemiological and contact tracing studies (primary studies) which were in general agreement with findings from viral culture studies. The period of communicability ranged from 9 days BSO to 5 days PSO, with most transmission occurring 3–5 days BSO to 5 days PSO.

- In a contact tracing study of 100 index cases and 2,761 close contacts in Taiwan, Cheng et al. reported that the secondary attack rate was 1.0% (95% CI: 0.6–1.6; n=1,818) when contacts were exposed to index cases within 5 days PSO.[26] When contacts were exposed to index cases after 5 days PSO, the secondary attack rate was 0.0% (95% CI: 0.0–0.4; n=852).
- In a study of 72 infector-infectee pairs in South Korea, Chun et al. estimated that the mean transmission-onset was 1.3 days PSO (95% CI: 0.38–2.55) and the median transmission-onset was 0.68 days PSO (95% CI: -0.09 to 1.73).[27] Transmission-onset peaked at 0.72 days BSO.
- In a study of 47 clusters (53 index patients and 100 secondary cases) in Beijing, China, Zhang et al. reported that 15 secondary cases were exposed to index patients up to 5 days BSO (n=2 clusters).[28]
- In an epidemiological study of 93 cases in Singapore and 135 cases in Tianjin, China, Tindale et al. estimated that infections occurred an average of 2.0 days BSO in Singapore and 3.7 days BSO in Tianjin.[29]
- In a contact tracing study of 15 cases in Wuxi, China, Gao et al. reported that transmission occurred from 2–9 days BSO.[30]

- Gong et al. studied three clusters (14 cases) in Shanghai, China, where 5 secondary cases were infected by index cases from 1–7 days BSO to 1 day PSO.[31]
- In a study of 243 cases in Singapore, Wei et al. determined that in 4 of 7 clusters, transmission occurred 1–3 days BSO, while timing of infection in the remaining 3 clusters could not be determined.[32]
- Xia et al. (pre-print) reviewed 74 secondary cases from Hubei Province, China. The majority of the secondary cases (73.0%) were infected BSO of first-generation cases, while 18.9% and 8.1% were infected on the same day of symptom-onset or PSO (latest was 15 days PSO), respectively. 66.2% of the secondary cases were infected within 3 days BSO, with 6.8% prior to 3 days BSO (earliest was 5 days BSO).[33]
- In a cluster (9 cases) investigation in Shanghai, China, Kong et al. reported that transmission occurred in secondary cases 3–4 days BSO in index cases; seven cases occurred due to exposures on the day of onset to 2 days PSO.[34] The secondary cases had additional contacts that could have contributed to transmission, but the authors attest risk was low since they were asymptomatic during a 14-day quarantine period (no positive RT-PCR tests).
- In a family cluster in Zhoushan, China, Li et al. reported that 4 of 5 familial contacts were possibly infected after exposure to the presymptomatic index case 4–7 days BSO.[35]
- In a study of a cluster of 8 cases in Hefei, China, Huang et al. reported that 6 of 7 secondary cases were likely exposed 1 day BSO in the index case, one case was exposed either 3 days BSO or 1 day PSO.[36]

Modelling Studies

Modelling studies were in agreement with other lines of evidence for the period of communicability of COVID-19. Specifically, modelling studies identified that the risk of transmission is highest just before and after the time of symptom-onset in index cases, with most transmission occurring approximately 3–5 days BSO to 8–10 days PSO (Figure 1).

SYSTEMATIC AND RAPID REVIEWS

One systematic review and meta-analysis and a rapid review modelled the period of communicability.

- Benefield et al. (pre-print), in a systematic review and meta-analysis of 32 studies and 715 patients, reported that the individual-level viral dynamics of SARS-CoV-2 show a clear pattern of a peak in viral load at or before the appearance of symptoms and a steady log-fold decline over the next 21 days.[37] The pooled median duration of viral RNA shedding (49 studies and 917 patients) in respiratory samples was 4.8 days PSO (95% CI: 4.4–5.1), with a 5th percentile of 0.5 days (95% CI: 0.46–0.58) and a 95th percentile of 43.7 days (95% CI: 38.6–48.9). The authors attest that RNA positivity represents presence of live and infectious virus, rejecting existing evidence that RNA-positivity does not always represent live virus; therefore, caution must be used when interpreting the authors' conclusions.
- In a rapid scoping review of 13 studies and through modelling, Byrne et al. reported the central tendency of the preclinical infectious period to range from about 0.5–4.0 days BSO with one study as an outlier at 8.2 days.[38]

PRIMARY STUDIES

Seven modelling studies examined the period of communicability. In most modelling studies, the risk of communicability peaked at symptom-onset in index cases.

- He et al. reported that infectiousness peaked at symptom-onset or day zero (95% CI: -0.9 to 0.9), decreasing rapidly by 7 days PSO.[39] The authors further estimated that the proportion of presymptomatic transmission was 44% (95% CI: 30–57). He et al. estimated that the proportion of transmission earlier than 7 days BSO was less than 0.1%, 1% at 5 days BSO or earlier, and 9% at 3 days BSO or earlier. The authors suggested that contact tracing should enquire about close contacts up to 2–3 days BSO. Slifka and Gao have raised concerns with the methodology and interpretation of findings in He et al.[40] Slifka and Gao contend that modelling studies tend to over-emphasize transmission at or before symptom-onset, due in part to smaller sample sizes during this period.
- After correcting coding in the He et al. model, Ashcroft et al. estimated that the proportion of presymptomatic infections traced at 1 day BSO in the index patient was 33% (95% CI: 19–51); at 2 days BSO was 61% (95% CI: 40–83); at 3 days BSO was 80% (95% CI: 57–96); at 4 days BSO was 91% (95% CI: 71–99); and at 5 days BSO was 97% (95% CI: 82–100).[41] The re-analysis and correction found a similar presymptomatic proportion of 45.6% (95% CI: 23.8–75.8) as He et al. The fraction of presymptomatic transmission was 3% at 5 days BSO or earlier and 20% at 3 days BSO or earlier. The authors suggest that contact tracing should enquire about close contacts beyond 3 days BSO, but do not define a specific end range.
- In a study of 1,178 patients and 15,648 contacts in China, Hu et al. (pre-print) modelled the period of communicability.[42] The greatest probability of transmission from index cases occurred 1.8 days BSO, with 95% of transmission occurring 8.8 days BSO to 9.5 days PSO.
- Prakash (pre-print), using published data on 1,251 patients, reported that infectiousness peaked prior to symptom-onset based on RT-PCR and live virus culture; however, the central tendency for this presymptomatic period was not reported but was approximately less than 2 days BSO (see Figure 3 in paper).[43] The proportion of presymptomatic transmission was 68.4% (95% CI: 67.0–69.7)
- Casey et al. (pre-print), in a modelling study that used published data, reported that the mean transmission time was from 2.9 days BSO (95% CI: 3.2–2.6) to 1.2 days PSO (95% CI: 0.9–1.6).[44] Using unweighted pooled estimates, the transmission peaked at 0.60 days BSO (95% CI: -3.01 to 1.81). The proportion of presymptomatic transmission from pooled estimates was 56.4% (34.9–78.0).
- Zhao developed a likelihood framework to estimate the presymptomatic transmission period from the serial interval observations from individual transmission events.[45] The estimated mean presymptomatic transmission period was 2.2 days BSO (95% CI: 1.3–4.7).
- Using mathematical modelling, with data on incubation periods and serial intervals, Zhang (pre-print) estimated that average presymptomatic transmission occurred 3.8 days BSO (SD: 6.1).[46]

SARS-CoV-2 RNA Shedding (RT-PCR Testing)

For this review, we avoided using cycle threshold (CT) values from RT-PCR testing to infer infectiousness, since individual studies use variable reaction conditions and target genes when correlating CT values in RT-PCR tests to respective live virus detection.[47,48] Therefore, comparisons among studies is not feasible.

Overall, studies investigating SARS-CoV-2 RNA detection were in agreement with studies detecting live virus or epidemiological studies. The detection of viral RNA decreased over time since symptom-onset, with most studies showing RNA detection up to 24 days PSO; however, there is no way to convert RNA shedding to infectiousness (Figure 1).

SYSTEMATIC REVIEWS

In seven systematic reviews and meta-analyses, the mean period of viral RNA shedding in respiratory samples was 17.0–28.7 days PSO (11.1–11.4 days in children). In two systematic reviews and meta-analyses, the median duration was 14.0–24.0 days PSO.

- In a systematic review of 133 studies, Park et al. reported that the median duration of viral RNA shedding in respiratory samples was 24.0 days PSO (IQR: 19), the mean ± SD duration was 28.7 days ± 15.8 days PSO (range: 5–95).[8]
- Walsh et al., in a review of 50 studies, reported that the viral load in URT samples was highest around the time of symptom-onset to a few days after, remained high for approximately 7 days PSO, and became undetectable within 14 days PSO.[49] Using 88 studies, the median duration of viral RNA shedding in URT samples was 14.5 days PSO (range: 1–53.5).
- 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) using a random-effects model.[9] URT viral RNA shedding was highest 0–5 days PSO, then decreases.
- In a systematic review and meta-analysis of 37 studies, Morone et al. reported that the median duration of viral RNA shedding from respiratory samples was 14 days PSO (IQR: 12).[50]
- In a systematic review and meta-analysis of 28 studies, Fontana et al. reported that the median duration of viral RNA shedding was 18.4 days PSO (95% CI: 15.5–21.3; range: 1–83).[10]
- Two systematic reviews focused on children (≤18 years).
    - In a systematic review of 17 studies of children, Xu et al. reported that the mean duration of viral RNA shedding in respiratory samples was 11.1 ± 5.8 days PSO.[51]
    - In a systematic review of 13 studies of children, Li et al. reported a pooled mean duration of viral RNA shedding was 11.4 days PSO (95% CI: 10.1–12.8).[52]

Limitations

We should acknowledge that a relatively large proportion (24%) of the research articles in this rapid review were non-peer-reviewed, pre-print articles. In addition, most of the systematic reviews we included used the same pre-print 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 some duplication of findings. Not all studies performed serial testing for the explicit purpose of determining the period of communicability; thus, some studies could underestimate the average duration of communicability.

In the case of epidemiological studies focusing on contact tracing, the evidence is still emerging and based mostly on small clusters. In contact tracing studies, it was not always possible to monitor all

contacts identified from the presymptomatic period of the index cases, likely leading to an underestimation of secondary attack rates attributed to exposure during this presymptomatic period. We must note that definitions for asymptomatic, presymptomatic and symptomatic patients varied among studies. In addition, studies varied in their definitions of index cases (e.g., symptomatic or asymptomatic, or both included) and not all studies tested asymptomatic contacts of index patients. The definitions of asymptomatic patients varied in studies, which could have led to overestimates and underestimates of secondary attack rates. In addition, there is likely time-dependent recall bias in determining close contacts, especially when looking further backward from date of symptom-onset. Furthermore, the definition of a contact varies among studies, leading to variability in estimates. In studies of asymptomatic index patients, it is unclear in some instances when potential exposure occurred; therefore, the date of first positive RT-PCR was day zero, potentially leading to shorter estimates of the period of viral RNA shedding. Clinical or surveillance definitions of asymptomatic, presymptomatic, and symptomatic patients are variable across studies, potentially affecting estimates of the period of communicability. Since sequencing of virus from index cases and secondary cases were not compared, it is possible that different strains were involved with infectee-infector pairs, thus not representing true transmission pairs.

There was a high degree of heterogeneity among studies used in meta-analyses, mostly due to varying methodologies and small sample sizes. Different studies also observed cell cultures for various periods of time (4 days to over 7 days) and used different cell lines, both factors that could affect the probability of detecting of live virus. The reaction conditions and specific gene targets used in RT-PCR assays varied among studies, making it difficult to compare studies and when performing meta-analyses.

Even when live virus is detected from patients, it is still not known if these patients are truly infective.[53] Factors to consider when determining infectiousness include viral loads, infectious dose, transmission route, and length of exposure. Given these limitations and the uncertainty associated with the period of presymptomatic infectiousness and prolonged shedding of live virus, a definitive period of communicability is difficult to state.

Period of Presymptomatic Transmission: Implications for Practice

Currently, Ontario recommends that the contact tracing period begins 48 hours prior to symptom-onset in the corresponding case or when the case had a positive sample collected (if asymptomatic at sample collection time).[54] This is aligned with other public health agencies in Canada and internationally.[55,56]

Under any scenario, extending the period >48 hours to trace close contacts may potentially identify and isolate additional exposed contacts, thereby, preventing further transmission. However, to our knowledge, there are no empirical studies testing the effectiveness of extending or shortening the presymptomatic period for contact tracing on reducing spread from exposed contacts. Given the relatively few primary studies of infector-infectee pairs assessing pre-symptomatic spread >2 days before symptom-onset, and their limitations to confidently identify the source case (vs the index case), there is insufficient evidence to extend the current pre-symptomatic period of communicability.

- In settings that are considered high-risk for transmission or where there are vulnerable populations (e.g., long-term care, congregate living, hospitals), an extension of the presymptomatic period of communicability to >48 hours could be considered to increase identification of exposed contacts. However, additional public health resources would be required to identify and trace potential contacts.

- In households, workplaces, and school environments where there has been ongoing exposure to a case, extending the presymptomatic period of communicability would likely not increase the effectiveness of contact tracing.

Conclusions

There are differences in the findings across included studies due to different designs and sample size; however, there were primary epidemiological studies identified that indicated individuals can be infectious up to 3–5 days prior to symptom-onset and epidemiological, live virus and modelling studies that indicated the period of communicability is approximately 8–10 days after symptom-onset, with infectiousness highest just before or after the time of symptom-onset.

PHO will continue to monitor the scientific evidence on the period of communicability of COVID-19, updating this document as necessary and making recommendations should a change in practice to contact tracing will be needed.

References

1. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Factors affecting COVID-19 period of communicability – what we know so far [Internet]. Toronto, ON: Queen's Printer for Ontario; 2021 [cited 2021 Feb 08]. Available from: https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/2021/02/wwksf-factors-affecting-period-communicability-en.pdf?la=en

2. Ryan KA, Bewley KR, Fotheringham SA, Brown P, Hall Y, Marriott AC, et al. Dose-dependent response to infection with SARS-CoV-2 in the ferret model: evidence of protection to re-challenge. bioRxiv 123810 [Preprint]. 2020 May 29 [cited 2021 Jan 06]. Available from: https://doi.org/10.1101/2020.05.29.123810

3. Zhang X, Wang J. Dose-response relation deduced for coronaviruses from COVID-19, SARS and MERS meta-analysis results and its application for infection risk assessment of aerosol transmission. Clin Infect Dis. 2020 Oct 29 [Epub ahead of print]. Available from: https://doi.org/10.1093/cid/ciaa1675

4. 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

5. Emerging Sciences Group of the Public Health Agency of Canada. How long are people with COVID-19 infectious? CCDR. 2020;46(11/12):435-36. Available from: https://www.canada.ca/content/dam/phac-aspc/documents/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2020-46/issue-11-12-nov-5-2020/ccdrv46i1112a12a-eng.pdf

6. Walsh KA, Spillane S, Comber L, Cardwell K, Harrington P, Connell J, et al. The duration of infectiousness of individuals infected with SARS-CoV-2. J Infect. 2020;86(6):847-56. Available from: https://doi.org/10.1016/j.jinf.2020.10.009

7. Singanayagam A, Patel M, Charlett A, Lopez Bernal J, Saliba V, Ellis J, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill. 2020;25(32):2001483. Available from: https://doi.org/10.2807/1560-7917.es.2020.25.32.2001483

8. 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

9. 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/10.1101/2020.07.25.20162107

10. 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

11. Basile K, McPhie K, Carter I, Alderson S, Rahman H, Donovan L, et al. Cell-based culture of SARS-CoV-2 informs infectivity and safe de-isolation assessments during COVID-19. Clin Infect Dis. 2020 Oct 24 [Epub ahead of print]. Available from: https://doi.org/10.1093/cid/ciaa1579

12. La Scola B, Le Bideau M, Andreani J, Hoang VT, Grimaldier C, Colson P, et al. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. Eur J Clin Microbiol Infect Dis. 2020;39(6):1059-61. Available from: https://doi.org/10.1007/s10096-020-03913-9

13. van Kampen JJA, van de Vijver DAMC, Fraaij PLA, Haagmans BL, Lamers MM, Okba N, et al. Shedding of infectious virus in hospitalized patients with coronavirus disease-2019 (COVID-19): duration and key determinants. Nat Commun. 2021;12;267. Available from. https://www.nature.com/articles/s41467-020-20568-4

14. Korea Centers for Disease Control and Prevention. Findings from investigation and analysis of re-positive cases. Cheongju: Korea Centers for Disease Control and Prevention; 2020 [modified 2020 Jun 03; cited 2021 Jan 06]. Available from: https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=0030&act=view&list_no=367267&nPage=1external%20icon

15. Folgueira MD, Luczkowiak J, Lasala F, Perez-Rivilla A, Delgado R. Persistent SARS-CoV-2 replication in severe COVID-19. medRxiv 20127837 [Preprint]. 2020 Jun 12 [cited 2021 Jan 06]. Available from: https://doi.org/10.1101/2020.06.10.20127837

16. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. Predicting infectious severe acute respiratory syndrome coronavirus 2 from diagnostic samples. Clin Infect Dis. 2020;71(10):2663-6. Available from: https://doi.org/10.1093/cid/ciaa638

17. Young BE, Ong SWX, Ng LFP, Anderson DE, Chia WN, Chia PY, et al. Viral dynamics and immune correlates of COVID-19 disease severity. Clin Infect Dis. 2020 Aug 28 [Epub ahead of print]. Available from: https://doi.org/10.1093/cid/ciaa1280

18. Perera RA, Tso E, Tsang OT, Tsang DN, Fung K, Leung YW, et al. SARS-CoV-2 virus culture from the upper respiratory tract: correlation with viral load, subgenomic viral RNA and duration of illness. medRxiv 20148783 [Preprint]. 2020 Jul 09 [cited 2021 Jan 06]. Available from: https://doi.org/10.1101/2020.07.08.20148783

19. Sohn Y, Jeong SJ, Chung WS, Hyun JH, Baek YJ, Cho Y, et al. Assessing viral shedding and infectivity of asymptomatic or mildly symptomatic patients with COVID-19 in a later phase. J Clin Med. 2020;9(9):2924. Available from: https://doi.org/10.3390/jcm9092924

20. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. N Engl J Med. 2020;382(22):2081-90. Available from: https://doi.org/10.1056/NEJMoa2008457

21. Madewell ZJ, Yang Y, Longini IM, Halloran ME, Dean NE. Household transmission of SARS-CoV-2: a systematic review and meta-analysis of secondary attack rate. JAMA Netw Open. 2020;3(12):e2031756. Available from: https://doi.org/10.1001/jamanetworkopen.2020.31756

22. Byambasuren O, Cardona M, Bell K, Clark J, McLaws ML, Glasziou P. Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis. JAMMI. 2020;5(4):223-4. Available from: https://doi.org/10.3138/jammi-2020-0030

23. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. PLoS Med. 2020;17(9):e1003346. Available from: https://dx.doi.org/10.1371/journal.pmed.1003346

24. Koh WC, Naing L, Chaw L, Rosledzana MA, Alikhan MF, Jamaludin SA, et al. What do we know about SARS-CoV-2 transmission? A systematic review and meta-analysis of the secondary attack rate and associated risk factors. PLoS ONE. 2020;15:e0240205. Available from: https://doi.org/10.1371/journal.pone.0240205

25. Qiu X, Nergiz AI, Maraolo AE, Bogoch II, Low N, Cevik M. Defining the role of asymptomatic and pre-symptomatic SARS-CoV-2 transmission: a living systematic review. medRxiv 20135194 [Preprint]. 2020 Oct 06 [cited 2021 Jan 06]. Available from: https://doi.org/10.1101/2020.09.01.20135194

26. Cheng HY, Jian SW, Liu DP, Ng TC, Huang WT; Taiwan COVID-19 Outbreak Investigation Team, et al. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. JAMA Intern Med. 2020;180(9):1156-63. Available from: https://doi.org/10.1001/jamainternmed.2020.2020

27. Chun JY, Baek G, Kim Y. Transmission onset distribution of COVID-19. Int J Infect Dis. 2020;99:403-7. Available from: https://doi.org/10.1016/j.ijid.2020.07.075

28. Zhang Y, Muscatello D, Tian Y, Chen Y, Li S, Duan W, et al. Role of presymptomatic transmission of COVID-19: evidence from Beijing, China. J Epidemiol Community Health. 2021;75(1):84-7. Available from: https://doi.org/10.1136/jech-2020-214635

29. Tindale LC, Stockdale JE, Coombe M, Garlock GS, Lau WYV, Saraswat M, et al. Evidence for transmission of COVID-19 prior to symptom onset. ELife. 2020;9:e57149. Available from: https://doi.org/10.7554/eLife.57149

30. Gao Y, Shi C, Chen Y, Shi P, Liu J, Xiao Y, et al. A cluster of the corona virus disease 2019 caused by incubation period transmission in Wuxi, China. J Infect. 2020;80(6):666-70. Available from: https://doi.org/10.1016/j.jinf.2020.03.042

31. Gong X, Xiao W, Cui Y, Wang Y, Kong D, Mao S, et al. Three infection clusters related with potential pre-symptomatic transmission of coronavirus disease (COVID-19), Shanghai, China, January to February 2020. Euro Surveill. 2020;25(33):2000228. Available from: https://doi.org/10.2807/1560-7917.ES.2020.25.33.2000228

32. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic transmission of SARS-CoV-2 – Singapore, January 23-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):411-5. Available from: https://doi.org/10.15585/mmwr.mm6914e1

33. Xia W, Liao J, Li C, Li Y, Qian X, Sun X, et al. Transmission of corona virus disease 2019 during the incubation period may lead to a quarantine loophole. medRxiv 20031955 [Preprint]. 2020 Mar 08 [cited 2021 Jan 06]. Available from: https://doi.org/10.1101/2020.03.06.20031955

34. Kong D, Zheng Y, Wu H, Pan H. Pre-symptomatic transmission of novel coronavirus in community settings. Influenza Other Resp Viruses. 2020;14(6):610-4. Available from: https://doi.org/10.1111/irv.12773

35. Li P, Fu JB, Li KF, Liu JN, Wang HL, Liu LJ, et al. Transmission of COVID-19 in the terminal stages of the incubation period: a familial cluster. Int J Infect Dis. 2020;96:452-3. Available from: https://doi.org/10.1016/j.ijid.2020.03.027

36. Huang L, Zhang X, Zhang X, Wei Z, Zhang L, Xu J, et al. Rapid asymptomatic transmission of COVID-19 during the incubation period demonstrating strong infectivity in a cluster of youngsters aged 16-23 years outside Wuhan and characteristics of young patients with COVID-19: a prospective contact-tracing study. J Infect. 2020;80(6):e1-13. Available from: https://doi.org/10.1016/j.jinf.2020.03.006

37. Benefield AE, Skrip LA, Clement A, Althouse RA, Chang S, Althouse BM. SARS-CoV-2 viral load peaks prior to symptom onset: a systematic review and individual-pooled analysis of coronavirus viral load from 66 studies. medRxiv 20202028 [Preprint]. 2020 Sep 23 [cited 2021 Jan 06]. Available from: https://doi.org/10.1101/2020.09.28.20202028

38. Byrne AW, McEvoy D, Collins AB, Hunt K, Casey M, Barber A, et al. Inferred duration of infectious period of SARS-CoV-2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic COVID-19 cases. BMJ Open. 2020;10(8):e039856. Available from: https://doi.org/10.1136/bmjopen-2020-039856

39. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020;26(5):672-5. Available from: https://doi.org/10.1038/s41591-020-0869-5

40. Slifka MK, Gao L. Is presymptomatic spread a major contributor to COVID-19 transmission? Nat Med. 2020;26(10):1531-3. Available from: https://www.nature.com/articles/s41591-020-1046-6

41. Ashcroft P, Huisman JS, Lehtinen S, Bouman JA, Althaus CL, Regoes RR, et al. COVID-19 infectivity profile correction. Swiss Med Wkly. 2020;150:w20336. Available from: https://doi.org/10.4414/smw.2020.20336

42. Hu S, Wang W, Wang Y, Litvinova M, Luo K, Ren L, et al. Infectivity, susceptibility, and risk factors associated with SARS-CoV-2 transmission under intensive contact tracing in Hunan, China. medRxiv 20094789 [Preprint]. 2020 May 12 [cited 2021 Jan 06]. Available from: https://doi.org/10.1101/2020.07.23.20160317

43. Prakash MK. Quantitative COVID-19 infectiousness estimate correlating with viral shedding and culturability suggests 68% pre-symptomatic transmissions. medRxiv 20094789 [Preprint]. 2020 Jul 24 [cited 2021 Jan 06]. Available from: https://doi.org/10.1101/2020.05.07.20094789

44. Casey M, Griffin J, McAloon CG, Byrne AW, Madden JM, McEvoy D, et al. Pre-symptomatic transmission of SARS-CoV-2 infection: a secondary analysis using published data. medRxiv 20094870 [Preprint]. 2020 Jun 11 [cited 2021 Jan 06]. Available from: https://doi.org/10.1101/2020.05.08.20094870

45. Zhao S. Estimating the time interval between transmission generations when negative values occur in the serial interval data: using COVID-19 as an example. Math Biosci Eng. 2020;17(4):3512-9. Available from: https://doi.org/10.3934/mbe.2020198

46. Zhang W. Estimating the presymptomatic transmission of COVID19 using incubation period and serial interval data. medRxiv 20051318 [Preprint]. 2020 Apr 06 [cited 2021 Jan 06]. Available from: https://doi.org/10.1101/2020.04.02.20051318

47. Rhee C, Kanjilal S, Baker M, Klompas M. Duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity: when is it safe to discontinue isolation? Clin Inf Dis. 2020 Aug 25 [Epub ahead of print]. Available from: https://doi.org/10.1093/cid/ciaa1249

48. Binnicker MJ. Can the SARS-CoV-2 PCR cycle threshold value and time from symptom onset to testing predict infectivity? Clin Infect Dis. 2020;71(10):2667-8. Available from: https://doi.org/10.1093/cid/ciaa735

49. 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

50. 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

51. 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

52. Li B, Zhang S, Zhang R, Chen X, Wang Y, Zhu C. Epidemiological and clinical characteristics of COVID-19 in children: a systematic review and meta-analysis. Front Pediatr. 2020;8:591132. Available from: https://doi.org/10.3389/fped.2020.591132

53. Pollock AM, Lancaster J. Asymptomatic transmission of COVID-19. BMJ. 2020;371:m4851. Available from: https://doi.org/10.1136/bmj.m4851

54. Ontario. Ministry of Health. Management of cases and contacts of COVID-19 in Ontario [Internet]. Version 11.0. Toronto, ON: Queen's Printer for Ontario; 2020 [modified 2021 Jan 12; cited 2021 Feb 08]. Available from: http://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/contact_mngmt/management_cases_contacts.pdf

55. World Health Organization. Contact tracing in the context of COVID-19: interim guidance [Internet]. Geneva: World Health Organization; 2021 [cited 2021 Feb 08]. Available from: https://www.who.int/publications/i/item/contact-tracing-in-the-context-of-covid-19

56. Public Health Agency of Canada. Updated: public health management of cases and contacts associated with COVID-19 [Internet]. Ottawa, ON: Government of Canada; 2020 [modified 2020 Dec 23; cited 2021 Feb 08]. Available from: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/interim-guidance-cases-contacts.html

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

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