COVID-19 WHO Scientific Reports

COVID-19 and the Use of Angiotensin-Converting Enzyme Inhibitors and Receptor Blockers

Scientific Brief

7 May 2020

Background

Concerns exists that angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) increase susceptibility to coronavirus SARS CoV-2 (the viral agent that causes the disease COVID-19) and the likelihood of severe COVID-19 illness.1 These concerns are based on considerations of biological plausibility,2 and the observation that there is an overrepresentation of patients with hypertension and other cardiovascular comorbidities among patients with COVID-19 who have poor outcomes.3 Millions of people around the world are on treatment with ACE-Is and ARBs for hypertension, heart failure, coronary artery disease, or kidney disease. Speculation about worse outcomes among patients on these medications during the COVID-19 pandemic has caused widespread anxiety among patients and their care providers. On the other hand, the harms of indiscriminate withdrawal of these medications on cardiovascular outcomes are well documented.4 There is also widespread speculation about the potential benefits of ACE-Is and ARBs, based on biological plausibility arguments and animal data and small clinical studies on patients with other viral respiratory infections.5

This brief summarizes the current evidence on the impact of ACE inhibitors or angiotensin receptor blockers on severe acute respiratory illness due to SARS CoV-2.

Methods

A rapid review was carried out using Ovid MEDLINE and the Cochrane Database of Systematic Reviews from 1 January 2003 to 24 April 2020 as well as the World Health Organization database of COVID-19 publications, clinicaltrials.gov, and medRxiv.org from inception to 17 April 2020 using terms for COVID-19, SARS virus, Middle East Respiratory Syndrome, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists. Additional citations were identified from hand-searching reference lists. Studies in all languages were included. Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale.

Review of the evidence: The rapid review identified 11 observational studies,6-16 eight of which were conducted in China,8-10, 12-16 along with single studies from Italy,11 the United Kingdom,7 and the United States.6 Nearly all studies included only patients with lab-confirmed COVID-19. No studies were found that were designed to directly assess whether ACE inhibitors or ARBs increase the risk of acquiring COVID-19. After adjustment for confounders, history of ACE inhibitor or ARB use was not found to be associated with increased severity of COVID-19 illness. There were no studies that address the potential benefits and harms of initiating ACE inhibitors or ARBs as treatment for patients with COVID-19.

Conclusion

There is low-certainty evidence that patients on long-term therapy with ACE inhibitors or ARBs are not at higher risk of poor outcomes from COVID-19.

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Estimating Mortality from COVID-19

Scientific Brief

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Background

An important characteristic of an infectious disease, particularly one caused by a novel pathogen like SARS-CoV-2, is its severity, the ultimate measure of which is its ability to cause death. Fatality rates help us understand the severity of a disease, identify at-risk populations, and evaluate quality of healthcare.

There are two measures used to assess the proportion of infected individuals with fatal outcomes. The first is infection fatality ratio (IFR), which estimates this proportion of deaths among all infected individuals. The second is case fatality ratio (CFR), which estimates this proportion of deaths among identified confirmed cases.

To measure IFR accurately, a complete picture of the number of infections of, and deaths caused by, the disease must be known. Consequently, at this early stage of the pandemic, most estimates of fatality ratios have been based on cases detected through surveillance and calculated using crude methods, giving rise to widely variable estimates of CFR by country – from less than 0.1% to over 25%.

For COVID-19, as for many infectious diseases, the true level of transmission is frequently underestimated because a substantial proportion of people with the infection are undetected either because they are asymptomatic or have only mild symptoms and thus typically fail to present at healthcare facilities [1,2]. There may also be neglected or under-served segments of the population who are less likely to access healthcare or testing. Under-detection of cases may be exacerbated during an epidemic, when testing capacity may be limited and restricted to people with severe cases and priority risk groups (such as frontline healthcare workers, elderly people and people with comorbidities) [3,4]. Cases may also be misdiagnosed and attributed to other diseases with similar clinical presentation, such as influenza.

Differences in mortality between groups of people and countries are important proxy indicators of relative risk of death that guide policy decisions regarding scarce medical resource allocation during the ongoing COVID-19 pandemic. This document is intended to help countries estimate CFR and, if possible, IFR, as appropriately and accurately as possible, while accounting for possible biases in their estimation.

A note on terminology: The acronym CFR, as applied to the measure of the number of deaths among all persons with a disease, is most commonly referred to as the ‘case fatality rate,’ although strictly speaking this term is incorrect because the term ‘rate’ is used to denote a time component, which is absent in the CFR. Some authors have attempted to rectify this inconsistency by using the term case fatality proportion, or case fatality ratio, which is not bound by the numerator being a subset of the denominator (i.e., the definition of a proportion). The term ‘case fatality risk,’ used more rarely, is only correct if the duration of the clinical illness is known. For the purposes of this document, we will use the term “case fatality ratio”.

COVID-19 case and death definitions: Countries have varying approaches to COVID-19 case definitions. Consequently, the numerator and the denominator of any formula used to calculate fatality rate will vary according to how they are defined. WHO recommends using the surveillance case definitions which are available in the WHO interim guidance on Global surveillance for COVID-19 [5].

A COVID-19 death is defined for surveillance purposes as a death resulting from a clinically compatible illness in a probable or confirmed COVID-19 case, unless there is a clear alternative

cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery between the illness and death [6].

Calculating IFR: The true severity of a disease can be described by the Infection Fatality Ratio:

Serological testing of a representative random sample of the population to detect evidence of exposure to a pathogen is an important method to estimate the true number of infected individuals [7,8,9]. Many such serological surveys are currently being undertaken worldwide [10], and some have thus far suggested substantial under-ascertainment of cases, with estimates of IFR converging at approximately 0.5 - 1% [10-12].

As serological studies require an investment of time and resources, there are many situations in which they may not be conducted timely, or even at all. Nevertheless, it remains crucial to monitor trends in severity in real time. In such situations, estimates need to be made with routinely available surveillance data, which generally consist of time-series of cases and deaths reported in aggregate.

Calculating CFR: Case fatality ratio (CFR) is the proportion of individuals diagnosed with a disease who die from that disease and is therefore a measure of severity among detected cases:

Reliable CFRs that can be used to assess the deadliness of an outbreak and evaluate any implemented public health measures are generally obtained at the end of an outbreak, after all cases have been resolved (affected individuals either died or recovered). However, this calculation may not hold in an ongoing epidemic, because it makes two assumptions:

Assumption 1: The likelihood of detecting cases and deaths is consistent over the course of the outbreak.

Early in an outbreak, surveillance tends to focus more on symptomatic patients who seek care, so milder and asymptomatic cases are less likely to be detected, leading to overestimation of CFR; this overestimation may decrease as testing and active case finding increase. One method to account for this is to remove from the analysis those cases that occurred before the establishment of robust surveillance, including application of clear case definitions (a method called left censoring).

Assumption 2: All detected cases have resolved (that is, reported cases have either recovered or died).

During an ongoing epidemic, some of the active cases already detected may subsequently die, leading to underestimation of CFR estimated before their death. This effect is accentuated in fast-growing epidemics (e.g. during the exponential growth phase of COVID-19).

Calculating CFR during an ongoing epidemic: CFR calculated using the above formula during ongoing epidemics provides a conditional, estimate of CFR and is influenced by lags in report dates for cases and deaths [13]. This leads to a wide variation in CFR estimates over the course of an epidemic, which tends toward a stable, final estimate of CFR as active cases are resolved.

One simple solution to mitigating the bias due to delays to case resolution during an ongoing outbreak is to restrict the analysis to resolved cases:

However, this method does not eliminate all biases related to delayed reporting. For example, differences in the time it takes for cases to resolve can bias this estimate. If people sick with the disease typically die quicker than they recover, CFR may be overestimated. If the reverse is true, it may be underestimated. Therefore, more sophisticated approaches that make use of statistical techniques to predict future outcomes among active cases based on the probabilities of past outcomes may be applied, including modified Kaplan-Meier survival analysis [14,15]. Two important drawbacks to such approaches are first, that they tend to require individual-level

data that are less accessible in real-time than aggregate case and death counts; and second, that they are less simple to do, generally requiring the application of advanced statistical methods.

Taking risk groups into account: The severity of COVID-19 has been widely reported to be influenced by age, sex and underlying comorbidities [10,16,17], and there is some evidence that other factors, such as ethnicity, are also independent risk factors [18]. Any attempt to capture a single measure of fatality in a population will fail to account for the underlying heterogeneities between different risk groups, and the important bias that occurs due to their different distributions within and between populations [19]. Therefore, efforts should be made to calculate risk-group-specific estimates of fatality risk in order to better describe the true patterns of fatality occurring in a population.

Potential bias in detection of cases and deaths: These biases may vary over the course of an outbreak:

- At the start of an outbreak, those cases detected are more likely to be severe or fatal. Patients with severe illness are more likely to present at health facilities and to be confirmed by laboratory test.
- Delays in reporting deaths can lead to underestimation of the CFR.
- COVID-19 cases and deaths occurring in the community that go undetected or are reported late because they were incorrectly attributed to other causes.
- If deaths are more likely to be reported than recoveries, an overestimation of CFR will occur. The reverse leads to underestimation.

It is unlikely that all deaths will be detected and correctly assigned, even though detecting deaths may be subject to less bias than case detection.

Conclusion

In the COVID-19 pandemic, we have seen broad variations in naïve estimations of CFR that may be misleading. Countries are difficult to compare for a number of reasons. They may be more or less likely to detect and report all COVID-19 deaths. Furthermore, they may be using different case definitions and testing strategies or counting cases differently (for example, with mild cases not being tested or counted). Variations in CFR also may be explained in part by the way time lags are handled. Differing quality of care or interventions being introduced at different stages of the illness also may play a role. Finally, the profile of patients (for example their age, sex, ethnicity and underlying comorbidities) may vary between countries.

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WHO continues to monitor the situation closely for any changes that may affect this scientific brief. Should any factors change, WHO will issue a further update. Otherwise, this scientific brief document will expire 2 years after the date of publication.

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Bacille Calmette-Guérin (BCG) vaccination and COVID-19

Scientific Brief

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Summary

There is no evidence that the Bacille Calmette-Guérin vaccine (BCG) protects people against infection with COVID-19 virus. Two clinical trials addressing this question are underway, and WHO will evaluate the evidence when it is available. In the absence of evidence, WHO does not recommend BCG vaccination for the prevention of COVID-19. WHO continues to recommend neonatal BCG vaccination in countries or settings with a high incidence of tuberculosis[1].

There is experimental evidence from both animal and human studies that the BCG vaccine has non-specific effects on the immune system. These effects have not been well characterized and their clinical relevance is unknown[2,3].

On 11 April 2020, WHO updated its ongoing evidence review of the major scientific databases and clinical trial repositories, using English, French and Chinese search terms for COVID-19, coronavirus, SARS-CoV-2 and BCG.

The review yielded three preprints (manuscripts posted online before peer-review), in which the authors compared the incidence of COVID-19 cases in countries where the BCG vaccine is used with countries where it is not used and observed that countries that routinely used the vaccine in neonates had less reported cases of COVID-19 to date. Such ecological studies are prone to significant bias from many confounders, including differences in national demographics and disease burden, testing rates for COVID-19 virus infections, and the stage of the pandemic in each country.

The review also yielded two registered protocols for clinical trials, both of which aim to study the effects of BCG vaccination given to health care workers directly involved in the care of patients with COVID-19[4,5].

BCG vaccination prevents severe forms of tuberculosis in children and diversion of local supplies may result in neonates not being vaccinated, resulting in an increase of disease and deaths from tuberculosis[6-8]. In the absence of evidence, WHO does not recommend BCG vaccination for the prevention of COVID-19. WHO continues to recommend neonatal BCG vaccination in countries or settings with a high incidence of tuberculosis.

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Breastfeeding and COVID-19

Scientific Brief

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Introduction

Breastfeeding is the cornerstone of infant and young child survival, nutrition and development and maternal health. The World Health Organization recommends exclusive breastfeeding for the first 6 months of life, followed by continued breastfeeding with appropriate complementary foods for up to 2 years and beyond.1 Early and uninterrupted skin-to-skin contact, rooming-in2 and kangaroo mother care3 also significantly improve neonatal survival and reduce morbidity and are recommended by WHO.

However, concerns have been raised about whether mothers with COVID-19 can transmit the SARS-CoV-2 virus to their infant or young child through breastfeeding. Recommendations on mother-infant contact and breastfeeding must be based on a full consideration of not only of the potential risks of COVID-19 infection of the infant, but also the risks of morbidity and mortality associated with not breastfeeding, the inappropriate use of infant formula milks, as well as the protective effects of skin-to-skin contact. This scientific brief examines the evidence to date on the risks of transmission of COVID-19 from an infected mother to her baby through breastfeeding as well as evidence on the risks to child health from not breastfeeding.

WHO recommendations: WHO recommends that mothers with suspected or confirmed COVID-19 should be encouraged to initiate or continue to breastfeed. Mothers should be counselled that the benefits of breastfeeding substantially outweigh the potential risks for transmission.4

Mother and infant should be enabled to remain together while rooming-in throughout the day and night and to practice skin-to-skin contact, including kangaroo mother care, especially immediately after birth and during establishment of breastfeeding, whether they or their infants have suspected or confirmed COVID-19.

Methods

A living systematic review of evidence that followed the procedures of the Cochrane handbook for systematic reviews of interventions was carried out with the latest search done on 15 May 2020 to identify studies including mothers with suspected or confirmed COVID-19 and their infants or young children.5 The search was conducted on Cochrane Library, EMBASE (OVID), PubMed (MEDLINE), Web of Science Core Collection (Clarivate Analytics) and the WHO Global Database. A total of 12,198 records were retrieved, 6945 were screened after removing duplicates, and 153 records with mother-infant dyads in which the mother had COVID-19 were included in full-text review.

Results

A total of 46 mother-infant dyads had breastmilk samples tested for COVID-19. All mothers had COVID-19, while 13 infants tested COVID-19 positive. Breastmilk samples from 43 mothers were negative for the COVID-19 virus while samples from 3 mothers tested positive for viral particles by RT-PCR. Among the 3 infants whose mothers' breastmilk tested positive for virual RNA particles, not live virus, one infant tested positive for COVID-19 but infant feeding practices were not reported. The two other infants tested negative for COVID-19; one was breastfed, and the other newborn was fed expressed breast milk after viral RNA particles were no longer detected. In the single child with COVID-19, it was unclear through which route or source the infant became infected, i.e. through breastmilk or droplet from a close contact with the infected mother.

A preprint article reported secretory immunoglobulin A (sIgA) immune response against the COVID-19 virus found in 12 of 15 breastmilk samples from mothers with COVID-19.6 The implications of this finding on the effect, duration and protection against COVID-19 for the child was not addressed.

Limitations: To date, studies of mother-infant dyads with data on feeding practices and COVID-19 infection have come from case reports, case series or a report of a family cluster. Other study designs such as cohort studies or case-control studies were eligible for inclusion, but none were identified. We are thus unable to measure and compare risks of infection based on feeding practices.

Although 1 of the 3 infants of mothers with viral particles in breast milk had COVID-19, it was unclear through which route or source the infant was infected, i.e., through breastfeeding or close contact with the mother or other infected person. RT-PCR detects and amplifies viral genetic material in samples, such as breastmilk, but does not provide information on viability or infectivity of the virus. Documented presence of replicative COVID-19 virus in cell culture from breast milk and infectivity in animal models are needed to consider breast milk as potentially infectious.

The presence of IgA in breast milk is one of the ways in which breastfeeding protects infants against infection and death. IgA antibodies with reactivity to the COVID-19 virus have been detected in breastmilk of mothers previously infected with COVID-19 but their strength and durability have not yet been adequately studied to address protection from COVID-19 among breastfed infants.

Discussion

Detection of COVID-19 viral RNA in breastmilk is not the same as finding viable and infective virus. Transmission of COVID-19 would need replicative and infectious virus being able to reach target sites in the infant and also to overcome infant defense systems. If in the future COVID-19 virus from breastmilk were shown to be replicative in cell culture it would need to reach target sites in the infant and overcome infant defense systems for transmission of COVID-19 to occur.

The implications of transmission risk need to be framed in terms of COVID-19 prevalence in breastfeeding mothers and the scope and severity of COVID-19 infection in infants when transmission occurs compared to the adverse consequences of separation and using breastmilk substitutes and also separation of newborns and young infants from mothers.

Children appear to be at low risk of COVID-19. Among the cases of confirmed COVID-19 in children, most have experienced only mild or asymptomatic illness.7,8 This is also the case with other zoonotic coronaviruses (SARS-CoV and MERS-CoV), which seem to affect children less commonly and to cause fewer symptoms and less severe disease compared with adults.9

Secretory IgA have been detected in breastmilk of mothers with previous COVID-19 infection. Although the strength and durability of sIgA reactive to COVID-19 have not yet been determined, multiple bioactive components have been identified in breastmilk that not only protect against infections but improve neurocognitive and immunologic development of the child since Lars A Hanson first described sIgA in breastmilk in 1961.10-12

Skin-to-skin contact and kangaroo mother care facilitate breastfeeding as well as improve thermoregulation, blood glucose control, and maternal-infant attachment, and decrease the risk in mortality and severe infection among low birth weight infants.13,14 Beyond the neonatal period, positive effects of mother-infant holding include improved sleep patterns, lower rates of behavioural problems in the child and higher quality parental interaction.15,16

Exclusively breastfed infants, the risk of mortality is 14-fold higher in infants who are not breastfed.17 Over 820 000 children's lives could be saved every year among children under 5

years, if all children 0-23 months were optimally breastfed. For mothers, breastfeeding protects against breast cancer and may protect against ovarian cancer and type 2 diabetes.18 On the other hand, children are at low risk of COVID-19.

Knowledge gaps: It is still not clear whether the virus can or cannot be transmitted though breast milk. Risk of transmission based on feeding practices have not been quantified, compared, or modelled against the benefits of breastfeeding and nurturing mother-infant interaction.

Conclusion

At present, data are not sufficient to conclude vertical transmission of COVID-19 through breastfeeding. In infants, the risk of COVID-19 infection is low, the infection is typically mild or asymptomatic, while the consequences of not breastfeeding and separation between mother and child can be significant. At this point it appears that COVID-19 in infants and children represents a much lower threat to survival and health than other infections that breastfeeding is protective against. The benefits of breastfeeding and nurturing mother-infant interaction to prevent infection and promote health and development are especially important when health and other community services are themselves disrupted or limited. Adherence to infection prevention and control measures is essential to prevent contact transmission between COVID-19 suspected or confirmed mothers and their newborns and young infants.

Based on available evidence, WHO recommendations on the initiation and continued breastfeeding of infants and young children also apply to mothers with suspected or confirmed COVID-19.

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this scientific brief will expire 2 years after the date of publication.

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The Use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) in Patients with COVID-19

Scientific Brief

19 April 2020

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs, and have a wide range of uses. NSAIDs include nonselective cyclooxygenase (COX) inhibitors (such as ibuprofen, aspirin (acetylsalicylate), diclofenac, and naproxen), as well as selective COX2 inhibitors (such as celecoxib, rofecoxib, etoricoxib, lumiracoxib, and valecoxib).

Concerns have been raised that NSAIDs may be associated with an increased risk of adverse effects when used in patients with acute viral respiratory infections, including COVID-19.1,2 This review aimed to assess the effects of prior and current use of NSAIDs in patients with acute viral respiratory infections on acute severe adverse events (including mortality, the acute respiratory distress syndrome (ARDS), acute organ failure, and opportunistic infections), on acute health care utilization (including hospitalization, intensive care unit (ICU) admission, supplemental oxygen therapy, and mechanical ventilation) as well as on quality of life and long-term survival.

Methods

A rapid systematic review was carried out on 20 March 2020 on NSAIDs and viral respiratory infections using MEDLINE, EMBASE, and WHO Global Database. The review included studies conducted in humans of any age with viral respiratory infections exposed to systemic NSAIDs of any kind. All studies on COVID-19, the Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) were included irrespective of their sample size.

Review of the evidence: A total of 73 studies were included (28 studies in adults, 46 studies in children, and one study in adults and children). All studies were concerned with acute viral respiratory infections or conditions commonly caused by respiratory viruses, but none specifically addressed COVID-19, SARS, or MERS. The review showed very low certainty evidence on mortality among adults and children.3 Effects of NSAIDs on the risk for ischemic and haemorrhagic stroke and myocardial infarction in adults with acute respiratory infections are unclear.4,5 Moderate to high certainty evidence showed little or no difference between ibuprofen and acetaminophen (paracetamol) among children with fever with regard to effects on death from all causes, hospitalization for any cause, acute renal failure, and acute gastrointestinal bleeding.6-9 Most studies report that no severe adverse events occurred, or that only mild or moderate adverse events were observed. 10-13 There was no evidence regarding the effects of NSAID use on acute health care utilization, explicit quality of life measures, or long-term survival.

Limitations: No direct evidence from patients with COVID-19, SARS, or MERS was available. Therefore, all evidence included should be considered indirect evidence with respect to the use of NSAIDs prior to or during the management of COVID-19. Only one randomized controlled trial included a sufficiently large number of participants to identify rare severe adverse events. The remaining evidence derives from smaller randomized controlled trials, which are likely to be underpowered for detecting rare severe adverse events, and from case-control and cohort studies with methodological limitations. Studies included not only patients with confirmed viral respiratory infections and known pathogens, but also those with conditions commonly caused by respiratory viruses, such as upper respiratory tract infections and fever in children. It is likely that not all participants had viral respiratory infections. NSAIDs are a diverse set of drugs with different risk profiles for different populations and conditions. Not all studies distinguished

between different types of NSAIDs. Some of the older studies are likely to have included patients taking specific NSAIDs that are no longer available owing to adverse effects.

Conclusion

At present, there is no evidence of severe adverse events, acute health care utilization, long-term survival, or quality of life in patients with COVID-19, as a result of the use of NSAIDs.

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Transmission of SARS-CoV-2: Implications for Infection Prevention Precautions

Scientific Brief

9 July 2020

This document is an update to the scientific brief published on 29 March 2020 entitled "Modes of transmission of virus causing COVID-19: implications for infection prevention and control (IPC) precaution recommendations" and includes new scientific evidence available on transmission of SARS-CoV-2, the virus that causes COVID-19.

Overview

This scientific brief provides an overview of the modes of transmission of SARS-CoV-2, what is known about when infected people transmit the virus, and the implications for infection prevention and control precautions within and outside health facilities. This scientific brief is not a systematic review. Rather, it reflects the consolidation of rapid reviews of publications in peer-reviewed journals and of non-peer-reviewed manuscripts on pre-print servers, undertaken by WHO and partners. Preprint findings should be interpreted with caution in the absence of peer review. This brief is also informed by several discussions via teleconferences with the WHO Health Emergencies Programme ad hoc Experts Advisory Panel for IPC Preparedness, Readiness and Response to COVID-19, the WHO ad hoc COVID-19 IPC Guidance Development Group (COVID-19 IPC GDG), and by review of external experts with relevant technical backgrounds.

The overarching aim of the global Strategic Preparedness and Response Plan for COVID-19(1) is to control COVID-19 by suppressing transmission of the virus and preventing associated illness and death. Current evidence suggests that SARS-CoV-2, the virus that causes COVID-19, is predominantly spread from person-to-person. Understanding how, when and in what types of settings SARS-CoV-2 spreads is critical to develop effective public health and infection prevention and control measures to break chains of transmission.

Modes of transmission

This section briefly describes possible modes of transmission for SARS-CoV-2, including contact, droplet, airborne, fomite, fecal-oral, bloodborne, mother-to-child, and animal-to-human transmission. Infection with SARS-CoV-2 primarily causes respiratory illness ranging from mild disease to severe disease and death, and some people infected with the virus never develop symptoms.

Contact and droplet transmission: Transmission of SARS-CoV-2 can occur through direct, indirect, or close contact with infected people through infected secretions such as saliva and respiratory secretions or their respiratory droplets, which are expelled when an infected person coughs, sneezes, talks or sings.(2-10) Respiratory droplets are >5-10 μm in diameter whereas droplets <5μm in diameter are referred to as droplet nuclei or aerosols.(11) Respiratory droplet transmission can occur when a person is in close contact (within 1 metre) with an infected person who has respiratory symptoms (e.g. coughing or sneezing) or who is talking or singing; in these circumstances, respiratory droplets that include virus can reach the mouth, nose or eyes of a susceptible person and can result in infection. Indirect contact transmission involving contact of a susceptible host with a contaminated object or surface (fomite transmission) may also be possible (see below).

Airborne transmission: Airborne transmission is defined as the spread of an infectious agent caused by the dissemination of droplet nuclei (aerosols) that remain infectious when suspended in air over long distances and time.(11) Airborne transmission of SARS-CoV-2 can occur during medical procedures that generate aerosols ("aerosol generating procedures").(12) WHO,

together with the scientific community, has been actively discussing and evaluating whether SARS-CoV-2 may also spread through aerosols in the absence of aerosol generating procedures, particularly in indoor settings with poor ventilation.

The physics of exhaled air and flow physics have generated hypotheses about possible mechanisms of SARS-CoV-2 transmission through aerosols.(13-16) These theories suggest that 1) a number of respiratory droplets generate microscopic aerosols (<5 μm) by evaporating, and 2) normal breathing and talking results in exhaled aerosols. Thus, a susceptible person could inhale aerosols, and could become infected if the aerosols contain the virus in sufficient quantity to cause infection within the recipient. However, the proportion of exhaled droplet nuclei or of respiratory droplets that evaporate to generate aerosols, and the infectious dose of viable SARS-CoV-2 required to cause infection in another person are not known, but it has been studied for other respiratory viruses.(17)

One experimental study quantified the amount of droplets of various sizes that remain airborne during normal speech. However, the authors acknowledge that this relies on the independent action hypothesis, which has not been validated for humans and SARS-CoV-2.(18) Another recent experimental model found that healthy individuals can produce aerosols through coughing and talking (19), and another model suggested high variability between individuals in terms of particle emission rates during speech, with increased rates correlated with increased amplitude of vocalization.(20) To date, transmission of SARS-CoV-2 by this type of aerosol route has not been demonstrated; much more research is needed given the possible implications of such route of transmission.

Experimental studies have generated aerosols of infectious samples using high-powered jet nebulizers under controlled laboratory conditions. These studies found SARS-CoV-2 virus RNA in air samples within aerosols for up to 3 hours in one study (21) and 16 hours in another, which also found viable replication-competent virus.(22) These findings were from experimentally induced aerosols that do not reflect normal human cough conditions.

Some studies conducted in health care settings where symptomatic COVID-19 patients were cared for, but where aerosol generating procedures were not performed, reported the presence of SARS-CoV-2 RNA in air samples (23-28), while other similar investigations in both health care and non-health care settings found no presence of SARS-CoV-2 RNA; no studies have found viable virus in air samples.(29-36) Within samples where SARS-CoV-2 RNA was found, the quantity of RNA detected was in extremely low numbers in large volumes of air and one study that found SARS-CoV-2 RNA in air samples reported inability to identify viable virus. (25) The detection of RNA using reverse transcription polymerase chain reaction (RT-PCR)-based assays is not necessarily indicative of replication- and infection-competent (viable) virus that could be transmissible and capable of causing infection.(37)

Recent clinical reports of health workers exposed to COVID-19 index cases, not in the presence of aerosol-generating procedures, found no nosocomial transmission when contact and droplet precautions were appropriately used, including the wearing of medical masks as a component of the personal protective equipment (PPE). (38, 39) These observations suggest that aerosol transmission did not occur in this context. Further studies are needed to determine whether it is possible to detect viable SARS-CoV-2 in air samples from settings where no procedures that generate aerosols are performed and what role aerosols might play in transmission.

Outside of medical facilities, some outbreak reports related to indoor crowded spaces (40) have suggested the possibility of aerosol transmission, combined with droplet transmission, for example, during choir practice (7), in restaurants (41) or in fitness classes.(42) In these events, short-range aerosol transmission, particularly in specific indoor locations, such as crowded and inadequately ventilated spaces over a prolonged period of time with infected persons cannot be ruled out. However, the detailed investigations of these clusters suggest that droplet and fomite transmission could also explain human-to-human transmission within these clusters.

Further, the close contact environments of these clusters may have facilitated transmission from a small number of cases to many other people (e.g., superspreading event), especially if hand hygiene was not performed and masks were not used when physical distancing was not maintained.(43)

Fomite transmission: Respiratory secretions or droplets expelled by infected individuals can contaminate surfaces and objects, creating fomites (contaminated surfaces). Viable SARS-CoV-2 virus and/or RNA detected by RT-PCR can be found on those surfaces for periods ranging from hours to days, depending on the ambient environment (including temperature and humidity) and the type of surface, in particular at high concentration in health care facilities where COVID-19 patients were being treated.(21, 23, 24, 26, 28, 31-33, 36, 44, 45) Therefore, transmission may also occur indirectly through touching surfaces in the immediate environment or objects contaminated with virus from an infected person (e.g. stethoscope or thermometer), followed by touching the mouth, nose, or eyes.

Despite consistent evidence as to SARS-CoV-2 contamination of surfaces and the survival of the virus on certain surfaces, there are no specific reports which have directly demonstrated fomite transmission. People who come into contact with potentially infectious surfaces often also have close contact with the infectious person, making the distinction between respiratory droplet and fomite transmission difficult to discern. However, fomite transmission is considered a likely mode of transmission for SARS-CoV-2, given consistent findings about environmental contamination in the vicinity of infected cases and the fact that other coronaviruses and respiratory viruses can transmit this way.

Other modes of transmission: SARS-CoV-2 RNA has also been detected in other biological samples, including the urine and feces of some patients.(46-50)One study found viable SARS-CoV-2 in the urine of one patient.(51)Three studies have cultured SARS-CoV-2 from stool specimens. (48, 52, 53) To date, however, there have been no published reports of transmission of SARS-CoV-2 through feces or urine.

Some studies have reported detection of SARS-CoV-2 RNA, in either plasma or serum, and the virus can replicate in blood cells. However, the role of bloodborne transmission remains uncertain; and low viral titers in plasma and serum suggest that the risk of transmission through this route may be low.(48, 54) Currently, there is no evidence for intrauterine transmission of SARS-CoV-2 from infected pregnant women to their fetuses, although data remain limited. WHO has recently published a scientific brief on breastfeeding and COVID-19.(55) This brief explains that viral RNA fragments have been found by RT-PCR testing in a few breast milk samples of mothers infected with SARS-CoV-2, but studies investigating whether the virus could be isolated, have found no viable virus. Transmission of SARS-CoV-2 from mother to child would necessitate replicative and infectious virus in breast milk being able to reach target sites in the infant and also to overcome infant defense systems. WHO recommends that mothers with suspected or confirmed COVID-19 should be encouraged to initiate or continue to breastfeed.(55)

Evidence to date shows that SARS-CoV-2 is most closely related to known betacoronaviruses in bats; the role of an intermediate host in facilitating transmission in the earliest known human cases remains unclear.(56, 57) In addition to investigations on the possible intermediate host(s) of SARS-CoV-2, there are also a number of studies underway to better understand susceptibility of SARS-CoV-2 in different animal species. Current evidence suggests that humans infected with SARS-CoV-2 can infect other mammals, including dogs(58), cats(59), and farmed mink.(60) However, it remains unclear if these infected mammals pose a significant risk for transmission to humans.

When do people infected with SARS-CoV-2 infect others? Knowing when an infected person can spread SARS-CoV-2 is just as important as how the virus spreads (described

above). WHO has recently published a scientific brief outlining what is known about when a person may be able to spread, based on the severity of their illness.(61)

In brief, evidence suggests that SARS-CoV-2 RNA can be detected in people 1-3 days before their symptom onset, with the highest viral loads, as measured by RT-PCR, observed around the day of symptom onset, followed by a gradual decline over time.(47, 62-65) The duration of RT-PCR positivity generally appears to be 1-2 weeks for asymptomatic persons, and up to 3 weeks or more for patients with mild to moderate disease.(62, 65-68) In patients with severe COVID-19 disease, it can be much longer.(47)

Detection of viral RNA does not necessarily mean that a person is infectious and able to transmit the virus to another person. Studies using viral culture of patient samples to assess the presence of infectious SARS-CoV-2 are currently limited. (61) Briefly, viable virus has been isolated from an asymptomatic case,(69) from patients with mild to moderate disease up to 8-9 days after symptom onset, and for longer from severely ill patients.(61) Full details about the duration of viral shedding can be found in the WHO guidance document on “Criteria for releasing COVID-19 patients from isolation”. (61) Additional studies are needed to determine the duration of viable virus shedding among infected patients.

SARS-CoV-2 infected persons who have symptoms can infect others primarily through droplets and close contact

SARS-CoV-2 transmission appears to mainly be spread via droplets and close contact with infected symptomatic cases. In an analysis of 75,465 COVID-19 cases in China, 78-85% of clusters occurred within household settings, suggesting that transmission occurs during close and prolonged contact.(6) A study of the first patients in the Republic of Korea showed that 9 of 13 secondary cases occurred among household contacts.(70) Outside of the household setting, those who had close physical contact, shared meals, or were in enclosed spaces for approximately one hour or more with symptomatic cases, such as in places of worship, gyms, or the workplace, were also at increased risk of infection.(7, 42, 71, 72) Other reports have supported this with similar findings of secondary transmission within families in other countries.(73, 74)

SARS-CoV-2 infected persons without symptoms can also infect others: Early data from China suggested that people without symptoms could infect others.(6) To better understand the role of transmission from infected people without symptoms, it is important to distinguish between transmission from people who are infected who never develop symptoms(75) (asymptomatic transmission) and transmission from people who are infected but have not developed symptoms yet (pre-symptomatic transmission). This distinction is important when developing public health strategies to control transmission.

The extent of truly asymptomatic infection in the community remains unknown. The proportion of people whose infection is asymptomatic likely varies with age due to the increasing prevalence of underlying conditions in older age groups (and thus increasing risk of developing severe disease with increasing age), and studies that show that children are less likely to show clinical symptoms compared to adults.(76) Early studies from the United States (77) and China (78) reported that many cases were asymptomatic, based on the lack of symptoms at the time of testing; however, 75-100% of these people later developed symptoms. A recent systematic review estimated that the proportion of truly asymptomatic cases ranges from 6% to 41%, with a pooled estimate of 16% (12%–20%).(79) However, all studies included in this systematic review have important limitations.(79) For example, some studies did not clearly describe how they followed up with persons who were asymptomatic at the time of testing to ascertain if they ever developed symptoms, and others defined “asymptomatic” very narrowly as persons who never developed fever or respiratory symptoms, rather than as those who did not develop any symptoms at all.(76, 80) A recent study from China that clearly and appropriately defined

asymptomatic infections suggests that the proportion of infected people who never developed symptoms was 23%.(81)

Multiple studies have shown that people infect others before they themselves became ill, (10, 42, 69, 82, 83) which is supported by available viral shedding data (see above). One study of transmission in Singapore reported that 6.4% of secondary cases resulted from pre-symptomatic transmission.(73) One modelling study, that inferred the date of transmission based on the estimated serial interval and incubation period, estimated that up to 44% (25-69%) of transmission may have occurred just before symptoms appeared.(62) It remains unclear why the magnitude of estimates from modelling studies differs from available empirical data.

Transmission from infected people without symptoms is difficult to study. However, information can be gathered from detailed contact tracing efforts, as well as epidemiologic investigations among cases and contacts. Information from contact tracing efforts reported to WHO by Member States, available transmission studies and a recent pre-print systematic reviews suggests that individuals without symptoms are less likely to transmit the virus than those who develop symptoms.(10, 81, 84, 85) Four individual studies from Brunei, Guangzhou China, Taiwan China and the Republic of Korea found that between 0% and 2.2% of people with asymptomatic infection infected anyone else, compared to 0.8%-15.4% of people with symptoms.(10, 72, 86, 87)

Remaining questions related to transmission: Many unanswered questions about transmission of SARS-CoV-2 remain, and research seeking to answer those questions is ongoing and is encouraged. Current evidence suggests that SARS-CoV-2 is primarily transmitted between people via respiratory droplets and contact routes – although aerosolization in medical settings where aerosol generating procedures are used is also another possible mode of transmission - and that transmission of COVID-19 is occurring from people who are pre-symptomatic or symptomatic to others in close contact (direct physical or face-to-face contact with a probable or confirmed case within one meter and for prolonged periods of time), when not wearing appropriate PPE. Transmission can also occur from people who are infected and remain asymptomatic, but the extent to which this occurs is not fully understood and requires further research as an urgent priority. The role and extent of airborne transmission outside of health care facilities, and in particular in close settings with poor ventilation, also requires further study.

As research continues, we expect to gain a better understanding about the relative importance of different transmission routes, including through droplets, physical contact and fomites; the role of airborne transmission in the absence of aerosol generating procedures; the dose of virus required for transmission to occur, the characteristics of people and situations that facilitate superspreading events such as those observed in various closed settings, the proportion of infected people who remain asymptomatic throughout the course of their infection; the proportion of truly asymptomatic persons who transmit the virus to others; the specific factors that drive asymptomatic and pre-symptomatic transmission; and the proportion of all infections that are transmitted from asymptomatic and pre-symptomatic individuals.

Implications for preventing transmission: Understanding how, when and in which settings infected people transmit the virus is important for developing and implementing control measures to break chains of transmission. While there is a great deal of scientific studies becoming available, all studies that investigate transmission should be interpreted bearing in mind the context and settings in which they took place, including the infection prevention interventions in place, the rigor of the methods used in the investigation and the limitations and biases of the study designs.

It is clear from available evidence and experience, that limiting close contact between infected people and others is central to breaking chains of transmission of the virus causing COVID-19. The prevention of transmission is best achieved by identifying suspect cases as quickly as possible, testing, and isolating infectious cases. (88, 89) In addition, it is critical to identify all close contacts of infected people (88) so that they can be quarantined (90) to limit onward spread and break chains of transmission. By quarantining close contacts, potential secondary cases will already be separated from others before they develop symptoms or they start shedding virus if they are infected, thus preventing the opportunity for further onward spread. The incubation period of COVID-19, which is the time between exposure to the virus and symptom onset, is on average 5-6 days, but can be as long as 14 days. (82, 91) Thus, quarantine should be in place for 14 days from the last exposure to a confirmed case. If it is not possible for a contact to quarantine in a separate living space, self-quarantine for 14 days at home is required; those in self-quarantine may require support during the use of physical distancing measures to prevent the spread of the virus.

Given that infected people without symptoms can transmit the virus, it is also prudent to encourage the use of fabric face masks in public places where there is community transmission[1] and where other prevention measures, such as physical distancing, are not possible.(12) Fabric masks, if made and worn properly, can serve as a barrier to droplets expelled from the wearer into the air and environment.(12) However, masks must be used as part of a comprehensive package of preventive measures, which includes frequent hand hygiene, physical distancing when possible, respiratory etiquette, environmental cleaning and disinfection. Recommended precautions also include avoiding indoor crowded gatherings as much as possible, in particular when physical distancing is not feasible, and ensuring good environmental ventilation in any closed setting. (92, 93)

Within health care facilities, including long term care facilities, based on the evidence and the advice by the COVID-19 IPC GDG, WHO continues to recommend droplet and contact precautions when caring for COVID-19 patients and airborne precautions when and where aerosol generating procedures are performed. WHO also recommends standard or transmission-based precautions for other patients using an approach guided by risk assessment.(94) These recommendations are consistent with other national and international guidelines, including those developed by the European Society of Intensive Care Medicine and Society of Critical Care Medicine (95) and by the Infectious Diseases Society of America. (96)

Furthermore, in areas with COVID-19 community transmission, WHO advises that health workers and caregivers working in clinical areas should continuously wear a medical mask during all routine activities throughout the entire shift.(12) In settings where aerosol-generating procedures are performed, they should wear an N95, FFP2 or FFP3 respirator. Other countries and organizations, including the United States Centers for Diseases Control and Prevention (97) and the European Centre for Disease Prevention and Control (98) recommend airborne precautions for any situation involving the care of COVID-19 patients. However, they also consider the use of medical masks as an acceptable option in case of shortages of respirators.

WHO guidance also emphasizes the importance of administrative and engineering controls in health care settings, as well as rational and appropriate use of all PPE (99) and training for staff on these recommendations (IPC for Novel Coronavirus [COVID-19] Course. Geneva; World Health Organization 2020, available at (https://openwho.org/courses/COVID-19-IPC-EN). WHO has also provided guidance on safe workplaces. (92)

Key points of the brief

Main findings

- Understanding how, when and in what types of settings SARS-CoV-2 spreads between people is critical to develop effective public health and infection prevention measures to break chains of transmission.
- Current evidence suggests that transmission of SARS-CoV-2 occurs primarily between people through direct, indirect, or close contact with infected people through infected secretions such as saliva and respiratory secretions, or through their respiratory droplets, which are expelled when an infected person coughs, sneezes, talks or sings.
- Airborne transmission of the virus can occur in health care settings where specific medical procedures, called aerosol generating procedures, generate very small droplets called aerosols. Some outbreak reports related to indoor crowded spaces have suggested the possibility of aerosol transmission, combined with droplet transmission, for example, during choir practice, in restaurants or in fitness classes.
- Respiratory droplets from infected individuals can also land on objects, creating fomites (contaminated surfaces). As environmental contamination has been documented by many reports, it is likely that people can also be infected by touching these surfaces and touching their eyes, nose or mouth before cleaning their hands.
- Based on what we currently know, transmission of COVID-19 is primarily occurring from people when they have symptoms, and can also occur just before they develop symptoms, when they are in close proximity to others for prolonged periods of time. While someone who never develops symptoms can also pass the virus to others, it is still not clear to what extent this occurs and more research is needed in this area.
- Urgent high-quality research is needed to elucidate the relative importance of different transmission routes; the role of airborne transmission in the absence of aerosol generating procedures; the dose of virus required for transmission to occur; the settings and risk factors for superspreading events; and the extent of asymptomatic and pre-symptomatic transmission.

How to prevent transmission

The overarching aim of the Strategic Preparedness and Response Plan for COVID-19(1) is to control COVID-19 by suppressing transmission of the virus and preventing associated illness and death. To the best of our understanding, the virus is primarily spread through contact and respiratory droplets. Under some circumstances airborne transmission may occur (such as when aerosol generating procedures are conducted in health care settings or potentially, in indoor crowded poorly ventilated settings elsewhere). More studies are urgently needed to investigate such instances and assess their actual significance for transmission of COVID-19.

To prevent transmission, WHO recommends a comprehensive set of measures including:

- Identify suspect cases as quickly as possible, test, and isolate all cases (infected people) in appropriate facilities;
- Identify and quarantine all close contacts of infected people and test those who develop symptoms so that they can be isolated if they are infected and require care;
- Use fabric masks in specific situations, for example, in public places where there is community transmission and where other prevention measures, such as physical distancing, are not possible;
- Use of contact and droplet precautions by health workers caring for suspected and confirmed COVID-19 patients, and use of airborne precautions when aerosol generating procedures are performed;

- Continuous use of a medical mask by health workers and caregivers working in all clinical areas, during all routine activities throughout the entire shift;
- At all times, practice frequent hand hygiene, physical distancing from others when possible, and respiratory etiquette; avoid crowded places, close-contact settings and confined and enclosed spaces with poor ventilation; wear fabric masks when in closed, overcrowded spaces to protect others; and ensure good environmental ventilation in all closed settings and appropriate environmental cleaning and disinfection.

WHO carefully monitors the emerging evidence about this critical topic and will update this scientific brief as more information becomes available.

[1]Defined by WHO as "experiencing larger outbreaks of local transmission defined through an assessment of factors including, but not limited to: large numbers of cases not linkable to transmission chains; large numbers of cases from sentinel surveillance; and/or multiple unrelated clusters in several areas of the country/territory/area" (https://www.who.int/publications-detail/global-surveillance-for-covid-19-caused-by-human-infection-with-covid-19-virus-interim-guidance)

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WHO continues to monitor the situation closely for any changes that may affect this scientific brief. Should any factors change, WHO will issue a further update. Otherwise, this scientific brief document will expire 2 years after the date of publication.

IMJ 2020; 66(2): 113-124.

WHAT TO DO IF SOMEONE IS SICK IN YOUR HOUSEHOLD

Life has to continue even where COVID-19 is spreading.

Here's how to stay safe.

1 ISOLATE THE SICK PERSON

Prepare a separate room or isolated space, and keep distance from others.

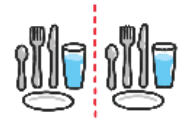
Keep the room well ventilated and open windows frequently.

2 REDUCE CONTACT WITH THE VIRUS

Identify one household member to be the contact person who is not at high risk and has the fewest contacts with people outside.

Wear a medical mask if in the same room as the sick person.

Use separate dishes, cups, eating utensils and bedding from the sick person.



Clean and disinfect frequently touched surfaces.

3 TAKE CARE OF THE SICK PERSON

Monitor the sick person's symptoms regularly.

Pay special attention if the person is at high risk for serious illness.

Ensure the sick person rests and stays hydrated.

! DANGER SIGNS

Call your healthcare provider immediately if you see any of these danger signs:

- Difficulty breathing
- Loss of speech or mobility
- Confusion
- Chest pain

REMEMBER, IT'S ALWAYS SAFER TO

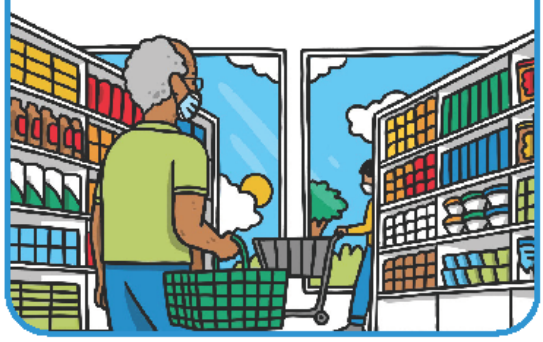
KNOW YOUR RISK.
LOWER YOUR RISK.

World Health Organization

SHOPPING FOR GROCERIES

Life has to continue even where COVID-19 is spreading. If online shopping is not an option, **here's how to stay safe.**

REDUCE YOUR RISK

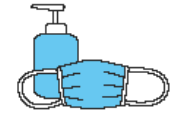


Go outside peak hours.

BEFORE YOU GO OUT

Always check on local regulations.

Bring sanitizer and wear your mask.



If you are in a high-risk group, wear a medical mask.

WHEN INSIDE STORES

Keep your shopping time short and make a list.

Keep at least 1 metre distance from others.

REMEMBER, IT'S ALWAYS SAFER TO

KNOW YOUR RISK.
LOWER YOUR RISK.

World Health Organization

DON'T PUT OFF NECESSARY MEDICAL APPOINTMENTS

Life has to continue even where COVID-19 is spreading.

Here's how to stay safe.

REDUCE YOUR RISK

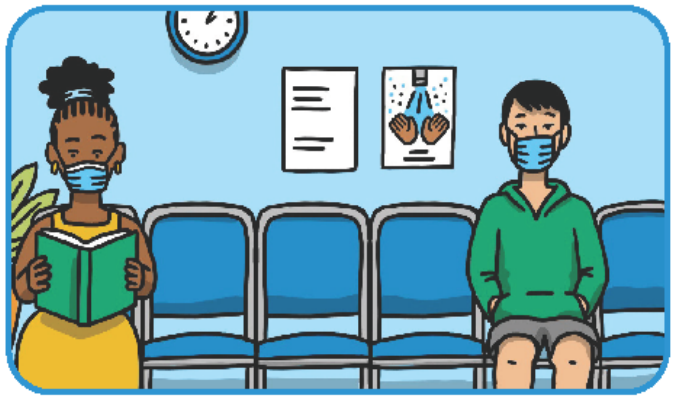
Call to check if a phone or telemedicine consultation is possible and appropriate. If not, schedule your appointment in advance.

BEFORE YOU GO OUT

Always check on local regulations.

Bring sanitizer and wear your mask.

If you are in a high-risk group, wear a medical mask.



WHILE WAITING FOR YOUR APPOINTMENT

Avoid crowded settings, maintain physical distance or ask to sit in a less crowded space.

REMEMBER, IT'S ALWAYS SAFER TO

KNOW YOUR RISK. LOWER YOUR RISK.

World Health Organization

HOW TO PREPARE IN CASE SOMEONE GETS SICK IN YOUR HOUSEHOLD

Life has to continue even where COVID-19 is spreading.

Here's how to stay safe.

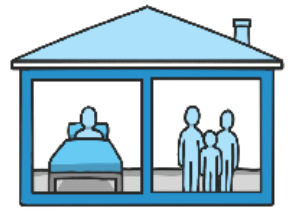
GET YOUR CONTACTS READY

For health information and care: your doctor, health facilities, health centre/hotline and emergency numbers.

For your support network: family, friends, neighbors, school or work.

WHAT SHOULD BE PREPARED

Stock up on supplies such as regular medicines, medical masks and cleaners/disinfectants.



Prepare a separate room or isolated space, and keep distance from others.

Put in place a support network for groceries, transport, childcare and other essentials.

REMEMBER, IT'S ALWAYS SAFER TO

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