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Expert Review of Vaccines

ISSN: (Print) (Online) Journal homepage: informahealthcare.com/journals/ierv20

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To cite this article: Timo Ulrichs, Morgane Rolland, Jianhong Wu, Marta C Nunes, Clotilde El Guerche-Séblain & Ayman Chit (2024) Changing epidemiology of COVID-19: potential future impact on vaccines and vaccination strategies, Expert Review of Vaccines, 23:1, 510-522, DOI: 10.1080/14760584.2024.2346589

To link to this article: https://doi.org/10.1080/14760584.2024.2346589

Published online: 06 May 2024.

EXPERT REVIEW OF VACCINES
2024, VOL. 23, NO. 1, 510–522
https://doi.org/10.1080/14760584.2024.2346589

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PERSPECTIVE

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Changing epidemiology of COVID-19: potential future impact on vaccines and vaccination strategies

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ABSTRACT

Introduction: COVID-19 was an unprecedented challenge worldwide; however, disease epidemiology has evolved, and COVID-19 no longer constitutes a public health emergency of international concern. Nonetheless, COVID-19 remains a global threat and uncertainties remain, including definition of the end of the pandemic and transition to endemicity, and understanding true rates of SARS-CoV-2 infection/transmission.

Areas covered: Six international experts convened (April 2023) to interpret changing COVID-19 epidemiology and public health challenges. We report the panel's recommendations and knowledge gaps in COVID-19 epidemiology, SARS-CoV-2 evolution, and future vaccination strategies, informed by peer-reviewed publications, surveillance data, health authority assessments, and clinical experience.

Expert opinion: High population SARS-CoV-2 immunity indicates the likely end to the pandemic's acute phase. Continued emergence of variants/sublineages that can evade the vaccine-induced antibody response are likely, but widespread immunity reduces the risk of disease severity. Continued surveillance is required to capture transition to endemicity, seasonality, and emergence of novel variants/sublineages, to inform future vaccination strategies. COVID-19 vaccination should be integrated into routine vaccination programs throughout life. Co-circulation with other respiratory viruses should be monitored to avoid a combined peak, which could overrun healthcare systems. Effective, combined vaccines and improved education may help overcome vaccine hesitancy/booster fatigue and increase vaccination uptake.

ARTICLE HISTORY
Received 12 January 2024
Accepted 19 April 2024

KEYWORDS
COVID-19; epidemiology; future strategies; vaccination; vaccine

1. Introduction

Coronavirus Disease 2019 (COVID-19) has posed an unprecedented challenge to public health worldwide. As of the 31st of December 2023, there have been more than 773 million cases of COVID-19 reported to the World Health Organization (WHO), with over 7 million deaths due to COVID-19 [1]. During the COVID-19 pandemic, our understanding of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) improved [2], due to research into the antigenicity, pathogenicity, and transmissibility of the virus. This enabled the development and implementation of successful COVID-19 vaccination strategies along with adequate public health measures across many countries. As of the 26th of November 2023, nearly 13.6 billion doses of COVID-19 vaccines have been administered [1]— saving tens of millions of lives globally and substantially altering the course of the pandemic [3].

SARS-CoV-2 has continued to evolve since its identification [4]. Previously circulating SARS-CoV-2 variants to the original Wuhan strain were Alpha, Beta, Gamma, Delta, and Omicron variants [4]. The initial variant, Alpha, had a single spike substitution, resulting in an approximately 20% growth advantage relative to preceding variants [5]. Subsequent variants increased transmissibility of the virus in humans. From October 2020 onwards, novel variants were distinguished by higher numbers of mutations in the spike (S) protein of the virus, particularly for Omicron, thus altering transmissibility and antigenicity [6]. The predominant Omicron variant has accounted for more than 98% of the publicly available sequences since February 2022 [7].

Vaccination against COVID-19 significantly reduces the development of severe symptoms after an infection with certain forms of the SARS-CoV-2 virus, including the ancestral Wuhan-1 strain [8]. However, some mutations have been shown to compromise the neutralization efficacy of existing vaccines against disease [8], particularly for the Omicron variant [9]. It is also possible that an undetected variant/sublineage could emerge with high transmissibility and novel antigenic properties [6]. As SARS-CoV-2 has evolved, there has been a need to develop novel formulations of COVID-19 vaccines to target new mutations and a need to propose new vaccination schedule recommendations. Importantly, vaccination schedules will largely depend on whether COVID-19 will follow a seasonal pattern similar to influenza.

An academic panel convened in April 2023 to discuss the current challenges of COVID-19 from a public health perspective. Complementing previous expert views [10,11], this report provides the panel's positions and recommendations, and corresponding evidence generation gaps regarding: the changing epidemiology and burden of COVID-19; SARS-CoV-2 evolution; and current and future COVID-19 vaccination strategies.

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Article highlights

- High population SARS-CoV-2 immunity indicates the likely end of the pandemic's acute phase; continued emergence of transmissible Omicron sublineages and novel variants which are able to evade the vaccine-induced antibody response are likely, but widespread immunity reduces the risk of disease severity.
- In 2023, we reached the end of the acute phase of the COVID-19 pandemic; it is now important to monitor the further development of the virus in the face of a widespread immunity in the human host population.
- Monitoring of the co-circulation of other respiratory viruses, specifically RSV and influenza, should be implemented to avoid a combined peak of viruses, which could overrun healthcare systems.
- COVID-19 vaccination should be integrated into routine vaccination programs throughout life, for a more people-centered approach.
- An effective combined vaccine together with improved vaccine-related education may help overcome vaccine hesitancy or booster fatigue and increase vaccination uptake.
- Vaccine recommendations could be released for different subpopulations, with additional booster vaccinations for adults aged 60 years or older and those with underlying risk factors, such as immunocompromised or pregnant individuals, or those with comorbidities.

2. Methods

An academic panel of six international infectious disease experts convened for an expert group meeting on 19 April 2023 in Copenhagen, Denmark. The objective of the meeting was to discuss and interpret the changing epidemiology and burden of COVID-19, SARS-CoV-2 evolution and current and future COVID-19 vaccination strategies. The panel's positions and recommendations described herein are informed by relevant peer-reviewed publications, surveillance data, and health authority assessments (manually searched from the literature, considering publications until February 2024), as well as clinical experience.

3. Positions and recommendations

3.1. COVID-19 epidemiology

In December 2019, several local health facilities in Wuhan, China, reported clusters of patients with pneumonia of an unknown cause, which was subsequently linked to SARS-CoV -2 and designated as COVID-19 [12]. SARS-CoV-2 spread rapidly following its emergence, and on 11 March 2020, the WHO declared the COVID-19 outbreak as a global pandemic [13]. The epidemiology of COVID-19 has evolved since the start of the pandemic, with a decreasing trend in COVID-19-related deaths and hospitalizations observed, and high levels of population immunity to SARS-CoV-2 [14]. This prompted the WHO Director-General to declare, on 5 May 2023, that COVID-19 is now an established and ongoing health issue, which no longer constitutes a public health emergency of international concern [14].

Nonetheless, COVID-19 remains a global threat. A slowing down of national surveillance, reporting systems, and lower testing capabilities [15,16] indicates a perception that the pandemic is over. However, there are still several uncertainties regarding the epidemiology of COVID-19: firstly, the definition of the end of a pandemic remains unclear, as does the definition of the transition to endemicity, along with predictions as to when this will occur; secondly, the true rates of population SARS-CoV-2 infections and transmissions; and thirdly, whether COVID-19 will become seasonal, i.e. whether it will have predictable fluctuations or patterns that recur or repeat over a certain period.

There have been several definitions for the endpoint of the COVID-19 pandemic, and agreement on a single definition has not been reached. The endpoint may be defined using epidemiological data, such as achieving herd immunity or endemicity. Epidemiologically, COVID-19 may be defined as endemic once the incidence of COVID-19 settles to a non-zero level, as determined by waning immunity, transmission rates of variants, vaccination rates, seasonality, and human behavior [17]. This level of endemic 'equilibrium' is a delicate balance between the extent of mitigation measures enforced and the incidence of disease that societies will accept [17]. On the other hand, pandemic historians believe the general public's consensus of when the pandemic is over, to be the true pandemic endpoint [18]. Additionally, differences exist in the continued persistence of COVID-19 and the subsequent immunity across the globe, which is largely dependent on how regions or countries approached their COVID-19 policies and guidance [19]. Transition to endemicity may not occur at the same time in all regions, and there is a risk of reactivation of the pandemic in countries with high population density and limited healthcare access. It is also worth noting that endemicity does not necessarily mean lower severity, for example endemic malaria still represents a serious health threat. In addition, a historical inconsistency in the trend of severity of successive SARS-CoV-2 variants over the course of the pandemic suggests that the severity of future variants remains uncertain [20].

Although high population SARS-CoV-2 immunity likely indicates the end to the pandemic's acute phase, established measures for disease management need to be maintained. Unbiased monitoring of SARS-CoV-2 transmission and infection rates should continue [14], since 'wavelets' (mini waves) may occur approximately every 3–4 months, resulting in milder infections rather than severe disease [21]. The magnitude of these wavelets will likely decrease over time as basic immunity is established, with seasonal exacerbations occurring during colder weather. Variant surveillance should be maintained to identify SARS-CoV-2 mutations and variants that are able to evade the vaccine-induced antibody response and risk driving further waves [14]. Particularly given the decline in clinical testing of patient samples, wastewater-based genomic surveillance is a strategy that may help monitoring mutations and lineages. Challenges associated with this approach are currently under investigation [22]. The utilization of public online dashboards that collect the most recent data and information concerning COVID-19 may be beneficial [1,23,24]. Further recommendations are listed in Table 1.

Knowledge gaps and evidence generation needs to include: robust active surveillance systems to provide accuracy regarding the number of COVID-19 cases; a definition of COVID-19 seasonality (particularly when seasons start to inform vaccination schedules); and simpler, more specific epidemiological modeling (Table 2).

Currently, COVID-19 is the leading cause of mortality via a single infectious agent, however, other pandemic pathogens are also a global threat, such as human immunodeficiency virus

Table 1. Panel position and recommendations (with supporting references).

Topic	Position and recommendations	References
COVID-19 epidemiology	The decreasing trend in COVID-19-related deaths and hospitalizations, and the high levels of population immunity to SARS-CoV-2 indicate the likely end of the acute phase of the pandemic.	[14]
	SARS-CoV-2 will likely become an endemic pathogen in the human population.	[25,26]
	The definition of endemicity is suggested to be once the COVID-19 incidence settles to a non-zero level, as determined by waning immunity, transmission rate of variants, vaccination rates, seasonality, and human behavior. Finding this level of endemic 'equilibrium' is a delicate balance between the extent of mitigation measures enforced and the incidence of disease that societies will accept.	[17]
	Transition to endemicity may not occur at the same time in all regions, and there is a risk of reactivation of the pandemic in countries with high population density and limited healthcare access.	
	Unbiased monitoring of SARS-CoV-2 transmission and infection rates should continue, via regular testing of sentinel populations or randomly selected representative samples of the general population, to allow for a comprehensive situational awareness.	[14]
	'Wavelets' (mini waves) may occur approximately every 3–4 months due to immune escape by new variants, resulting in milder infections rather than severe disease.	[21]
	The magnitude of the wavelets will likely decrease over time as basic immunity is established, with seasonal exacerbations occurring during colder weather.	
	Variant surveillance should be maintained to identify SARS-CoV-2 mutations and variants that are able to evade the vaccine-induced antibody response and risk driving further waves.	[14]
SARS-CoV-2 evolution	COVID-19 resulting from Omicron infection is perceived to be less severe than previous variants [27,28]. However, current estimates of disease severity may be confounded by protection conferred by immunity from previous infection and vaccines.	[29]
	Continued emergence of more transmissible Omicron lineages and sublineages that are able to evade the vaccine-induced antibody response is likely, particularly due to increasing population immunity.	[7]
	A novel variant may still emerge, but widespread population immunity reduces the chance of a major increase in disease severity.	[30]
	Modeling to predict novel mutations is challenging, but has been beneficial in predicting epitope loss and potential vaccination targets.	[31–33]
	To date, most variants have been selectively driven by altered transmissibility or immune escape. Mutations outside of the receptor binding domain and those that affect viral infectivity and replication have not been extensively studied and require further research.	[6]
Burden of COVID-19	Estimates of infection rates may be affected by recent changes to testing capacities and practices, with many countries having discontinued most routine testing.	[15,16]
	The broader impact of COVID-19 vaccines, beyond protection from severe disease, needs to be better communicated. These benefits include the need to protect healthcare systems and avoid COVID-19-related absenteeism from school or work.	
	The definition of post-acute COVID-19 sequalae (also referred to as long COVID), needs to be redefined and standardized, to include the duration of post-acute COVID-19 sequalae, and its specific symptoms, to aid our understanding of the disease and its management.	
	There is no strategy or therapeutic approach to manage post-acute COVID-19 sequalae; potential management options need to be studied urgently among different subpopulations.	
	Co-circulation of COVID-19, RSV, and influenza should be monitored closely to avoid a combined peak, which could overrun healthcare systems. Future combination vaccines should be explored to provide potential management options.	
COVID-19 vaccine effectiveness and disease management	Reduced duration of protection with current COVID-19 vaccines is due to SARS-CoV-2 evolution and varying antigenicity, which is challenging for vaccine development. Learnings gained from the pandemic so far should be used to develop future COVID-19 vaccines with broader and more durable protection.	
	Recent evidence suggesting lower relative COVID-19 vaccine effectiveness with emerging variants should be viewed cautiously. Original reference populations in clinical trials included infection- and vaccination-naïve individuals, whereas current populations are better protected due to previous natural infection or vaccination, which leads to improvements in efficacy data and adds bias to the data on vaccine effectiveness.	
	Comparisons between the current population (which has some immunity due to natural infection and vaccinations) compared with the previous populations (no immunity due to no prior natural infection or vaccination) are imbalanced and introduce an unknown bias, as the infection rates are likely to be higher in unvaccinated individuals. This imbalance in infection rates presents a challenge when combined with the reduced level of national surveillance and reporting.	
	There are still individuals who are not vaccinated and certain at-risk populations, for whom additional management options such as antiviral drugs are needed.	
Future COVID-19 vaccination strategies	COVID-19 vaccination recommendations are likely to be continually updated for several more years using a variant-chasing approach and will focus on protection of at-risk groups (e.g. elderly individuals, and those with comorbidities or who are immunocompromised).	
	Uptake of COVID-19 booster vaccinations has waned considerably over time. Local vaccination strategies must consider vaccine and booster coverage, along with the patient's opinions and emotions regarding vaccination with COVID-19.	
	If 12-month duration of protection can be demonstrated, administration of COVID-19 vaccines between September and October (in the Northern Hemisphere) of each year would be ideal to protect against the winter peak.	
	Whether or not COVID-19 becomes seasonal, future COVID-19 vaccination strategies may be integrated into existing frameworks for seasonal influenza vaccination, independent of COVID-19 epidemiology, for economic reasons and to optimize vaccine uptake.	
	An effective combined COVID-19/influenza vaccine may help to overcome vaccine hesitancy or booster fatigue.	

(*Continued*)

Table 1. (Continued).

Topic	Position and recommendations	References
Future COVID-19 vaccine development needs	Next-generation COVID-19 vaccines: Broad cross-reactivity against several SARS-CoV-2 variants is a key requirement, although this should not be at the expense of efficacy against existing variants. Longer duration of protection is required. However, demonstrating durability of protection with a new vaccine is challenging due to regular COVID-19 waves (every 3–4 months), the impact of vaccination timing and emerging variants, and confounding factors such as heterologous versus homologous vaccination and the different number of vaccine doses. Clinical studies assessing immunogenicity should consider the impact of natural immunity in a diverse population of individuals, since many individuals in current populations will have had previous natural infection(s). To increase global coverage and improve vaccine equality, next-generation COVID-19 vaccines must be accessible. Vaccines that are less expensive and have improved thermostability could benefit low/middle-income countries, which typically have higher temperatures and challenges with cold storage of mRNA vaccines. Intra-nasal vaccine administration could be a route to reducing viral transmission, along with additional benefits such as a decreased need for trained medical personnel, and less distress for children and individuals who have needle phobia. Pan-sarbecovirus vaccines: A pan-sarbecovirus vaccine targeting SARS-CoV-2 and other sarbecoviruses (e.g. SARS-CoV-1) with high zoonotic potential will be valuable for stockpiling and immunizing priority populations during the emergence phase of a new virus while a specific vaccine is in development. There are practical challenges involved with the development of pan-sarbecovirus vaccines, including extending shelf-life or stability (to maximize stockpiling capabilities), and regulatory considerations for how the assessment of clinical outcomes will be measured following vaccination against sarbecoviruses that are not currently in circulation. Development of a pan-betacoronavirus vaccine that provides broad functional protection against both SARS-CoV-2 and MERS would be challenging, due to differences between the viruses in host selectivity and tissue toxicity. Future vaccines in the US and EU: The formulations of COVID-19 vaccines were updated to a monovalent COVID-19 vaccine with an XBB-sublineage of the Omicron variant (XBB.1.5) and were implemented in Autumn 2023, for the start of the 2023/2024 vaccination program, following approval of emergency use in the US in September 2023; however, it is important that their superior performance characteristics and additional value compared with prior bivalent mRNA vaccines continue to be demonstrated (most importantly broad cross-reactivity and duration of protection).	[34] [35–37]

COVID-19, coronavirus disease 2019; EU, European Union; MERS, Middle East respiratory syndrome coronavirus; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(HIV) [39], with an estimated 39 million people living with HIV and 1.3 million people newly diagnosed with HIV in 2022 [40]. Persistence of viral reservoirs is the main obstacle against achieving eradication or long-term remission of HIV [41]. Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is also a major global threat. Until the COVID-19 pandemic, TB was the leading cause of mortality from a single infectious agent, with higher mortality rates than with HIV/AIDS [41]. The global incidence of TB remains high, with 6.4 million people newly diagnosed with TB in 2021 [42]. Regarding bacterial infections, the emergence of multidrug resistant strains adds to future healthcare challenges. Other pathogen-transmitted diseases that pose a major threat include malaria and dengue, and the number of people at risk is increasing with global warming [43,44]. Nevertheless, pathogens with human-to-human transmission remain the greatest threat in terms of future pandemics.

3.2. SARS-CoV-2 evolution

The ancestral Wuhan-1 strain was first identified in 2019 [12] and has since continued to evolve, with the emergence of new variants driving multiple pandemic waves [4]. The main variants to date have included the Alpha lineage (mainly B.1.1.7), the Delta lineage (B.1.617.2 and all AY sublineages), and the most recent Omicron lineage (B.1.1.519 and all BA sublineages), each of which has had a selective advantage compared with the previous predominant variant [45]. Many studies reported COVID-19 resulting from Omicron infection to be less severe compared with COVID-19 resulting from previous SARS-CoV-2 variants [27,28], whereas others found comparable severities [46]. Whilst not entirely conclusive, these observations indicate that disease severity is at least partially reduced by immunity from previous infection and vaccines [29]. Continued emergence of transmissible Omicron lineages and sublineages that are able to evade the vaccine-induced antibody response is likely [7], but widespread population immunity reduces the chance of increases in disease severity [30].

The clinical severity of COVID-19 is also reduced as a result of biological changes resulting from mutations accumulated in the Omicron lineage, particularly those that decrease membrane fusogenicity and therefore replication capacity in the lower respiratory tract [47,48]. This is further evidenced by the fact that the Omicron variant that first emerged in South Africa caused a milder clinical severity of COVID-19 disease [49], despite the low level of vaccine coverage [50]. It is also worth noting that some later Omicron sublineages revealed increased fusogenicity, yet this may not result in the clinical severity of infections, supporting the role of immunity in the severity of SARS-CoV-2 infection [49].

Modeling to predict novel mutations is challenging but has been beneficial to predict epitope loss and potential vaccination targets [31–33]. Unprecedented SARS-CoV-2 genome sequencing and modeling generated globally have revealed advantageous mutations and have guided laboratory

Table 2. Knowledge gaps and evidence generation needs.

Topic	Knowledge gaps and evidence generation needs	References
COVID-19 epidemiology	Robust active surveillance systems (including comprehensive and complementary data from different sources, e.g. wastewater surveillance, hospital admissions, and emergency department visits) are needed to provide accurate estimates of the numbers of cases to better inform the current epidemiology of COVID-19. COVID-19 seasonality needs to be defined, particularly when seasons start, to better inform vaccine recommendations and strategies. COVID-19 epidemiological modeling is increasingly complex. Future strategies may move away from a 'one-size-fits-all' model to the development and application of simpler models that are designed to address specific questions.	
SARS-CoV-2 evolution	Additional knowledge is needed about mutations affecting viral infectivity and replication, as well as mutations in structural proteins other than the spike protein, such as the membrane, envelope, and nucleocapsid proteins. There is limited understanding of circulating SARS-CoV-2 and SARS-CoV-2 evolution in asymptomatic individuals, who are less likely to be tested and have viral sequencing performed to identify variants. Continued modeling is required for the purpose of predicting novel SARS-CoV-2 mutations and variants that could lead to new COVID-19 waves.	
Burden of COVID-19	Cost-effectiveness modeling should consider the anticipated lifespan of a population, the effects of post-acute COVID-19 sequalae, as well as the impact of COVID-19-related mental health and work/school absenteeism. There is a need for further assessment of the benefits of COVID-19 vaccination for post-acute COVID-19 sequalae (also referred to as long COVID): comparing the characteristics of post-acute COVID-19 sequalae among individuals who are vaccinated versus unvaccinated and investigating the effect of COVID-19 vaccination in individuals with existing post-acute COVID-19 sequalae. Active surveillance should be maintained to monitor co-circulation of influenza, RSV, and COVID-19 to prepare for a potential combined peak.	[38]
COVID-19 vaccine effectiveness and disease management	Vaccine effectiveness should focus on a diverse population (including immunocompromised individuals) and outcomes used to measure vaccine effectiveness should include long-term efficacy. There are different reasons for waning immunity, which need to be better understood. Immunity translates into a longer duration of protection in some individuals compared with others, which needs to be better understood. Prediction modeling of vaccine impact should provide threshold levels for parameters such as efficacy and transmissibility.	
Future COVID-19 vaccination strategies	A duration of protection of approximately 12 months from severe disease needs to be demonstrated in order to enable COVID-19 vaccinations to be annualized. Models that inform COVID-19 vaccination strategies must include social, behavioral, demographic, in-host (e.g. existing immunity), and socioeconomic factors, viral transmission and burden (asymptomatic cases, deaths, hospitalizations, major sequelae, post-acute COVID-19 sequalae), and genomic surveillance factors specific to an individual country/population. Models should be developed to inform COVID-19 vaccination requirements and strategies in special settings such as mass gathering events. Modeling may be used to further increase our knowledge of the benefits of mass vaccination, address issues of geographical vaccine equity, and calculate requirements for vaccine stockpiles.	
Future COVID-19 vaccine development needs	Next-generation COVID-19 vaccines: Need to demonstrate: cross-protection against the full breadth of SARS-CoV-2 variants (Wuhan to Omicron) plus emerging variants, more durable and longer protection compared with bivalent mRNA vaccines, prevention or reduction in virus transmission as well as disease, safety/tolerability, and ease of use (i.e. no contraindications). Pan-sarbecovirus vaccines: Future pan-sarbecovirus vaccines would require clinical testing to at least Phase 2 for regulatory consideration. Extended shelf-life or stability would need to be demonstrated for the purpose of stockpiling for use in future pandemics.	

COVID-19, coronavirus disease 2019; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

experiments, which have led to a better understanding of the intrinsic properties of the interactions between the virus and the host [7,33,51]. Multiple advantageous mutations have been detected within the SARS-CoV-2 spike protein that have changed the transmissibility and infectivity of SARS-CoV-2, and mortality associated with COVID-19 [9,51,52]. Mutations outside of the receptor binding domain and those that affect viral infectivity and replication have not been extensively studied and require further research [6] (Table 1).

Recent work following a systems approach demonstrates how different variants convergently evolved strategies to enhance viral replication and transmission by remodeling the host, through modulation of viral and host protein expression and phosphorylation and changes in virus-host protein–protein interactions [53]. Convergent evolution has been observed since the emergence of variants, and a combination of genetic sites have repeatedly mutated across lineages [54]. The predominant Omicron variant has high transmissibility and immune evasion, with many Omicron lineages emerging over time. One study found that five substitutions were recurrently acquired, particularly in younger Omicron lineages, which increased viral fitness [55]. Importantly, mutations on the S protein have been shown to compromise the efficacy of existing vaccines [9,30,54,56–58] consequently impacting vaccine recommendations. Understanding the mechanisms by which SARS-CoV-2 evolves to overcome human immune barriers may help to identify future vaccination targets.

Knowledge gaps exist regarding mutations, particularly those that affect viral infectivity and replication, or structural

proteins other than the S protein. Additionally, there is limited understanding of circulating SARS-CoV-2 and SARS-CoV-2 evolution in asymptomatic individuals. There is a need for continued modeling to predict novel SARS-CoV-2 mutations and variants that could lead to new COVID-19 waves (Table 2).

3.3. Burden of COVID-19

COVID-19 vaccination has successfully protected individuals against symptomatic infection, hospitalization and mortality [59]. Despite effective vaccines, SARS-CoV-2 transmission continues. However, overall symptom severity and frequency in many areas is shifting to a milder presentation compared with the start of the pandemic due to increased population immunity, from both previous infections and vaccinations [60,61]. For many people, COVID-19 has become no more than an occasional inconvenience, involving a few days of symptoms and a short isolation period [62].

Meanwhile, the slowing of national surveillance, reporting systems and lower testing capabilities [15,16] and demand [63] are a challenge to determine the true current burden of COVID-19, which is still associated with a risk of mortality. COVID-19 has a greater case-fatality rate and mortality risk than influenza [64,65], which is likely driven by its continuous circulation throughout the year compared with predictable seasonal peaks for influenza. As of the 31st of December 2023, over 7 million deaths due to COVID-19 have been reported to the WHO, globally [1]. Many countries have now discontinued routine testing and, as a result, estimates of infection rates may be affected [15,16].

The COVID-19 pandemic has had a substantial psychosocial impact on many individuals. In March 2022, 2 years on from the initial COVID-19 pandemic outbreak, depression, and anxiety symptoms remained at a similar level to those reported when lockdown first eased. In a national study of 70,000 adults living in the UK, only 35% of adults aged 18–29 felt in control of their mental health, compared with 47% of adults aged 30–59, and 61% of older adults [66]. Among people in vulnerable groups (such as individuals who face systemic exclusion and discrimination, individuals who are stateless, incarcerated, live in inadequate housing, or that have chronic health conditions), the pandemic substantially magnified gaps in inequality, with potentially negative implications on their long-term physical, socioeconomic, and mental wellbeing [67,68].

In addition, many individuals continue to experience post-acute COVID-19 sequalae (also referred to as long COVID). The clinical definition of post-acute COVID-19 sequalae has evolved and is currently described by the WHO as 'continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation' [14]. However, post-acute COVID-19 sequalae needs to be redefined and standardized, to include the duration of post-acute COVID-19 sequalae, and its specific symptoms, to aid our understanding of the disease and its management. An estimated 1.9 million in the UK (2.9% of the population) are experiencing self-reported post-acute COVID-19 sequalae [69], and one in 10 individuals with post-acute COVID-19 sequalae stopped working [70]. Current efforts to assess the prevalence of post-acute COVID-19 sequalae and its clinical manifestations are hampered by non-standardized study designs, differences in data quality, and a lack of appropriate comparative methods [71].

Finally, we have now moved into an important phase of the COVID-19 pandemic, where population immunity is affected by SARS-CoV-2 immune escape, and where co-circulation of influenza, respiratory syncytial virus (RSV), or other respiratory viruses [72] has the potential to overrun healthcare systems as a result of a combined peak. Co-circulation of COVID-19, RSV and influenza must be closely monitored to avoid this. The broader impact of the benefits of vaccination against COVID-19 beyond protection from severe disease must be communicated more effectively, such as protection of healthcare systems and prevention of COVID-19-related absenteeism from school or work (Table 1).

Knowledge gaps include the need for cost-effectiveness modeling to understand the impact of COVID-19-related mental health problems and school or work absenteeism, and the need for greater understanding of the benefits of COVID-19 vaccination in preventing against post-acute COVID-19 sequalae (Table 2).

3.4. COVID-19 vaccine effectiveness and disease management

The initial COVID-19 vaccines developed (BNT162b2, mRNA-1273, ChAdOx1, and Ad26.COV2-S), were designed to target the S protein of the ancestral Wuhan-1 strain and were highly effective at preventing symptomatic SARS-CoV-2 infections in clinical trials [58]. However, identification of SARS-CoV-2 variants began even before the initial vaccines were approved. Subsequent mutations on the SARS-CoV-2 S protein have been verified to compromise the efficacy of existing COVID-19 vaccines [9,54,56–58]. In particular, the current predominant Omicron variant has been shown to evade antibody-mediated neutralization more efficiently than the Delta variant [73]. Indeed, lower protection with monovalent mRNA vaccines against the Omicron variant led to the approval of bivalent mRNA booster vaccines (Pfizer – BioNTech and Moderna), containing an ancestral SARS-CoV-2 strain plus an updated component of the Omicron BA.4 and BA.5 sublineages [74]. However, as of October 2023, the most recent update from the US Food and Drug Administration (FDA) granted approval for emergency use of monovalent XBB.1.5 COVID-19 vaccines against Omicron, which was the latest variant of concern available [75].

Continuous SARS-CoV-2 evolution, coupled with waning antibodies and vaccine efficacy [76]), are clearly challenges to vaccine development. Longstanding challenges in the development of effective vaccines against highly mutable viruses are the ability of viruses to evolve and evade the neutralizing antibody response [76].

The effectiveness of current bivalent mRNA booster vaccines against future SARS-CoV-2 variants remains to be seen. Emerging evidence suggests that the BA.5 bivalent mRNA booster does not produce robust neutralization against the emerged Omicron BA.2.75.2, BQ.1.1, or XBB.1 sublineages [77].

However, current population comparisons have unknown bias, since infection rates are higher in unvaccinated individuals, compared with previous clinical trials involving infection- and vaccination-naïve individuals (Table 1).

Novel mutations, such as those having led to the emergence of XBB.1.5, XBB.1.9, XBB.1.16, and EG.5.1 sublineages [78–80], are of increasing concern. While the predominance of different variants continues to evolve over time, vaccine composition should be updated to reflect this; for example, in June 2023 FDA guidance stated that a new monovalent COVID-19 vaccine with an XBB-sublineage of the Omicron variant would be implemented in the US in time for the commencement of the 2023/2024 season vaccination program in Autumn. This was later approved in September 2023 [37].

Knowledge gaps include: the need for vaccine effectiveness evaluations to focus on a more diverse population and reflect longer-term outcomes; better understanding of the reasons for waning immunity; and prediction modeling of vaccine impact to provide thresholds for efficacy and transmissibility (Table 2).

3.5. Future COVID-19 vaccination strategies

There has been a need to update the COVID-19 vaccine recommendations as the pandemic and SARS-CoV-2 have evolved. Current vaccine recommendations reflect that most of the population has immunity from either vaccination or previous SARS-CoV-2 infection, or both, and emphasize the importance of vaccinating those who remain at risk of severe disease [81]. In March 2023, the WHO's Strategic Advisory Group of Experts on Immunization revised the roadmap for prioritizing COVID-19 vaccines to include three priority groups (high; medium; and low priority). The highest priority risk group includes: older adults; adults with significant comorbidities (e.g. diabetes and heart disease); immunocompromised individuals (including people of any age group above ≥6 months e.g. people living with HIV, and transplant recipients); pregnant individuals; and frontline health workers [82]. Individuals with medium priority include healthy younger adults (ages 18–49 or 18–59 years; cutoff decided by countries) and children/adolescents aged 6 months to 17 years with severe obesity or comorbidities with higher risk of severe COVID-19; those with low priority are healthy children/adolescents [82].

The planning of future COVID-19 vaccination strategies is based on a country's epidemiological situation, the effectiveness of previously administered vaccinations, the potential availability of new, updated and more effective vaccines, and the identification of at-risk groups [81]. COVID-19 vaccination recommendations are likely to be continually updated for several more years. In April 2023, the US FDA simplified the COVID-19 vaccination schedule for most individuals, authorizing the current bivalent mRNA vaccines to be used for all doses administered to individuals aged ≥6 months, including as an additional dose or doses for specific populations [74]. From July 2023, the FDA advised that vaccination composition should be updated to a monovalent COVID-19 vaccine with an XBB sublineage of the Omicron variant, with a preference for XBB.1.5, in time for the autumn 2023 vaccination program. By September 2023, the FDA had granted approval for emergency use of monovalent XBB.1.5 COVID-19 vaccines in the US [37]. The European Medicines Agency (EMA) also advised that monovalent vaccines should be implemented [36]. However, in the European Union, each country considers its own specific situation and may decide to use approved, available vaccines differently [83]. Administration of annual COVID-19 vaccines between September and October of each year would be advisable to protect against a possible winter peak in the Northern Hemisphere (Table 1).

Preventative public health strategies introduced in 2020 to curb SARS-CoV-2 transmission also effectively prevented transmission of common respiratory viruses such as influenza [84]. With most COVID-19 public health measures now lifted, co-circulation of influenza and COVID-19 is of increasing concern [85]. In May 2023, the WHO recommended that COVID-19 vaccination is integrated into routine vaccination programs throughout life [14,86,87]. Therefore, coadministration of COVID-19 and influenza vaccines has received increasing interest, given that this provides many logistic and economic advantages, has been shown to be effective and well tolerated, and may optimize vaccine uptake by overcoming vaccine hesitancy and booster fatigue [88,89] (Table 1).

Factors that may underlie vaccine hesitancy include safety concerns, education status, and injection fear [90,91], as well as doubts and lack of knowledge among vaccinating physicians [92]. Regardless of the socioeconomic status of a country, information about the increasingly sophisticated RNA vaccine technology (not only mRNA but also self-amplifying [sa]RNA-based vaccines) needs to be conveyed to improve acceptance. Educational material could be used to assist healthcare professionals in explaining the technology to their patients. It may also help raise awareness among the general population of the risks associated with vaccine-preventable diseases compared with the low risk associated with vaccination itself. Also, the utilization of public online dashboards that track vaccine effectiveness may be beneficial in increasing vaccine uptake [93]. Taken together, interventions that improve knowledge around, and confidence in, vaccination-associated benefits could enhance vaccine uptake.

To inform COVID-19 vaccination strategies, modeling is required that considers social, behavioral, demographic, in-host, socioeconomic, viral transmission and burden, and genomic surveillance factors specific to an individual country or population. There is a particular need for focus on social settings such as mass gathering events. Modeling may also assist to address issues of geographical vaccine equity and calculate requirements for vaccine stockpiles. Inequities and limited or delayed access to vaccines [94] and diagnostic testing [95] have impacted health outcomes, particularly in low-to-middle income countries. Demonstration of approximately 12 months' duration of protection from severe disease would allow for the implementation of annual COVID-19 vaccinations (Table 2).

3.6. Future COVID-19 vaccine development needs

With the likely continued evolution of SARS-CoV-2, vaccine developers are focusing on several strategies for next-generation COVID-19 vaccines [96]. One such strategy is a variant chasing approach, which relies on the rapid adaptation of existing mRNA vaccines to variant ready vaccines

targeting the circulating SARS-CoV-2 variant [77]. However, timing is critical, even with the extraordinary speed at which mRNA vaccines are produced – the fastest turnaround time is several months [96]. A variant-chasing strategy has rapidly declining effectiveness with greater time elapsed following variant emergence [97]. Therefore, the key challenge is to determine the future booster sequence before new variants begin to dominate [77]. Indeed, even as of March 2024, within the current XBB.1.5 vaccine season, new variants, including BA.2.86, have emerged with different antigenic and neutralization characteristics [98,99].

Another factor that needs to be considered with the practice of repeated booster mRNA vaccinations is a potential shift in the mRNA vaccine-induced immune response toward an increase in anti-SARS-CoV-2 spike receptor binding domain-specific immunoglobulin (Ig)G4 antibodies [100]. Whilst elevated IgG4 antibody levels do not appear to be associated with a higher rate of breakthrough infections, potential long-term effects on immune responses against SARS-CoV-2 following repeated booster vaccinations remain unknown [100].

Recent emerging evidence has indicated that the ancestral Wuhan-1 spike in the current bivalent mRNA vaccine is the cause of deep immunological imprinting that prevents broadening of antibodies and should be removed from the expected XBB sublineage-specific vaccine [101,102]. A second approach is the development of next-generation COVID-19 vaccines capable of eliciting broad, durable, cross-reactive protection across SARS-CoV-2 variants, i.e. vaccines that are 'mutation-proof' [54,58]. Several mechanisms for cross-protection have been proposed, such as the inclusion of S protein epitopes from several variants, or highly conserved epitopes or structural proteins that elicit a cellular response [96,103]. The ultimate strategy, however, would be to develop vaccines that can protect against all sarbecoviruses – a pan-sarbecovirus vaccine. During the last 20 years, SARS-CoV-2 was the third major human infectious disease outbreak that has been caused by zoonotic coronaviruses, after SARS-CoV-1 between 2002 and 2003, and Middle East respiratory syndrome (MERS) coronavirus in 2012. Several other coronaviruses currently found in animals also have a risk of spillover to humans [104], with the potential to lead to future novel epidemics. Therefore, developing a pan-sarbecovirus vaccine with high zoonotic potential, that provides broad protection against existing SARS-CoV-2 variants and those that are evolving, as well as novel coronaviruses that may emerge in the future, is paramount. However, development, and evaluation of a pan-betacoronavirus vaccine that provides broad functional protection against both SARS-CoV-2 and MERS is more challenging, due to differences between the viruses in host selectivity and tissue toxicity [34]. Practical challenges also exist including the need to extend shelf-life and stability, along with regulatory considerations for vaccination against sarbecoviruses that are not currently circulating. Future pan-sarbecovirus vaccines would require clinical testing to at least Phase 2 and would need to demonstrate extended shelf-life and stability to allow for stockpiling for use in future pandemics (Table 2).

Scientific discussions are ongoing regarding the potential approaches for pan-sarbecovirus vaccines [105]; emerging preclinical models are exploring hypotheses and frameworks for potential pan-sarbecovirus vaccines [106–108]. An important consideration is that the antibody evasion capability of some Omicron sublineages have been shown to exceed that of SARS-CoV-1 [109]. Regardless of the approach used, there are several key performance characteristics that would increase the likelihood of including a next-generation COVID-19 vaccine in vaccination recommendations, such as broad cross-reactivity, longer duration of protection, accessibility, and route of administration (Table 1). Next generation COVID-19 vaccines must demonstrate cross-protection across all SARS-CoV-2 variants (Wuhan to Omicron), along with emerging variants, offer more durable and longer protection compared with bivalent mRNA vaccines, prevent or reduce virus transmission as well as disease, and demonstrate safety/tolerability and ease of use (Table 2).

An additional factor to consider for future COVID-19 vaccine development is the evaluation of vaccine effectiveness. Initial trials for vaccines against COVID-19 were designed to evaluate the efficacy of the vaccine in a naïve population, prior to the identification of the most recent, advantageous variants [110–112]. Following the FDA's Vaccines and Related Biological Products Advisory Committee meeting and European Centre for Disease Prevention and Control and EMA's statement in June 2023, it was recommended that the vaccine composition was updated to a monovalent COVID-19 vaccine with an Omicron XBB-sublineage (XBB.1.5) in time for the Autumn 2023 vaccination program [35,36]. As of September 2023, monovalent XBB.1.5 COVID-19 vaccines were approved for emergency use in the US [37]. In October 2023, the FDA released further guidance on the efficacy considerations for future COVID-19 vaccine trials, stating that the primary endpoints should include virologically confirmed acute cases of COVID-19, or laboratory confirmed SARS-CoV-2 infection (symptomatic or asymptomatic) [113]. However, future trials and studies still need to consider the evolved population immunity due to the emergence of new variants as well as the population immunity due to prior infections with SARS-CoV-2.

Aside from mRNA vaccines, lipid nanoparticle (LNP)-encapsulated saRNA vaccines may present an effective future RNA-based alternative. Preclinical studies have demonstrated protective immunization with saRNA vaccines against infectious diseases including influenza, RSV, HIV-1, Ebola, and rabies [114]. COVAC1 is a first-in-human trial to test the safety and immunogenicity of an saRNA vaccine against SARS-CoV-2 (LNP-nCoVsaRNA) [115]. In Phase 2a of the study, 216 healthy individuals (aged 20–73 years) with or without previous immunity to the virus received two doses of LNP-nCoVsaRNA, 1 µg followed by 10 µg approximately 14 weeks later [116]. Reactions following vaccination were dose- and age-dependent, with better tolerability in older participants, and the authors report that no vaccination-related serious adverse events occurred. Even after a single 1 µg dose, seroconversion rates were promising [116], indicating that saRNA vaccines may serve as a low-cost booster alternative to mRNA vaccines that can be administered at low doses. However, the effectiveness and safety of this technology will require further investigation.

4. Conclusions

The COVID-19 pandemic has highlighted the need for a greater level of preparedness for a future viral pandemic. The global scientific community has come a long way since the beginning of the pandemic in understanding the complex and changing dynamics of SARS-CoV-2 and the subsequent impact on COVID-19 vaccine development. Although the WHO have declared that COVID-19 is no longer a public health emergency of international concern, COVID-19 remains a global concern, particularly due to the continued evolution of SARS-CoV-2 and the potential emergence of variants that are able to evade the vaccine-induced antibody response. Continued surveillance and monitoring are required to allow for a comprehensive situational awareness, including the transition to endemicity, seasonality, and emergence of new and more transmissible variants, which can inform future vaccination recommendations and development of COVID-19 vaccines. Monitoring the co-circulation of other respiratory viruses, specifically RSV and influenza, should be implemented to prevent a combined peak of both viruses, which could lead to healthcare systems being overrun. An effective combined COVID-19/influenza vaccine, combined with improvements in vaccine-related education, may help overcome vaccine hesitancy or booster fatigue and increase vaccination uptake.

WHO 2023 vaccine recommendations describe the importance of an integrated approach to vaccination against COVID-19, in combination with existing vaccination programs, for a more people-centered approach. As per FDA recommendations, the COVID-19 vaccine composition was updated to a monovalent COVID-19 vaccine, which corresponds to the Omicron variant XBB-1.5, to commence the 2023/2024 season vaccination program in Autumn. Future vaccine recommendations will likely focus on prioritizing vaccination of those still at risk of severe disease, and further integrating COVID-19 vaccination into routine vaccination programs throughout life. Vaccine recommendations could be released for different subpopulations, with additional booster vaccinations offered to adults aged 60 years or older and those with underlying risk factors, such as immunocompromised individuals or those with comorbidities. Regular annual vaccinations should be offered to children, those with underlying risk factors, and individuals that are pregnant. Further results and dynamic adaptation of the existing recommendations will be required. Potential use of saRNA vaccines against SARS-CoV-2 will depend on future studies evaluating the effectiveness and safety of this technology.

5. Expert opinion

Although we have likely reached the end of the acute phase of the COVID-19 pandemic, as evidenced by high levels of immunity to SARS-CoV-2 in the population, particularly in high-income countries, monitoring of SARS-CoV-2 transmission and infection rates should continue. The continued emergence of additional transmissible variants which are able to evade the vaccine-induced antibody response are expected. However, widespread population immunity reduces the likelihood of severe infection and subsequent hospitalization. Nevertheless, it remains possible that new variants/sublineages could emerge with high transmissibility and novel antigenic properties, which could lead to an increase in the burden of COVID-19 disease (deaths, hospitalizations, and long-term sequelae). The slowing down of surveillance, reporting systems, and lower testing capabilities as well as demands, combined with scaled-back national vaccination programs and a lower willingness of the public to continue to be vaccinated (for reasons such as vaccine hesitancy and booster fatigue), may make such an event more difficult to predict, detect, and manage.

The WHO recommends that COVID-19 vaccination should be integrated into routine vaccination programs throughout life. However, it is still not clear what the optimal vaccination strategy is (e.g. a population vs targeted 'at-risk' approach, variant-chasing vs cross-protection), and how best to adapt and administer vaccines given the continuous evolution of the SARS-CoV-2 virus (i.e. emergence of mutations that affect transmissibility and infectivity), and the current unpredictability of COVID-19 outbreaks. While it makes sense to relax the monitoring of mild cases of COVID-19, as compared with the extent of monitoring in the height of the pandemic, monitoring of the circulation of all respiratory viruses is important, to avoid another pandemic, or a combined peak, which could overrun healthcare systems. Effective combined vaccines and interventions to raise awareness and understanding of vaccine-related benefits may help overcome vaccine hesitancy/booster fatigue and increase vaccination uptake.

While we have learned so much about how to monitor and manage SARS-CoV-2 infections in such a short time, many challenges remain. For example, we need to understand more about the long-term consequences of SARS-CoV-2 infection for both physical and mental health, and their impact on working/school life, as well as how to manage these consequences. There is also a need to better understand how the SARS-CoV-2 virus is changing in terms of both its structure and biological features, and how this may affect clinical relevance.

For vaccine development, it will be important to determine the optimal antigenic targets to elicit protective immunity, reasons for waning immunity with existing vaccines, and how best to assess and determine the effectiveness of new vaccines in the context of a highly immunized and/or previously infected population. The unprecedented success of mRNA vaccines notwithstanding, the development of self-amplifying (sa)RNA vaccines holds promise of further improving vaccine-induced immunity. From a global perspective, a major issue particularly in low-to-middle income countries is vaccine inequity. If the effectiveness and safety of SARS-CoV-2 saRNA vaccines can be confirmed in current and upcoming clinical studies, their potential to induce immunity at a lower dose could positively impact vaccine inequity. In combination with the low cost associated with saRNA vaccines, this may help improve accessibility of vaccines beyond high-income countries.

Over the next 5–10 years, it is hoped that advances in COVID-19 vaccines will further reduce the burden of the disease. As well as protecting against existing variants and sublineages, future vaccines would need to protect against the severe consequences of infection (Long and/or Post-COVID) and have an excellent safety profile. Additionally, vaccines should strive to further reduce viral transmission, which in

part would be due to eliciting a broad, durable cross-protection across existing and potential future SARS-CoV-2 variants. They will also need to be relatively easy to manufacture, store, distribute, and administer, and be affordable. Whether an improved vaccine is attained within this timeframe remains to be seen, but there are many candidates in development.

Acknowledgments

Medical writing support was provided by Emily Evans, BMedSc, of Ashfield Medcomms, an Inizio company, and funded by Sanofi.

Funding

Medical writing support for the development of this manuscript was funded by Sanofi. The expert group meeting prior to compiling this paper was convened and funded by Sanofi.

Declaration of interest

M Rolland is funded through a cooperative agreement between The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., and the U.S. Department of the Army, and reports consultancy fees from Sanofi, which were paid to the Henry M. Jackson Foundation for the Advancement of Military Medicine, and travel fees received from Sanofi during the conduct of the study. MC Nunes received grants from BMGF, EDCTP, Sanofi, AstraZeneca, and Pfizer; honoraria from Sanofi; expert testimony fees from Sanofi; participated in an advisory board for Sanofi and a committee for Gavi. C Guerche-Séblain and A Chit are employees of Sanofi and may be stock or shareholders in Sanofi. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All authors contributed equally to the review, interpretation of the relevant literature, and writing/revision of the article.

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