

## The COVID-19 pandemic: diverse contexts; different epidemics—how and why?

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### ABSTRACT

It is very exceptional that a new disease becomes a true pandemic. Since its emergence in Wuhan, China, in late 2019, SARS-CoV-2, the virus that causes COVID-19, has spread to nearly all countries of the world in only a few months. However, in different countries, the COVID-19 epidemic takes variable shapes and forms in how it affects communities. Until now the insights gained on COVID-19 have been largely dominated by the COVID-19 epidemics and the lockdowns in China, Europe, and the United States. But this variety of global trajectories is little described, analysed, or understood. In only a few months, an enormous amount of scientific evidence on SARS-CoV-2 and COVID-19 has been uncovered (knowns). But important knowledge gaps remain (unknowns). An important missing piece of the COVID-19 puzzle can be solved by learning from the variety of ways the COVID-19 epidemic is unfolding across the globe. This paper tries to make sense of this variability—by exploring the important role that context plays in these different COVID-19 epidemics; by comparing COVID-19 epidemics with other respiratory diseases, including other coronaviruses that circulate continuously; and by highlighting the critical unknowns and uncertainties that remain. These unknowns and uncertainties require a deeper understanding of the variable trajectories of COVID-19. Unraveling them will be important for discerning potential future scenarios, such as the first wave in virgin territories still untouched by COVID-19 and for future waves elsewhere.

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## SUMMARY BOX

- **SARS-CoV-2, the virus that causes COVID-19, has spread to nearly all countries of the world in only a few months. It is unique that an emerging respiratory virus becomes a pandemic, and can continue human-to-human transmission unabated, probably permanently.**
- **Depending on the context, the trajectory and the impact of the COVID-19 epidemic vary widely across affected countries. This is in fact the case with most infectious diseases.**
- **Despite limited initial knowledge on COVID-19, most societies have deployed draconian measures, including lockdowns, to contain the virus and mitigate its impact. This had variable success, but invariably with profound socioeconomic collateral effects.**
- **Through research and rapid sharing of its findings, progressively more insights on SARS-CoV-2 and COVID-19 have been uncovered (knowns), mainly based on evidence from China, Europe, and the US; however, important knowledge gaps remain (unknowns).**
- **The different COVID-19 epidemics and the responses unfolding in the Global South are little described, analysed, or understood. Insights from these less researched contexts are important for discerning potential future scenarios, not only for the first wave in virgin territories still untouched by COVID-19, but also for future waves.**
- **More understanding of lived experiences of people in a variety of contexts is necessary to get a full global picture and allow learning from this variety. [BMJ Global Health and Emerging Voices for Global Health have launched a call](#) for such on-the-ground narratives and analyses on the epidemics of, and responses to, COVID-19.**

## INTRODUCTION

Late in 2019, a cluster of acute respiratory disease in Wuhan, China, was attributed to a new coronavirus,[1-3] later named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2),[4] transmitted from human to human. It was soon discovered that the virus is easily transmitted, can cause severe disease, and can be quite lethal especially in the elderly and those with co-morbidities.[5-8] The new human disease is called COVID-19 (Coronavirus Disease-2019).[9] Soon it became clear that its global spread was unstoppable. Even with draconian containment measures, such as strict movement restrictions, a so-called lockdown, it spread to other Chinese provinces and neighbouring countries first, then to Europe, and the Americas. Within a few months, it reached almost all countries and was declared a pandemic by the World Health Organization (WHO).[10] Table 1 summarises key events in the unfolding of the COVID-19 pandemic, from December 2019 to May 2020.

This progression is quite unique. New human pathogens emerge frequently from an animal host, but most emerging pathogens cause only a few cases of the disease in humans, a local cluster of cases, or a local outbreak. Due to a variety of factors, human-to-human transmission stops at some point, and the virus can only re-emerge as a human pathogen from its animal host. Only very rarely does an emerging pathogen become a pandemic and is transmitted continuously within the human species. Over the past decades, a totally new pathogen emerged, caused serious disease, and spread around the globe continuously only once before: the Human Immunodeficiency Virus (HIV). HIV has infected more than 70 million individuals over the last 40 years.[18] It seems increasingly likely that SARS-CoV-2 transmission will be continuing. All countries are now facing their own “COVID-19 epidemic.”

In only a few months the scientific community has started to learn the virus’s characteristics and its manifestations in different contexts.[19] But we fail to understand fully why the virus spreads at different speeds and affects populations differently. Our main objective is to make sense of those different expressions of the COVID-19 pandemic, to understand why COVID-19 follows variable trajectories in ways that are often quite different from the collective image created by the mediatisation of the dramatic COVID-19 epidemics in densely populated areas in the Global North.

We start by exploring the role of context, followed by a brief summary of what is already known at the time of writing about SARS-CoV-2 and COVID-19. We then compare these knowns with what is known of some other viral respiratory pathogens and identify the critical unknowns. We also discuss the coping strategies and collective strategies implemented to contain and mitigate the effect of the epidemic. We finally look ahead to potential future scenarios.

**Table 1: Key events in the COVID-19 pandemic, December 2019–May 2020**

Month	Key events
<b>December 2019</b>	<ul style="list-style-type: none"> <li>• Clusters of pneumonia of unknown origin in Wuhan, China.</li> <li>• Human infection probably began sometime between 9 October and 20 December 2019.[11]</li> <li>• WHO alerted of a novel coronavirus on 31 December 2019.</li> <li>• Several cases in Hubei Province, China, and probably already spread to surrounding areas.</li> <li>• The virus may have already been spreading in France late December 2019.[12]</li> </ul>
<b>January 2020</b>	<ul style="list-style-type: none"> <li>• First case outside China reported in Thailand on 13 January 2020.</li> <li>• Cases reported in at least 24 countries, mostly in South and Southeast Asia; also in Europe, the US, Canada, and the United Arab Emirates (UAE).[13]</li> <li>• The “new disease” declared a “Public Health Emergency of International Concern” on 30 January 2020.</li> <li>• Mostly “imported cases only,” mainly travellers from China. Soon “export” of virus from other countries started.</li> <li>• The Wuhan lockdown,[14] which later inspired a series of lockdowns across the world.</li> </ul>
<b>February 2020</b>	<ul style="list-style-type: none"> <li>• The new disease named COVID-19 on 11 February 2020.</li> <li>• Cruise ship Princess Diamond quarantined near Japan, sparking media attention.</li> <li>• Epidemic in China peaked with ~80,000 cases and 2,900 deaths (80% of cases restricted to the Hubei Province).[15]</li> <li>• Local epidemics of varying attack rates and case fatality rates (CFR) in 58 countries with imported cases causing “local transmission” reported from 20 countries.</li> <li>• South Korea, Italy, and Iran emerged as new epicentres.</li> </ul>
<b>March 2020</b>	<ul style="list-style-type: none"> <li>• Europe engulfed with local epidemics.</li> <li>• Over 170 countries were affected worldwide.</li> <li>• The epidemic in China seemed to have plateaued.</li> <li>• WHO declared the epidemic a pandemic.</li> <li>• China partially lifted lockdown while India instituted the world’s biggest complete lockdown affecting ~1.4 billion people.[16]</li> </ul>
<b>April 2020</b>	<ul style="list-style-type: none"> <li>• COVID-19 cases crossed 1 million with more than 50,000 deaths.</li> <li>• The US emerged as the most affected country with epicentre in New York.</li> <li>• Aerosols implicated in the transmission (prompting “mass masking” of the general public).</li> <li>• WHO warned that Africa will be the future epicentre of COVID-19.</li> </ul>
<b>May 2020</b>	<ul style="list-style-type: none"> <li>• South America became the new epicentre of COVID-19.</li> <li>• More than 325,000 deaths globally with ~5 million cases in 216 countries/territories/areas.</li> <li>• At the time of writing (end of May 2020), no effective medication and/or vaccine exist.</li> <li>• The pandemic appeared to have slowed down in countries such as South Korea, Italy, Spain, France, and the rest of Europe.</li> <li>• In Africa, the number of cases seemed to fall short of forecasts.</li> <li>• Tremendous socioeconomic fallouts after an estimated 4.5 billion persons (more than half of humanity) subjected to social distancing norms and/or lockdowns.[17]</li> </ul>

## THE UNFOLDING COVID-19 PANDEMIC: IMPORTANCE OF CONTEXT

Initially, human-to-human transmission was documented in family/friends clusters.[20-25] Progressively it became clear that super-spreading events, typically during social gatherings such as parties, religious services, weddings, sports events, and carnival celebrations, have played an important role.[26-29] Dense transmission has also been documented in hospitals [30] and nursing homes possibly through aerosols.[31, 32]

SARS-CoV-2 has spread around the world through international travellers. The timing of the introduction of SARS-CoV-2 has largely depended on the intensity of connections with locations with ongoing COVID-19 epidemics; thus it reached big urban centres first and, within these, often the most affluent groups, the “jet setters” or “VIPs.” From there, the virus has spread at variable speeds to other population groups.

As of May 2020, the most explosive COVID-19 epidemics observed have been in densely populated areas in temperate climates in relatively affluent countries, where quite draconian lockdowns have been implemented. The COVID-19 epidemic and the lockdowns have been covered intensively in the media and have shaped our collective image of the COVID-19 epidemic, both in the general public and in the scientific community.

The COVID-19 epidemic has spread more slowly and less intensively in rural areas in the US and Europe, in the megacities of Africa and the Indian subcontinent, and the rural areas of low and lower-middle income countries (LICs/LMICs). Not only the media but also the scientific community has paid much less attention to these realities, emerging later and spreading more slowly.

The dominant thinking has been that it is only a question of time before dramatic epidemics similar to those in Europe and the US occur everywhere. This thinking, spread globally by international public health networks, has been substantiated by predictive mathematical models based largely on the epidemics of the Global North.

However, what has been observed elsewhere is quite different although not necessarily less consequential. Transmission follows patterns of human mobility, reaching highly connected cities first and spreading through dense networks. The virus is then seeded more occasionally to less connected societies, progressively reaching even peripheral communities.

The dramatic effects of the COVID-19 epidemic may manifest in peculiar ways in different contexts. In the early stages of the COVID-19 epidemic in sub-Saharan Africa, the virus first affected the urban elites with international connections. From there it was seeded to other sections of the society more slowly. In contrast, the collateral effects of a lockdown, even partial in many cases, are mostly felt by the urban poor, as “stay home” orders abruptly intensify hardship for those earning their daily living in the informal urban economy. Governments of LICs/LMICs lack the budgetary space to grant generous benefit packages to counter the socioeconomic consequences. International agencies are very thinly spread, as the pandemic has been concurrent everywhere. Donor countries have focussed mainly on their own COVID-19 epidemics.

The epidemic is thus playing out differently in different contexts. The spread of SARS-CoV-2 has been obviously slower and less intensive in certain contexts. Many factors might explain those different SARS-CoV-2 transmission dynamics. Climate, population structure, social practices, pre-existing immunity, and many other variables that have been explored are summarised in Table 2.

**Table 2: Contextual variables potentially influencing transmission of SARS-CoV-2**

<b>Variable</b>	<b>Elements</b>	<b>Range (variation/extremes)</b>	
<b>Population density</b>	People per km <sup>2</sup>	Big European/ US/Chinese cities	Rural areas
	People per household Indoor space (m <sup>2</sup> ) per person		Megacities with urban slums
<b>Social demography</b>	Age structure: proportion of elderly & children Household composition: nuclear vs. multi-generational	Italy, Europe	Sub-Saharan Africa, Southeast Asia
	Mixing patterns, including mode of transport Forms of religious and social events		
<b>Social practices</b>	Mode of greeting and social contact (shaking hands, kissing, hugging, etc.)	High income countries or areas	Slums
	Handwashing, water, and sanitation Ventilation and air conditioning		
<b>Geography</b>	Climate Urbanization rate	Europe, US	Sub-Saharan Africa, Brazil, India
	Air traffic intensity Population movements Road networks		
<b>Pre-existing immunity</b>	Prior exposure to other coronaviruses, BCG vaccine, etc. Non-specific immunity?	High income countries	Low income countries in tropical climates
<b>Genetic factors</b>	ACE variability		
	HLA variability		

BCG: Bacillus Calmette–Guérin, ACE: Angiotensin-Converting Enzyme, HLA: Human Leukocyte Antigen, US: United States

Although all these variables probably play some role, many uncertainties remain. It is difficult to assess how much these variables influence transmission in different contexts. It is even more difficult to assess how they interact and change over time and influence transmission among different social groups, resulting in the peculiar COVID-19 epidemic in any particular context.

## INSIGHTS FROM OTHER VIRUSES

We do not attempt to give a complete overview of viruses but select only those viruses that emerged recently and caused epidemics such as Ebola, that have obvious similarities in transmission patterns such as influenza and measles, or that are closely related such as other coronaviruses.

## Emerging viral respiratory pathogens

Respiratory viruses such as SARS-CoV, MERS-CoV, and avian influenza A and also Ebola have originated from animal hosts and caused human diseases (Table 3). These viruses do not continuously circulate from human to human. They create an outbreak only when there is interspecies cross-over transmission, most frequently from bats to another animal host. When a virus causes acute disease with high lethality, continuous transmission is difficult. The rapid killing of the virus’s human host hampers further transmission.

**Table 3: Examples of emerging human respiratory viral diseases without sustained human-to-human transmission**

Virus	Originating animal host	Characteristics	No. of cases; CFR
SARS-CoV	Bat	<ul style="list-style-type: none"> <li>• First emerged in China in November 2002.[33]</li> <li>• Causes SARS (Severe Acute Respiratory Syndrome).</li> <li>• Transmission through super-spreading events in healthcare facilities.[34]</li> </ul>	8422 cases; CFR:10% [35]
MERS-CoV	Bat	<ul style="list-style-type: none"> <li>• First emerged in the Middle East in 2012.[36]</li> <li>• Causes MERS (Middle East Respiratory Syndrome).</li> <li>• Outbreaks from 2012 to 2019 in Saudi Arabia and one outbreak in South Korea (2015).</li> </ul>	2502 cases; CFR: 34% [36]
Avian influenza A (H5N1 and H7N9)	Birds/poultry	<ul style="list-style-type: none"> <li>• Subtypes of influenza viruses detected in birds (having killed millions of poultry) but with “pandemic potential” (WHO).[37]</li> <li>• H5N1 first detected in humans in 1997 in China with widespread emergence in 2003–2004; no sustained community-level transmission.[37]</li> <li>• H7N9 first detected in humans in China in 2013.[38]</li> </ul>	H5N1: 649 cases; CFR: 60% [39] H7N9: 571 cases; CFR: 37% [38]
Ebola virus	Bat	<ul style="list-style-type: none"> <li>• First appeared in 1976 and caused over 20 documented “major” outbreaks.[40]</li> <li>• Largest epidemics in 2014–16 in Guinea, Liberia, and Sierra Leone.</li> <li>• Ongoing epidemic in the Democratic Republic of Congo.</li> </ul>	Over 30,000 cases; average CFR: 50% [40]

CFR: case fatality rates

The first human case of a disease from an emerging viral pathogen, the “index case” or “patient zero,” is invariably someone in close contact with the originating animal host or an intermediary animal host. If this contact occurs in a remote rural community the spread is usually slow, at low intensity, and could fade out before the pathogen gets a chance to spread to another community. The spread can suddenly intensify if seeded in a densely-populated community, frequently in a particular context such as a hospital or during a social event, often referred to as a super-spreading event. When the spread reaches a city, it can become a major outbreak, from where it can spread further; this happened with

SARS-CoV in Hong Kong in 2003 and with Ebola in Conakry, Freetown, and Monrovia in 2014–16.[41, 42] But at some stage human-to-human transmission is interrupted and the outbreak stops.

Only very exceptionally can a new viral pathogen sustain continuous human-to-human transmission. Other viral diseases such as measles and influenza are “old” diseases; they have been studied in great depth. What can we learn from them?

### **Measles and influenza: the importance of context**

It is thought that measles emerged between 10,000 and 20,000 years ago in the Middle East when the first cities were created and people lived in close contact with domesticated animals. It is assumed that in such an environment a cross-over occurred from a cattle pathogen, the rinderpest virus,[43] to become the human measles virus. Measles has since spread around the globe in continuous human-to-human transmission. The latest episodes of the global spread of measles have been documented. The most dramatic epidemic occurred when measles, along with other viruses such as smallpox and influenza, was introduced in the Americas by European conquerors, contributing to a massive die-off of up to 90% of the original population.[44]

It seems that for the moment the best comparison of transmission dynamics of SARS-CoV-2 is with influenza. Influenza typically causes yearly seasonal epidemics in temperate climates during winter with less seasonal patterns in tropical or sub-tropical regions.[45, 46] In hotter climates, such as in sub-Saharan Africa [45] or South and Southeast Asia [46] it is transmitted year-round at a lower level of intensity as a common respiratory infection, often not identified as influenza. Such different epidemic patterns of influenza are still incompletely understood but thought to be associated with temperature and humidity and human behavioural factors such as indoor crowding.

But, in contrast to SARS-CoV-2, the influenza virus is not new. Influenza is a very old disease, certainly circulating for several centuries. It has infected most human beings living on the planet already, many of them several times. An influenza episode causes some immunity but does not produce durable protection. The virus also mutates, giving rise to a new dominant strain every flu season. Influenza is every year a slightly different virus (due to antigenic drift as a result of progressive mutations) with major differences every few decades (antigenic shift as a result of recombination with novel strains).

One such antigenic shift resulted in the 1918 H1N1 “Spanish” Influenza pandemic, which had an estimated case fatality rate (CFR) of 2–3%, killing millions.[47] Box 1 summarises some key facts about H1N1, including factors thought to be associated with its high CFR.

**Box 1: Pandemic H1N1 Influenza, 1918–2009**

- The 1918 H1N1 virus probably infected one-third of the world’s population at that time (or ~500 million people).[48]
- The pandemic had three waves in quick succession; the second wave, in 1919, was worse than the first wave.[48]
- High mortality, especially in younger persons (5–15 years; ~25% of total deaths) in the 1918 pandemic, may have been due to antibody-dependent enhancement and “cytokine storms.”[48] Another possible explanation is that older persons had some protective cross-immunity from previous influenza outbreaks while younger persons did not.
- H1N1 continued to circulate along with seasonal influenza viruses, often recombining to produce more severe local outbreaks, including other pandemics between 1918 and 2009, giving it the nickname “mother of all pandemics.”
- The original 1918 H1N1 strain was replaced by A(H1N1)pdm09 virus that resulted from an antigenic shift and caused the 2009 H1N1 influenza pandemic.
- The 2009 H1N1 virus originated in pigs in central Mexico in March 2009 and was responsible for an estimated 284,000 deaths worldwide with an estimated CFR <0.1%. [49, 50]
- During the 2009 pandemic mortality was much lower than in the 1918 pandemic. Higher mortality in persons younger than 65 years was related to cytokine storms.[51] A role of protective cross-immunity from previous influenza strains in older persons has been suggested.
- After August 2010, the A(H1N1)pdm09 virus appeared to have integrated with circulating strains of influenza and continues to cause localised seasonal influenza outbreaks worldwide.[52]

The comparison between COVID-19 and influenza is certainly imperfect. The two may be similar in several ways, but SARS-CoV-2 is a new pathogen and influenza is not. At the time of writing (May 2020), SARS-CoV-2 has triggered an immune response in over five million confirmed infections (and probably in many more), definitely too few to create anything close to herd immunity for SARS-CoV-2. Calculations using an estimated reproductive number (R0) for SARS-CoV-2 suggest that herd immunity would require at least 60% of the population to have protective immunity (see Box 2).[53]

Like COVID-19, measles and influenza have different epidemic patterns in different contexts. This also is the case for cholera, tuberculosis (TB), HIV/AIDS, and most infectious diseases. The difference in patterns is most pronounced and so is easily understood with vector-borne and water-borne diseases. Epidemic patterns are also different for air-borne infections, although they are less easily understood. Transmission of respiratory viruses is influenced by factors related to the virus and the human host but also by factors related to the natural and human environment (Table 4).

**Table 4: Factors related to transmission patterns and severity of respiratory viruses**

Factor	Variables
<b>Virus</b>	<ul style="list-style-type: none"> <li>• Infection efficiency, transmissibility.</li> <li>• Capacity to survive outside the human body (including in aerosols, in droplets, on surfaces, in stools, in intermediate animal hosts, etc.)</li> <li>• Potential to shed virus from an infected person, asymptomatic or diseased.</li> <li>• Genetic stability or variability (affecting the potential of long-lasting immunity).</li> <li>• Viral load determines the incubation period with the formula high load -&gt; short incubation period -&gt; high severity.</li> </ul>
<b>Human host</b>	<ul style="list-style-type: none"> <li>• Human susceptibility to the virus; transfer of parental immunity to newborns.</li> <li>• Route and efficiency of human-to-human transmission.</li> <li>• Presence and capacity of asymptomatic carriers to transmit the virus.</li> <li>• Immunity created after infection, its robustness, and how long-lasting it is.</li> <li>• Severity and duration of the disease: proportion symptomatic, lethality (CFR).</li> <li>• Pathogenicity and disease spectrum; disease pattern according to age and co-morbidities, and related potential to spread.</li> </ul>
<b>Natural environment</b>	<ul style="list-style-type: none"> <li>• Temperature, humidity, and seasonal changes in climate affecting the stability and transmission potential of the virus and human susceptibility.</li> <li>• Increasing extreme weather conditions such as droughts and severe storms, as well as global climate change may also affect transmission patterns.</li> <li>• Air pollution may also play a role in the transmission and stability of the virus.</li> </ul>
<b>Human environment/ social geography</b>	<ul style="list-style-type: none"> <li>• Demographic variables such as population density, age structure, and household composition.</li> <li>• Mixing patterns within households, including bed sleeping patterns, related to housing conditions and hygiene practices.</li> <li>• House construction with solid walls or permeable walls (thatched walls, straw mats).</li> <li>• Mixing patterns among households related to settlement patterns: social networks, urban-rural differences, working conditions, religious practices, and commuting patterns.</li> <li>• Variables related to built environments, road infrastructure, and socioeconomic conditions.</li> <li>• Mobility between communities, including international travel.</li> <li>• Crowding institutions: e.g., elderly homes, extended families, boarding schools, child institutions, seclusion during tribal ceremonies, hospitals, nursing homes, military barracks, and prisons.</li> </ul>

However, although we observe different transmission patterns and associate them with observable explanatory variables, we are quite unable to explain fully which factor has which influence, how these factors vary among different social groups, and how interdependent or isolated they are. We are certainly unable to fully model all these variables mathematically to explain the epidemic pattern across a variety of different contexts. Too many variables and their interrelations are difficult to quantify, and when all these factors change over time while the pathogen continues to spread in diverse societies, the complexity becomes daunting.

This situation is a bit less daunting for measles, as several variables are well known and rather constant across individuals and contexts. Although at present measles transmission patterns are strongly influenced by vaccination, its natural transmission pattern, before the introduction of vaccines, has been well described in most communities. Measles is mostly a childhood disease, but this is not the case in very remote communities, where measles transmission had been interrupted for

extended periods (such as the Faroe Islands).[54, 55] In fact, measles affected all age groups when reaching new territories, causing dramatic first-time epidemics, a phenomenon called “virgin soil epidemic.”[56, 57]

The latest stages of the global dissemination of measles, including in Australia, the Fiji islands, and the Arctic countries, occurred in the 19<sup>th</sup> and the mid-20<sup>th</sup> centuries. These first-wave epidemics have been well documented.[44, 58] Fortunately, measles infection creates robust protective immunity and after a first wave becomes a typical childhood disease, affecting only those without any prior immunity.[59] Human-to-human transmission of measles virus in a community stops when too few people without protective immunity remain. When herd immunity is reached, the virus cannot find new susceptible human hosts.[60, 61] But transmission of measles continues elsewhere, from where it can be re-introduced after a number of years when the population without immunity has grown large enough to allow human-to-human transmission again.

The epidemic patterns of measles are easily understood as measles is highly infectious, spreads through relatively superficial contact, creates disease in almost every infected person, and leaves lifelong natural immunity. Measles circulation, prior to vaccination, was continuous only in large urban areas with high birth rates; local transmission halted everywhere else once the pool of susceptible children became too small. Periodic re-introduction occurred typically every 3 to 5 years but sometimes only after 10 or 15 years in isolated rural communities (such as among nomadic groups in the Sahel), causing epidemics among all those without acquired immunity or those who had lost maternal antibodies.[62] These diverse patterns of measles epidemics have been fundamentally changed by variable coverage of measles vaccination. They still can help us make sense of the diversity of COVID-19 epidemics being observed in 2020.

Although SARS-CoV-2 is quite different from measles, we have discussed measles transmission at some length because it illustrates convincingly that the transmission pattern of a respiratory viral disease is strongly influenced by the demographic composition, density, and mixing patterns of the population and the connectedness to big urban centres. Measles transmission is continuous only in some large urban areas. It presents in short epidemics everywhere else with variable periodicity depending on human geography. This transmission pattern may well be a bit similar for COVID-19.

But it took thousands of years for measles to reach all human communities while SARS-CoV-2 spread to all countries in only a few months, despite measles being much more transmissible than SARS-CoV-2. Factors such as increased air travel and more dense community structures play bigger roles for SARS-CoV-2 than they did for measles.

### **Comparison with other pathogenic coronaviruses**

SARS-CoV-2 has many close relatives. Six other human coronaviruses (HCoV) are known to infect humans. SARS-CoV and MERS-CoV (causing SARS and MERS respectively) are very rare and do not continuously circulate among humans. The other four (HCoV-229E, HCoV-OC43, HCoV-HKU1, and HCoV-NL63) cause the common cold or diarrhoea and continuously circulate and mutate frequently.[63, 64] They can cause disease in the same person repeatedly. The typical coronavirus remains localised to the epithelium of the upper respiratory tract, causes mild disease, and elicits a poor immune response, hence the high rate of reinfection (in contrast to SARS-CoV and MERS-CoV, which go deeper into the lungs and hence are relatively less contagious). There is no cross-immunity between HCoV-229E and HCoV-OC43, and new strains arise continually by mutation selection.[65]

### **COPING STRATEGIES AND COLLECTIVE STRATEGIES**

How a virus spreads and its disease progresses depend not only on the variables described above (Table 4) but also on the human reactions deployed when people are confronted with a disease outbreak or the threat of an outbreak. All these variables combined result in what unfolds as “the epidemic” and the diverse ways it affects communities.

What a population experiences during an epidemic is not fully characterised by the numbers of known infections and deaths at the scale of a country. Such numbers hide regional and local differences, especially in large and diverse countries. The epidemic reaches the different geographical areas of a country at different moments and with different intensities. It affects different communities in variable ways, influencing how these communities perceive it and react to it. What constitutes a local COVID-19 epidemic is thus also characterised by the perceptions and the reactions it triggers in the different sections of the society.

Even before the virus reaches a community, the threat of an epidemic already causes fear, stress, and anxiety. Consequently, the threat or arrival of the epidemic also triggers responses, early or late, with various degrees of intensity and effectiveness. The response to an epidemic can be divided into individual and household actions (coping strategies), and collectively organised strategies (collective strategies). Coping strategies are the actions people and families take when disease threatens and sickness occurs, including the ways they try to protect themselves from contagion. Collective strategies are voluntary or mandated measures deployed by organised communities and public authorities in response to an epidemic. These include, among others, isolation of the sick or the healthy, implementation of hygiene practices, and physical distancing measures. They can also

include mobility restrictions such as quarantine and *cordon sanitaire*. Coping strategies and collective strategies also include treatment of the sick, which critically depends on the availability and effectiveness of diagnostic and therapeutic tools, and performance of the health system. Collective strategies also include research being deployed to further scientific insight and the development of diagnostic and therapeutic tools, potentially including a vaccine. Implementation of these measures depends not only on resources available but also on the understanding and interpretation of the disease by both the scientific community and the community at large, influenced by the information people receive from scientists, public authorities, and the media. This information is interpreted within belief systems and influenced by rumours, increasingly so over social media, including waves of fake news, recently labelled “infodemics.”[66]

Coping strategies and collective strategies start immediately, while there are still many unknowns. Progressively, as the pandemic unfolds and scientists interpret observations in the laboratory, in the clinic, and in society, more insights are gained on the virus; its interaction with humans; its spread across communities; and its consequences for infected individuals, communities, and entire countries. These insights inform in real time the collective strategies taken by communities and public authorities. Table 5 lists measures recommended by the WHO for preventing transmission and slowing down the COVID-19 epidemic.[67-69] “Lockdown,” first employed in early 2020 in Wuhan, China, is the label often given to the bundle of containment and mitigation measures promoted or imposed by public authorities, although the specific measures may vary greatly between countries. In China, lockdown was very strictly applied and enforced. It clearly had an impact, resulting in total interruption of transmission locally. [70, 71]

**Table 5: Measures recommended by the WHO for preventing transmission and slowing down the COVID-19 epidemic, 2020**

<b>Implementation level</b>	<b>Intervention</b>
<b>Individual</b>	<ul style="list-style-type: none"> <li>• Hand hygiene: handwashing or use of hydroalcoholic solution.</li> <li>• Physical distancing.</li> <li>• Respiratory etiquette.</li> <li>• Masks for infected and symptomatic individuals.</li> </ul>
<b>Community</b>	<ul style="list-style-type: none"> <li>• Mass masking with surgical and/or homemade masks by everyone in public spaces.</li> <li>• Avoid crowding and mass gatherings.</li> </ul>
<b>Public authorities</b>	<ul style="list-style-type: none"> <li>• Tracing, testing, and isolating cases and providing them with appropriate care.</li> <li>• Tracking, quarantining, and monitoring of asymptomatic contacts.</li> <li>• Protecting health workers and vulnerable groups.</li> <li>• Environmental cleaning and sanitising.</li> <li>• Closures of schools, places of worship, sporting events, non-essential shops.</li> <li>• Workplace closures and other measures: work from home where possible and/or reduction in workforce capacity.</li> <li>• Public transportation closures.</li> <li>• Stay-at-home orders.</li> <li>• Limiting national and international travel.</li> <li>• Maintaining essential health services.</li> <li>• Ensuring continuity of essential social and economic functions and services.</li> </ul>

This list or catalogue of measures is quite comprehensive; it includes all measures that at first sight seem to reduce transmission opportunities for a respiratory virus. However, knowledge is lacking about the effectiveness of each measure in different contexts as the transmission of SARS-CoV-2 is still incompletely understood.

The WHO recommends that the appropriate combination of measures in a given country at any one time will depend on the phase of the pandemic, categorised in four transmission scenarios (no cases, first cases, first clusters, and community transmission).[68] As a global health agency, the WHO recommends a “generic catalogue” of measures from which all countries can select and adapt to their own contexts. However, under pressure to act and with little time to consider variable options, the global recommendations were often adopted as a “blueprint” with limited consideration for the capacity of the public health system and the socioeconomic context.[69, 72]

The initial lockdown in China much inspired the collective strategies in other communities and societies where the virus was introduced later. This has been referred to as “global mimicry”[73]. As the current pandemic has been highly mediated and politicised, many of the collective strategies taken are partly “copy/paste” from those taken early on at the beginning of the COVID-19 epidemics (strong path dependency).

Some epidemiologists in Northern Europe (including the United Kingdom (UK),[74] Sweden,[75] and the Netherlands [76]) pleaded against strict containment measures and proposed that building up herd immunity against SARS-CoV-2 might be wiser. Towards early April 2020, it became increasingly clear that reaching herd immunity in the short term was illusive. Most countries thus backed off from the herd immunity approach to combating COVID-19 and implemented lockdowns.[77] The intensity of the lockdowns has been variable, ranging from very strict (“Chinese, Wuhan style”), over intermediary (“French/Italian/New York City (NYC) style” and “Hong Kong style”), to relaxed (“Swedish style”), to piecemeal.

The effectiveness of such measures largely depends on how intensely and at what stage of the outbreak they are applied. This is quite variable across countries, depending on the understanding and motivation of the population (“willingness to adhere”), on the trust they have in government advice (“willingness to comply”), and on the degree of enforcement by public authorities. The feasibility of different population groups following these measures depends largely on their perceived risk (severity, contagiousness) of the disease and socioeconomic and living conditions. It is more difficult for people living in crowded shacks in urban slums to practise physical distancing measures and strict hand hygiene when water is scarce than for people living in wealthier parts of a city.

### **Collateral effects of the response**

Every intervention against the COVID-19 epidemic has a certain degree of effect and comes at a cost with collateral effects. Each collective strategy: (1) has intended and unintended consequences (some are more or less desirable); (2) is more or less feasible and/or acceptable in a given context and for certain subgroups in that society; (3) has a cost not only in financial terms but in many other ways, such as restrictions on movement and behaviour, stress, uncertainty, and others. These costs are more or less acceptable, depending on the perception of the risk and many societal factors; (4) can be implemented with more or less intensity; and (5) can be enforced more or less vigorously.

The balance between benefit and cost is crucial in judging whether measures are appropriate, which is very context specific. Furthermore benefits and costs are also related to the positionality with which they are analysed; benefits for whom and costs borne by whom. More wealthy societies with strong social safety nets can afford increased temporary unemployment. This is much more consequential in poorer countries, especially in fragile and conflict-affected settings, where large proportions of the population live precarious lives and where public authorities cannot implement generous mitigation measures at scale.

The adherence to hygiene and distancing measures depends not only on living conditions but also on risk perception and cultural norms. Mass masking has been readily accepted in some Asian countries, where it was already broadly practised even before the COVID-19 epidemic. It remains more controversial in Western societies, some of which even have legal bans on veiling in public places.

Lockdowns are unprecedented and have triggered intensive public debate. Also, once a lockdown is started, rationalised, explained, and enforced, it is difficult to decide when to relax or stop it. The balance between positive and negative effects evolves with the evolution of the epidemic over time. Moreover, the application and effectiveness of lockdowns depend on the context, including an area's carrying capacity.

Not surprisingly, the impact of lighter lockdowns on the transmission is much less impressive; they decrease transmission but do not stop it. Quite rapidly, the justification for lockdowns shifted from stopping transmission to “flattening the curve.” Together with the impossibility of sustaining lockdowns over very long periods, their usefulness has been increasingly questioned. Exit scenarios, usually some form of progressive relaxation, are implemented with the knowledge that transmission will be facilitated again. Ultimately, the balance of positive and negative effects of any collective strategy depends on the communities and societies in which they are implemented.

## **KNOWN AND UNKNOWN ABOUT SARS-COV-2/COVID-19**

### **What we already know**

The available information on SARS-CoV-2 and the spectrum of COVID-19 disease are summarised in Table 6 and Table 8. There are still many unknowns about the virus and its transmission, including the influence of the natural and social environments. But it is increasingly becoming clear that most transmission happens indoors and that super-spreading events trigger intensive dissemination.

The virology and immunology of SARS-CoV-2/COVID-19 are being studied intensively. This is critical not only to understand what will potentially happen in future waves but also for the development of a vaccine. Some scientists and companies are very upbeat about the possibility of producing a vaccine in record time. Having a vaccine is one thing, but how effective it is, is quite another. At the time of writing (May 2020), a vaccine doesn't exist. As acquired immunity after a natural infection is probably not very robust (Table 6), it will also be challenging to trigger robust immunity with a vaccine, but perhaps it is not impossible. Many questions remain, some of which are summarised in Table 7.

Regarding the severity of COVID-19, initial fears of very high mortality have also lessened. It has progressively become clear that many infections remain asymptomatic, that severe disease is rare in children and young adults, and that mortality is heavily concentrated in the very old and those with co-morbidities. Table 8 summarises a fuller overview of the present state of knowledge regarding COVID-19.

With COVID-19 epidemics unfolding rapidly in the northern hemisphere, several of the variables in the transmission of SARS-CoV-2 and the disease spectrum of COVID-19 could be quantified. This allows for mathematical modelling. Several models have been quickly developed, leading to predictions of the speed of transmission and the burden of COVID-19 (Box 2). Predictive models developed by the Imperial College [125]; the Center for Disease Dynamics, Economics & Policy (CCDEP) and Johns Hopkins University [126]; the Institute for Health Metrics and Evaluation (IHME) [127]; Harvard University [128]; and the WHO,[129] including an “African model,”[130] are a few that are influencing containment strategies around the world.

**Table 6: Knowns, uncertainties, and unknowns about SARS-CoV-2, as of May 2020**

Factor	Available information
<b>Origin of SARS-CoV-2</b>	<ul style="list-style-type: none"> <li>• Most probably from bats via intermediate animal hosts to index case.[63, 78]</li> <li>• All subsequent cases resulted from human-to-human transmission.</li> </ul>
<b>Transmission</b>	<ul style="list-style-type: none"> <li>• Mainly through respiratory droplets from infected persons [79]; by hands, after contamination at nose, mouth, or eyes; also through air on exposure to sneezing or coughing from an infected person at close distance.</li> <li>• Through aerosols, while singing/talking loudly in congregations, groups, parties, karaoke, etc., especially in poorly ventilated spaces.[26, 80]</li> <li>• Through fomites.[81]</li> <li>• Possibly via faecal-oral route [82, 83]; detection in sewage.[84-86]</li> <li>• Related to peak in upper respiratory tract viral load prior to symptom onset in pre-symptomatic (pauci-symptomatic) persons.[80, 87, 88]</li> <li>• Transmission dynamics in asymptomatic persons not fully elucidated although viral shedding occurs.[89]</li> </ul>
<b>Influence of climate and/or air pollution on transmission</b>	<ul style="list-style-type: none"> <li>• Influence of climate on the capacity of the virus to survive outside human body (in air, in droplets, on surfaces, etc.) and to spread has been speculative.</li> <li>• May spread more readily in milder/colder climate [90, 91]; although variability of the reproductive number could not be explained by temperature or humidity.[92]</li> <li>• Existing levels of air pollution may play a role; air pollutants, such as particulate matter, nitrogen dioxide, and carbon monoxide, are likely a factor facilitating longevity of virus particles.[93]</li> <li>• Elevated exposure to common particulate matter can alter host immunity to respiratory viral infections.[93]</li> </ul>
<b>Immunity – protective antibodies</b>	<ul style="list-style-type: none"> <li>• IgM and IgA antibody response 5–10 days after onset of symptoms, does not depend on clinical severity, correlates with virus neutralisation; IgG is observed ~14 days after onset of symptoms,[94, 95] may or may not correspond to protective immunity. Whether antibody response is long lasting has remained unclear.</li> <li>• Re-challenge in rhesus macaques showed immunity post primary infection.[96] How protective immunity after first infection is against subsequent infection with an identical or mutated strain has been uncertain.</li> <li>• Incidental reports showed recovered persons positive by Real-Time PCR,[97, 98] later attributed to testing errors.</li> </ul>
<b>Seroprevalence to SARS-CoV-2</b>	<ul style="list-style-type: none"> <li>• Reported estimates for seroprevalence range between 0.4 and 59.3% [99]; differences in timing of the sero-survey, the use of assay kits with varying sensitivity/specificity, and different methods for detection may contribute to this large variation.[100]</li> <li>• Seemingly high seroprevalence may be due to cross-reactive epitopes between SARS-CoV-2 and other HCoV.[101, 102]</li> <li>• Whether seroprevalence implies immune protection is unclear, yet, some countries have considered use of “immunity passports.”[103]</li> <li>• For herd immunity to be effectively achieved, an estimated seroprevalence of 60% of the population will be required.[53] Other studies estimate between 5.66% and 85% seroprevalence in different countries.[104-106]</li> </ul>
<b>Rate of variability/mutation in SARS-CoV-2</b>	<ul style="list-style-type: none"> <li>• Mutation rate: <math>\sim 10^{-3}</math> substitutions per year per site [107, 108]; 13 mutation sites have been identified as of May 2020, suggesting selective mutations.[109]</li> <li>• The low mutation rate suggests that a vaccine would be a single vaccine rather than a new vaccine every year like the flu vaccine.[110]</li> <li>• Ten different circulating clades (<a href="http://nextstrain.org">nextstrain.org</a>; <a href="http://www.gisaid.org">www.gisaid.org</a>),[111] as of May 2020.</li> </ul>

PCR: Polymerase Chain Reaction; HCoV: Human Coronaviruses

**Table 7: Questions and considerations in case a COVID-19 vaccine is developed**

Question	Considerations
<b>If a vaccine is developed?</b>	<ul style="list-style-type: none"> <li>• What type of vaccine will it be (live/non-live, classic killed, DNA, or recombinant)?</li> <li>• Will it need special manufacture and transport conditions (such as cold chain)?</li> <li>• How robust will be vaccine-acquired immunity? After how many doses?</li> <li>• How protective will it be against infection?</li> <li>• For how long will vaccine-acquired immunity last? And hence: How often will the vaccine have to be administered? Only once? Or yearly?</li> <li>• Will there be any adverse effects?</li> </ul>
<b>Acquired immunity is not very strong; hence, what is the consequence regarding herd immunity?</b>	<ul style="list-style-type: none"> <li>• To achieve herd immunity, how efficient will the vaccine need to be?</li> <li>• What proportion of the population (critical population) will need to be vaccinated?</li> <li>• How long will it take to effectively vaccinate the critical population?</li> <li>• Will vaccination be acceptable in the population? Or will vaccine hesitancy reduce uptake?</li> </ul>
<b>What are the socioeconomic implications?</b>	<ul style="list-style-type: none"> <li>• Which countries will get the vaccine first (implications for LICs/LMICs)?</li> <li>• How expensive will the vaccine be?</li> <li>• Will vaccination be made mandatory, especially for international travel?</li> </ul>

**Table 8: Knowns, uncertainties, and unknowns about COVID-19, as of May 2020**

Factor	Available information
<b>Disease spectrum</b>	<ul style="list-style-type: none"> <li>• Many different estimates: <ul style="list-style-type: none"> <li>• Initially it was estimated that among infected, 30% remained asymptomatic, 55–80% had mild/moderate disease, 10–14% had severe disease, and 5–6% became critically ill.[15, 112-114].</li> <li>• Very variable estimates for remaining totally asymptomatic (estimated 5–80% [95, 115-117]).</li> </ul> </li> <li>• What determines that an infection remains asymptomatic?</li> <li>• Quasi-absence of disease in children: why?</li> </ul>
<b>Case fatality rate (CFR)</b>	<ul style="list-style-type: none"> <li>• Initial estimates CFR: 2–3%; comparisons: influenza 0.1%; common cold: 0%; SARS: 9–10%; MERS: 30% [118].</li> <li>• Calculated infection fatality rates (cIFR) and calculated CFR (cCFR) on the Princess Diamond were 1.3% and 2.6% respectively (for all ages combined), and projected cIFR and cCFR for China were between 0.6–0.66% and 1.2–1.38% respectively.[112, 119] In Gangel, Germany: cCFR of 0.37%.[120]</li> <li>• CFR is influenced significantly by age; male sex; co-morbidities; body-mass index (BMI) and/or fitness; and adequacy of supportive treatment, mainly oxygen therapy.[121, 122] Also, as in certain other viral diseases such as measles, possibly influenced by the dose of virus in initial infectious inoculum (see Box 3).</li> <li>• CFR and IFR vary depending on population distribution. March 2020, estimated IFR UK: 0.9%, Italy: 1.14–6.22% initial estimate which increased to 9.26%, Spain: 6.16%, France: 4.21%.[123, 124]</li> </ul>
<b>Medication/ treatment options</b>	<ul style="list-style-type: none"> <li>• Treatments being used: hydroxychloroquine and chloroquine, remdesivir, azithromycin, convalescent plasma, and other antivirals.</li> <li>• At the time of writing (May 2020), no proven effective treatment. Many clinical trials ongoing.</li> <li>• Oxygen therapy most essential component of case management. Low oxygen saturation a dominant feature of COVID-19, curiously dissociated from dyspnoea. In most cases, oxygen can be administered through a facial mask. In very advanced disease, oxygen administered through artificial ventilation, requiring sophisticated equipment and highly skilled personnel.</li> </ul>

**Box 2: On the use of mathematical models during epidemics**

A dominant way of studying the transmission dynamics of an infectious disease such as COVID-19, and predicting the amplitude and peak of the epidemic in a population (city, province, country) and analysing the effect of control measures is using mathematical models. Based on available data and several assumptions, a model attempts to predict the course of the epidemic, the expected number of infections, clinical cases, and deaths over time. Critical is the effective reproductive number ( $R_t$ ). When  $R_t > 1$  the number of cases in a population increases; when  $R_t < 1$  the number of cases decreases. A relatively simple and widely used model is the SEIR model, as used in the two papers recently published in BMJ Global Health on COVID-19 in Africa.[130, 131] There are many more types of models, with varying degrees of complexity.

The use of such models has strengths and limitations. Building a mathematical model implies trade-offs between accuracy, transparency, flexibility, and timeliness. A difficulty, in general, is that the parameters on which the model is based, the so-called assumptions are frequently uncertain (Table 8) and predictions can vary widely if any of the parameters are modestly different. This uncertainty is captured in a sensitivity analysis, leading to various possible quantitative outcomes, usually expressed as a range of plausible possibilities, between “worst-case” and “best-case” scenarios.

With a new disease such as COVID-19, certainly at the start of the outbreak, the parameters had to be based on very limited data from a particular context. However, many variables can widely differ across communities as they critically depend on contextual factors (Table 2). In mathematical models, all such uncertainties and unknowns are somehow hidden in the complex formulae of the model, as a quasi “black box.” Few people have the knowledge and skill to “open up the black box.”

As uncertainties in COVID-19 are large, the range of possibilities produced by a model is wide, with the worst-case scenario typically predicting catastrophic numbers of cases and deaths. Such predictions are often misunderstood by journalists, practitioners, and policy makers, with worst-case estimates getting the most attention,[132] not specifying the huge uncertainties.

**Critical unknowns and uncertainties**

Although the COVID-19 pandemic triggered unprecedented research efforts globally, with over 30,000 scientific papers published between January and April 2020, there are still critical unknowns and many uncertainties.

Table 6 and Table 8 summarise many of the knowns, but their relative importance or weight is not clear. For instance, the virus can spread via droplets, hands, aerosols, fomites, and possibly through the environment. However, the relative importance of these in various contexts is much less clear. These factors undoubtedly vary between settings, whether in hospitals, in elderly homes, or at mass events. The weight of the variables also probably differs between the seeding and initial spread in a community and the spread when it suddenly amplifies and intensifies. The importance of each variable probably also depends on climatic conditions, not only outdoors, but also on microclimates indoors, influenced by ventilation and air conditioning and built environments.

Important knowledge gaps in SARS-CoV-2 and COVID-19 include:

- Why are there such different transmission patterns? What parameters contribute most to the differences in patterns?
- Will human-to-human transmission continue permanently? Is immunity long-lasting?
- What is the role of children in transmission?
- What will happen in future waves?
- What proportion of the population will undergo infection before the transmission will slow down or be interrupted as a result of population immunity?
- Will herd immunity be reached at any time?
- Why are there such large variations in the spectrum and severity of the disease?
- Which mechanisms are at play in severe disease?

We summarise the critical unknowns in Table 9 along some elements to consider in addressing the unknowns and thoughts on their importance.

**Table 9: Some critical unknowns in SARS-CoV-2 transmission**

Critical unknowns	Considerations
<p><b>Which transmission patterns will occur and will human-to-human transmission continue permanently?</b></p> <p><b>This will strongly depend on:</b></p> <p><b>How strong will the acquired immunity after a first infection with SARS-CoV-2 be and how long will it last?</b></p>	<ul style="list-style-type: none"> <li>• Seasonal transmission in temperate climate?</li> <li>• Continuous tides, with ups and downs?</li> <li>• The experience from China and some other countries showed that “local elimination” is possible but risk of re-introduction remains.</li> <li>• Increasingly unlikely that elimination everywhere is possible.</li> </ul> <p>• Evidence of acquired immunity against subsequent infections has been limited.</p> <p>• Measurable antibodies have been observed in most persons who have recovered from COVID-19,[106] and research in animal models has suggested limited possibility of re-infection.[96]</p> <p>• It is still unclear as to how robust the immunity is and how long it will last.</p> <p>• Debate on use, practicality, and ethics of “immunity passports” for those recovered from COVID-19 has been ongoing.[103, 133]</p>
<p><b>How stable is the virus (mutation) and do the different clades seen worldwide have any effect on the transmission potential/severity of the disease?</b></p>	<ul style="list-style-type: none"> <li>• If the virus mutates quickly and different strains develop, then antibody-dependent enhancement (ADE) might be an important risk, as in dengue with its four different strains. If so, then in subsequent waves progressively more severe cases could occur.</li> <li>• This has been reported for the Spanish flu, where the second and third waves were characterised by a more severe disease pattern.[47, 48]</li> </ul>
<p><b>What is the role of children in transmission?</b></p>	<ul style="list-style-type: none"> <li>• Children have quasi-universally presented less severe disease. However, their susceptibility to infection remains unclear, with large heterogeneity reported between studies.[134, 135]</li> <li>• Their role in transmission has remained unclear, but evidence points to a more modest role in transmission than adults.</li> </ul>
<p><b>How significant are asymptomatic carriers in transmission?</b></p>	<ul style="list-style-type: none"> <li>• There have been several reports of asymptomatic transmission [136, 137] and estimates based on modelling.[88]</li> <li>• Increasing consensus that asymptomatic carriers play an important role in transmission.</li> </ul>

Uncertainty remains, leading to controversy and directly influencing the choice of containment measures. Controversy continues regarding when and where lockdown or more selective measures are equally effective with lower societal effects.

### **Relationship between the dose of the initial infectious inoculum, transmission dynamics, and severity of the COVID-19 disease**

New evidence is being discovered rapidly. Some evidence comes from field observations and ecological studies; other evidence results from scientific experiments or observations in the laboratory and the clinic. Sense-making by combining insights from different observations and through the lens of various disciplines can lead to hypotheses that can be tested and verified or refuted. One such hypothesis is that there is a relationship between the dose of virus in the infectious inoculum and the severity of COVID-19 disease. Several intriguing observations in the current pandemic could be (partially) explained by such a relationship. We develop this hypothesis in Box 3, as an example of possible further research, to create new insight which may influence control strategies.

#### **Box 3: Relationship between the dose of the initial infectious inoculum, transmission dynamics, and severity of the COVID-19 disease**

##### **Hypothesis:**

The dose of the virus in the initial inoculum may be a missing link between the variation observed in the transmission dynamics and the spectrum of the COVID-19 disease. It is plausible that:

- Viral dose in inoculum is related to severity of disease.
- Severity of disease is related to viral shedding and transmission potential.

This hypothesis plays out potentially at three levels:

- At individual level: A person infected with a small dose of viral inoculum will on average develop milder disease than a person infected with a high viral inoculum and vice versa.
- At cluster level: A person with asymptomatic infection or mild disease will on average spread lower doses of virus in droplets and aerosols and is less likely to transmit disease; when the person transmits, the newly infected person is more likely to have milder disease than if infected by a severely ill person, who spreads on an average higher doses of virus. This causes clusters and chains of milder cases or of more severe cases.
- At community level: In certain contexts, such as dense urban centres in moderate climates during the season when people live mostly indoors, the potential for intensive transmission and explosive outbreaks is high, especially during indoor super-spreading events. In other contexts, such as in rural areas or in regions with hot and humid climate where people live mostly outdoors, intensive transmission and explosive outbreaks are less likely.

This viral inoculum theory is consistent with many observations from the early stages of the COVID-19 pandemic, but it is not easy to test scientifically.

## **POTENTIAL FUTURE SCENARIOS OF COVID-19**

As COVID-19 is a new disease, we should make a distinction between (1) the current 2019–2020 “virgin soil pandemic” caused by SARS-CoV-2, specifically in how it will further spread around the globe in the first wave, and (2) the potential future transmission in subsequent waves. In some countries, transmission will continue at lower levels. In other countries, such as China, the virus may have been eliminated but can be re-introduced in identical or mutated form.

For the current first wave, using influenza and the common cold as reasonable comparisons, it is possible that the major epidemics, as witnessed in Wuhan, northern Italy, or New York, will typically occur in temperate climates in the winter season. Some predict that such epidemics will last between 8 and 10 weeks (but this is just a plausible and reasonable comparison in analogy with seasonal influenza). It is possible/likely that in hotter climates the transmission may become continuous, year-round at lower levels. It is increasingly clear that hot climate does not exclude super-spreading events as observed in Guayaquil, Ecuador, and in various cities in Brazil. Ventilation, air-conditioning, and crowded places may still create favourable environments for intensive transmission. It is also quite possible that the more difficult spread of SARS-CoV-2 in such climates may, in certain communities, be compensated for by human factors such as higher population density, closer human contacts, and lesser hygiene (as, for instance, exist in urban slums in mega cities in low income countries). How all this plays out in sub-Saharan Africa, in its slums and remote areas, is still largely unknown. With SARS-CoV-2, transmission scenarios are mainly based on mathematical models despite their serious limitations (Box 2).

As the virus continues to circulate, it will progressively be less of a “new disease” during subsequent waves. The immunity caused by the first epidemic will influence how the virus spreads and causes disease. Whether later waves will become progressively milder or worse, as observed in the 1918–19 Spanish flu, is a matter of intense speculation. Both views seem plausible and the two are not necessarily mutually exclusive. Indeed, immunity should be defined on two levels, individual immunity and herd immunity. Individual immunity will dictate how mild or severe the disease will be in subsequent infections. Herd immunity could be defined in different communities/regions/countries that, in theory, could be fenced off, allowing only limited interaction with other areas, impacting the spread of the virus to more vulnerable populations.

The future is unknown, but we can think of likely futures and critical elements therein.

Some obvious critical elements are:

- Will there be an effective vaccine? How soon? How effective? How available at scale? How acceptable?
- Will there be an effective treatment? How soon? How effective? How available at scale?
- Will future waves be less severe? More severe?
- Will there be more “precision lockdowns”?

## CONCLUSION

The current first wave is unfolding in the absence of effective biomedical tools (no vaccine, no effective antiviral or immune-modulating medicine, only supportive treatment such as oxygen therapy). This comes close to what can be called a “natural evolution” of the COVID-19 pandemic, mostly modified by the containment measures deployed (Table 5) and the effect of supportive treatment.

Progressively, we can learn more about the direct health effects of COVID-19 (morbidity and mortality), about appropriate individual and collective measures,[132] the various degrees of societal disruption, and the collateral effects on other essential health services (e.g., reluctance to use health services for other health problems, because of “corona fear”). Our growing knowledge may enable us to progressively improve our response.

Learning from the variety of ways the COVID-19 epidemic is unfolding across the globe provides important “ecological evidence” and creates insights into its epidemiology and impacts. Until now the insights gained on COVID-19 have been largely dominated by the COVID-19 epidemics in the Global North. More understanding of lived experiences of people in a variety of contexts, where the epidemic is spreading more slowly and with different impacts, is necessary to get a full global picture and allow learning from this variety. This is an important missing piece of the COVID-19 puzzle. BMJ Global Health and Emerging Voices for Global Health have launched a call (<https://blogs.bmj.com/bmjgh/2020/05/26/from-models-to-narratives-and-back-a-call-for-on-the-ground-analyses-of-covid-19-spread-and-response-in-africa/>) for such on-the-ground narratives and analyses of the spread of and response to COVID-19, local narratives and analyses that will hopefully help to further enrich our understanding of how and why the COVID-19 pandemic continues to unfold in multiple local epidemics along diverse trajectories around the globe.

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## **CONTRIBUTORS**

WVD, RD, EW, and YA conceived and designed the study.

RD, GV, YA, and WVD searched the literature and screened for new emerging evidence.

WVD, RD, and YA drafted successive versions of the manuscript and coordinated inputs from all co-authors.

YA, SA, KV, BI, RvdP, and HK contributed to writing the manuscript.

AD, JPD, PI, SVdB, DN, GB, IVE, MAAA, JAK, VDB, KB, PA, AK, SA-A, PNS, JJM, PM, and SA-M reviewed successive versions of the manuscript and oriented it, with a field-based and local gaze from Guinea, Benin, Cambodia, Belgium, India, the UK, Mali, Canada, Burkina Faso, Germany, the US, Guinea-Bissau, the Democratic Republic of Congo, Yemen, and Australia.

All authors commented on subsequent versions of the manuscript and approved the final version.

WVD attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted

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## COMPETING INTERESTS

None declared

## PATIENT AND PUBLIC INVOLVEMENT

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## PATIENT CONSENT FOR PUBLICATION

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