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From the common cold to COVID-19

Expert review by

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Introduction

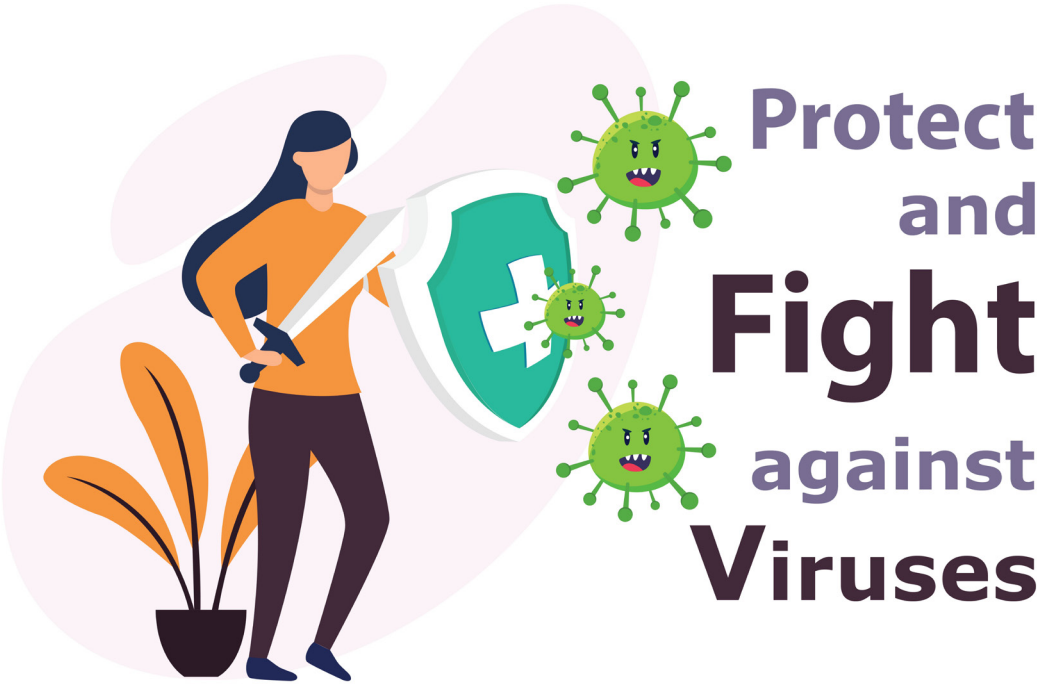
This review provides a background to understanding the current coronavirus (CoV) disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It does not attempt to provide a thorough understanding of a situation that no-one fully understands yet, but rather aims to provide a framework into which emerging epidemiological and clinical facts can be fitted.

It does provide, as we enter the season of colds and influenza in South Africa, a focus on priorities and treatment approaches in the clinical management of a condition that might lead patients to ask: "Is this a cold/flu or COVID-19?"

LEARNING OBJECTIVES

You will learn:

- Current understanding of SARS-CoV-2 and the COVID-19 pandemic
- A framework within which emerging epidemiological and clinical facts can be considered
- How to differentiate the symptoms of the common cold from those of COVID-19
- The criteria for self-isolation and management of COVID-19 at home.



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When were coronaviruses first discovered?

CoV infections in human beings were first described in 1960 in patients with a common cold which, in approximately 25% of cases, was caused by the coronavirus species 229E, OC43, NL63 and HKU1. Other aetiologies of common cold include (predominantly) rhinoviruses, as well as mild manifestations of other respiratory viruses.

In 2003, a new CoV was identified as causing respiratory distress and death during an outbreak that had originated in southern China in late 2002, but that had later spread to North America and Europe before being contained through stringent public health measures in mid-2003. This virus that caused this severe acute respiratory syndrome, named SARS-CoV, belongs to the genus betacoronavirus. Overall, 8 096 cases from SARS occurred, with a relatively high case fatality rate of 9%, resulting in 774 deaths.

A new CoV, Middle East respiratory syndrome-related coronavirus (MERS-CoV), was isolated from a patient with severe respiratory disease in Saudi Arabia in 2012. MERS causes respiratory failure, acute renal impairment and has a case fatality rate of 37.1%. To date the virus has caused 2 494 cases of illness and 858 deaths, but seems poorly adapted to ongoing person-to-person transmission.

In 2019, SARS-CoV-2 was identified as the aetiological agent of COVID-19.

How are different coronaviruses transmitted?

Coronaviruses 229E, OC43, NL63 and HKU1 are well adapted and circulate widely in human populations. Most cases of disease caused by these coronaviruses are common cold-like and mild, with rare exceptions especially in immune-compromised individuals (Figure 1).[1] Infection is spread by droplet and contact transmission from contaminated surfaces and objects (so-called 'fomites').

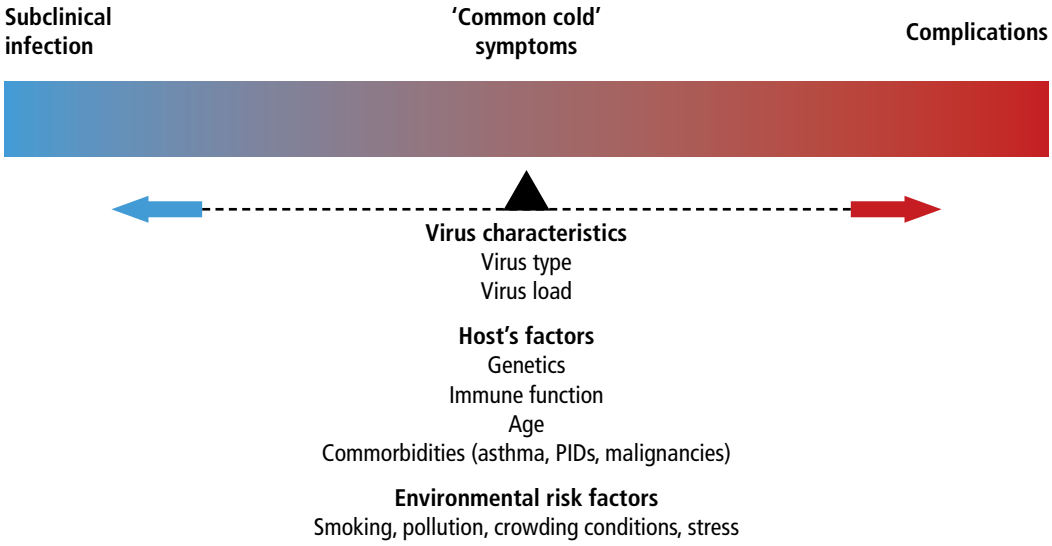

Figure 1. Common cold[1]
Common cold symptoms and possible complications result from a dynamic interplay between the infecting virus' characteristics and the host's immune response. In the majority of cases, the cold is a relatively mild and self-limiting illness. However, affected individuals with defective immunity, either because of an underlying condition (i.e. asthma, immunodeficiency, young or old age) or as a result of environmental conditions (i.e. smoking, stress, pollution), may experience severe or even fatal complications.

The common cold is the most frequently observed infectious disease in humans, with an average of 4-8 episodes occurring per year in children and 3-5 episodes in adults. Up to one-quarter of cases of common cold may be caused by one of the four established human coronaviruses. Two of these, NL63 and 229E, belong to the genus alphacoronavirus, and the other two, OC43 and HKU1, to genus betacoronavirus.[2] These coronaviruses typically have a peak of infection in the colder months.

What are the intermediate hosts, and how did these coronaviruses spread to humans?

SARS-CoV-1 and MERS-CoV are not well adapted to human hosts and do not circulate in human populations for prolonged periods of time. This is now likely to be different for SARS-CoV-2

All four human coronaviruses associated with the common cold are thought to have originated from animals a long time ago: NL63 and 229E from bats, and OC43 and HKU1 from rodents. SARS-CoV-1 and MERS-CoV are not well adapted to human hosts and do not circulate in human populations for prolonged periods of time. This is now likely to be different for SARS-CoV-2. It's very high transmissibility makes control of the ongoing pandemic so difficult; it is well possible that over time it will evolve into another endemic human virus, probably with much reduced mortality due to pre-existing partial immunity. SARS-CoV-1 and MERS-CoV are acquired by humans through exposure to civets and camels, respectively. Civets are apparently not naturally infected with SARS-CoV, but became infected further to exposure to infected bats, presumably in 'wet markets' or breeding farms under circumstances of poor hygiene and animal welfare. In contrast, camels in many regions seem to carry MERS-CoV. Yet a close relative of MERS-CoV was identified in a South African bat, making an ultimate bat origin likely too. SARS-CoV and MERS-CoV are sustained permanently in non-human vertebrate reservoirs with only occasional spillovers into the human population (Figure 2).[3]

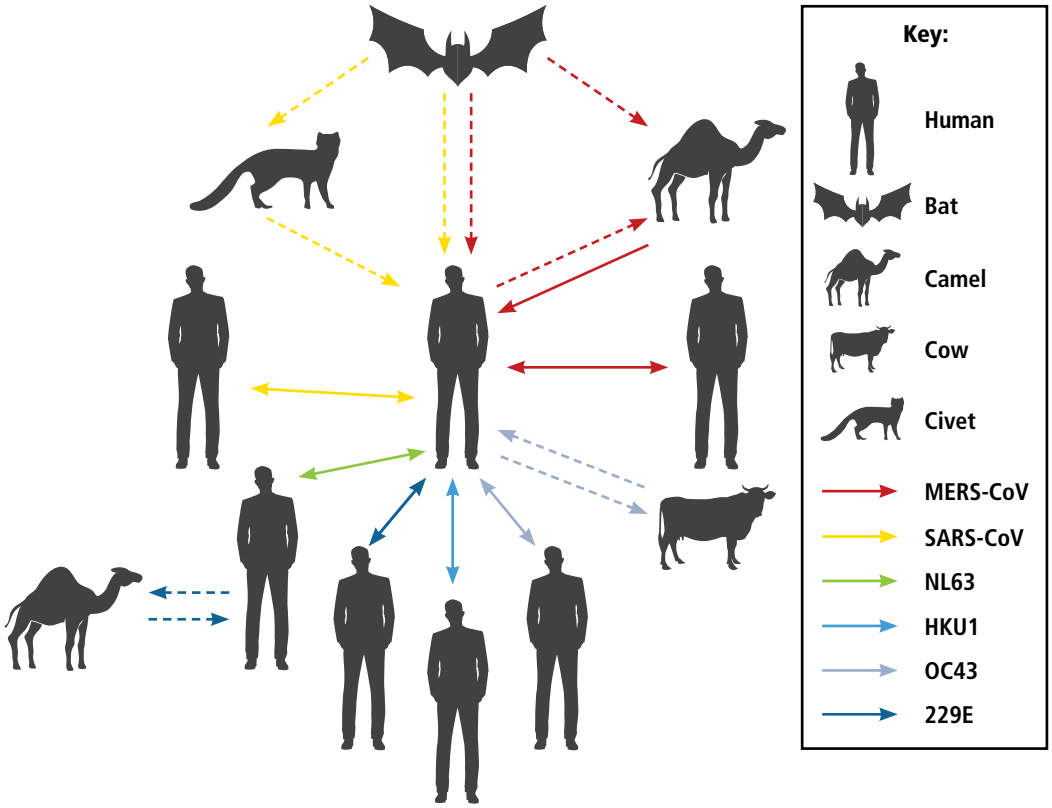

Figure 2. Intra- and inter-species transmission of human coronaviruses[3]
Red, yellow, green, blue, brown and purple arrows represent transmission of MERS-CoV, SARS-CoV, NL63, HKU1, OC43, and 229E, respectively, between bats, camels, cows, humans, and masked palm civets. Unbroken arrows represent confirmed transmission between the two species in question, and broken arrows represent suspected transmission.

Why are these viruses called coronaviruses?

Coronaviruses were named because of their 'crown-like' appearance under an electron microscope. They belong to the family 'coronaviridae' and have positive-sense single-stranded RNA genomes.[4] Their mutation rates are not as high as, for example, that of HIV; yet typically, when a virus is not well adapted to its host it can still evolve rapidly. The mutation rate remains but the selection pressure changes, resulting in more rapid evolution.

To date, variations between different clades are not known to influence transmissibility or pathogenicity, yet sequencing of human isolates from different regions remains important for molecular epidemiology and to ensure that any developed diagnostic test, vaccine or antiviral agent remains effective for longer periods and is not rendered ineffective by genetic mutation. The relatively low mutation rate of coronaviruses also means that vaccines and antivirals are unlikely to become ineffective quickly as a result of genetic mutation.

What causes the severe symptoms of SARS-CoV-2?

The COVID-19 pandemic and the severe nature of the illness are because SARS-CoV-2 is newly introduced to the human population, is easily transmissible and is pathogenic. Ongoing studies are underway, so only a few additional factors can be highlighted:

- *In vitro* study shows that SARS-CoV-2 has a 10- to 20-fold higher affinity for the ACE2 receptor than SARS-CoV (Figure 3),[5] resulting in more effective binding of viral particles to human cells carrying this receptor including, but not limited to, cells of the respiratory tract
- The 'spike' protein on the viral membrane interacts with the human cell so that viral RNA is released into the host cell, as is the case with all viruses
- The ACE2 receptor is found primarily in the lower respiratory tract yet SARS-CoV-2 also efficiently infects above the vocal cords; it must be noted, however, that there is a great deal of discussion in the literature as to where variations of the ACE2 receptor are located and in what concentrations.

The relatively low mutation rate of coronaviruses also means that vaccines and antivirals are unlikely to become ineffective quickly as a result of genetic mutation

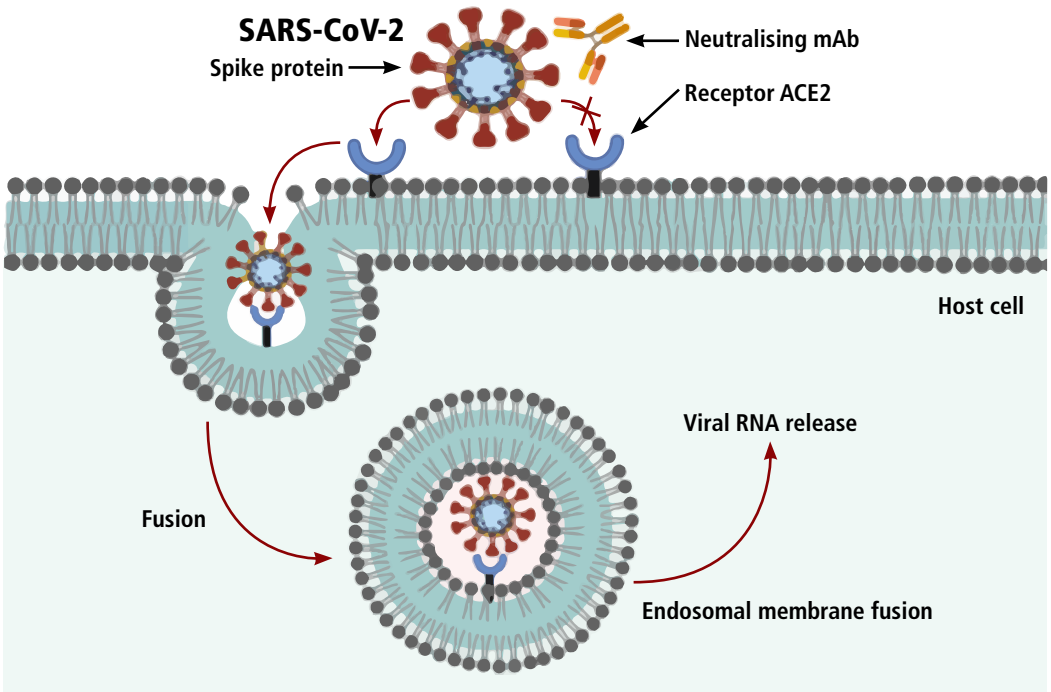

Figure 3. Schematic representation of SARS-CoV-2 neutralisation mechanism[5]
Interaction of the viral spike protein and the cellular receptor is required for membrane fusion and entry into the target cell. The monoclonal antibodies targeting the SARS-CoV-2 spike protein could potentially inhibit the virus binding to its cellular receptor, thereby preventing its entry into the cell.

How to distinguish the common cold from COVID-19?

Today's approach to the common cold is to regard it as a viral, self-limiting inflammatory condition involving variable sites of the upper airways, including the throat, larynx and sinuses. The viral infection may involve sites beyond the upper respiratory tract such as the trachea and bronchi.[6]

Signs and symptoms of the common cold

Cough, runny nose, fever, sore throat, nausea, sleep disturbance and sweats are the typical cluster of signs and symptoms occurring in patients with the common cold. Acute bronchitis shares many of the above symptoms and it is difficult to distinguish it from the common cold.

Treating the common cold

Patients visiting clinicians with a severe common cold have traditionally only wanted symptom relief, whereas they may be anxious now and looking for reassurance that it is 'only a cold'. Traditional treatment recommendations are an anti-inflammatory and anti-cough. Later treatment of lingering symptoms involves mucolytics, decongestants and even antibiotics if secondary bacterial infection is suspected.

Signs and symptoms of COVID-19

The distinguishing symptom of severe COVID-19 infection is 'shortness of breath'

The distinguishing symptom of severe COVID-19 infection is 'shortness of breath'; in a small percentage of patients, predominantly but not exclusively those over 60 years old and patients with chronic illnesses such as diabetes or hypertension, infection may lead to severe and often fatal manifestations including acute respiratory distress syndrome. The National Institute for Communicable Diseases (NICD) notes that the symptoms currently reported for patients with COVID-19 have included mild to severe respiratory illness with cough, sore throat, shortness of breath or fever ≥38°C (measured) or history of fever (subjective).

The complete clinical picture of COVID-19 is still not clear. Reports have ranged from infected individuals with few or no symptoms, to others who are severely ill and dying. Pneumonia that develops as a result of SARS-CoV-2 is characterised by fever, dry cough and shortness of breath. Gastrointestinal symptoms are less common than the respiratory effects, and include nausea, vomiting, abdominal discomfort and diarrhoea. Interestingly, gastrointestinal symptoms can precede the typical respiratory symptoms.[7] This is plausible as the ACE2 receptor is present on the enterocytes of the ileum and colon. There is mild to moderate hepatic injury, expressed by raised transaminases, hypoproteinaemia and prolonged prothrombin time. This hepatic injury is likely due to direct injury of the intrahepatic bile ducts. Neurological symptoms are also seen, such as dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia and seizure.[8] In people with asthma, COPD or any other condition causing 'shortness of breath', the COVID-19 virus may increase the severity of the underlying disease, as well as in other existing comorbidities such as hypertension, diabetes and cardiovascular disease.[9-11]

A potential COVID-19 case – what do I do now?

South Africa's NICD is continually updating their testing, clinical management and public health guidelines, in line with the improving understanding of the disease globally and nationally. It is suggested that at the time of reading, refer to https://www.nicd.ac.za/diseases-a-z-index/covid-19/covid-19-guidelines/ for determining testing eligibility. COVID-19 is a notifiable medical condition with specific requirements and forms available on the NICD website.

A patient with mild disease or a person under investigation (PUI) may be considered for management at home, provided they are able to self-isolate safely and are at low risk of developing severe disease. The criteria for management at home are provided in Table 1.

Once a patient is confirmed as being infected with COVID-19, the necessary

NICD notification forms must be completed. It is vital that all appropriate steps are taken to prevent onward transmission. In approximately 10% of patients with mild disease the severity will increase; all patients should be given details of how to contact their doctor's practice at the first sign of clinical deterioration.

Table 1. Criteria for management at home (for age >12 years*)[11]

Mild disease
• SpO_2 ≥95%
• Respiratory rate <25
• Heart rate <120
• Temperature 36-39°C
• Mental status normal
Able to safely self-isolate
• Separate bedroom available for patient to self-isolate in
• Patient able to contact, and return to, healthcare facility in case of deterioration
Not at high risk of deterioration
• Age <65 years
• No severe cardiac or pulmonary comorbidities
• No other debilitating comorbidities (e.g. cancer)

*For ages 5-12: use respiratory rate <30 and heart rate <130. For younger ages, use age-appropriate normal values.

KEY LEARNINGS

- Coronaviruses 229E, OC43, NL63 and HKU1 circulate widely in human populations and in 25% of cases may be the cause of the common cold, the most frequently observed infectious disease in humans
- Coronaviruses typically have a peak of infection in the colder months
- SARS-CoV and MERS-CoV are not well adapted to human hosts and do not circulate in human populations for prolonged periods of time
- SARS-CoV-2 is new to the human population and is easily transmissible, with a high affinity for the ACE2 receptor
- The distinguishing symptom of COVID-19 infection is 'shortness of breath'
- The NICD is continually updating its clinical management guidelines.

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