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Unit No. 1

COVID-19: WHERE ARE WE NOW?

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ABSTRACT

When severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in December 2019, coronavirus disease (COVID-19) rapidly evolved into a global health crisis, prompting the WHO to declare it a pandemic in March 2020. Initially, the response relied on non-pharmaceutical interventions such as masking and physical distancing, which proved unsustainable in the long term. The rapid development and deployment of mRNA vaccines in late 2020 marked a crucial turning point in the fight against the virus. These vaccines, particularly those updated for evolving variants, have significantly mitigated severe outcomes and hospitalisations. As of September 2024, COVID-19 is endemic and continues to circulate, with smaller waves driven by increasingly transmissible variants. Despite reduced virulence compared to earlier strains, the virus still poses a substantial burden due to its high transmissibility and the persistence of long COVID – a condition causing prolonged neurological, neuropsychiatric, and physical symptoms in survivors. Vaccination remains critical for managing both acute and long-term complications, with updated boosters providing enhanced protection against severe illness and reducing the risk of long COVID. Nevertheless, challenges such as vaccine hesitancy, perceived low risk of severe disease, and logistical barriers have impacted vaccination uptake. Family physicians play a vital role in addressing these issues by providing clear vaccination directives, building confidence in vaccine safety and efficacy, and improving convenience through co-administration with other vaccines. This paper highlights the ongoing challenges and strategies to manage COVID-19 and emphasises the importance of continued vigilance and vaccination efforts in mitigating the impact of the pandemic.

Keywords: Immunisation; Pandemics; Post-Acute COVID-19 Syndrome; SARS-CoV-2; Vaccines

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INTRODUCTION

On 8 December 2019, a novel RNA coronavirus – subsequently named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) – emerged in Wuhan, China. It primarily caused pneumonia and respiratory failure and was highly contagious.[1] COVID-19 swiftly spread globally and led to the World Health Organization (WHO) declaring it a public health emergency of international concern (PHEIC) on 30 January 2020 and a pandemic on 11 March 2020. By 2 October 2020, 10 months after its onset, COVID-19 had caused more than 34 million cases and over 1 million deaths.[1]

Initially, only supportive treatment was available and initial antiviral therapies were of uncertain benefit. Prevention could only be done via non-pharmaceutical interventions like masking, physical distancing, and travel restrictions. These non-pharmaceutical interventions, though effective in stopping the spread of SARS-CoV-2 in some countries,[1] were unsustainable over the long-term given their psychological and socioeconomic impact.

Another form of prevention was urgently required, and vaccines were developed in record time. The genetic sequence of SARS-CoV-2 was released on 10 January 2020, within weeks of the virus' emergence.[1] By late 2020, highly-efficacious vaccines were available.[2] The breakthrough technology was vaccination based on mRNA that encodes for SARS-CoV-2 spike protein, which is the main target for neutralising antibodies.[2] The mRNA platform enabled not only rapid vaccine production but also allowed rapid changes to the mRNA to encode different spike proteins. The latter would prove to be essential for addressing viral evolution and mutation, which has resulted in the alpha, beta, gamma, delta, and omicron variants.[3]

Vaccination rollout, though patchy, was overall successful given the tremendous motivation of the public and governments to dampen pandemic spread. As the large waves of infections subsided owing to vaccination, the population impact and pressure on healthcare systems exerted by COVID-19 were sufficiently mitigated for WHO to declare the PHEIC over on 5 May 2023. This meant that public life, social interactions, and commercial dealings could revert to pre-pandemic norms.

Post-PHEIC however does not mean that COVID-19 cases have been eliminated. On the contrary, as of September 2024, COVID-19 has become endemic, with smaller waves rather than larger ones. Case numbers may even rise due to waning immunity after vaccination or natural infection, coupled with the emergence of new viral variants that evade vaccination-induced immunity. Additionally, after acute COVID-19 infections, many patients develop systemic complications in a syndrome now termed long

COVID. This paper aims to provide an overview of the current healthcare burden of COVID-19 and long COVID primarily in adults, to alert family physicians about the ongoing threat of COVID-19. Family physicians can in turn help patients avoid being complacent about the ongoing risk of COVID-19 infection. In addition, this paper will outline vaccination recommendations and strategies that family physicians can use to improve COVID-19 vaccine uptake.

BURDEN OF DISEASE

Acute COVID-19 Disease

In the initial stages of the pandemic, the world's population, apart from SARS-CoV-1 survivors with cross-clade memory immunity,[4] had no immunity against SARS-CoV-2 infection. This, coupled with the virulence of the initial ancestral (wild-type) strain of SARS-CoV-2, meant that fulminant pneumonia and acute respiratory distress syndrome developed in many individuals with high case fatality rates. The large number of patients quickly overwhelmed health systems, including those in developed, high-income countries. As a result, in the first two years of the COVID-19 pandemic from 2020-2021, global age-standardised all-cause disability-adjusted life-years (DALY) rates increased 4.1 percent in 2020 and 7.2 percent in 2021, reversing the decline seen between 2010 and 2019.[5] In 2021, COVID-19 became the leading cause of DALYs globally (212 million DALYs), outpacing ischaemic heart disease, neonatal disorders, and stroke.[5] On a similar note, global all-cause mortality increased by 5.1 percent from 2020-2021, reversing age-standardised mortality rate decline between 1950 and 2019.[6] Not unexpectedly, the economic burden was tremendous owing to the COVID-19 pandemic on both nations and individuals (average direct medical costs were US $1,264 to US $79,315).[7]

With subsequent waves of COVID-19, different variants become dominant, with current variants being less virulent than the early strains, accompanied by decreases in hospitalisation, ICU utilisation, and mortality.[8] Presently, when patients require hospitalisation, morbidity and mortality associated with COVID-19 are like influenza,[9] or worse than influenza.[10] Among hospitalised patients, omicron-variant infection now results in 12.90 percent risk of ICU admission, 5.80 percent risk of receiving invasive mechanical ventilation, and 7.10 percent risk of death.[8] Older age and lack of vaccination are associated with higher mortality risk.[11]

Compared to earlier SARS-CoV-2 strains, the decreased virulence of current strains is currently counterbalanced by increased contagiousness.[12] Each person infected by the omicron variant would infect about nine others,[12] compared to 2.5 for wild-type SARS-CoV-2.[1] As of 9 September 2024, >776 million cases of COVID-19 and >7 million deaths have been reported, with >238,000 cases and >4,300 deaths in the last 28 days (WHO COVID-19 dashboard, https://data.who.int/dashboards/covid19, accessed 9 September 2024).

Post-acute COVID-19 Disease (Long COVID)

Post-acute COVID-19 complications came to the forefront as increasing numbers of survivors manifested smouldering neurological (e.g., brain fog, memory issues, attention disorder), neuropsychiatric (e.g., sleep disorder, anxiety, depression), and physical (e.g., fatigue, headache, myalgia, respiratory problems, anosmia, dysgeusia) complications that lasted on average nine months for hospitalised patients and four months for non-hospitalised patients[13-17] after the acute phase has resolved. About 20 percent of patients have symptoms lasting three months after their acute infection and 15 percent of patients have symptoms lasting 12 months.[13,18] Patients typically have increased healthcare utilisation in terms of outpatient visits (increased by 11-240 percent), diagnostic tests (increased by 35-603 percent), and hospitalisations (increased by up to 438 percent).[19] Following the duration of symptoms, increased healthcare utilisation could also be maintained up to 12 months after acute COVID-19 infection.[20]

The cumulative number of people affected by long COVID is estimated to be in the millions, with significant morbidity, including among the working-age population.[21] For instance, data from Italy and the USA from January 2020 to April 2023 showed that there were 14.4 million cases with 2.3 million quality-adjusted life years lost due to long COVID, resulting in a productivity loss of 49 billion international dollars (equivalent to the purchasing power of 49 billion US dollars).[22]

VACCINATION COVERAGE AND RECOMMENDATIONS

Vaccination remains effective against infection and severe disease if patients receive variant-updated vaccines.[23,24] Among the general adult population, due to high antigenic divergence and antibody evasion of SARS-CoV-2 variants,[25,26] people who only received vaccination against the ancestral wild-type COVID-19 had minimal protection against the later omicron sub-lineages.[27,28] About 3-13 percent of patients infected with older variants are reinfected.[29]

Bivalent booster vaccination reestablished protection against critical illness, hospital admission, emergency department or urgent care visits, and outpatient encounters.[28] Patients with chronic lung disease (including asthma, chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis) remained at elevated risk of infection, hospitalisation, and severe COVID-19 when newer variants like delta and omicron were circulating, even when previously vaccinated against the ancestral strains of COVID-19. These risks were reduced when patients received booster vaccination.[30] Specifically, among the general adult population, an XBB-variant adapted mRNA vaccine could prevent 62 percent of COVID-19 hospitalisation and 58 percent of emergency department/urgent care visits, with older vaccines having no protective effect.[31]

Antivirals, while effective at reducing acute complications of hospitalisation and mortality,[32] do not seem to reduce any post-acute symptom or complication (cardiovascular, neurological, respiratory, autoimmune).[33] In contrast, vaccination may reduce long COVID not only by decreasing the number of infections, but also by decreasing the incidence of post-acute complications after infection. Vaccination with two doses prior to infection has been associated with a 36.9 percent reduction in the risk of getting long COVID and getting a third booster dose prior to infection was associated with a larger 68.7 percent reduction in the risk of getting long COVID.[34]

Vaccination also has a good safety profile. Anaphylaxis with COVID-19 mRNA vaccines and inactivated whole-virus COVID-19 vaccines were less likely than other vaccines (typhoid, encephalitis, hepatitis B, cholera, hepatitis A, influenza), though serotype 5 adenovirus (Ad5)-vectored COVID-19 vaccine-associated anaphylaxis were linked with the highest fatality rate of 15 percent.[35] Myocarditis risk remains low and uncertain,[36] and seems to be lower than with smallpox (vaccinia) vaccination.[37] Guillain-Barré syndrome, an acute immune-mediated inflammatory disease of the peripheral nerves, is also very rare after COVID-19 vaccination, with a pooled incidence between 0.23 to 9.8 per million doses,[38] though adenovirus-vectored vaccines showed an increased risk of GBS that was about seven times higher compared with mRNA-based vaccines.[39]

Revaccination would both address waning immunity and provide an opportunity to receive a variant-updated vaccine. Immunity against SARS-CoV-2 infection wanes six months after vaccination, natural infection, or both (i.e., hybrid immunity).[40-43] Naturally-acquired immunity against re-infection appears to wane more for omicron variants compared to pre-omicron variants.[44] Booster immunisation with variant-updated vaccines tends to increase the duration of protection to at least 360 days,[41] suggesting that re-vaccination could be done annually.

Adults at elevated risk of severe disease include those who are older in age or who have comorbid conditions.[45] Pregnant women are at risk of both severe disease and COVID-19-related pregnancy complications.[46] In line with the available evidence, WHO's Strategic Advisory Group of Experts on Immunisation recommends vaccination based on vaccination history and risk for severe COVID-19 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice, accessed 9 September 2024):

- All adults who have not previously received at least one dose of a COVID-19 vaccine should receive COVID-19 vaccination.
- Among adults who have previously received at least one dose of a COVID-19 vaccine, those over 50 years old, those with comorbidities, and health workers with direct patient contact should be revaccinated 12 months after the most recent dose.
- Pregnant women should get revaccinated in each pregnancy.
- Revaccination is not routinely recommended for younger healthy adults who have previously received at least one dose of a COVID-19 vaccine.

STRATEGIES TO IMPROVE VACCINE UPTAKE

COVID-19 continues to pose a significant risk to both individual and public health, with ongoing transmission worldwide. In addition to maintaining good hygiene practices, such as regular handwashing, revaccination is crucial for sustaining immunity and reducing case numbers, helping to prevent the overwhelming of healthcare systems. However, several factors have slowed vaccination uptake in the post-PHEIC era, including a low perceived risk of severe illness from COVID-19, concerns over vaccine efficacy and side effects, distrust, and logistical barriers.[47,48]

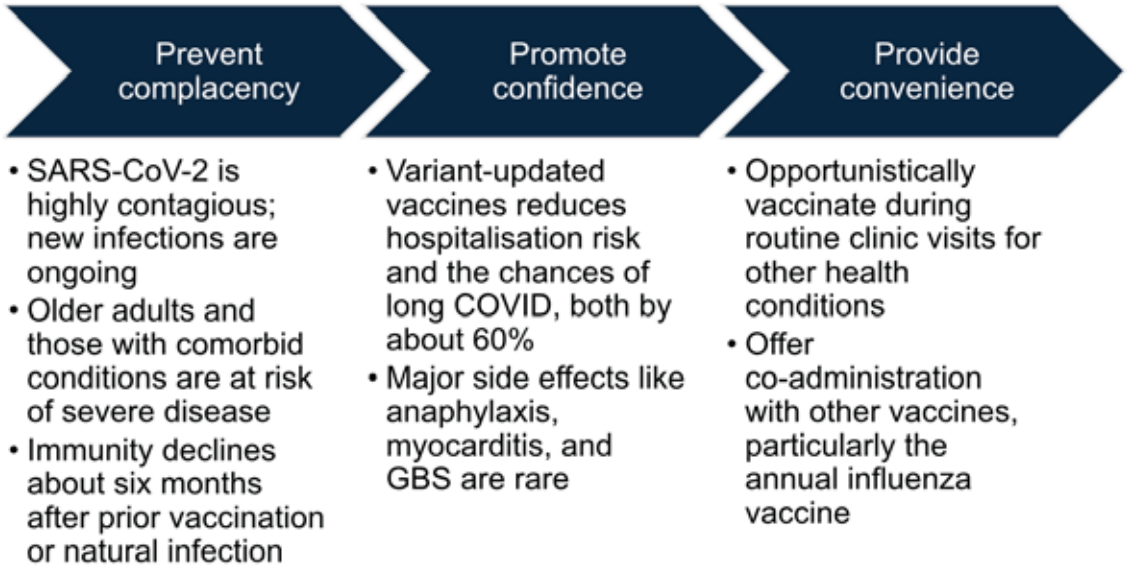
As described by WHO's Strategic Advisory Group of Experts on Immunisation's 3C model of vaccine hesitancy (i.e., delay in acceptance or refusal of vaccines despite the availability of vaccination services), this can be due to complacency, confidence, and convenience barriers.[49] Each of the three latter terms are defined below:

- Complacency: An overly optimistic view of personal health and a low perceived risk of infection or serious illness.
- Confidence: Distrust in vaccine effectiveness and/or safety.
- Convenience: Structural obstacles and challenges related to access.

To improve vaccine uptake, family physicians can adopt strategies to overcome each of the three "C"s (see **Figure 1**).

- Complacency: Provide a clear directive (e.g., "you are due for a COVID vaccine booster") rather than using a participatory approach (e.g., "are you interested in getting a COVID vaccine booster?"), as this enhances the effectiveness of physician recommendations.[50] Counsel patients about their risk of getting COVID-19 and if they have elevated risk of severe disease (e.g., due to age, presence of comorbidities). Protection against SARS-CoV-2 infection wanes about six months after vaccination, or natural infection.[40-43] If available, use a patient decision aid such as the Relative Risk Tool, which visually depicts the relative risks associated with COVID-19 vaccination and infection, compared to other common activities (https://www.covidtaser.com/relativerisk).[51]
- Confidence: Inform patients that booster vaccination could prevent about 60 percent of COVID-19 hospitalisations and emergency department/urgent care visits, with older vaccines having no protective effect.[31] Similarly, booster vaccination prior to infection could

Figure 1. A stepwise approach to COVID-19 vaccination for primary care physicians



prevent about 60 percent of long COVID.[34] Reassure patients that major side effects like anaphylaxis, myocarditis, and GBS are rare.[35,36,38]

- Convenience: Opportunistically vaccinate during routine clinic visits for other health conditions. Compared with separate vaccinations, coadministration with the seasonal influenza vaccine is time-saving, and is particularly suitable given similar annual vaccination schedules and preservation of efficacy and safety for both vaccines.[52,53]

CONCLUSION

COVID-19 remains a disease of high burden despite having moved towards an endemic state like for influenza. Given the reduction or removal of non-pharmaceutical interventions like physical distancing or mask-wearing, vaccination has become the primary method for protection. However, COVID-19 vaccination hesitancy needs to be overcome by preventing complacency through counselling patients about their risk of COVID-19 and severe complications, promoting confidence by informing patients about the effectiveness and safety of vaccination, and providing convenience through opportunistic vaccination and vaccine co-administration.

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LEARNING POINTS

- **SARS-CoV-2 continues to evolve into highly contagious variants that tend to evade immunity.**
- **COVID-19 remains a significant global health burden, with long COVID causing neurological, neuropsychiatric, and physical difficulties beyond the acute phase.**
- **Vaccination before infection helps reduce disease severity, hospitalisation, and the risk of long COVID.**
- **Immunity from vaccination or natural infection wanes over time, particularly against newer variants.**
- **Variant-updated booster vaccinations restore protection and can be safely co-administered with annual seasonal influenza vaccines.**