

# COVID-19 Report

## Finding the evidence for you

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

**This information is intended for health care professionals.**

### Clinical Description & Epidemiology

#### How long does viral shedding persist in symptomatic COVID-19 patients?

- Evidence of viral shedding is limited to studies using real-time PCR to detect viral RNA. The significance of detected viral RNA is clinically unclear. Viral culture to determine if the RNA represents viable virus is rarely found in the literature.<sup>1</sup>
- A retrospective cohort study of 191 patients from numerous Wuhan hospitals showed, of the 118 who survived with complete follow-up data, the median time of viral shedding from symptom onset was 20 days (longest = 37 days) determined by PCR (throat swab). Survivors who were in critical condition had a median shed time of 24 days.<sup>2</sup>
- 1 asymptomatic and 9 symptomatic children with COVID-19 were followed by RT-PCR on nasopharyngeal (NP) and rectal swabs. Of the 8 positives on initial rectal swab, 5 had subsequent positive rectal swabs at least 2 weeks after NP swabs tested negative (most >3 weeks). This suggests that fecal shedding can occur even after negative NP swabs are documented.<sup>3</sup> However, to date there is no evidence for fecal-oral transmission.

#### How long does viral shedding persist in COVID-19 in asymptomatic patients? Is there any evidence that can help predict transmissibility?

- In a group of German evacuees from Wuhan, China, 2 patients remained well for 7 days after testing positive for SARS-CoV-2 by RT-PCR. Samples from these patients were cytopathogenic to Caco-2 cells, an indication of potential infectivity.<sup>1</sup>

- In a report detailing screening of close contacts from China, time between first positive RT-PCR to first negative was up to 21 days in asymptomatic patients with a median time of 9.5 days<sup>2</sup>. Viral load in asymptomatic patient swabs was also similar to patients with symptoms.<sup>3</sup>
- Using contact information from 94 patients, an estimate of incubation time, and RT-PCR data, a preprint article notes that the viral load peaks around symptom onset and decreases thereafter. Authors estimate that infectiousness starts 2-3 days before symptom onset, peaking on or just before the onset and declining rapidly within 7 days of illness onset.<sup>4</sup>

**How common is anosmia and/or dysgeusia in COVID-19? Are these symptoms helpful in differentiating COVID-19 from other respiratory infections?**

- Anosmia and impaired taste are known to occur in viral URIs.<sup>1</sup> Recent media attention has focused on the utility of using these symptoms to predict infection with SARS-CoV-2.
- A recent survey of 59 hospitalized patients in Italy reported 20 (34%) complained of at least one taste or olfactory disorder, and 11 (19%) complained of both.<sup>2</sup> In a preprint retrospective case series of 214 hospitalized patients with COVID-19 in Wuhan, China, 12 patients (5.6%) had hypogeusia and 11 patients (5.1%) had hyposmia.<sup>3</sup>
- Researchers at Kings College in London have estimated the rate of anosmia in COVID-19, using self-reported symptoms from 400,000 people via an online app, may be as high as 59%, but this data lacks scientific validation.<sup>4</sup>
- At this time, there is no robust evidence that supports using these symptoms to accurately predict COVID-19 infection.

**What is the risk posed by COVID-19 to prospective organ recipients and donors? Is there evidence of transmissibility of SARS-CoV-2 in the process of transplantation? Should donors and/or recipients be screened prior to transplant?**

- No research is available regarding exact risk of transmissibility of SARS-CoV-2 from donor to recipient in the process of transplantation, but expert opinion indicates plausibility.<sup>1</sup>
- Numerous guidelines have been produced on this topic and there is consensus that donor and recipients should be screened prior to transplant.
- From a Canadian perspective, the Organ Donation and Transplantation Expert Advisory Committee ([ODTEAC](#)) has made recommendations to consider postponing or suspending renal transplants, and to assess medical urgency for liver transplant on a case-by-case basis. It is recommended to screen both donor and recipient and

to not use organs from donors who are confirmed positive for COVID-19 or who meet high-risk criteria. Transplants are to be deferred for positive recipients.<sup>2</sup>

- In Manitoba, latest updates can be found at [Shared Health Manitoba](#). Of note, all non-urgent surgical procedures in Manitoba were suspended effective March 23, 2020.

## Diagnostics & Surveillance

**What role does serology play in monitoring COVID-19 disease progression and population surveillance? Has SARS-CoV-2 serology been applied to "return to work" policies?**

- IgM and IgG antibodies against SARS-CoV-2 may be detected as early as 2-4 days post symptom onset.<sup>1</sup> However, seroconversion usually occurs after 10-13 days post symptom onset for IgM and 12-14 days for IgG.<sup>1,2,3,4</sup>
- Severe COVID-19 has been associated with an early and strong IgM response.<sup>5,6</sup>
- In one study, only 4.3% of close contacts of COVID-19 cases with negative nasopharyngeal RT-PCR were positive for IgG and/or IgM.<sup>1</sup>
- Serology may play a role in population surveillance and "return to work" policies, but this has not yet been studied nor implemented.

**What Point of Care Testing (POCT) is currently available for SARS-CoV-2?**

- The use of POCT is ideal for emerging outbreaks due to decreased turn-around time (0.5-1 hours), technical simplicity, and portability which would be particularly beneficial for rural and remote settings.<sup>1</sup>
- Currently, the only product approved for use in Canada is the Gene Xpert Xpress SARS-CoV-2, with six other systems pending approval.<sup>2</sup>
- This test, among most others on the market, utilizes a nucleic acid amplification approach (e.g.: RT-PCR).<sup>3</sup>

**What laboratory findings are consistent with COVID-19?**

- The most frequent laboratory abnormalities include: lymphopenia, increased LDH, increased CRP and ESR, increased D-dimer, anemia, and decreased serum albumin.<sup>1,2</sup>
- In addition to the derangements above, severe cases are marked by: thrombocytopenia, transaminase elevation, and increased procalcitonin. However, the latter likely indicates bacterial superinfection.<sup>1,3</sup>

- A minority of COVID-19 cases are associated with myocarditis and increased troponin.
- In one study, 15 of 21 (71%) patients with fatal COVID-19 fulfilled the criteria for DIC with increased fibrinogen degradation products.<sup>4</sup>

## Therapeutics

### What is Favipiravir and what is the evidence for its use in treating COVID-19?

- Favipiravir (Avigan) is a novel RNA dependent RNA polymerase (RdRp) inhibitor that is used to treat influenza in China.<sup>1</sup>
- In the preprint of a randomized study comparing Favipiravir to Umefenovir (also known as Arbidol, an influenza medication used in China and Russia), Favipiravir had a higher 7-day rate of recovery (71% vs. 56%), but did not alter mortality or need for intubation.<sup>2</sup>
- Favipiravir adverse reactions include diarrhea, hepatitis, uricemia, and psychiatric symptoms.<sup>2</sup>
- Results from large placebo-controlled trials are not yet available and Favipiravir is not widely available in North America.

### What is the evidence for convalescent plasma in treating COVID-19?

- The use of convalescent plasma for respiratory viral infections remains controversial.<sup>1</sup> Pooled data from SARS-CoV-1 and severe Influenza suggests that convalescent plasma decreases mortality.<sup>2</sup>
- In SARS-CoV-2, two small observational studies of 5 and 10 critically-ill patients demonstrated clinical improvement and reduced viral loads after receiving convalescent plasma, with no patient deaths.<sup>3,4</sup>
- Clinical trials are currently ongoing. Reasons for caution include transfusion reactions such as TRALI,<sup>5</sup> and theoretical risks such as antibody-dependent enhancement.<sup>6</sup>

### What is the evidence for pre- and post-exposure prophylaxis for preventing COVID-19?

- No robust evidence is currently available for the use of any medication as pre- or post-exposure prophylaxis in COVID-19.
- Ongoing RCTs are examining the use of Lopinavir/Ritonavir, Hydroxychloroquine, and Arbidol in preventing COVID-19.<sup>1,2,3</sup>

- Extrapolation from other coronaviruses such as MERS-CoV suggests possible benefit of antiviral prophylaxis, with one study citing 40% reduction in infection with Lopinavir/Ritonavir.<sup>4</sup>
- Several articles highlight the potential for hydroxychloroquine to prevent COVID-19.<sup>5</sup>
- A Canadian RCT of hydroxychloroquine as post-exposure prophylaxis is currently enrolling participants: <https://www.covid-19research.ca/home>

## Infection Prevention & Control

*This week we reviewed evidence for ways to minimize secondary infections in the household contacts of both patients with COVID-19, and of healthcare workers. Note: Some of the best evidence comes from studies of SARS and influenza, which are transmitted similarly, but aren't identical. Importantly, COVID-19, is likely infectious for a period prior to the onset of symptoms.<sup>1</sup> Hence, pre-emptive measures when an individual has been exposed to a case, or has travelled, are reasonable.*

### **What strategies can be adopted to minimize the risk of secondary infections with respiratory viruses in household contacts?**

- Isolation of the index case within a separate room from other household members, keeping the room well-ventilated (open window, if possible, with a fan), flushing with the toilet lid closed, use of own personal products, and frequent hand washing have all been shown to reduce the risk of secondary household infection. Disinfection of shared surfaces may further reduce the risk. These interventions are most effective if implemented as soon as possible.<sup>1,2</sup>
- Care of the index case should be provided by a single household caregiver to reduce household spread. If possible, choose a caregiver who is younger and does not have medical comorbidities.
- Evidence is conflicting for the benefit of face masks worn by isolated cases or household contacts. Although some health agencies recommend the use of masks in this setting, other interventions should be prioritized given the current mask shortage. If you are going to wear a mask at home, be aware that mask changes and frequent adjustments may actually put you at increased risk, and hand washing around these moments is essential.<sup>2</sup>
- Guidelines for self-isolation of patients with COVID-19 in Manitoba: [https://www.gov.mb.ca/asset\\_library/en/coronavirus/coronavirus\\_selfisolation.pdf](https://www.gov.mb.ca/asset_library/en/coronavirus/coronavirus_selfisolation.pdf)

### **What measures can healthcare workers undertake to minimize any risk of transmitting the infection to members of their household?**

- Viral contamination of healthcare workers' personal protective equipment (PPE), clothing, and skin can occur while caring for individuals with acute viral infections.<sup>1</sup> Doffing of PPE is one mechanism for viral transfer to skin and clothing.<sup>2</sup>
- While the effectiveness of interventions (e.g. changing clothes or showering after a hospital shift) has not been investigated, some of these precautions were adopted during the SARS outbreak and may have contributed to lower rates of secondary infections in household contacts of healthcare workers.
- In light of this, it is a reasonable precaution to develop a post-work routine that includes changing clothes before leaving work and showering upon arriving home.
- Shared Health recommends changing clothes before going home, dedicating a pair of shoes for work only, and following normal laundry practices. ([Shared Health MB Guidelines](#))

## Public Health Interventions

### What process is involved in vaccine development?

- Without any proven effective treatment for SARS-CoV-2, there is an urgency for vaccine development. Vaccines can stagnate the progression of an outbreak, decrease transmission, and prevent future outbreaks. However, this is a long process on the scale of years.<sup>1</sup>
- Steps in vaccine development:<sup>2,3</sup>
  - (1) Starts with analyzing and understanding the virus itself to determine potential targets for candidate vaccines.
  - (2) Potential vaccines are developed and tested in non-clinical (preclinical) laboratory and/or animal settings, evaluating for effectiveness and safety.
  - (3) Successful candidates move onwards to clinical human trials: Phase I, II, and III. The sequential phases include increasing number of trial participants. Phase I evaluates vaccine safety and whether it produces an immune response. Phase II includes the intended target population. Phase III is a large-scale trial to evaluate efficacy and safety.
  - (4) Regulatory and review process and includes validation of manufacturing process.
  - (5) Final steps are manufacturing and quality control.
  - Monitoring continues after vaccines are licensed and administered for any adverse effects that may not have been apparent during trial and initial administration.
- On the road to vaccine development, several challenges can be expected due to the extensive development process which ensures safe, quality and effective vaccine

development.<sup>1</sup>

### **What are the different types of candidate SARS-CoV-2 vaccines?**

There are over 50 potential vaccine candidates in the pipeline globally that include a wide range of different technologies. The following is not an exhaustive list but includes a description of the most common types.

Whole virus vaccines.<sup>1,2</sup>

- Includes whole-cell killed, live attenuated, and vectored vaccines. The first two types make use of the original virus. Virus vector-based vaccines use a different live virus to express heterologous antigens from the virus of interest to promote immunity.
- Whole virus vaccines present multiple antigenic components to the host, thus promoting a diverse immunogenic response. They can also stimulate toll-like receptors (TLRs).
- Whole virus vaccines requires extensive additional testing to confirm their safety.

Subunit vaccines

- Subunit vaccines utilize one or more antigens specific to the virus that have strong immunogenicity to promote an immunogenic response from the host. Many of the candidate SARS-CoV-2 vaccines use the viral S protein as the subunit of choice. This is the surface exposed protein that mediates the interaction with the host cell through the ACE2 receptor.<sup>1,2</sup>
- This type of vaccine is safer and easier to produce, but often requires adjuvants. Adjuvants are substances that enhance the immunogenicity of highly purified antigens.<sup>3</sup>

Nucleic acid vaccines

- Includes DNA and mRNA vaccines. DNA vaccines are generally comprised of plasmid DNA molecules that encode one or more antigens. The DNA is taken up by cells and expressed in their nucleus, producing the characteristic antigen proteins, which then triggers an immunogenic response.<sup>4</sup>
- DNA vaccines come with the risk of causing mutations in the host genome.<sup>1</sup> mRNA vaccines work similarly, but do not integrate into the host genome, thus are safer.<sup>5</sup>

### **Are there any candidate SARS-CoV-2 vaccines in human clinical trials?**

- Currently there are two candidate vaccines in Phase I trials, one that is recruiting volunteers for Phase I trial, and one that is hoping to begin Phase I trial in April. Brief details of these are discussed below. There are many other vaccine candidates hoping to begin Phase I trials over the next few months.

### **mRNA-1273** [1,2](#)

Developer: Moderna Therapeutics and US National Institute of Allergy and Infectious Diseases (NIAID)

Type of vaccine: messenger RNA (mRNA) vaccine

Current development stage: Phase I human trial, funding by Coalition for Epidemic Preparedness Innovations (CEPI). Plan is to enroll 45 healthy adults to receive two doses separated by 1 month. First patient received their first dose on March 16, 2020. They hope to start Phase II trial in the Spring. If successful, the vaccine will likely not be commercially available for at least 12-18 months, but the company believes that it might be available for emergency use by Fall 2020.

### **Ad5-nCoV** [3](#)

Developer: CanSino and Institute of Biotechnology of the Academy of Military Medical Sciences

Type of vaccine: viral vector vaccine using the Adenovirus type 5 vector

Current development stage: Began Phase I human trial on March 16, 2020, and is studying low, medium, and high doses of the vaccine.

### **ChAdOx1** [3,4](#)

Developer: University of Oxford - Oxford Vaccine Group and the Jenner Institute

Type of vaccine: viral vector vaccine using a chimpanzee adenovirus vaccine vector to express the SARS-CoV-2 spike protein

Current development stage: Preclinical, but recruitment for Phase I human trial began at the end of March 2020. They are simultaneously working on scale-up of vaccine production.

### **INO-4800** [1,5](#)

Developer: Inovio Pharmaceuticals

Type of vaccine: DNA vaccine

Current development stage: preclinical, but they are collaborating with CEPI to begin Phase I trials in USA and with Beijing Advance for Phase I trials in China sometime in April. The company is targeting to scale up production with a goal of 1 million doses by the end of 2020, for either further trial use or emergency use.





## Pediatric Corner

### What is the risk of transmission of SARS-CoV-2 on playgrounds?

- To date there has not been any published literature specifically examining the transmission risk of SARS-CoV-2 on playgrounds. As discussed in the 1st edition of the COVID-19 Report, in an experimental laboratory setting, SARS-CoV-2 virus particles can be found on steel and plastic for up to 72 hours.<sup>1</sup>
- Other respiratory viruses have been shown to spread via playgrounds.
- A study in China investigated playgrounds as the reservoir for hand, foot and mouth disease (HFMD) outbreaks.<sup>2</sup> Enterovirus nucleic acid was detected on surfaces of several different playgrounds, suggesting possible transmission of virus when touched.
- In a case-control study of preschoolers, playgrounds were associated with HFMD with a 57% attributable fraction.<sup>3</sup> The authors observed a dose-response relationship with the number of different playgrounds children attended.
- As of Saturday, March 28, 2020, all public play structures in Winnipeg have been closed.<sup>4</sup>

### How does the clinical presentation differ in neonates and infants with COVID-19?

- In a Chinese national-wide case-series, illness severity ranged from asymptomatic infection to critical illness including ARDS and sepsis.<sup>1</sup> 10.5% of 379 infants with suspected COVID-19 developed severe-critical infections.
- As of April 1, 2020, three infant deaths associated with COVID-19 have been reported.
- Initial presentations may include non-specific symptoms such as temperature instability, poor feeding, lethargy, and emesis,<sup>2,3</sup> which can progress to predominantly respiratory symptoms including tachypnea, hypoxia, and cough.<sup>4</sup>
- Duration of illness seems to correlate with disease severity: 4-5 days in mild cases,<sup>2</sup> and 10-20+ days in severe-critical cases.<sup>4</sup>
- All documented positive cases in infants and neonates are believed to be due to familial or caregiver transmission.<sup>2,3</sup>

pandemic where rapid dissemination of information is essential, we have included information from evolving medical literature which may be awaiting peer-review.

This report was produced by a collaboration of fellows, residents, medical students, faculty leads, and librarians from the University of Manitoba and the Medical Microbiology and Infectious Diseases community.

Acknowledgement to this week's contributors (alphabetical order):

Fellows: Carl Boodman, Thomas Fear, Santana Lee, Milena Semproni, Robert Taylor

Residents: Karen Ballinger

Medical Students: Karam Al-Bayati, Emma Avery, Lauren Bath, Sandeep Devgan, Ihor Hayda, Roy Hutchings, Josh Jones, Suhyun Kim, Daniel Kroft, Tony Mao, Andrew McDermid, Pam McIntosh, Amanallah Montazeripouragha, Kari Parsons, Lana Tennenhouse, Neil Reed, Prabjot Singh, Sarah Tougas, Kayan Xu, Albert Yeung, Antonia Zhu

Librarians: Nicole Askin, Maureen Babb, Orvie Dingwall, Mê-Linh Lê, Janice Linton, Hal Loewen, Caroline Monnin, Christine Neilson, Angela Osterreicher, Janet Rothney

Staff Advisor: Dr. Jared Bullard

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**Email:** [mbcovid19report@gmail.com](mailto:mbcovid19report@gmail.com)

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