

## Commentary

## Vaccination Uncertainties and COVID-19 Prospects in 2021

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As we pass the first anniversary of the World Health Organization's (WHO) declaration of a Public Health Emergency of International Concern (1), we look back at the impact of coronavirus disease 2019 (COVID-19) in 2020 and the prospects for the pandemic in 2021.

The almost inverse correlation between pre-COVID-19 assessed preparedness (2) and actual performance (3) one year since the world first learned of the pandemic potential of the COVID-19 virus (4) is a stark reminder of Robert Burns's "The best laid schemes o' Mice an' Men / Gang aft agley." Going forward, we clearly need to bridge this disconnect and identify reliable indicators of true preparedness that are widely applicable and can stand the test of a real outbreak.

In the past year we have observed unprecedented public health and social measures (PHSMs) including lockdowns and travel restrictions (5). The health impact could have been much larger without these sustained drastic interventions, but the societal and economic cost has still not yet been fully realized. Although affected earliest in the pandemic, the rapid implementation of effective measures in China resulted in domestic elimination of infections by March 2020 (6) with only very occasional case clusters observed thereafter, leading to one of the lowest rates of infection per capita worldwide (7) and without the need for sustained PHSMs since.

COVID-19 vaccines are eagerly anticipated to bring an "end" to the pandemic, although the virus may continue to circulate and is likely to cause seasonal epidemics in the post-vaccination era (8). We must be vigilant for the emergence of new variants, especially those arising from convergent evolution, that are more transmissible, virulent, or could escape vaccine immunity. As administration of COVID-19 vaccinations is rolled out in more countries, we should begin to see reductions in case numbers and hospitalizations, and the opportunity to relax some PHSMs that have been in place for much of the past year. However, with delays in vaccine availability and

fatigue with physical distancing measures, we are concerned that there could be more COVID-19 deaths in 2021 than 2020. With a resurgence in case numbers in many parts of the world, we urgently need to vaccinate older adults, other target groups such as healthcare workers and front-line workers in essential services and ultimately the whole adult population.

If high vaccination coverage is achieved and vaccines have high effectiveness against infection, we should see herd immunity preventing large epidemics although smaller outbreaks would remain a risk. On the other hand, even if coverage of a vaccine with insufficiently high efficacy reaches high levels, herd immunity will be difficult to achieve. In China, vaccination efforts have so far focused on high-risk working populations (9), leaving older adults vulnerable to infection if outbreaks recur. However, if vaccination coverage does not reach high levels, or if the vaccines prevent disease development but not infections (10) and specifically do not limit transmission, a more concerning scenario may play out where PHSMs need to be maintained for much longer to protect healthcare systems against surges in cases. Achieving high vaccine coverage will be hindered by vaccine hesitancy (11), which can be a particular problem with novel vaccines against a coronavirus that are licensed under emergency approvals with a rapid development timeline.

While we are encouraged by the successes of several promising vaccines with high efficacy against symptomatic disease in interim analyses of phase 3 trials, others have unsurprisingly been reporting more variable data. Even amongst those that have already been approved for emergency rollout, studies addressing extended use in population subgroups (e.g. the extremes of age, immunocompromised groups, and pregnant mothers), the optimal dosing interval between prime and booster, head-to-head comparisons between vaccines, and possible mixed use of vaccines between different technology platforms as first or second booster are ongoing. Therefore, many uncertainties remain as the pandemic threat

necessitates immediate vaccine deployment. Post-marketing pharmacovigilance and safety monitoring, as well as vaccine effectiveness studies, will help us further finetune immunization strategies.

As such, openness and transparency are the only sure way of countering vaccine hesitancy. Full and systematic disclosure of data from clinical trials and post-rollout empirical studies is needed to determine the safety and efficacy of each vaccine for different population groups, preferably in the international peer reviewed literature in parallel with regulatory submissions at the national level.

It is expected that the protection from vaccination against COVID-19 would not be lifelong, although data on waning of the neutralizing antibody after vaccination have been mixed (12–13). It is worrying to see a surge of COVID-19 cases in countries with high attack rates in their first waves (14–15). Revaccination may be needed sooner or later to prevent vaccinated or infected individuals from reinfection, although development of new vaccines would become essential if new virus variants emerge capable of escaping from vaccine-induced immune protection (16).

Despite the uncertainties in efficacy and safety, vaccines are expected to be the single most effective intervention to bring the COVID-19 pandemic to a resolution. To achieve fair and equitable access to vaccines, ethical principles should be upheld to overcome vaccination nationalism and, at the same time, to guarantee efficient access for individuals/countries in greater need (17–18). The moral imperative for equitable access to vaccines ultimately also serves the utilitarian purpose of self-protection by vaccinating others.

**Funding:** The Health and Medical Research Fund, Food and Health Bureau, Government of the Hong Kong Special Administrative Region (grant no. COVID190118). BJC and GML are supported by the AIR@innoHK program of Hong Kong SAR Government.

**Conflicts of Interest:** BJC consults for Roche and Sanofi Pasteur. The authors report no other potential conflicts of interest.

doi: 10.46234/ccdcw2021.044

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Submitted: January 27, 2021; Accepted: January 31, 2021

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