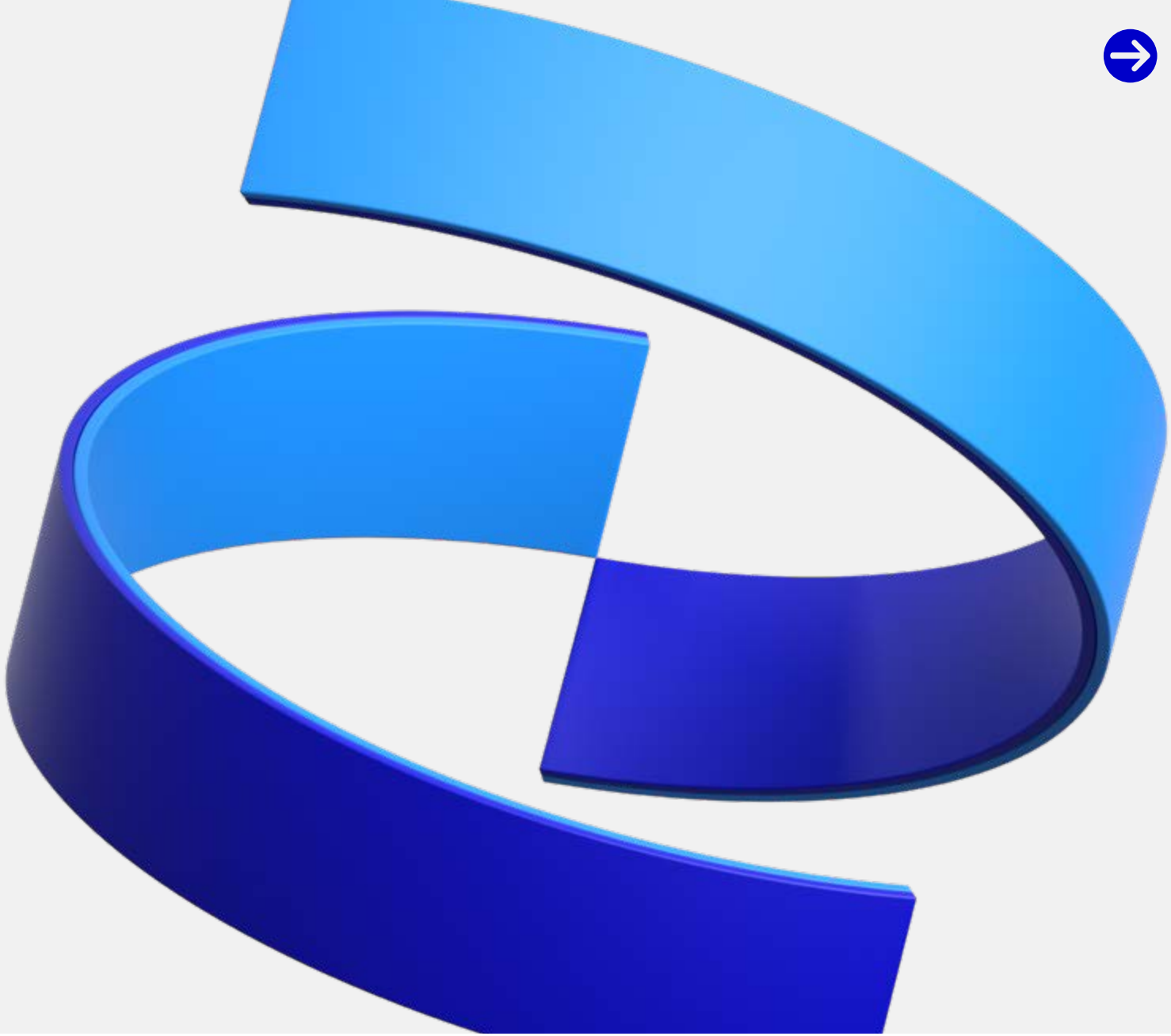
COVID 19: Clinical Presentation



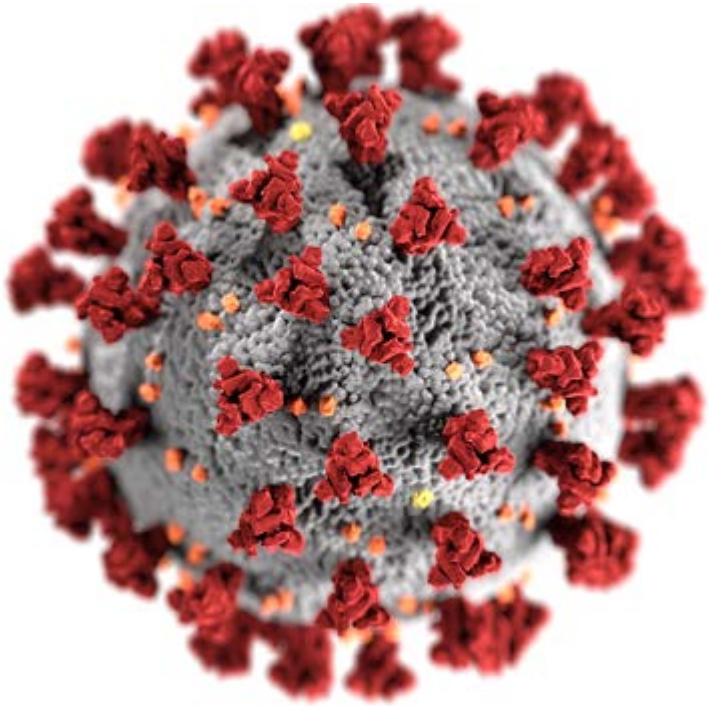
Content: Clinical Presentation

- SARS-CoV-2 Infection: COVID-19
- COVID-19 Epidemiology
- COVID-19 Disease Course and Symptoms
- Risk Factors for Severe COVID-19 Infection
- Hospitalization with COVID-19: Presenting Symptoms
- Special Populations: Paediatrics
- Special Populations: Immunosuppressed Patients
- Special Populations: Pregnancy
- Summary

SARS-CoV-2 Infection: COVID-19

SARS-CoV-2 Infection: COVID-19

- On 11 February 2020, WHO officials announced a new infectious disease named **COVID-19** caused by severe acute respiratory syndrome coronavirus 2 **(SARS-CoV-2)**[1]
- 'CO' stands for corona, 'VI' for virus, and 'D' for disease and the 19 for the year 2019 when it was first diagnosed[2]
- Guidelines agreed by the WHO, the World Organisation for Animal Health and the Food and Agriculture Organisation of the United Nations stated that the disease name must:
  - Be pronounceable
  - Be related to the disease
  - Not refer to a geographical location, animal, individual or group of people

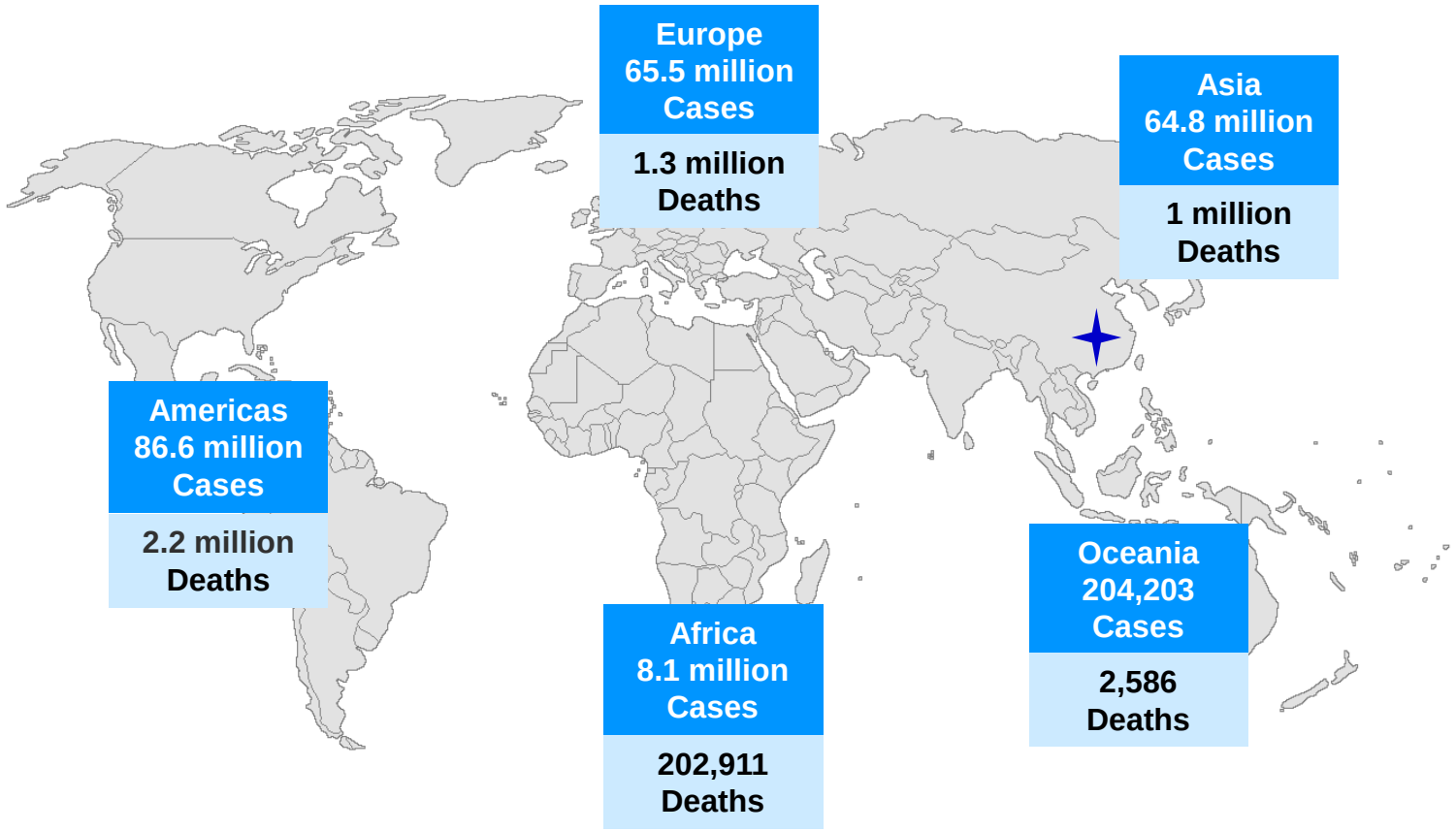


Permission to use image received (CDC)

1. Who Director-General's remarks at media briefing on 2019-nCOV,11 February 2020. [Online] Available from https://www.who.int/director-general/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 [Accessed 30 July 2021] 2. CDC About COVID-19 [Online] Available from https://www.cdc.gov/coronavirus/2019-ncov/your-health/about-covid-19/basics-covid-19.html

COVID-19 Epidemiology

Global COVID-19 Cases and Deaths Recorded up to September 16 2021[1]



- Following the emergence of the first case of infection in China, cases of SARS-CoV-2 infection spread rapidly across the globe
- Over 200 countries have reported cases of COVID-19
- Over 225 million cases reported Worldwide
- Over 4.6 million deaths

1. ECDC. COVID-19 situation update worldwide, as of week 36 2021. [Online] Available from: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases [Accessed 16 September 2021];

Top 10 Countries by Confirmed Cases and Deaths

Cases of, and deaths from, COVID-19 continue to increase globally

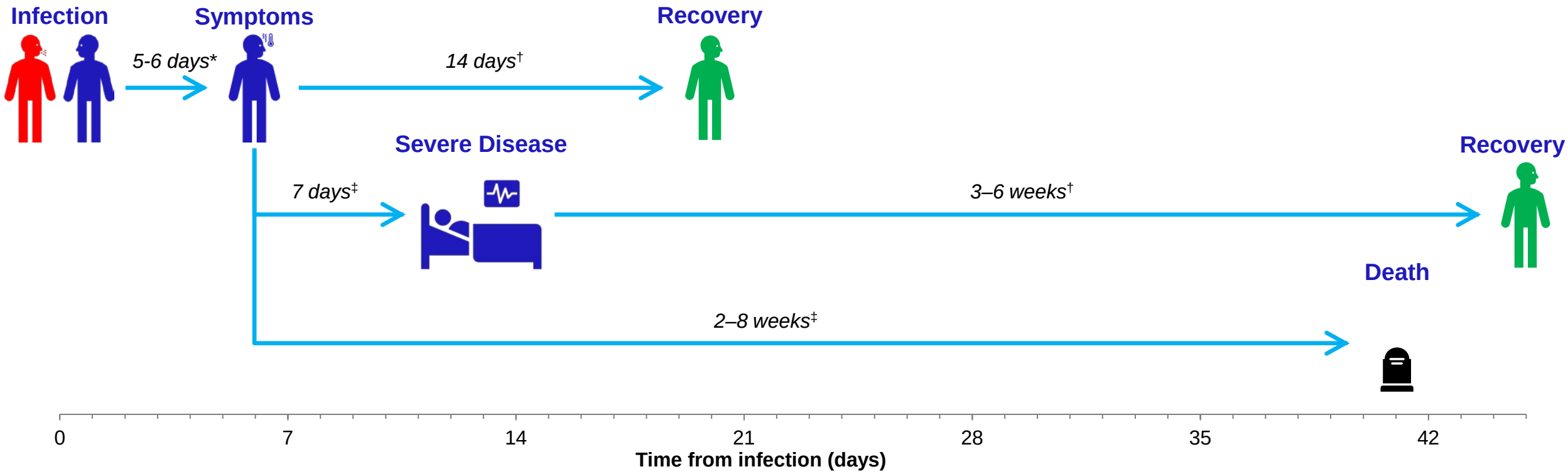
Confirmed Cases Global: 213,912,908	
US:	38,223,029
India:	32,558,530
Brazil:	20,645,537
France:	6,757,783
Russia:	6,709,605
UK:	6,621,799
Turkey:	6,273,651
Argentina:	5,155,079
Colombia:	4,897,150
Spain:	4,815,205

Deaths Global: 4,463,734	
US:	632,272
Brazil:	576,645
India:	436,365
Mexico:	255,452
Peru:	197,944
Russia:	175,328
UK:	132,323
Indonesia:	129,293
Italy:	128,914
Colombia:	124,474

Our World in Data. Coronavirus (COVID-19) Cases [online]. Available from https://ourworldindata.org/covid-cases [Accessed August 2021]

COVID-19 Disease Course and Symptoms

COVID-19 Disease Course

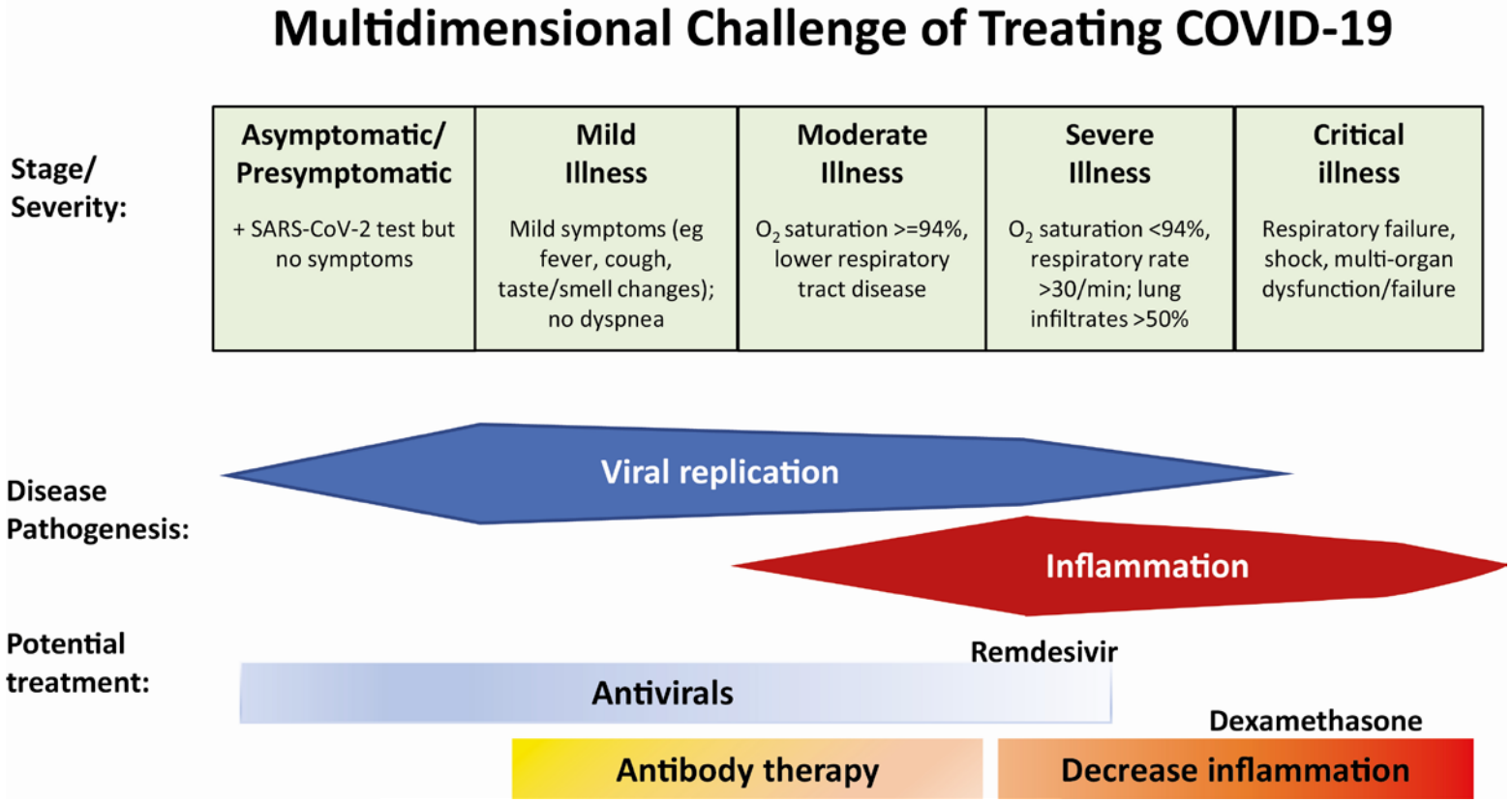


*mean; † median; ‡ unknown average type

1. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19): 16–24 February 2020 [online] Available at https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf [Accessed August 2021]

Signs and Symptoms Over the Disease Course

- The signs and symptoms experienced by patients are determined by the disease pathogenesis, with milder illness correlating with viral replication, and more severe illness correlating with the body's inflammatory response



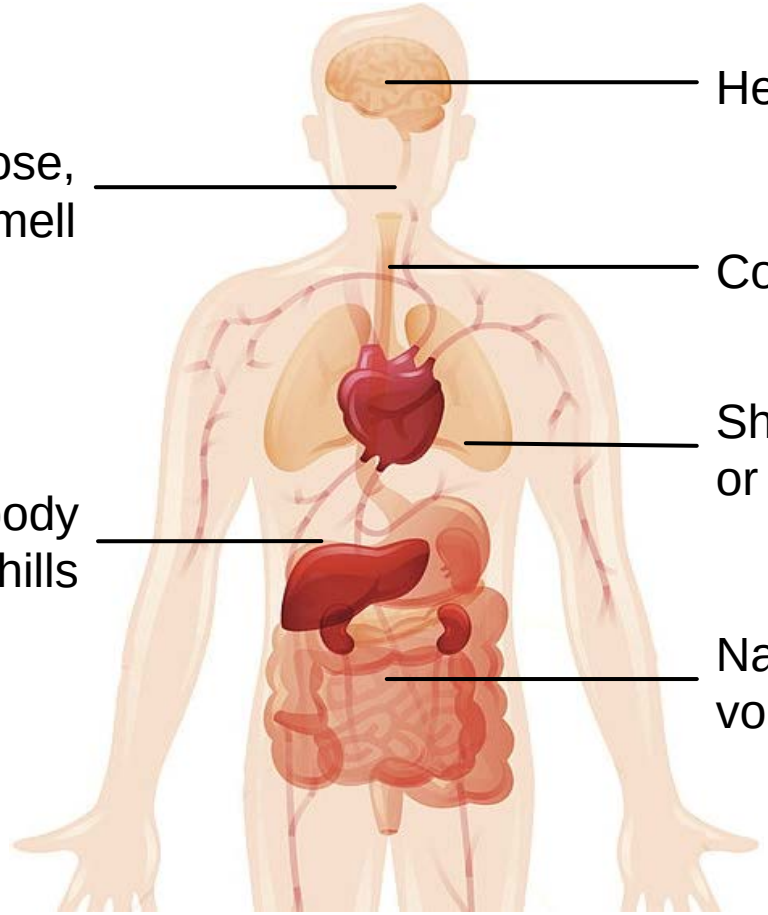
Permission to use image received
Adapted from Gandhi RT, et al. Clinical Infectious Diseases. 2020 doi: 10.1093/cid/ciaa1132.

Clinical Symptoms Reported Across the Global Population*

Symptom	Studies Reporting (n)	% of Presenting Symptoms
Fever	144	59
Cough	139	55
Dyspnea	99	31
Sore throat	62	14
Headache	76	12
Fatigue	78	28
Myalgia	69	17
Sputum/secretion	57	25
Diarrhea	85	10
Chest pain	27	11
Nasal congestion	19	5
Hemoptysis	17	2
Rhinorrhea	32	8
Abdominal pain	16	5
Confusion	7	6
Anorexia	18	20

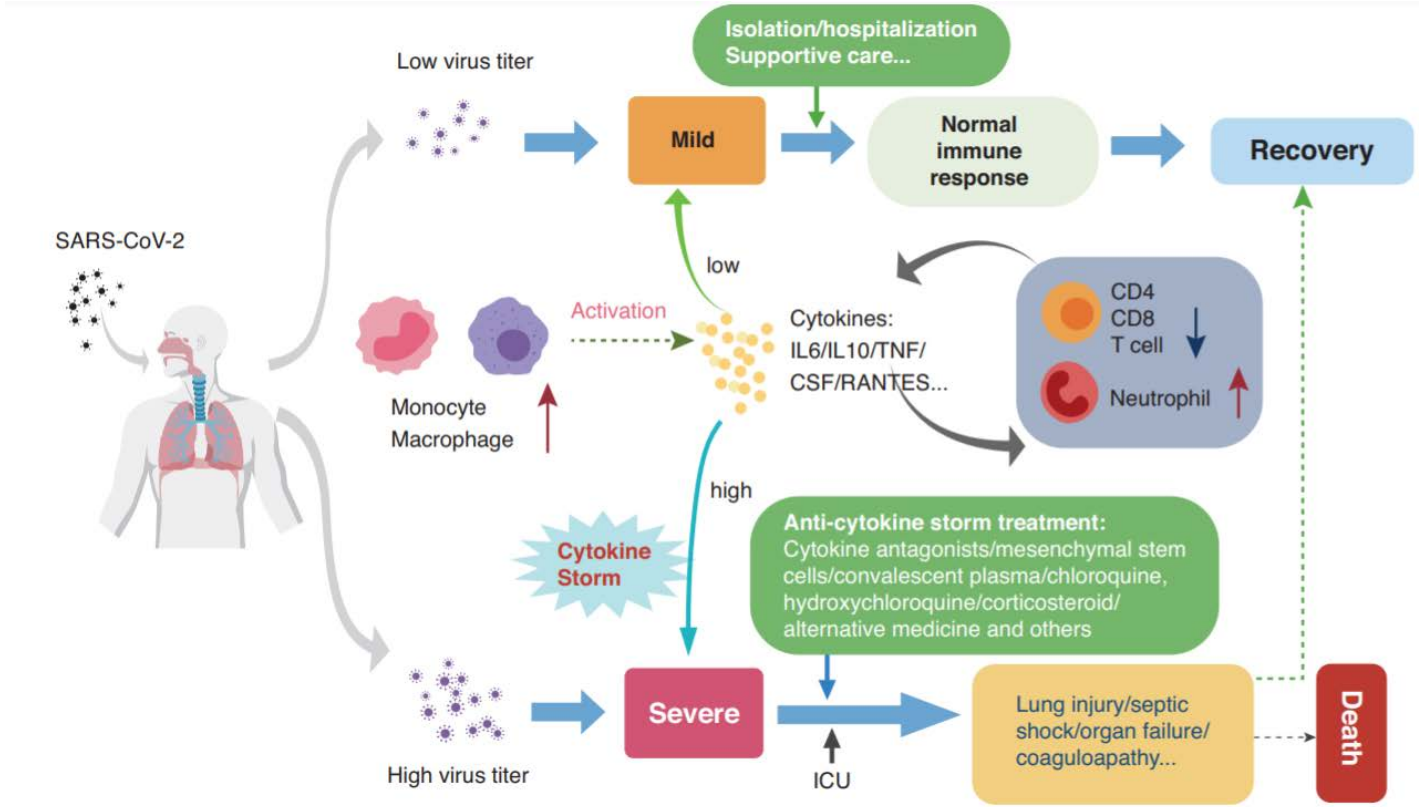
*Data from a systemic review of most common clinical manifestations in patients diagnosed with COVID-19 that included 152 publications, a total of 41,409 individuals from at least 23 countries; Percentages rounded to nearest integer value
Mesquita R et al. Clinical manifestations of COVID-19 in the general population: systematic review. Wien Klin Wochenschr. 2021 Apr;133(7-8):377-382.

Primary Symptoms of COVID-19[1,2]



1. Li L, et al. J Med Virol. 2020;92:577–83; 2. CDC. Symptoms of coronavirus. [Online] Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html [Accessed 30 July 2021].

Inflammatory Response



- Monocytes and macrophages can be infected by SARS-CoV-2
- Monocytes from COVID-19 patients show an activated phenotype, and can produce cytokines IL-6, IL-10 and TNF
- A high level of cytokines triggers a cytokine storm, leading to more severe disease, and possibly death

CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; CSF, colony stimulating factor; ICU, intensive care unit; IL, interleukin; RANTES, regulated on activation, normal t cell expressed and secreted; TNF, tumor necrosis factor.
Adapted from Wang J, et al. J Leukonc Biol 2020;108:17.

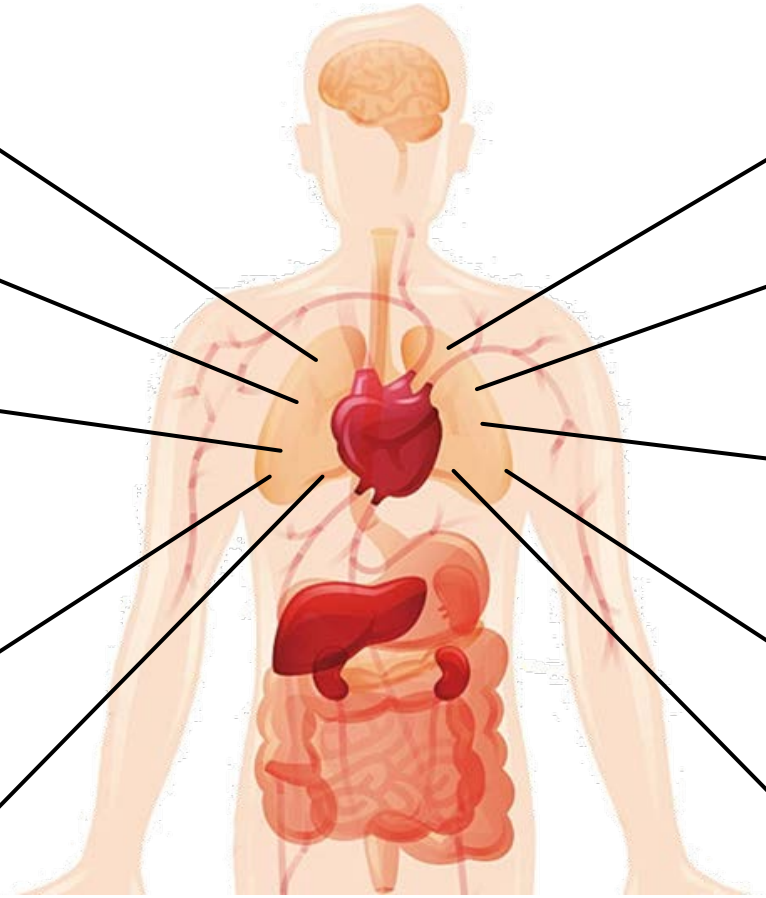
Pulmonary Manifestations of COVID-19

Symptoms[1]

- Fatigue
- Cough
- Dyspnea

Signs[2]

- Increased breathing rate
- Decreased oxygen saturation



- Sputum production
- Respiratory failure
- Acute Respiratory Distress Syndrome (ARDS)
- Low PaO_2/FiO_2
- Imaging shows lung infiltrates

PaO_2/FiO_2, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen

1. Johnson KD, et al. *Front Med (Lausanne).* 2020;7:526. 2. NIH COVID-19 Treatment Guidelines. Clinical Spectrum of SARS-CoV-2 Infection. Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ [Accessed 30 July 2021].

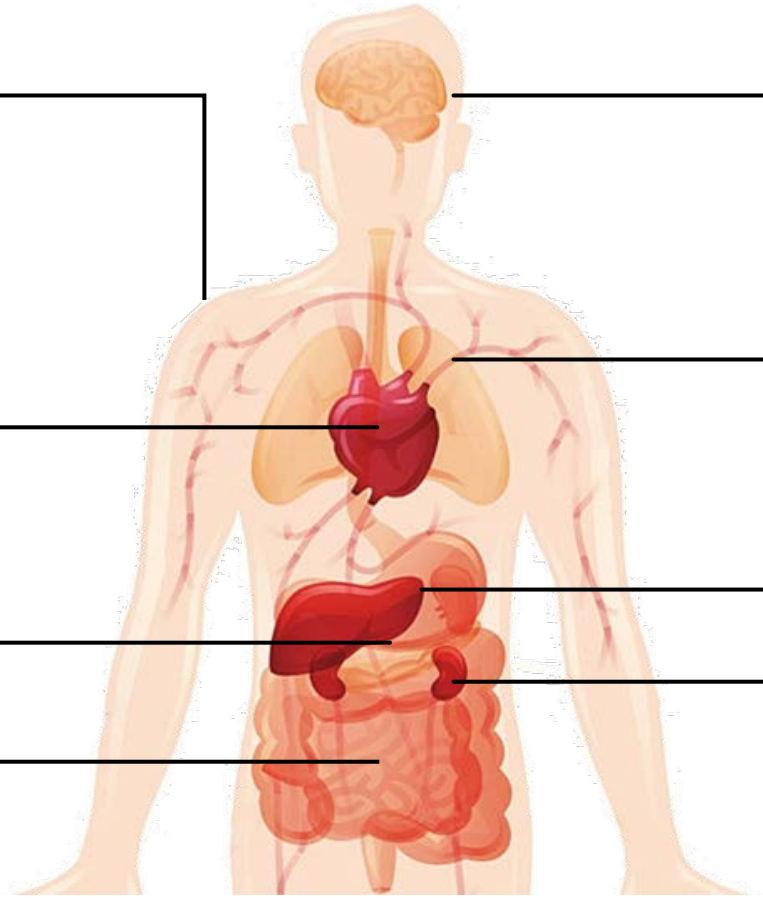
Extrapulmonary Manifestations of COVID-19

Dermatologic
- Petechiae
- Livedo reticularis
- Erythematous rash
- Urticaria
- Vesicles
- Pernio-like lesions

Cardiac
- Takotsubo cardiomyopathy
- Myocardial injury/myocarditis
- Cardiac arrhythmias
- Cardiogenic shock
- Myocardial ischemia
- Acute cor pulmonale

Endocrine
- Hyperglycemia
- Diabetic ketoacidosis

Gastrointestinal
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Anorexia



Neurologic
- Headaches
- Dizziness
- Encephalopathy
- Guillain-Barré
- Ageusia
- Myalgia
- Anosmia
- Stroke

Cardiovascular
- Deep vein thrombosis
- Pulmonary embolism
- Catheter-related thrombosis

Hepatic
- Elevated ALT/AST
- Elevated bilirubin

Renal
- Acute kidney injury
- Proteinuria
- Hematuria

Gupta A, et al. Nat Med 2020;26:1017.

NIH Guidelines: The COVID-19 Severity Spectrum

Stage	Characteristics
Asymptomatic or pre-symptomatic	Positive test for SARS-CoV-2 but no symptoms
Mild illness	Varied symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain) but no shortness of breath, dyspnea or abnormal imaging
Moderate illness	SpO_2 ≥94% and evidence of lower respiratory disease during clinical assessment or imaging
Severe illness	SpO_2 <94%, PaO_2/FiO_2 <300mmHg, respiratory rate >30 breaths/min, or lung infiltrates >50% on imaging
Critical illness	Respiratory failure, septic shock, and/or multiorgan dysfunction

NIH, National Institutes of Health; PaO_2/FiO_2 , ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; SpO_2, oxygen saturation.

NIH COVID-19 Treatment Guidelines. Clinical Spectrum of SARS-CoV-2 Infection. Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ [Accessed 30 July 2021].

Overview of Disease Course

- Data suggest that:
  - 80% of cases are asymptomatic or mild[1],
  - 15% are severe[1], and
  - 5% are critical[1]
- Data on the percentage of people with COVID-19 who require hospital admission is difficult to estimate, as people who are asymptomatic may not get tested and confirmed as being infected[2]
  - A recent study based on US COVID-19 cases estimated the infection-hospitalization ratio at 2.1%, although varies based on age and race[2]
- Of hospitalized patients:
  - Median hospital stay has been estimated at 5 days[3]
  - 86.4% recover[3]
  - 21.9% admitted to ICU[3]
  - 16.9% required invasive mechanical ventilation[3]
  - 13.6% die[3]

1. World Health Organisation. Coronavirus disease (COVID-19): Similarities and differences with influenza 2020 [online] Available from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19-similarities-and-differences-with-influenza [Accessed September 2021]; 2. Menachemi N, et al. J Public Health Manag Pract. 2021;27:246–50; 3. Di Fusco M, et al. J Med Econ. 2021;24:308–17

Risk Factors For Severe COVID-19 Infection

Risk Factors For Severe Illness from COVID-19 Infection

- **Older adults:** risk increases with age from 50 years onwards, those aged ≥85 years are at the highest risk
- **Racial/ethnic minority groups and people with disabilities:** risk increases with increase in likelihood of comorbidities, reduced healthcare access and increased likelihood of living in a congregate setting
- **People with medical conditions:** including cancer, chronic kidney disease, chronic lung diseases, dementia and other neurological conditions, diabetes, down syndrome, heart conditions, HIV, immunocompromised, liver disease, obesity, SCD, transplant recipient, CVD
- **Pregnant and recently pregnant people:** Pregnant people with COVID-19 are more likely to experience preterm birth and other poor outcomes related to pregnancy versus pregnant people without COVID-19

CDC [online] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Last accessed August 2021

Hospitalization with COVID-19: Presenting Symptoms

Presenting Symptoms: Hospitalized Patients

Symptom	Prevalence
Fever	71.6
Shortness of breath	71.2
Cough	68.9
Fatigue	45.5
Confusion	26.7
Cough (sputum)	26.2
Muscle ache	20.6
Diarrhoea	20.4
Nausea/vomiting	19.8
Chest pain	14.6
Headache	12.5
Wheeze	10.9
Abdominal pain	10.2
Sore throat	9.8

Symptoms associated with viral pneumonia

Docherty AB, et al. BMJ 2020;369:m1985; Verity R, et al. Lancet Infect Dis. 2020;20:669–77

Special Population: Paediatrics

COVID-19 in Children: Clinical Characteristics

- Children appear more likely to be asymptomatic than adults
  - Studies describe rates of asymptomatic infection as high as 13%, but true prevalence remains unknown
- Most commonly reported symptoms in children similar to those in adults
  - Fever, cough, shortness of breath, myalgia, fatigue and headache
  - Sore throat or pharyngeal erythema (5–50%), myalgia (10–25%), rhinorrhea/nasal congestion (4–30%) and headache (3–28%) have also been described
  - Gastrointestinal pain, nausea/vomiting and diarrhoea seem to occur less commonly in children (5–10%)
  - Anosmia and ageusia have not yet been reported
    - possibly due to challenges eliciting this type of symptomatology from younger children
- The overlap of symptoms with other respiratory tract viral infections common in children, such as influenza and respiratory syncytial virus, poses additional challenges to recognition of COVID-19.

Rajapakse N, Dixit D. Paediatr Int Child Health 2021 Feb;41(1):36–55.

Children with COVID-19: A Systematic Review

- A meta-analysis of 48 studies[1] in paediatric patients with COVID-19 (n=5,829), exploring most common clinical and laboratory findings
- Children of all ages at risk of COVID-19[1]
- Main illness classifications[1]:
  - Asymptomatic: 20% (95% CI: 14–26%)
  - Mild: 33% (95% CI: 23–43%)
  - Moderate: 51% (95% CI: 42–61%)
- The most prevalent symptom was fever, followed by cough, nasal symptoms, diarrhea, and nausea/vomiting[2]

Features	
Typical Clinical Manifestations	
Fever	51%
Cough	41%
Laboratory Findings	
Normal white blood cell count	69%
Lymphopenia	16%
Elevated creatine-kinase myoglobulin bound (CK-MB)	37%
Imaging	
Normal chest imaging	41%
Ground-glass opacities	36%

1. Cui X et al. J Med Virol 2021;93(2):1057–69; 2. de Souza TH et al. Pediatr Pulmonol 2020;55(8):1892–9.

Special Population: Immunosuppressed Patients

COVID-19 and Immunocompromised Patients

- Due to impaired immune defenses from both underlying disease and treatment, immunocompromised patients with respiratory virus infection are at risk of:[1]
  - More severe infection[1]
  - Increased rates of bacterial and fungal superinfection[1]
- Similar concerns exist regarding immunosuppressed patients infected with SARS-CoV-2[1,2]
- However, association between COVID-19 and intense cytokine release raises the possibility that immunosuppression may temper the exuberant inflammatory response in this infection[1]
- Important issues remain, specifically[1]
  - Possibility of atypical clinical manifestations in the immunocompromised[1]
  - Attributable risk of immunosuppression versus other comorbidities on COVID-19 severity[1]
- Patients with cancer appear to have an increased risk of severe outcomes[1,2]
- Well-treated HIV is not associated with an excess risk of severe COVID-19[3]

1. Fung M, Babik JM. Clin Infect Dis 2021;72(2):340–50; 2. CDC. People with Certain Medical Conditions. [Online] Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html [Accessed 30 July 2021].3. CDC. Guidance for COVID-19 and People with HIV. [Online]https://clinicalinfo.hiv.gov/en/guidelines/covid-19-and-persons-hiv-interim-guidance/interim-guidance-covid-19-and-persons-hiv

Special Population: Pregnancy

COVID-19 in Pregnancy

- Pregnant people are at greater risk of having severe illness following COVID-19 infection, particularly if there are other factors that put them at greater risk – such as having underlying medical conditions[1]
- Compared with pregnant people without COVID-19, those with COVID-19 are more likely to experience adverse pregnancy outcomes, including:[1,2]
  - Preterm birth[1,2]
  - Pregnancy loss[1]
  - Stillbirth[2]
  - Preeclampsia[2]
- In addition, compared with pregnant people with mild COVID-19, those with severe COVID-19 during pregnancy are at greater risk of:[2]
  - Gestational diabetes[2]
  - Low birth weight[2]

1. CDC. Pregnant and Recently Pregnant People at Increased Risk for Severe Illness from COVID-19 [online]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnant-people.html [Accessed August 2021];
2. Wei SQ, et al. CMAJ 2021;193:E540–8

Summary

Summary: Clinical Presentation

- COVID-19 primarily impacts the respiratory system, though most organ systems can be involved[1]
  - Symptom onset ranges from 2–14 days after exposure to SARS-CoV-2[3]
- Patients are at risk of disease transmission before onset of symptoms[4]
- Patients infected with SARS-CoV-2 can be asymptomatic or present with a range of clinical signs and symptoms ranging from mild to critical[1,3,4]
- The patient journey varies according to disease severity[5]
- Children appear more likely to be asymptomatic than adults, yet the commonly reported symptoms in children are similar to those in adults[6]
- Due to impaired immune defenses from both underlying disease and treatment, immunocompromised patients with respiratory virus infection are at risk of more severe infection and increased rates of bacterial and fungal superinfection[7]
- Compared with pregnant people without COVID-19, those with COVID-19 are more likely to experience adverse pregnancy outcomes, including preterm birth, pregnancy loss, stillbirth and preeclampsia[8,9]

1. Li L, et al. J Med Virol 2020;92:577–83; 2. NIH COVID-19 Treatment Guidelines. Clinical Spectrum of SARS-CoV-2 Infection. [Online] Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ [Accessed 30 July 2021]; 3. Docherty AB, et al. BMJ 2020;369:m1985; 4. Zhang J, et al. Lancet Infect Dis 2020;20:793–802. 4. CDC. Symptoms of coronavirus. [Online] Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html [Accessed 30 July 2021]. 5. 1. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19): 16–24 February 2020 [online] Available at https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf [Accessed August 2021]; 6. Rajapakse N, Dixit D. Paediatr Int Child Health 2021 Feb;41(1):36–55. 7. Fung M, Babik JM. Clin Infect Dis 2021;72(2):340–50; 8 CDC. Pregnant and Recently Pregnant People at Increased Risk for Severe Illness from COVID-19 [online]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnant-people.html [Accessed August 2021]; 9. Wei SQ, et al. CMAJ 2021;193:E540–8