Perspective

After the pandemic: perspectives on the future trajectory of COVID-19

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There is a realistic expectation that the global effort in vaccination will bring the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) under control. Nonetheless, uncertainties remain about the type of long-term association that the virus will establish with the human population and, in particular, whether coronavirus disease 2019 (COVID-19) will become an endemic disease. Although the trajectory is difficult to predict, the conditions, concepts and variables that influence this transition can be anticipated. Persistence of SARS-CoV-2 as an endemic virus, perhaps with seasonal epidemic peaks, may be fuelled by pockets of susceptible individuals and waning immunity after infection or vaccination, changes in the virus through antigenic drift that diminish protection and re-entries from zoonotic reservoirs. Here we review relevant observations from previous epidemics and discuss the potential evolution of SARS-CoV-2 as it adapts during persistent transmission in the presence of a level of population immunity. Lack of effective surveillance or adequate response could enable the emergence of new epidemic or pandemic patterns from an endemic infection of SARS-CoV-2. There are key pieces of data that are urgently needed in order to make good decisions; we outline these and propose a way forward.

Early in 2020, the world observed a sharp increase in the reported number of SARS-CoV-2 infections. The rapid accumulation of cases contrasted not only with the historical numbers of the SARS-CoV outbreak in 2003, but also with the numbers from the pandemic in 2009 caused by influenza H1N1, with the caveat that perhaps cases of an H1N1 infections were underdiagnosed (Fig. 1). The pattern and impact of the pandemic revealed flaws in the worldwide response to the infection—some local of which were in nature, whereas others were more systematic across many different countries.

With the ongoing deployment of several highly effective SARS-CoV-2 vaccines in many countries, there is an expectation that this virus will disappear. However, two reasons temper our hope in reaching this conclusion: patchy vaccine coverage due to disparities in global access to vaccines and vaccine hesitancy, and vaccines may not always block virus transmission (despite reducing the burden of disease). In addition, although mass vaccine deployment may signal the end of the pandemic, the end of the pandemic does not necessarily equate to the end of SARS-CoV-2. Thus, it is critical to consider what the new equilibrium between humans and this virus and its evolutionary descendants might be. The goal of this Perspective is to discuss the probable transition to a new phase of SARS-CoV-2 infection in humans as an endemic pathogen, perhaps with intermittent epidemic peaks (Box 1). We base our assessment on ongoing data from the COVID-19 pandemic and observations from previous epidemics. We highlight the role of the dynamic interactions between changes in population immunity and ongoing viral evolution and immune escape in shaping the future association of SARS-CoV-2 with humans. We also discuss the possibility that the virus will retain considerable virulence long term. We believe that a thorough understanding of this transition period, and informed guesses about the future of the pandemic are necessary to inform the next steps for public health. It is with that goal in mind that we identify key gaps in our current knowledge and tools with the hope of refining our response as well as guiding scientific initiatives.

Observations from previous pandemics

We believe that it is pertinent to use observations from past infectious disease epidemics to help to predict what the evolutionary future of

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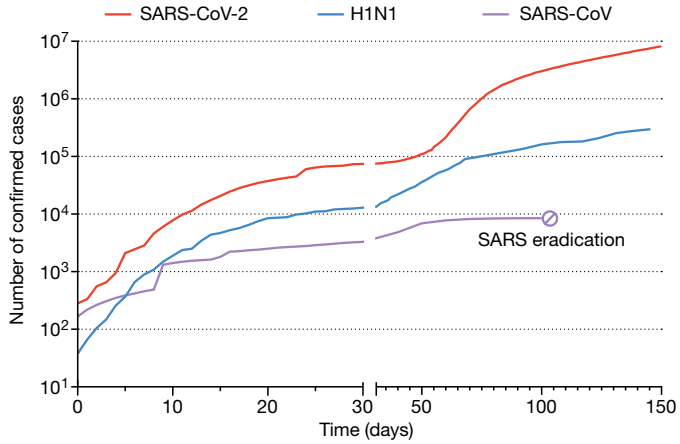

Fig. 1 | Ominous signs in the early days of the pandemic. Towards the end of January 2020, there was an alarming increase in the reported number of SARS-CoV-2 infections (red) that contrasted not only with the growth of historical cases of SARS-CoV in 2003 (purple; counts starting from 19 March 2003), but also with growth curves for the 2009 swine H1N1 infection (blue; counts starting from 24 April 2009). However, each pandemic was probably broader than currently estimated. Data are from Github (https://github.com/CSSEGISandData/COVID-19) and the World Health Organization.

this pathogen could look like. Key questions include whether COVID-19 will become a familiar but high impact seasonal disease similar to influenza and whether SARS-CoV-2 will become more or less virulent than it is currently. Such comparisons are not as straightforward as they might initially seem. In contrast to the coronaviruses that cause the common cold (HCoV-229E, HCoV-HKU1, HCoV-NL63 and HCoV-OC43), SARS-CoV-2 has a higher virulence, yet it also differs from the even-more-serious coronaviruses severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in that asymptomatic transmission is frequent. Thus, comparisons to other coronaviruses do not enable a definitive prediction of the future behaviour of SARS-CoV-2. At a first glance, SARS-CoV-2 seemingly has a capacity to evolve that outstrips that seen in the other human coronaviruses. We do not know whether this reflects a lack of comparable data for the other viruses that have entered the human population long ago, a recent zoonotic origin that has resulted in a strong selection pressure for adaptation to transmission and/or immune evasion in the human host. Indeed, recent studies have shown that seasonal coronaviruses (such as HCoV-229E) have also experienced antigenic evolution in recent decades[1]. The overall uncertainty of these parameters makes it difficult to accurately predict the future post-pandemic equilibrium between SARS-CoV-2 and the human population.

A more meaningful comparison can be made with the emergence of new human influenza viruses, particularly the H1N1 influenza A virus that caused the global pandemic of 1918/1919. In the Northern Hemisphere, the 1918/1919 pandemic was associated with a relatively mild wave in the spring followed by a much more severe wave in the autumn. Although an infection fatality rate of around 2% is commonly cited for the devastating autumn wave, the accuracy of this number is difficult to assess[2]. However, both of these waves fell outside of the usual human influenza season (beginning in March and September, respectively), suggesting that the climatic factors that probably drive seasonality are less important when a new virus enters a very large population of susceptible hosts with little or no pre-existing immunity to the pathogen[3,4]. The same appears to be true of SARS-CoV-2. Although there have been suggestions of emerging seasonality, the reality is that the current changing patterns of the incidence of COVID-19 could better reflect the differing extent and timing of non-pharmaceutical interventions such as social distancing. Major 'summer' (or tropical climate) outbreaks have been reported in such locations as Brazil, India and South Africa.

Although it is possible that SARS-CoV-2 may eventually evolve into a winter seasonal virus such as influenza and the common-cold coronaviruses, this may not occur until there is more widespread population immunity and fewer susceptible hosts in regions that have the optimal climatic conditions for transmission[3]. If SARS-CoV-2 does not become mostly seasonal, implications for the timing of vaccination and vaccine booster campaigns will be considerable.

Box 1

Definition of terms

Definitions are adapted in part from https://www.cdc.gov/mmwr/preview/mmwrhtml/su48a7.htm.

Endemic disease A disease that is constantly present with an incidence that waxes or wanes over a relatively prolonged period (often years of decades).

Epidemic Occurrence of a disease in a pattern that is clearly in excess of normal expectations. Can also refer to a new disease occurring regionally without evolution into a pandemic.

Pandemic An epidemic in which a disease spreads worldwide, crossing international boundaries and spreading between continents.

Transmissibility The likelihood that a pathogen will spread from an infected individual to an uninfected individual.

Virulence The capacity to cause severe illness once the pathogen infects a host.

Fitness Reproductive success, in this context the capacity of a virus to produce infectious progeny in a given environment.

Control An acceptable reduction in a disease in the setting of ongoing epidemic or endemic transmission.

Elimination of disease Diminution to zero of a disease in the setting of ongoing epidemic or endemic transmission.

Elimination of infection Diminution to zero of an infection in the human population. This goal is particularly difficult to attain when there are reservoirs of zoonotic transmission in contact with humans or vector species, as is observed for bird species and the transmission of influenza.

Eradication Permanent reduction to zero of the worldwide incidence of an infection caused by a specific agent as a result of deliberate efforts; intervention measures are therefore no longer needed.

Extinction Absence of a pathogen in humans, animal reservoirs or laboratory sources. Extinction has not been attained for any pathogen as stocks of smallpox and rinderpest are still held in some laboratories.

Viral evolution, transmission and disease severity

In general, transmission of respiratory viruses is mediated by replication in, and shedding from, the upper respiratory tract, whereas severe disease is associated with the invasion of and replication in the lower respiratory tract. Mutations that increase virus replication in both respiratory sites could be selectively favoured if they not only increase the transmissibility but may also result in higher virulence, causing more-severe disease. Notably, mutations that increase replication only in the upper respiratory tract could be selected based on higher transmissibility but may decrease virulence. Indeed, experiments in ferrets with avian influenza H5N1 virus (which is highly virulent, but

poorly transmissible in humans) gave rise to viruses with increased transmissibility and decreased virulence. This is due to changes in the receptor specificity that favour replication in the upper respiratory tract to the detriment of replication in the lower respiratory tract[5]. However, in the case of SARS-CoV-2, mutations that further optimize the use of the human angiotensin-converting enzyme 2 (ACE2) as a virus receptor (which is present in both the upper and lower respiratory tract) or alter the capacity of co-receptors to influence tropism and infection are likely to increase both transmission and virulence[6,7]. By contrast, mutations that increase replication at 33 °C, the temperature of the human upper respiratory tract, while decreasing replication at 37 °C, the temperature of the lower respiratory tract, are expected to increase transmission but decrease virulence. A 'wild card' mutation that—for example—enables the evasion of innate immunity could have profound effects on both transmission and virulence or even the nature of disease. The likelihood that one or all of these changes may occur, or have already occurred, is not possible to predict with certainty given the paucity of data on the status of the virus and disease worldwide.

What about the evolution of SARS-CoV-2 during the pandemic? A reasonable expectation early in the pandemic was that the virus could evolve to develop increased transmissibility, reflecting adaptations to propagation in the new human host. Such a process probably occurred during the large outbreak of Ebola virus in western Africa, resulting in the fixation of mutations that increased affinity of the virus for the human cellular receptor[8]. It is now clear that the D614G substitution in SARS-CoV-2 increased transmission, leading to its emergence as a dominant strain; in addition, the mutations in the recent B.1.1.7 (Alpha) and B.1.617.2 (Delta) variants have further increased transmission in humans, enabling these variants to successively become dominant in every region in which they have been introduced[9]. Compared with influenza virus, SARS-CoV-2 has shown an unprecedented capacity to evolve global variants that outcompete regional variants in extremely short time windows and before considerable selective pressure owing to pre-existing immunity. However, whether the SARS-CoV-2 virus will eventually evolve into a more virulent virus is less predictable, as virulence is not necessarily a selectable phenotypic trait that increases the fitness of the virus.

Lessons for understanding the evolution of SARS-CoV-2 can again be tentatively drawn from the 1918/1919 influenza pandemic. The autumn wave of the influenza pandemic was associated with far higher virulence than the spring wave. Thereafter, the 1918/1919 virus continued to cause epidemics until the 1950s when it was replaced by a novel zoonotic H2N2 influenza A virus. Importantly, some of these later seasonal epidemics of H1N1 were also associated with relatively high virulence due to ongoing antigenic drift: two of the worst outbreaks of influenza in the twentieth century in terms of excess deaths occurred in 1928–1929 and 1934–1936, respectively, and were due to descendants of the 1918/1919 H1N1 pandemic influenza virus[10]. Moreover, it is well-documented that bacterial co-infections increase the severity of the disease caused in humans by influenza virus. In this respect, we still do not know well the consequences of co-infections of SARS-CoV-2 with other human pathogens, including influenza virus, the circulation of which was markedly decreased during the SARS-CoV-2 pandemic, but that is likely to be a prevalent human respiratory pathogen when many of the measures adopted to mitigate the spread of SARS-CoV-2 in humans are lifted.

The severity of disease caused by SARS-CoV-2 is bound to decrease with increasing population immunity. Even in individuals who are not fully protected from infection by vaccination or previous infection, pre-existing immunity is likely to reduce the severity of symptoms after infection, and to prevent future severe pandemics arising from antigenically related coronaviruses that are circulating in bats and other possible animal reservoirs. Nevertheless, the evolution of the virus to the low level of virulence seen in common-cold coronaviruses may not occur or may take several decades to manifest. More broadly, many years of data and theory have told us that it is probably naive to make strong predictions about the evolution of virulence in any complex system[11].

SARS-CoV-2 will evolve and evade immunity

The emergence of new virus variants that imperil the control of the pandemic is a prominent theme in public discourse. These new variants are defined by the US Centers for Disease Control and Prevention as variants of interest, variants of concern or variants of high consequence (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html#Interest). At present, the B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma) and and B.1.617.2 (Delta) variants that are circulating in the USA and worldwide are variants of concern. In the context of the evolving pandemic, there is a need to review the expectation of how SARS-CoV-2 could evolve to a form that might derail the control of the pandemic or alter the nature of an ensuing endemic or combined endemic/epidemic phase.

The *Coronaviridae* family is characterized by relatively high replication fidelity compared with other RNA viruses, defined by the processivity of their polymerases as required by their exceptionally large genomes[12]. On this basis, there had been opinions that SARS-CoV-2 evolution would be limited, in turn ensuring the durability of vaccines and therapeutics and supporting optimism that population immunity can end the pandemic. However, although—on average—SARS-CoV-2 evolves (perhaps 3–4 times) more slowly than influenza virus[13], the virus is accumulating mutations more rapidly than might be expected given its relative replication fidelity with approximately two mutations fixed per month[14] and far higher rates of change are seen in some of the variants of concern. Coronaviruses also have a high rate of viral RNA recombination[15]; thus, humans who are infected with two variants of SARS-CoV-2 may acquire multiple mutations from both variants at the same time. We also cannot exclude potential recombination events in the future between SARS-CoV-2 and other human coronaviruses. In addition, prolonged infections of immunosuppressed individuals who cannot efficiently clear the infection may provide an opportunity for the accumulation of multiple mutations. Furthermore, vaccination may not be effective in individuals with compromised immunity[16]. Thus, there may be stochastic events in the emergence of future variants based on the infection of a limited number of immunosuppressed or vaccine-unresponsive persons. In the USA alone there are an estimated 10 million individuals with potential limitations to their immune response.

Why are we witnessing the emergence of variants despite the relatively fastidious replication machinery of coronaviruses? The speed of evolution of a viral pathogen is not only dependent on the background mutation rate, but also on the virus generation time, the duration of infection, the number of variants that develop during the infection of an individual, the structural and functional constraints in specific regions of viral proteins, and the extent and strength of natural selection acting on the virus. In addition, the greater the number of individuals infected with the virus, the larger the pool and diversity of mutant viruses that is generated. Although transmission events between two hosts routinely generate bottlenecks that purify away most of the low-frequency mutant viruses, large numbers of transmission events may enable the transmission of a more fit virus, with the global spread of B.1.1.7 (Alpha) and now the spread of B.1.617 (Delta) in India serving as important examples[17–20].

Functional domains in viral proteins that can accept mutations without losing their overall structure and function are sites of potentially selectable mutations. The region of the spike protein of SARS-CoV-2 that interacts with the human ACE2 receptor exhibits particular structural and functional plasticity[21,22]. With new selection pressures generated by vaccines or immunity to natural infection—or by the use of antivirals—the possibility of viral adaptations to overcome immune and/or antiviral pressure will probably be a continuing reality. There is a risk of

viral diversification in the currently uncontrolled or incompletely controlled pandemic in many regions of the world. In this regard, the level of knowledge of the effect of mutations outside of the viral spike protein is in its infancy, which limits the ability to predict the evolutionary pathways that the virus will follow in the future.

A rapid transition to an endemic phase may decrease the number of circulating virus variants by limiting the extensive exploration of the fitness landscape that takes place during the pandemic phase. Hence, the nature of the future equilibrium between SARS-CoV-2 and humans relies on both the speed and inclusivity of responses to the pandemic across diverse geographies and cultures, as this directly influences the speed of the emergence of problematic variants.

Understanding the transition to an endemic phase, with potential seasonal peaks, would benefit from new tools that can forecast what virus variants may emerge and spread. Spreading variants can be predicted to some extent from epidemiological and biological data, including ACE2 binding measured in the context of deep-scanning mutagenesis of the viral spike protein[23]. Immune escape is beginning to drive the spread of virus variants at a time in the pandemic when high levels of vaccine- and infection-induced immunity have not yet been achieved worldwide[24]. Full containment of the pandemic minimizes the likelihood of SARS-CoV-2 adapting to the host by reducing the length of transmission chains[25]. This appears unlikely to be the case unless very high levels of vaccination can be accomplished worldwide.

Interspecies spread

SARS-CoV-2 does not only infect humans; it also has pantropic properties[26]. SARS-CoV-2 infections have been established in a range of animal species, including bats, cats, dogs, ferrets, hamsters, deer mice, otters, white-tailed deer and various nonhuman primates[27–29]. Zoonotic transmission from humans to animals has been documented in farmed mink, dogs and cats[29–32] as well as in lions and tigers in zoos[33]. Thus, the host range of SARS-CoV-2 extends to a variety of mammalian species, including those maintaining large populations in the wild. Virus evolution can occur in animal hosts, generating a suite of genomic changes in addition to those seen during human-to-human transfer (Fig. 2). As expected, mutations related to species specificity occur in the receptor-binding domain (RBD) of the spike protein and are important, because changes to this region may enable immune escape and/or confer a transmission or fitness advantage. Variation in the N-terminal domain or in or near the furin-cleavage site represent other mutational hotspots in the spike protein that are common to variants of concern and after interspecies transfers (Fig. 2). However, the effect of mutations outside of the spike protein in these interspecies adaptations has not yet been examined and is a wild card that may limit the predictability of the course of the pandemic.

Infected animals can be the source of two evolutionarily related problems. First, upon animal infection, the human virus can undergo evolution that could introduce adaptive mutations. An example of such an event occurred in mink in Denmark and the Netherlands[30,34]. Human-to-animal transfer resulted in the introduction of an adaptive substitution, Y453F, and the subsequent outbreak of this variant in humans (referred to as the 'mink variant', B.1.1.298). The Y453F substitution is in the RBD of the spike protein and increases the affinity of the spike protein for human ACE2 compared with the original SARS-CoV-2 strain, suggesting an avenue for the enhanced transmission or pathogenicity of SARS-CoV-2[35]. Second, an animal coronavirus infection in animals carrying SARS-CoV-2 may pose a serious risk for the generation of hybrid viruses through recombination between viral genomes. These hybrid viruses could have new properties related to immune evasion or virulence. Genomic recombination—which is frequently observed in coronaviruses[15]—may have played a part in the evolution of SARS-CoV-2 (https://virological.org/t/recombinant-sars-cov-2-genomes-involving-lineage-b-1-1-7-in-the-uk/658), including potential recombination with diverse coronaviruses that are present in a variety of animal species. New variants that can be transmitted back to humans in an interspecies 'ping pong' of infections could contribute to further SARS-CoV-2 diversification, as it is the case for influenza A viruses[36]. Infection and propagation of SARS-CoV-2 in nonhuman species could lead to sequence alterations, interspecies transmission and adaptations that could compromise human immunity or affect virulence and that could diminish binding to monoclonal antibodies that are in clinical use[37,38]. As an example, one RBD substitution—N501Y—that occurs in B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma) and other emerging variants of concern enables the productive infection of laboratory mice and possible expansion of the host range to wild mice[39–41]. This mutation also diminished neutralization by a monoclonal antibody in clinical trials[42].

Establishment of SARS-CoV-2 in other species could provide a refuge for the virus to re-emerge in human populations in an evolutionarily distinct form—for example, upon waning of vaccine coverage or diminished natural or vaccine-induced immunity that occurs over time. It is also possible that after decades of separate circulation of SARS-CoV-2 in humans and animals, the human viruses will have diverged antigenically owing to immune pressure, but the animal viruses may not have. This could lead to a population of young individuals born in post-pandemic years with no pre-existing immunity against the old SARS-CoV-2 strains who are therefore susceptible to infection with the animal SARS-CoV-2 viruses that are antigenically related to the original SARS-CoV-2 pandemic strain. In fact, this is the most likely explanation of the pandemic in 2009 caused by a swine influenza virus, which is a descendant of the human H1N1 viruses from the 1918/1919 pandemic virus, but which is antigenically related to the H1N1 viruses that circulated in humans in the beginning of the twentieth century[43]. The potential for such events demands active research into possible susceptible secondary reservoir hosts, and the development of therapeutic and prophylactic interventions that are agnostic to variations in the virus sequence. It is important to recognize that such solutions need to be on the shelf against the possible emergence of a highly problematic strain of SARS-CoV-2, as the speed with which the virus has spread during this pandemic shows the limitations of even an exceptionally fast response in the development of vaccines or therapeutics[44].

The role of vaccines and the correlates of protection

The remarkably rapid development of safe and highly effective vaccines that mitigate the burden of COVID-19 is an historic achievement. Nevertheless, fundamental questions remain as to the mechanism(s) of protection against the disease, the extent of protection against asymptomatic infection and the duration of vaccine-induced humoral and cellular immunity. The effects of potential differences between the immunity induced by the vaccines compared with natural infection and between different COVID-19 vaccines also remain unclear.

Policies to guide vaccine campaigns in the fight against any virus benefit when a test of immunity that correlates with vaccine efficacy can be identified. Antibody assays that measure the neutralization of antigen binding are typically used to determine the rates of seroconversion after vaccine administration, but these may not be fully useful as correlates of protection in an individual because antibodies also restrict viral infection according to their effector functions[45–47] and $CD4^+$ and $CD8^+$ T cell responses are critical for antiviral immunity[48]. Recently, $CD4^+$ T cells have been reported to shape the development of humoral and $CD8^+$ T cell responses to the spike protein after vaccination with an mRNA vaccine[49]. Assays for neutralizing antibodies elicited by the spike protein have been the primary measure of immunity induced by the SARS-CoV-2 vaccines. Most neutralization assays are variable across assay systems and cell lines[50,51], which limits their use to define a correlate that spans clinical studies of different vaccines, and they do not distinguish between responses to different epitopes on the spike

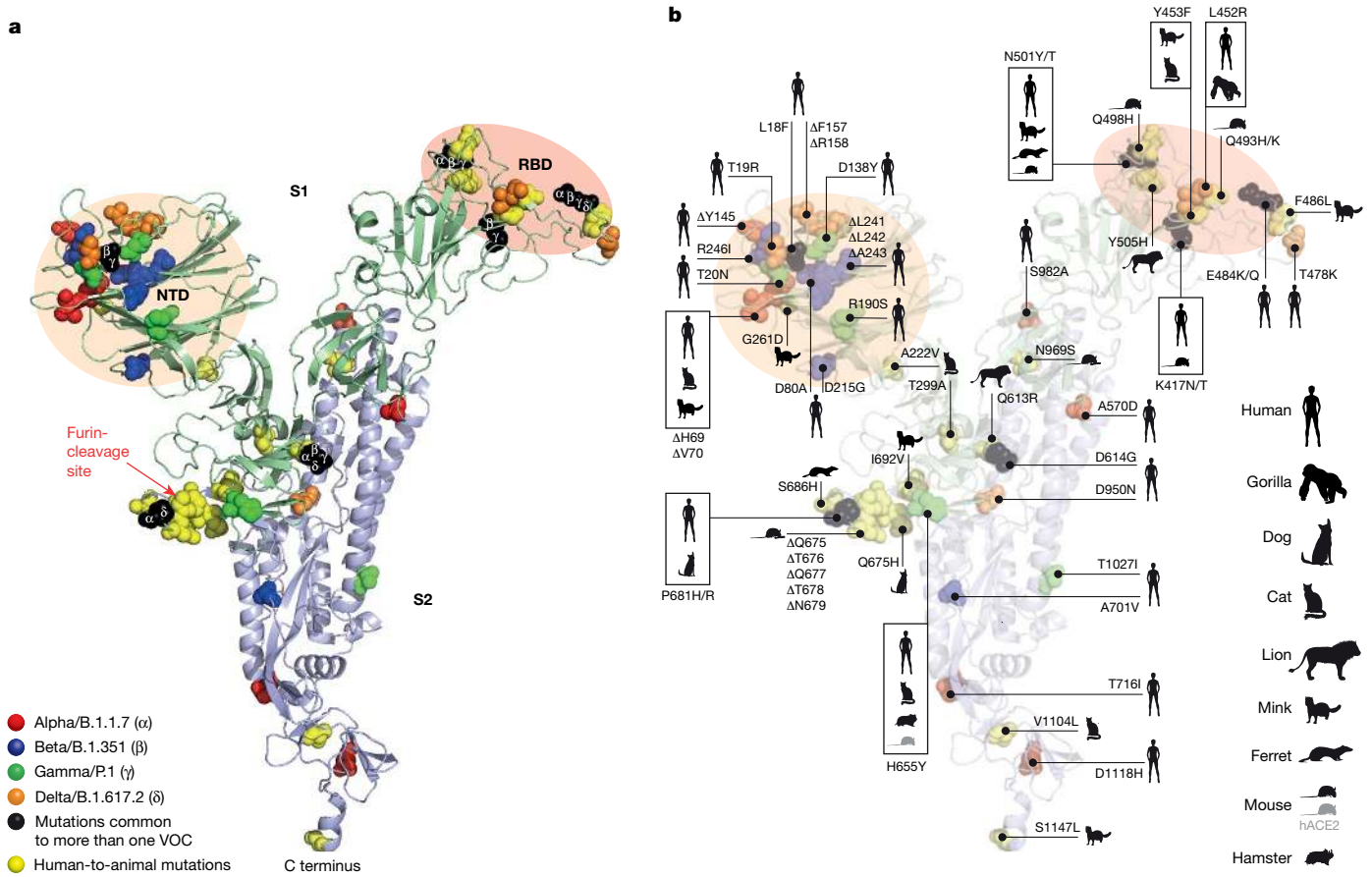

Fig. 2 | Mutations arising in the spike protein of SARS-CoV-2 upon sustained transmission between humans and between humans and animals. Black thick lines show mutations shared between infection in humans and animals. Thin lines indicate mutations limited to infection in humans or animals. Homology modelling of the SARS-CoV-2 spike used reference sequence QHD43416.1 and a closed pre-fusion configuration of the spike trimer (Protein Data Bank (PDB) 6VXX)[81] as a template. NTD, N-terminal domain; VOC, variant of concern. The figure is adapted from https://virological.org/t/mutations-arising-in-sars-cov-2-spike-on-sustained-human-to-human-transmission-and-human-to-animal-passage/578.

protein, some of which are highly immunodominant[52]. The establishment of an international standard by the World Health Organization to enable the normalization of data from different assays is an important step towards addressing this issue (www.who.int/teams/blueprint/covid-19). A recent model that relates the efficacy of immunization with mRNA, adenoviral vector and other SARS-CoV-2 vaccines to neutralizing titres supports that these titres have predictive value[53].

Notably, as observed for influenza A virus, regions of the spike protein of SARS-CoV-2 that elicit the most potent neutralization responses are also the most variable in emerging variants of concern. Indeed, vaccine-induced and natural immunity—as measured by neutralization assays—is reduced against some variants. Although vaccines are effective against current variants, the impact of such changes on the prevention of COVID-19, especially severe illness, requires continuous assessment. At a minimum, the longevity of protection is likely to be affected, assuming that antibodies are the primary defence mechanism. The level of total antibody in serum after natural infection decreases with a half-life of about 50–100 days[52,54,55] and vaccine-induced antibodies also peak shortly after immunization. However, waning antibody levels after vaccination cannot be equated to renewed susceptibility to disease because the immune system has been primed to rapidly mount memory B and T cell responses that mitigate the consequences of repeated infection.

More information about the mechanisms of immune protection against COVID-19 that are poorly understood, such as mucosal immunity and innate immune barriers, as well as the impact of immune protection on the transmission of SARS-CoV-2 is essential to inform vaccine policies to control the pandemic and for the need for boosters or a next-generation of vaccines as the pandemic transitions to an endemic or epidemic pattern.

Lessons from vaccination against respiratory viruses

The challenges for SARS-CoV-2 vaccine programmes have instructive similarities and potential differences from experiences with other viral vaccines. Vaccines against 17 viral pathogens are approved in the USA. The effects of vaccines can be divided into control, elimination of disease, elimination of infection, and eradication and extinction (Box 1). The first aim of SARS-CoV-2 vaccine programmes is the rapid control of new infections in as many geographical regions as possible, an outcome that depends on the widespread—both within counties and worldwide—uptake of vaccines that effectively reduce transmission. Control also requires broad access to rapid diagnostic methods and surveillance to detect ongoing transmission. Of note, highly effective vaccines can achieve the elimination of disease even if the infection is not eliminated. Smallpox is the only example of vaccine-mediated eradication of an infection in humans, which required a global initiative that combined high levels of vaccine coverage, active surveillance and rapid and targeted vaccination efforts in regions in which outbreaks occurred. The importance of combining sustained immunization campaigns with effective surveillance and rapid molecular diagnosis are hard-learned lessons, as illustrated by the failure to eliminate polio despite the lack of an animal reservoir and the availability of two effective vaccines.

Experiences with viruses that are transmitted by respiratory droplets and/or aerosols but that have persisted in the human population despite the availability of effective vaccines point to obstacles and inform about SARS-CoV-2 vaccine strategies. Considerable achievements in the elimination both of the disease and infections caused by such viruses—including measles, mumps and rubella—have been made in many, but often not in all, geographical regions. Even in optimal circumstances, communities that are under-vaccinated owing to poor access or that resist vaccination serve as reservoirs for the reintroduction of pathogens and disease outbreaks when vaccination coverage falls at the population level.

A lesson from experience with measles, mumps, rubella and varicella vaccines is the importance of two-dose regimens. Because respiratory transmission is efficient, even a low incidence of primary vaccine failure, defined as no seroconversion to the first dose, leaves enough susceptible individuals in the population to support outbreaks. Secondary vaccine failure, defined as disease despite seroconversion, occurs with single-dose regimens that elicited antibodies after one dose, as was observed with the varicella vaccine and also occurs in some cases with two doses of varicella or mumps vaccines[56]. Under these circumstances, the vaccinated individuals benefit from protection against severe illness, but breakthrough infections remain a source of transmission. Limited information about SARS-CoV-2 vaccines suggests that this pattern of breakthroughs, albeit with markedly reduced severity, may occur but with a frequency that is as yet undetermined at the population level.

In the case of measles, even though the viral fusion protein is genetically stable—in contrast to the spike protein of SARS-CoV-2—virus entry is highly efficient and population immunity of 92–95% is required to eliminate transmission, as confirmed by recent outbreaks of measles despite high vaccine coverage[57]. Measles has a very high basic reproductive number (R_0) with transmission from one case to fifteen susceptible individuals, whereas the R_0 value for SARS-CoV-2 has been modelled at 2.2–5.7 for the Wuhan reference strain[58]. As long as estimates of transmission of variants of concern remain below measles, control may occur with lower levels of population immunity. Notably—and in contrast to measles—the occurrence of asymptomatic SARS-CoV-2 infections will interfere with rapid outbreak recognition and provide an avenue for spread within populations and across geographical regions. In this regard, SARS-CoV-2 is more similar to polio, or rubella, for which a strategy of universal and repeated vaccination campaigns rather than outbreak control has been necessary to eliminate congenital disease[59].

Childhood vaccines also demonstrate the difficulty of defining immune correlates of protection against breakthrough infections that re-introduce the virus into the community. For example, receiving two doses of measles vaccine correlates with protection even though neutralizing antibody titres may be low and not be boosted by additional doses[57]. Occurrence of varicella in vaccinated adults appears to reflect lower cellular immune responses, which are not measured by neutralization assays[60]. The occurrence of mumps in highly vaccinated groups is attributed to waning immunity. Administration of a third dose of vaccine appears to reduce the spread in outbreaks, but an antibody-based immune correlate that would allow targeted revaccination of those at risk has not been established despite extensive study[61]. These experiences predict that maintaining the benefits of SARS-CoV-2 vaccine programmes will require not only the monitoring of the duration of immunity as determined by serological assays, but also the ongoing local surveillance for infections in vaccinated populations coupled with the tracking of vaccine coverage rates within the community so that gaps can be rapidly addressed. Notably, the only way to identify correlates of protection will be the consistent application of robust and reproducible assays of both T- and B-cell-mediated immunity in vaccine recipients under conditions in which exposures can be documented. Such an effort will be technically challenging for vaccine producers and studies of one vaccine may not inform immune correlates for a different type of vaccine. This presents a major unaddressed challenge to understanding the mechanisms of vaccine protection and the new equilibrium between humans and SARS-CoV-2 that is currently evolving as vaccine coverage is extended. A large study on college campuses is designed to address this challenge (ClinicalTrials.gov NCT04811664). In addition, elimination of SARS-CoV-2 is unlikely without immunization of children who may be vectors for asymptomatic transmission. Decades of childhood vaccine experience documents that even with high coverage—sufficient to eliminate disease and infection in almost all individuals—protection of unvaccinated people by herd immunity is not guaranteed when reintroductions occur. Reintroductions of SARS-CoV-2 have the added challenge that these may result from either human or zoonotic sources or both, whereas endemic childhood viruses do not have animal reservoirs.

Large-scale SARS-CoV-2 vaccine programmes have already had an enormous impact on the burden of COVID-19 disease. Although SARS-CoV-2 may become endemic without being associated with severe disease[62], viruses with pathogenic potential may continue to circulate, causing local outbreaks or more widespread epidemics, and requiring vaccine campaigns and possibly ring prophylaxis[63] using monoclonal antibodies to eliminate the disease.

The paradigm of antigenic drift and shift in influenza

The experience with influenza A and B vaccines offers a perspective for COVID-19 vaccines when transmission is associated with the capacity of the target virus to undergo seasonal antigenic drift and periodic antigenic shift, which may be caused by recombination in the case of SARS-CoV-2[64] (as opposed to segment re-assortment in the influenza viruses). Antigenic drift is common to all four antigenically distinct circulating influenza A and B viruses. Most of the key mutations that lead to antigenic drift are located in the globular head of the haemagglutinin (HA), which comprises the receptor-binding motif—which, similar to SARS-CoV-2, appears to be the most structurally and functionally plastic region[21]—possibly enhancing the efficacy of antibody selection of variants that may evade natural or vaccine-induced immunity.

The degree of antigenic variation or 'antigenic distance' between the HA and neuraminidase proteins of influenza is the basis for needing to update the composition of influenza vaccines frequently. This distance is typically measured in an haemagglutination inhibition assay using ferret or human antisera generated against the influenza vaccine and circulating strains[65]. Whenever the fold change in titres of antisera in the haemagglutination inhibition assay generated against vaccine strains and tested against circulating strains exceeds 8–10-fold, it typically signals the need to 'upgrade' the vaccine composition (Fig. 3a, b). This exercise is performed for all four viruses that are part of the influenza vaccine mixture—currently H1N1, H3N2, influenza B Yamagata lineage and influenza B Victoria lineage. The need to update vaccines results from the fact that the most variable region of HA (and neuraminidase) is also the immunodominant region and, reciprocally, because the response to more conserved regions elicits antibodies endowed with poor neutralizing activity. It is worth noting that for SARS-CoV-2, the introduction of more than ten mutations in some of the variants of concern such as B.1.351 (Beta)—which has led to a reduced neutralizing titre of antisera from vaccinated donors of approximately tenfold (Fig. 3d, f)—is comparable to the extent of antigenic drift in influenza A and B viruses that typically requires a change in the viruses selected for vaccine production. Indeed, several vaccines were shown to provide modest efficacy against the B.1.351 (Beta) variant[66,67]. As a consequence of the reduced efficacy, the composition of SARS-CoV-2 mRNA vaccines—such as the one developed by Moderna—was recently adapted to match the B.1.351 (Beta) variant and clinical trials testing the immunogenicity of such vaccines are underway (Clinical Trials.gov NCT04785144). Antigenic drift was also shown to occur in human endemic coronaviruses such as HCoV-229E[1] (Fig. 3e, f).

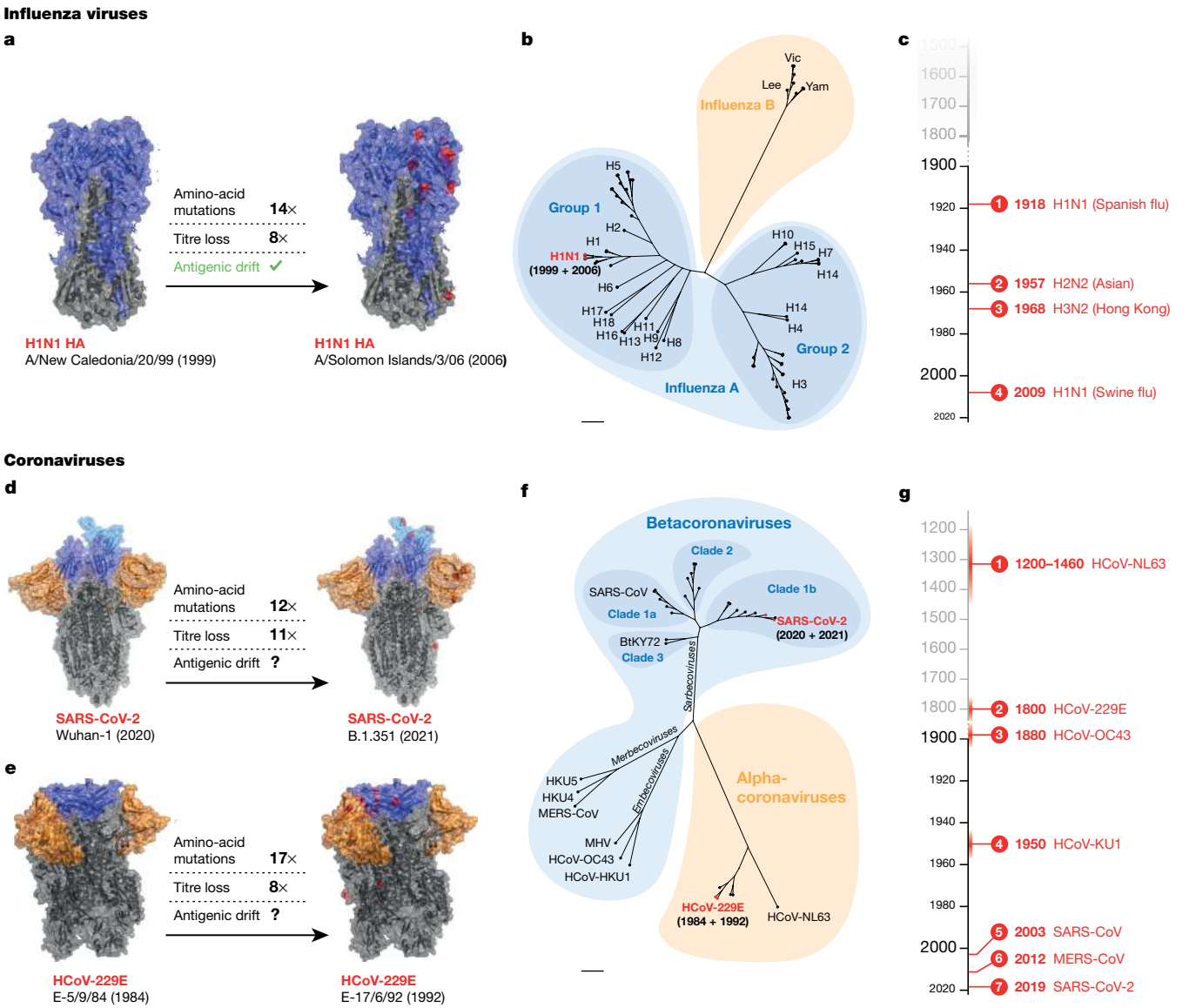

Fig. 3 | The antigenic drift paradigm of influenza viruses and coronaviruses. a, Structural models of the HA protein of influenza A virus H1N1 from 1999 and 2006 isolates (PDBs 5C0S and 6CF7, respectively), in which mutated residues are highlighted in red and are shown on a single monomer of each trimer. Loss of neutralization titres against parental and drifted strains of H1N1, as previously described[65]. **b**, Protein distance of major glycoproteins of influenza viruses. Dendrograms show the protein distance of HA amino acid sequences that are representative of the variability of each virus family. Shown are HAs from all 18 influenza A virus subtypes (multiple strains shown for H1, H3 and H5) and of HAs from influenza B virus from the ancestral virus from 1940 and the two Victoria and Yamagata lineages. Scale bar, 0.100. **c**, Timeline of influenza pandemics. **d**, **e**, The spike ectodomain of SARS-CoV-2 (**d**; PDB 6VYb; spike in the open conformation) and the spike ectodomain of HCoV-229E (**e**; PDB 6U7H), in which mutated residues are highlighted in red and are shown on a single monomer of each trimer. Loss of neutralization titres against parental and drifted strains of SARS-CoV-2 and HCoV-229E by serum antibodies elicited against the parental strains, as determined previously[1,82]. **f**, Protein distance of spike glycoproteins of human and animal coronaviruses. Sarbecoviruses are shown according to the phylogenetic definition of RBD clades[83]. Scale bar, 0.100. **g**, Timeline of the emergence of human coronaviruses. The emergence of common-cold coronaviruses is approximate and based on molecular clock dating[84]. Highlighted in red in **b** and **f** are viral strains used in **a**, **d** and **e**.

It remains to be established whether the evolution of SARS-CoV-2 will be accelerated by increasing immunity or whether—by contrast—the reduced circulation of the virus that is expected to occur as a consequence of widespread vaccination may slow down the accumulation of mutations[68]. In the case in which SARS-CoV-2 will become endemic and will continue to evolve, revaccination scenarios need to be envisioned. These may require the revaccination with the same vaccine or boosting/vaccination with a vaccine based on the most prevalent circulating variants. More difficult to predict is how often revaccinations will be needed and recommended for specific risk groups or for the general population.

As it is the case for influenza, it will be important to assess the possible influence of original antigenic sin in trapping the antibody response by the first response made to the parent antigen[69,70]. This is a phenomenon in which the immune response to subsequent infection or vaccination is biased towards responses imprinted in an individual's immune system by the persistence of memory B and T cells elicited by previous infections with related viruses. If this holds true for SARS-CoV-2, it might reduce the immunogenicity of vaccines against the variable sites of the spike protein, possibly boosting the response to the most conserved regions, which could be a potential beneficial outcome if cross-reactive antibodies have a protective role[71]. In this respect, even previous immunity

against other human betacoronaviruses could shape subsequent immunity to SARS-CoV-2 infection or from vaccination[72].

Another lesson from the evolution of influenza viruses is that multiple lineages of the same virus can co-exist and co-circulate. This is the case for the two co-circulating lineages of influenza B virus that originated from a common progenitor in the 1970s, which has led to the independently evolving Victoria and Yamagata lineages and resulted in a decision to convert the traditional trivalent influenza vaccine into a quadrivalent vaccine[73]. This decision was driven by the difficulty of predicting which of the two lineages would prevail during each season. The co-circulation of different SARS-CoV-2 lineages in the same or different geographical areas may complicate decisions on which lineages merit incorporation into new vaccines and whether these vaccines will need to evolve into multivalent formats that target several variants, like influenza vaccines. It is as yet undetermined how many strains of SARS-CoV-2 will need to be considered when planning an effective long-term vaccine strategy. It is worth noting that until now, a relatively limited set of mutations have independently emerged in multiple variants, pointing to a convergent and potentially constrained evolution of SARS-CoV-2 for immune escape.

A second, but no less important, aspect of the evolution of influenza viruses that may occur with SARS-CoV-2 is antigenic shift—that is, the introduction, through recombination, of antigenically novel forms for viral antigens. In the case of influenza, this involves the acquisition of new genome segments from zoonotic (particularly avian) viruses and has occurred at least four times in the past century: in 1918 (H1N1), in 1957 (H2N2), in 1968 (H3N2) and in 2009 (H1N1) (Fig. 3c). As a parallel, animal betacoronaviruses have already entered the human population five times, including in: 2003 (SARS-CoV), 2012 (MERS-CoV) and 2019 (SARS-CoV-2), and at some earlier time in the case of NL63-CoV and HKU1-CoV, with both MERS-CoV and SARS-CoV associated with severe disease (Fig. 3g). MERS-CoV has caused spill-over events from camels to humans since 2012 but has not evolved into a form associated with high levels of human-to-human transmission. There were exceptions, such as in South Korea, where a single imported case resulted in almost 200 infections in a hospital setting[74]. Therefore, the risk for MERS-CoV evolving into a more transmissible virus should not be underestimated. Notably, the level of sequence similarity between the spike proteins of SARS-CoV and SARS-CoV-2 is 76%, which is close to the 80% similarity between the pre-pandemic H1N1 strain (A/Solomon Island/03/06) and the pandemic H1N1 swine influenza strain (A/California/04/09). The risk for new sarbecoviruses to cause future zoonotic infections is considerable as this has already occurred twice in the past 20 years. Coronaviruses isolated from bats can efficiently multiply in human lung tissue[75]. This calls for aggressive development of countermeasures based on pan-reactive vaccines or therapeutics that can be stockpiled and be ready for deployment to avoid the health and economic devastation seen in this pandemic.

In summary, the very recent emergence of SARS-CoV-2 has not given much time to understand the role and consequences of antigenic drift and shift. These are critical analyses to establish the future needs and requirements for revaccination.

Three possible scenarios of the future of COVID-19

The first—and most worrisome—scenario is that we will not gain rapid control of this pandemic and thus will face a future with ongoing manifestations of severe disease combined with high levels of infection that, in turn, could foster further evolution of the virus. Vaccinations and previous infection could achieve long-term herd immunity, but we will need a very broad application of vaccines worldwide combined with comprehensive disease surveillance by accurate and readily available diagnostic assays or devices[76].

A second and more likely scenario is the transition to an epidemic seasonal disease such as influenza. Effective therapies that prevent progression of COVID-19 disease (for example, monoclonal antibodies that reduce hospitalization and death by 70–85%) may bring the burden of SARS-CoV-2 infection to levels that are equivalent or even lower than influenza. However, we should remember that the annual mortality burden of influenza, in non-pandemic years, is estimated to be between 250,000 and 500,000 deaths, with up to 650,000 all-cause deaths globally, comprising around 2% of all annual respiratory deaths (two thirds among people who are 65 years and older)[77]. This is an extremely important health burden and equates to a relatively 'optimistic' view of the future of the COVID-19 pandemic.

A third scenario is the transition to an endemic disease similar to other human coronavirus infections that have a much lower disease impact than influenza or SARS-CoV-2. There is, however, limited data on the global burden of disease by common human coronaviruses[78] and as noted in above, it is not possible to predict with confidence whether further adaptations of SARS-CoV-2 to humans will increase or decrease its intrinsic virulence.

Box 2

Current key gaps in developing an effective global response

Research questions

Epidemiology

- What are the effects of geographical and socioeconomic variations in vaccine coverage and disease on the ability to convert the pandemic to an endemic or epidemic disease?
- What is the contribution of immunosuppressed populations to the rapid evolution of SARS-CoV-2?

Virology

- What are the mechanisms by which viruses adapt to different hosts, thereby crossing species barriers?
- Is viral sequence evolution effectively reduced by vaccination?

Immunology

- What are the correlates of protection for vaccines and natural immunity? The assessment of protection will require the coherent application of reproducible immunologic assays in populations to follow disease incidence and severity.
- What is the impact of antigenic drift?
- What are the criteria for the renewal or boosting of vaccines?
- What is the role of mucosal immunity in limiting viral shedding and preventing severe disease?

Tools and technologies

Surveillance

- Globally accessible diagnostics and deep-sequencing tools to establish continuous and sustained global surveillance of disease and variants.

Vaccines

- Pan-sarbecovirus vaccines and monoclonal antibodies that will address both SARS-CoV-2 variants and the future introduction of pandemic coronaviruses into the human population.

Therapeutics

- Next-generation therapeutics in the form of cheap oral antiviral agents.
- Long-acting monoclonal antibody prophylaxis for persons not likely to achieve effective vaccination.
- Addressing inequalities in pandemic healthcare and access worldwide to the most effective vaccines and therapeutics.

To better predict which scenario is likely to emerge and to better equip the world with an appropriate response, we propose several key questions that need to be answered and critical tools that need to be developed (Box 2). These comprise gaps in our knowledge in terms of epidemiology, immunology and virology, and missing surveillance, prophylactic and therapeutic tools.

This pandemic has shown both the importance of initiatives in individual countries and the interdependence of the world, and the necessity of global cooperation for pandemic control. It is the investment by a limited number of countries that has led to the biomedical discoveries that have brought forward the tools to interrupt the spread of the pandemic[79]. Yet, the lack of international structures for the implementation of these tools has brought into focus the disparities between advantaged and disadvantaged groups both within countries and between countries. This highlights the current inadequacies in healthcare delivery systems and access to new biomedical interventions[80]. Global health leaders will need to be vigilant with respect to the trajectory of SARS-CoV-2 in the near future while assessing the strategies and approaches used in the pandemic to develop more effective structures and processes to ensure a more effective and equitable response for the future.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-021-03792-w.

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