University of Manitoba

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6th Edition

COVID-19 Report

Finding the evidence for you

A weekly report to answer clinically relevant questions by summarizing the most recent evidence.

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Clinical Description & Epidemiology

What are the cutaneous manifestations seen in COVID-19? Do cutaneous manifestations provide a useful predictor of SARS-CoV-2 infection?

- At this time, cutaneous manifestations seen in COVID-19 are incompletely characterized. A large descriptive study from China found unspecified rash to be rare (0.2%).[1] However, a more recent descriptive study from Italy with a specific focus on dermatologic manifestations described 18 of 88 (20.4%) patients with cutaneous manifestations. Of these, 14 patients had an erythematous rash, 3 had generalized urticaria, and 1 had a chicken pox-like vesicular rash.[2] There was no clear correlation with disease severity.
- There are numerous case reports detailing ischemic and coagulopathic cutaneous manifestations of COVID-19. A case report from China noted dermatologic changes associated with ischemia and coagulopathy in the limbs and digits of critically ill adult COVID-19 patients, but the pathogenesis of these changes remains unclear.[3] The report noted the possibility of antiphospholipid syndrome, disseminated intravascular coagulation, heparin induced thrombocytopenia, or thrombotic microangiopathy developing in the context of COVID-19. A case series describing three purpuric skin rashes showed complement-mediated microvascular injury on biopsy.[4] Diffuse, petechial rash was noted in the context of thrombocytopenia in a case report from Thailand.[5]

- COVID-19 associated acro-ischemia has been noted in more than a dozen otherwise asymptomatic Italian children including a 13-year-old boy in Italy with acrocyanosis on the toes.[6] There was progression to bullous lesions, followed by the development of black crusting, and finally regression.

Is there evidence of multiple strains or strain mutation in SARS-CoV-2? What are the possible implications of strain mutations of SARS-CoV-2 on the evolution of the COVID-19 pandemic?

- Like other RNA viruses, SARS-CoV-2 appears to undergo frequent mutations. There are several "hot spots" for mutation within the SARS-CoV-2 genome.[1]
- Many SARS-CoV-2 strains and sub-strains have been identified but estimates of the exact number vary significantly. Homology is high among these strains at the nucleotide level (99.9-100%) and amino acid level (99.79%-100%).[1] Preprint *in vitro* data of 11 Chinese SARS-CoV-2 isolates suggest certain mutations may cause a 270-fold increase in viral load, correlating with higher rates of cell death.[2] However, there is no data on whether mutations in SARS-CoV-2 strains correlate with changes in clinical presentation or outcome.
- SARS-CoV-2 will continue to evolve. Mutations may lead to increased transmissibility and virulence as well as immune evasion.[3,4] Further research on diagnosis, treatment, and vaccine development should take strain variability into account.[4]

What is the incidence of cardiac complications in COVID-19? How does this compare to rates seen with SARS-CoV and MERS?

- Incidence of cardiac injury (defined as elevation of high-sensitivity cardiac troponin I to >99th percentile of the upper reference limit) ranges from 7-28% in hospitalized COVID-19 patients. Cardiac injury appears to be associated with significantly higher mortality in affected patients (51% vs. 4.5% in one review).[1]
- The incidence of arrhythmia was 16.7% in a Chinese cohort of 138 hospitalized COVID-19 patients.[2] In another cohort of 191 inpatients from China, prevalence of heart failure was 23%.[3] A report of critically ill COVID-19 patients from Washington state found that 7 of 21 (33%) had evidence of de novo cardiomyopathy.[4]
- SARS-CoV and MERS were also associated with cardiac complications. In a review, SARS was associated with tachycardia (72%) and reversible cardiomegaly (10.7%) with no clinical evidence of heart failure.[5] Reports on MERS also noted cardiac arrhythmias in up to 15.7% of patients.
- On April 20, 2020, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, and the American College of

Emergency Physicians released a consensus statement on the management of acute myocardial infarction during the COVID-19 pandemic. They emphasize that percutaneous coronary intervention (PCI) remains the standard of care in managing patients with ST-elevation MI, with appropriate personal protective equipment utilized by healthcare providers.[6]

Does SARS-CoV-2 cause clinical disease in pets or farm animals? Is transmission possible from pets/farm animals to owners/handlers?

- As of April 22, 2020, a global total of seven companion and captive animals (four cats, two dogs, and a tiger) are reported to have tested positive for SARS-CoV-2 following close contact with infected humans.[1,2] Four of the felines showed mild respiratory symptoms.[1]
- A recent laboratory study suggested cats and ferrets are susceptible to SARS-CoV-2 infection and may be capable of transmitting the virus to other cats under ideal laboratory conditions.[3] The cats in the study did not develop clinical signs of disease. The same study reported dogs, pigs, chickens, and ducks were less susceptible to SARS-CoV-2 infection and incapable of transmission of the virus under laboratory settings. To date, there is no evidence of transmission between companion animals outside of the laboratory setting.
- There is currently no evidence that companion animals or livestock transmit SARS-CoV-2 to humans or participate in the spread of the pandemic.[1,2]
- The CDC has provided interim guidance for pet owners[4] and the Canadian Food Inspection Agency has provided recommendations for livestock producers regarding the management of domestic and farm animals during the COVID-19 pandemic.[5] They recommend that people with confirmed or suspected COVID-19 should restrict their interactions with animals.

Diagnostics & Surveillance

What is the probability of false negative SARS-CoV-2 testing?

- Accuracy of RT-PCR is influenced by a number of factors such as the platforms and protocols used,[1] disease severity,[2] specimen type,[3] and time of collection.[3,4,5] For further details on each of these factors, please see March 27,2020 newsletter.
- Generally, the sensitivity of RT-PCR for SARS-CoV-2 is highest when performed as close as possible to time of symptom onset.[3,4] However, false negatives can still occur, particularly in the week immediately following symptom onset. False negatives also seem to be more common later in the disease course as symptoms

begin to wane. This may impact the practice of serial monitoring for viral clearance and may account for the observed “recurrence” in those thought to have initially cleared the virus.[5,6]

Why is viral isolation in cell culture important? What information does it give us compared to RT-PCR?

- SARS-CoV-2 is most commonly grown in the Vero-E6 cell line using minimum essential medium or Dulbecco's modified eagle medium and incubated at 37°C. Cytopathic effects have been observed 72 hours post infection of Vero-E6 cells.[1,2,3,4]
- Isolation of the virus is critical for the development of new diagnostic tests and therapeutics including:
    - Validation of RT-PCR assays for SARS-CoV-2 detection
    - Drug susceptibility testing against SARS-CoV-2
    - Vaccine development for active immunization
    - Development of plaque reduction neutralization assays to determine long-term immunity

What are the consequences on diagnostic laboratory testing when public resources are focused on SARS-CoV-2?

- During viral pandemics, it is expected that diagnostic laboratories alter routine testing protocols and infrastructure in response to the atypical demands placed on them, irrespective of testing volume.[1,2]
- For instance, across Canadian laboratories, many routine tests that are normally run once a week are now being run every two weeks to allow for more timely SARS-CoV-2 testing. In Manitoba, assays performed mostly for academic purposes have been suspended.
- Besides the changes made by diagnostic laboratories, there has been a significant decrease in sample volumes for many standard tests at tertiary hospitals from January to March, a trend that is anticipated to continue in April.

Therapeutics

What is the evidence for vitamin D supplementation in preventing or treating COVID-19?

- Vitamin D has been speculated to have protective effects against SARS-CoV-2 infection due to its immunomodulatory properties and potential antiviral effects.[1]
- Recent epidemiological studies suggest that hypovitaminosis D is associated with higher rates of COVID-19 attributed morbidity and mortality.[2,3,4] However, the

evidence from these studies is weak due to significant difficulties with case ascertainment and confounder bias.
- Two randomized controlled trials in Europe will soon be investigating the role of vitamin D supplementation in mitigating COVID-19 attributed mortality and morbidity.[5,6,7]
- There is currently no recommendation for vitamin D supplementation in preventing or treating COVID-19. As part of good general health, it is recommended to supplement your diet with the daily recommended dose of vitamin D if you are at risk for deficiency.

Many COVID-19 investigational therapies are only available through clinical trials. What ethical issues should be considered for populations that face barriers to trial enrolment?

- Randomized controlled trials (RCTs) are often organized through urban tertiary care centres with online support, thus excluding rural populations and those without reliable internet connection. Other perceived enrollment barriers include, but are not limited to, patient socioeconomic status and ethnicity.[1,2]
- Research is expedited during outbreaks and this can create additional ethical difficulties, especially regarding community acceptability of randomization and placebo control. The West African Ebola epidemic reinforced the notion that local political will was essential for successful completion of clinical trials.[3]
- Providing experimental medications on compassionate grounds to those unable to participate in controlled trials should not be done without consideration of risks including potential for drug adverse reactions and harm, lack of adequate monitoring, and the limitation of drug availability for formal trials.[4,5]

How do COVID-19 guidelines address Advanced Care Planning and what resources are available?

- Most COVID-19 treatment guidelines do not specifically address Advance Care Planning (ACP).
- In general, outpatient ACP discussions increase concordance of patient preference with care received, increase Advance Directive completion, and improve patient and family perception of end-of-life discussions.[1,2,3]
- The current pandemic reinforces the notion that ACP discussions are a fundamental aspect of outpatient family medicine, especially for patients with life-limiting conditions.
- To facilitate ACP discussions over phone or videoconference, in the context of the SARS-CoV-2 pandemic, a two page handout is available here. For additional ACP

resources relating to COVID-19, please see Speak Up Canada and Virtual Hospice Canada.

Infection Prevention & Control

When are people with SARS-CoV-2 infection no longer contagious? How has this been determined in viral respiratory illnesses prior to COVID-19?

- Thus far, we do not have robust data to reliably determine when a patient infected with SARS-CoV-2 is no longer contagious. Studies of viral shedding and transmission in SARS-CoV-2 and other respiratory illnesses have provided some information, but many limitations remain.
- Viral shedding can be measured by PCR or culture. PCR measures the presence of viral genetic material, but does not indicate whether this material is "viable" or infectious.[1] Viral culture can determine if a virus can replicate within cells, and the superiority of culture for determining the presence of infectious virus has been demonstrated in animal models of influenza.[2] However, it is a more complex and less sensitive method than PCR-based testing and results of either method do not necessarily correlate with whether a person can transmit virus or not.
- For some illnesses, such as influenza A, levels of viral shedding measured by PCR decrease predictably in relation to the resolution of clinical illness.[3] However, in a study investigating transmission among household contacts, the infectious period of the virus did not correlate well with viral shedding measured by PCR.[4] Furthermore, even closely related influenza A and B have different periods of viral shedding relative to symptoms, so it is difficult to make generalizations among different viral respiratory illnesses. Additionally, patient age and immune status have an effect on duration of viral shedding.[5]

What can epidemiologic data tell us about the infective period of COVID-19?

- The viral shedding and transmission patterns of SARS-CoV-2 appear more similar to those of influenza, compared to SARS-CoV or MERS. With SARS-CoV-2 infection, viral load and contagiousness seem to peak around symptom onset.[1,2]
- A retrospective study of transmission pairs of COVID-19 estimated that the infectious period starts 2.3 days prior to symptom onset, peaks around the time of symptom onset, and declines within 7 days.[2] One caveat is that the measured period of infectivity in this study may have been influenced by hospitalization and self-isolation procedures.

What do we know about the infective period of SARS-CoV-2 infection from studies of viral shedding?

- Based on multiple studies, SARS-CoV-2 detection by PCR tends to peak around the time of symptom onset but can stay positive at a low level for extended periods. One study showed viral shedding in hospitalized patients measured by PCR lasting a median of 20 days, with a maximum of 37 days in one patient.[1] Similarly, PCR detection persisted for up to 28 days post symptom onset in a small prospective case series of German patients with mild COVID-19 disease.[2] However, virus isolation by culture was successful only up to 8 days post symptom onset, and only in those with higher RNA copy levels measured by PCR.
- To date, there has not been a study of live viral isolation in severe COVID-19 cases. However, it has been observed that severe cases of COVID-19 have higher viral loads and a longer period of viral shedding measured by PCR compared to mild or moderate cases.[3,4]

How are different jurisdictions approaching the issue of discontinuing precautions and allowing for return to work after SARS-CoV-2 infection?

- The decision to discontinue self-isolation and precautions for positive cases who have experienced symptom resolution has been made in different jurisdictions by either a test-based strategy (two negative specimens by PCR collected ≥24 hours apart) or a non-test-based strategy (based on the number of days since symptom onset and resolution).[1,2]
- Several centers have adopted more complex hybrid approaches, accounting for potential differences in risk of transmission on account of immune compromise, age, or occupation.[3]

- Without a clear understanding of infectivity, there is no universal strategy for discontinuing precautions or instituting back-to-work policies. Decisions need to incorporate local testing capacity, workforce demands, unique patient circumstances, and evolving evidence. Further, specific cases may demand a more cautious approach, including healthcare workers, immunocompromised patients, and patients who are being transferred to high-risk settings such as long-term care homes.
- Even after isolation precautions are discontinued, affected individuals should continue to adhere to practices such as physical distancing, hand hygiene, and wearing a face mask when appropriate.
- Current Guidelines in Manitoba: For hospitalized patients, isolation precautions are discontinued in consultation with the Infection Prevention and Control service.

What personal protective equipment (PPE) is appropriate for home healthcare workers in the setting of COVID-19?

- Patients requiring care at home may be predisposed to infectious disease acquisition and adverse outcomes due to factors such as age and comorbidities.[1*] Home healthcare workers (HCWs) have been implicated in the spread of infections such as MRSA to their patients.[2] Conversely, home HCWs face unique challenges, such as a lack of control over the care environment, which can limit infection prevention by environmental/engineering strategies. This places greater importance on individual use of PPE.[3,4]
- Unfortunately, no data has been published on this issue in COVID-19. However, because of the potential for asymptomatic spread of COVID-19, all home visits should be considered a potential risk to both the patient and HCW.
- Shared Health Guidelines in Manitoba state that a medical mask and eye protection should be used by HCWs for all home visits. Gloves and gowns are only required for confirmed or suspected COVID-19 clients and where they are required per routine practice.

1* Smith PW, Hewlett, AL. Epidemiology and Prevention of Infections in Home Healthcare. In: Mayhall CG. Hospital epidemiology and infection control. 4th edition. Philadelphia, PA. Lippincott Williams & Wilkins; 2012 Feb 20.

Public Health Interventions

Assuming that SARS-CoV-2 will not spontaneously disappear, what indicators should be used to determine when to decrease or increase public health measures?

- There is currently no concrete evidence in the literature regarding what metrics should be used to determine when public health measures can be lifted. The World Health Organization has recommended that restrictions be lifted in a stepwise incremental fashion, once a steady state of low-level or no transmission has been achieved.[1] The WHO has outlined six criteria for lifting measures:
    - COVID-19 transmission is controlled
    - Sufficient health system and public health capacity is in place
    - Outbreak risks in high-vulnerability settings are minimized
    - Workplace preventive measures are established
    - Risk of imported cases is managed
    - Communities are fully engaged

- Some studies have suggested that public health measures could be “turned on and off” based on indicators in the population.[2,3] There are several indicators proposed:
    - Prevalence of cases.[4] To use this indicator, extensive testing must be in place. For example, a modelling study using R_0 = 2.2 and USA data found

that physical distancing measures should be turned on when COVID-19 prevalence reaches 35 per 10,000 and turned off at 5 cases per 10,000.[4]

    - ICU bed occupancy.[2,3] Of note, ICU bed use lags behind SARS-CoV-2 transmission more than the other indicators. To deal with this, an Ontario modelling study suggested that public health measures be turned on when 40% of available ICU beds are filled with COVID-19 cases.[3]
    - Instantaneous reproduction number (R_t),[5] which is the average number of secondary cases due to a single primary case at time *t*. A modelling study in mainland China recommended maintaining $R_t < 1$ to determine adjustments to public health interventions.

- Concerns have been raised that a second outbreak may occur once public health measures are relaxed. One modelling study, using data from China, calculated that maintaining social distancing for one extra month would delay the peak of a possible resurgence by two months.[6] However, there are many challenges with maintaining ongoing strict public health measures. Close monitoring of the local epidemiology and good communication with the public will be important as measures are re-evaluated.

What is the evidence for the order in which public health measures should be relaxed?

- There is no clear evidence on the optimal order of public health measure cessation. As China eases restrictions, their course of action and the ensuing second wave or lack thereof may provide some guidance for the rest of the world.
- China's current approach includes:[1]
    - Removal of travel restrictions in the province of Hubei (including Wuhan).
    - Extensive testing and contact tracing to find new infections.
    - Maintenance of social distancing practices.
    - Keeping the country closed to non-citizens to prevent cases from being imported and imposing mandatory 14-day quarantine on returning residents.
    - Allowing residents of Hubei to return to work and reopening factories, while universities, schools, and child-care centres remain closed.
- As governments look at easing restrictions, it is important for them to work with the community and businesses on ways this can be done safely and to maximize the chances of success. British Columbia, for example, is working with the restaurant sector to develop ways of reopening restaurants while maintaining social distancing.[2]

What is the evidence on transmission of SARS-CoV-2 in grade schools?

- Many countries have closed schools to decrease the transmission of SARS-CoV-2 from and within the school setting.[1] This measure is based on data from previous viral outbreaks as SARS-CoV-2 specific data is limited.
- Evidence from previous outbreaks:
    - Coronavirus outbreaks (SARS, MERS): Limited evidence is available on the transmission of SARS and MERS within schools, though some studies suggest there was minimal to no transmission in schools.[1]
    - H1N1 Influenza Pandemic: Transmission rates were high within schools as children were the main vectors of transmission.[1,2,3] School closures decreased contact among children which decreased and delayed the peak of the outbreak.[1,3] This was effective due to a low R_0 (<2), early implementation, and a higher attack rate in children than adults.[1,4]
- There is limited evidence regarding the transmission and contact patterns of SARS-CoV-2 within schools. The current understanding is that children are more likely to be mildly symptomatic or asymptomatic, but the relationship between the severity of symptoms and the transmission of SARS-CoV-2 is still unclear.[5] Younger people appear to have a lower attack rate than adults, which is in contrast to previous Influenza outbreaks. Modelling studies have demonstrated conflicting data about the effectiveness of school closures in the context of SARS-CoV-2.[1,6]

What needs to be in place to allow learning in an in-class setting to resume?

- Currently, there is no data available on the efficacy of implementing social distancing interventions in schools during infectious disease outbreaks.[1]
- In 2009, the World Health Organization suggested several school interventions to help reduce transmission of the H1N1 Pandemic Influenza virus.[2] These interventions could be considered to allow reopening of schools during the COVID-19 pandemic:
    - Promote consistent and correct hand hygiene and respiratory etiquette.
    - Students and staff should stay home if are sick. If they become sick while at school, they should be isolated immediately and sent home.
    - All surfaces shared by students or staff are to be cleaned regularly with soap & water, household cleaning products, or disinfectants.
    - Ensure all classrooms and hallways are well ventilated. Natural ventilation can be achieved by keeping windows open.
    - Limit gatherings in confined spaces (e.g. lunchrooms or assembly halls).
    - Collaboration between schools and national/local health authorities with the dissemination of public health messages to parents, students, and staff.

- Planning at a school and regional level for the maintenance of essential services and supplies that are critical in reducing viral transmission.

Pediatric Corner

Are healthcare providers who work in pediatrics at a higher risk of contracting COVID-19 when compared to adult care providers?

- There has been concern that children could be disproportionately responsible for SARS-CoV-2 transmission due to milder clinical presentation or asymptomatic infections.[1,2] The infection rate amongst pediatric healthcare workers (HCWs) as compared to adult care providers is of interest to help determine if children are driving ongoing SARS-CoV-2 transmission and to determine if pediatric HCWs are at a higher risk of developing COVID-19.
- Data determining the rate of pediatric HCW infection in comparison to adult HCWs is extremely limited. A preprint study from Spain found that 38% of tested hospital employees (791 of 2,085) were positive for SARS-CoV-2.[3] Of the tested employees, 109 worked within pediatric/neonatal environments and 53 (48.6%) were COVID-19 positive, which is 6.7% of the overall SARS-CoV-2 positive employees. It is not clear if the HCWs acquired their infection from occupational exposure.
- While data is limited, current evidence suggests that the infection rate in pediatric HCWs is similar to that of adult HCWs, which does not support the hypothesis that children are disproportionately responsible for transmission of SARS-CoV-2, although this may not hold true outside of the occupational setting. Despite this, in the WHO-China Joint Mission Report completed February 16-24, there were no confirmed cases of asymptomatic child to adult transmission in China.[4]

Are adolescents presenting for testing or requiring hospitalization for COVID-19? What is known about adolescents and infection with SARS-CoV-2?

- In Manitoba, there is a substantially higher number of COVID-19 cases in the 20-29 year age group compared to the 10-19 year age group.[1] This is also seen in other jurisdictions.[2] It is not clear from current evidence how much of this difference is accounted for by asymptomatic or mildly symptomatic cases or differences in testing between these age groups.

- In a study of 46,506 confirmed COVID-19 cases in Italy, those aged 7-19 years were the least likely to require hospitalization.[3] In a study of USA cases <18 years old, there were 745 cases with known hospitalization status of which there was little variation in the percentage of patients hospitalized within the four age categories of 1-4, 5-9, 10-14, and 15-17 years.[4]
- One study compared 14 individuals aged 10-24 years and 32 individuals aged 25-35 years hospitalized with confirmed COVID-19 in China.[5] A greater proportion of those aged 25-35 had derangements in all categories of lab values at admission with the exception of elevated D-dimer and total bilirubin. A smaller proportion of those aged 10-24 required oxygen therapy.

The information presented reflects the data that is currently available to us. In the context of a pandemic where rapid dissemination of information is essential, we have included information from evolving medical literature which may be awaiting peer-review.

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