Emerging Evidence on COVID-19

Evidence Brief on Infectiousness and Symptom Onset

Introduction

Is there a difference in risk of transmission from persons who are pre- and asymptomatic infected cases compared to symptomatic cases?

Case studies, case series, contact and cluster investigations, and large population studies have demonstrated that transmission from pre- and asymptomatic cases frequently occur. This review aimed to summarize the literature up to May 29, 2020.

Key Points

- Literature from healthcare settings highlight that transmission of COVID-19 is complex and related to the situation, duration of exposure, and individual factors.
    - Potential asymptomatic transmission has been documented in healthcare settings among facility residents, healthcare workers, and visitors (Arons et al., 2020; McMichael et al., 2020). One outbreak in a skilled nursing facility in Washington State found that over half of residents who had positive results were asymptomatic at time of testing and that viable virus could be cultured from pre-symptomatic cases up to six days prior to symptom development (Arons et al., 2020).
    - Another study was unable to demonstrate that asymptomatic transmission occurred among close contacts and in healthcare settings (Canova et al., 2020). This study had low power, which may not have been sufficient to estimate a risk of transmission.
- Asymptomatic transmission has been shown to occur and may be linked to time spent in close contact with an infected person and other attributes of the scenario under which transmission occurred.
    - In a meta-analysis of mild (n=8) and asymptomatic cases (n=36), high rates of transmission were observed in situations of close quarters such as meals/family events, talking while travelling in car, private meetings, and prayer service (Prakash, 2020a). It is likely that in such situations, asymptomatic spread is facilitated via contact (contamination of hands and fomites) as well as droplet generation via talking and singing.
- The estimated viral load in aerosols emitted by patients while breathing normally was on average 0.34-11.5 copies/cm^3 while the corresponding numbers for patients exhibiting respiratory symptoms were much higher at 10,900-366,00 copies/cm^3 per cough (Riediker & Tsai, 2020). An individual spending time in a room with a person breathing normally (i.e. not exhibiting respiratory symptoms) was still likely to inhale tens to hundreds of copies of the virus.

- The proportion of transmission events from pre- and asymptomatic individuals in epidemiological investigations are highly variable (range <10-73%) (Table 1). Predictive models estimate 40-80% of transmission events occur from pre- and asymptomatic individuals (Ferretti et al., 2020; Javid & Balaban, 2020; Li et al., 2020).
- Transmission probabilities for symptomatic and asymptomatic cases may be very similar:
    - An analysis reported no significant difference in transmission rates between symptomatic and asymptomatic patients (6.3/100 and 4.1/100, respectively) (Yin & Jin, 2020).
    - Similar SARS-CoV-2 upper respiratory viral loads have been reported among asymptomatic and symptomatic patients (Zou et al., 2020).

Overview of the Evidence

There are few studies that directly compare transmission potential and infectivity between cases exhibiting respiratory symptoms and cases not exhibiting respiratory symptoms. For the purposes of this review the majority of evidence on this topic has been extrapolated from studies comparing symptomatic and pre-symptomatic/asymptomatic cases in general as well as in the healthcare setting.

Evidence on this subject is mainly described via case reports and contact tracing studies, which are at high risk of bias and thus are considered of low quality. Many studies are pre-publications and have not undergone a peer-review process. Overall, the outcomes should be interpreted with caution.

There were no risk assessments or studies that estimated the risk of infection for healthcare workers from caring for pre- or asymptomatic patients compared to symptomatic patients.

Estimates are changing as new research becomes available and there are many knowledge gaps. New research addressing these gaps could significantly change our understanding of SARS-CoV-2 infectivity among symptomatic and asymptomatic cases. More evidence demonstrating cultivatable virus from asymptomatic, pre-symptomatic, and symptomatic infections is required to determine infectiousness at different stages with greater certainty.

CONTENTS

EVIDENCE OF PRE- AND ASYMPTOMATIC TRANSMISSION POTENTIAL

It is important to keep in mind that transmission between cases depends on context and multiple factors. Individuals exhibiting respiratory symptoms are much more likely to isolate than asymptomatic individuals, explaining the high rates of pre- and asymptomatic transmission reported in this literature. Transmission studies of pre- and asymptomatic cases have shown that pre- and asymptomatic transmission does occur at high proportions in this pandemic, both in the general population and within healthcare settings. Thus, cases not exhibiting obvious signs of infection, including droplet generating events such as coughing and sneezing, can still be highly infectious.

Table 1: Studies providing evidence related to infectivity and transmission potential of pre- and asymptomatic infections. An indicator of the quality of evidence is provided (low, moderate, high) based on the risk of bias in the study design and reporting.

Reference	Key Outcomes	Quality
Pre-symptomatic transmission estimations		
(Arons et al., 2020)	Outbreak investigation of residents of a skilled nursing facility in Washington, US April 3, 2020 end date - Forty-eight (63%) of residents that participated in point-prevalence surveys tested positive. - Twenty-four were pre-symptomatic and two were asymptomatic. - Viable virus was isolated from specimens collected 6 days before to 9 days after onset of symptoms. - This indicates that pre- and asymptomatic infection was a major factor in the transmission of SARS-CoV-2 within the facility.	Low
(Du et al., 2020) *Preprint*	Case review of publically available data in China Review of 468 infector–infectee pairs identified via contact tracing January 21-February 8, 2020 - 59 infector-infectee pairs (12.6%) indicated that the infectee had symptoms earlier than the infector. - These negative serial intervals suggest that pre-symptomatic transmission likely occurred.	Low
(Chun, Baek, & Kim, 2020) *Preprint*	Case review of publically available data in South Korea Review of 72 infector-infectee transmission pairs January 23-March 31, 2020 - The pre-symptomatic transmission proportion was 37% (16–52% 95%CI).	Low
(He et al., 2020) *Preprint*	Contact tracing study in Vietnam, Malaysia, Japan, China, Taiwan, USA, Singapore Study of 77 infector–infectee transmission pairs	Low

	December 18-March 5, 2020 -Estimated that 44% (25-69% 95%CI) of secondary cases were infected during the index cases' pre-symptomatic stage.	
(Pham et al., 2020) *Preprint*	Case review of publically available data in Vietnam Review of 33 infector-infectee transmission pairs April 15 – May 1, 2020 - Serial intervals were calculated from infector-infectee pairs and used to estimate the proportion of pre-symptomatic transmission events. - 27.5% (15.7%-40.0% 95%CI) of transmissions occurred pre-symptomatically.	Low
(Wei et al., 2020)	Contact tracing study of 243 cases and seven clusters in Singapore January 23-March 16, 2020 - Seven clusters of cases with probable pre-symptomatic transmission were identified. - The overall proportion of transmission from pre-symptomatic cases comprised 6.3% of overall transmission.	Low
(Xia et al., 2020) *Preprint*	Investigation of 50 clusters in China Symptom onset prior to January 25, 2020 - Investigated 124 cases where the secondary case contact with the first generation case occurred before symptom onset. The infectious curve showed that in 73.0% of the infectees, their date of being infected was before symptom onset of their infectors, particularly in the last 3 days of the incubation period.	Moderate
(Casey et al., 2020) *Preprint*	Secondary analysis of published data reporting serial interval or generation time originating from Hong Kong, Tianjin, Singapore, Mainland China excluding Hubei, mixed sources, Shenzhen, northern Italy and Wuhan December 1, 2019 – April 15, 2020 - Subtracted incubation period from serial interval or generation time to infer pre-symptomatic infectious period and to estimate the proportion of pre-symptomatic transmission. - Pre-symptomatic transmission was estimated to be 56.1% based on serial interval estimates and 65.5% based on generation time estimates.	Low
(Prakash, 2020b) *Preprint*	Secondary analysis of published data Includes 1251 individuals reported in the literature - Estimated that 68.4% (67.0-69.7% 95%CI) of infections are caused by pre-symptomatic infectors.	Low
(Nishiura, Linton, & Akhmetzhanov, 2020)	Log-normal distributed Bayesian model built from case review of published research and investigation reports Study of 28 infector-infectee pairs February 12, 2020 end date - Accounting for right truncation and analyzing all pairs, authors estimated a serial interval of 4.0 days (3.1-4.9 95%CI).	Low

	- This interval is shorter than preliminary estimates of the incubation period of approximately 5 days. - This suggests that pre-symptomatic transmission may make up a substantial proportion of secondary transmission.	
Asymptomatic transmission estimates		
(McMichael et al., 2020)	Outbreak investigation of residents, healthcare workers, and visitors of a long-term care facility in Washington, US March 18, 2020 end date - In total, 167 confirmed cases of COVID-19, including 101 residents, 50 health care personnel, and 16 visitors were found to be epidemiologically linked to the facility. - No symptoms were documented in 7 (6.9%) of residents.	Low
(Yin & Jin, 2020)	Re-analysis of case and contact data in Ningbo, China Analysis of 157 symptomatic cases and 30 asymptomatic cases January 21st to March 6th, 2020 -Transmission rates for the symptomatic and asymptomatic patients were 0.063 and 0.041 respectively (no significant difference). - Odds of transmitting to a healthy individual by a symptomatic patient is 1.2 times of that by an asymptomatic patient (not statistically significant).	Low
(Danis et al., 2020)	Cluster investigation in the French Alps with exportation and spread to several countries in Europe. Pre-symptomatic index case and 15 contacts in chalet; 172 contacts identified overall of cases. January 25, 2020 onward - Attack rate from asymptomatic index case 12/15 (75%) over 4 days contact; 1/15 asymptomatic. Only 1 of the 172 subsequent contacts was positive. - Viral load in one symptomatic case similar to asymptomatic case.	Low
(Wang et al., 2020)	Retrospective study in China Study of 125 patients confirmed by real-time RT-PCR. January 20 to February 18, 2020. - 22.4% of cases reported no known exposure to ill individuals.	Low
(Wong et al., 2020)	Case review in travelers and returning residents to Brunei Review of 53 symptomatic infector-infectee pairs. March 5 – April 24, 2020 -Twenty-one cases (39.6%) had a SI of ≤3.0 days and 6 (11.3%) had zero or negative SI values, suggesting potential infectivity when asymptomatic.	Low
(Zou et al., 2020)	Viral load study of 17 symptomatic patients and one asymptomatic patient in China January 7 –26, 2020 - Analyzed the viral load in nasal and throat swabs.	Low

	- The viral load detected in the asymptomatic patient was similar to that in the symptomatic patients. This suggests the transmission potential of asymptomatic or pauci- symptomatic patients.	
(Li et al., 2020) *Preprint*	Mathematical model that simulates the spatiotemporal dynamics of infections in China January 10 – February 8, 2020 - Estimated 86% of all infections were undocumented prior to the Wuhan travel shutdown, and that per person, these undocumented infections (many of whom were likely not severely symptomatic) were 55% as contagious as documented infections and the source of infection for 79% of documented cases.	Low
(Riediker & Tsai, 2020) *Preprint*	A one-compartment model was used to estimate the virus load concentration for a perfectly mixed room of volume 50 m^3 with one patient as source - The cumulative total emission per breath from normal breathing patients was 0.34 copies/cm^3 (air) for an average patient, and 11.5 copies/cm^3 for high emitters. - Virus emissions from coughing patients were much higher with a cumulative total emission per cough of 19,400 copies/cm^3 for an average patient and 651,315 copies/cm^3 for high emitters. - A person spending time in a room with an average emitting patient breathing normally has a high probability of inhaling tens to hundreds of copies of the virus even when practicing distancing. The probability is higher in the presence of a high emitter or if the patient is a coughing high emitter. - Conclude that the high predicted virus concentrations may be why frequent community transmission from asymptomatic cases and high rates of infection in medical staff have been reported. - Authors recommend strict respiratory protection when being in a room with a patient, whether the patient is symptomatic or not.	Low
(Aguirre-Duarte, 2020) *Preprint*	Systematic Review and narrative report of Cluster/contact investigations. Primary studies of the ability of asymptomatic carriers to infect others. Nine articles reported on 83 asymptomatic or pre-symptomatic persons. Published in indexed journals January 1 to March 31, 2020. - While no specific estimates reported, there is evidence that asymptomatic and pre-symptomatic people can infect others with COVID-19.	Moderate
(Prakash, 2020a) *Preprint*	This synthesis is not conducted using standard systematic review methodology although a thorough search was conducted. Twenty situations that resulted in 418 infections across 32 instances from 44 individuals (eight had mild symptoms, 36 were asymptomatic). Situation (transmission rate): • Meals/ family events (15.7% to 66.7%) • Meetings (One hour private meeting, 72.7% (CI 43.6-98.0%))	Moderate

	• Open work space with people movement (78.7% (70.3-85.3%)) • Singing (e.g. Two hour practice 86.7% (76.2- 93.2%) • Prayer service (resulted in one to seven secondary infections per infected individual) • Travelling in a car (closed environment) and talking had a high risk (100% (20-100%)) • Public transportation, wearing a mask with no talking (~0%) • Hotels (53.3% (30.1-75.2%))/cruise ships (28.1% (27.3-29.0%)) where space is shared for days • Direct interaction with an infected sales agent (25.0% (10.2-49.5%)) • Nightclub, attack rate among direct contacts >50%, among patrons of the nightclub (6.27% (5.15-7.61%)) • Restaurant overall attack rate (9.9% (5.3-17.7%) vs. those in the flow of the air conditioner (45.0% (25.8- 65.8%))	

Methods:

A daily scan of the literature (published and pre-published) is conducted by the Emerging Sciences Group, PHAC. The scan has compiled COVID-19 literature since the beginning of the outbreak and is updated daily. Searches to retrieve relevant COVID-19 literature are conducted in Pubmed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN, Research Square and cross-referenced with the literature on the WHO COVID literature list, and COVID-19 information centers run by Lancet, BMJ, Elsevier and Wiley. The daily summary and full scan results are maintained in a refworks database and an excel list that can be searched. Targeted keyword searches were done using a combination of the terms "outbreak", "hospital", "long-term care" and "nursing". Previous evidence summaries and briefs on asymptomatic infection, super-spreading events, and infectious period, were used to gather evidence related to respiratory symptoms and infectivity. This review contains research published up to May 29, 2020. Each potentially relevant reference was examined to confirm it had relevant data and relevant data is extracted into the review.

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