

## Perspectives

## Vaccinate with Confidence and Finish Strong

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China's sustained containment of the coronavirus disease 2019 (COVID-19) epidemic has spared over 99% of the mainland of China's 1.4 billion people from exposure to and infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its variants for an astonishing two and a half years. Although the whole-of-government, whole-of-society containment effort has its own socioeconomic costs, the now-called dynamic COVID-zero strategy purchased a rare commodity — tranquil time with relatively little suffering and death from COVID-19 to develop and deploy tools for escaping the pandemic: diagnostics, vaccines, antivirals, and knowledge (1).

During this two and a half years, China's vaccine industry developed, tested domestically, tested overseas, received regulatory approval, received the World Health Organization (WHO) emergency use listing, and produced over 5 billion doses of COVID-19 vaccines for domestic and international use. China's immunization programs have vaccinated over 1.3 billion people, most with boosted primary series vaccination, protecting more than 90% of the population with the China-produced vaccines.

With an overarching strategy of achieving broad and deep vaccine-induced population immunity strong enough to prevent suffering and death from COVID-19, there is precious little time left to finish the vaccination campaign (2). The last 10% in any vaccination campaign is the most difficult to reach, and in our case, the last 10% is also a critically important group to protect because the last 10% has an enrichment of people with comorbidities, many of whom are elderly and will suffer the most from COVID-19 if infected. A systematic review of the association of common comorbidities with severe or fatal COVID-19 shows that obesity, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, respiratory disease, kidney disease, and malignancy are risk factors, with obesity being the most prevalent and respiratory disease being the most strongly predictive (3).

Because SARS-CoV-2 is not amenable to herd immunity from any of the current generation vaccines

or from natural infection, everyone needs to be individually protected by vaccination (4). With little indirect protection, effective population immunity must be built one person at a time until all are protected — a daunting task for a large-population country.

China-produced COVID-19 vaccines have performance characteristics in common with all of the first-generation COVID-19 vaccines, regardless of technical platform. All approved COVID-19 vaccines are safe and effective; all are most protective against severe/critical/fatal COVID-19; none are highly effective at blocking infection and transmission; all have waning protection after a few months; all require one or more booster doses to maintain protection; booster doses restore protection and people with immunocompromising conditions need additional doses; and all are associated with some loss of protection from Omicron.

Real-world evidence shows that the vaccines produced and widely used in China are up to the job of protection. They have the greatest effectiveness where it is needed the most — prevention of serious, critical, and fatal COVID-19 among people of all ages and regardless of comorbidities. They are among the least reactogenic vaccines in existence, and after over 3.4 billion doses used in the mainland of China, they are associated with no serious safety concern other than the exceedingly rare serious allergic reactions that all vaccines are associated with. A population-based study of inactivated vaccine safety among people 60 years or older in Hong Kong Special Administrative Region (SAR), China found no increased risk of adverse events of special interest, regardless of whether the vaccinee is older or younger than 80 years, and regardless of the presence of comorbidities (5).

The first large-scale, real-world vaccine effectiveness (VE) study of China-produced inactivated vaccine was conducted in Chile and published in mid-2021. Dr. Jara and colleagues showed that among both working-age and elderly adults, primary-series, non-boosted inactivated vaccine was 86% to 88% effective against hospitalization, 89% to 90% effective against critical

care unit admission, and 86% effective against fatal COVID-19 (6).

The most recently published overseas VE study of China-produced inactivated vaccine was in Abu Dhabi, where Dr. Al Kaabi and colleagues demonstrated primary-series, non-boosted inactivated VE against Delta and Omicron COVID-19 was 80% against hospitalization, 86% against critical care unit admission, and 84% against fatal COVID-19, and was slightly more effective in people with comorbidities compared with people without comorbidities. The Abu Dhabi team concluded that the inactivated vaccine “was effective in preventing and reducing COVID-19 related hospitalizations and critical care admissions, as well as mortality,” and that waning protection “confirmed the need for booster doses (7).”

Now, the most relevant evidence on population immunity in China comes from domestic evidence because of China’s nearly unique situation of having only vaccine-induced immunity — essentially no hybrid immunity. During the dynamic COVID-zero period, there have been numerous small-to-moderate COVID-19 importation outbreaks and two large importation outbreaks (Jilin and Shanghai). Each outbreak and every infection probes the adequacy of population immunity to prevent serious/critical/fatal COVID-19. It is the job of the immunization program to gather evidence with these immunity probes for updating vaccination and prevention and control strategies.

The 2021 Ruili Delta-variant outbreak happened early in the vaccination campaign and allowed measurement of VE for two inactivated and the Ad5-vectored vaccine. Careful analysis of 686 virus-exposed close contacts showed that primary-series, non-boosted VE of the three most used vaccines in China provided roughly equivalent and strong protection from serious and critical Delta COVID-19, with VEs of 68% to 77% against pneumonia and 100% against severe COVID-19, with no deaths (8). Analysis of the 2021 Guangdong Delta outbreak found vaccine effectiveness of 78% against pneumonia and 100% VE against severe/critical COVID-19 (9). Similarly, in the Henan Delta-variant outbreak, non-boosted primary-series VE against COVID-19 pneumonia and severe COVID-19 were 62% and 82%, respectively (10).

The Jilin Omicron BA.2 outbreak demonstrated that regardless of age group, primary series vaccination was associated with an impressive 9-fold reduction in severe COVID-19 and a 4-fold reduction in critical COVID-19, and that homologous boosting was

associated with 44-fold and complete reductions in severe and critical COVID-19 (11). The relative impact of a booster dose of inactivated vaccine was further shown in a case-case study in an outbreak in Henan Province in early 2022 with 405 Delta infections and 421 Omicron infections. Compared with primary vaccination 6-months before infection, a homologous booster dose reduced Delta COVID-19 pneumonia by an additional 82%, primary series alone reduced Omicron pneumonia by 66%, and there were too few boosted Omicron pneumonia cases (2 cases) to estimate relative VE (12).

One of the most important and directly relevant assessments of China-produced inactivated COVID-19 vaccine effectiveness in an infection-naïve population is Dr. McMenamin and colleagues’ evaluation of the serious and fatal COVID-19 cases in the 2022 Omicron BA.2 outbreak in Hong Kong SAR, China (13). She and her team found that homologous-boosted inactivated vaccine was 98% effective at preventing severe/fatal COVID-19 — on par with homologous boosted mRNA vaccine. Without boosting, inactivated primary series vaccination was 70% effective, showing that boosting is important for optimal protection. Three-dose inactivated vaccine effectiveness against severe/fatal COVID-19 was very high among the elderly, with three-dose VEs of 97%, 95%, and 97% for people in their 60s, 70s, and 80s or older.

Another study in Hong Kong that spanned the Delta and Omicron periods assessed VE and safety of inactivated COVID-19 vaccine in people with kidney diseases, including individuals on hemodialysis and kidney transplant recipients (14). In this study, Dr. Cheng and colleagues found identical two and three-dose vaccine effectiveness in renal disease patients as did Dr. McMenamin in the general population: two-dose VE of 70% and three-dose VE of 97%. Their safety analysis also found no concerns about the safety of the inactivated vaccine. Similarly, Dr. Wan and colleagues used a case-control study in the Hong Kong outbreak to estimate VE against hospitalization, intensive care admission, and fatal COVID-19 from Omicron BA.2 infection in people with diabetes. These scientists found that the VE of three doses of inactivated vaccine was 86% against hospitalization, 94% against ICU admission, and 96% against all-cause mortality (15).

The recent Shanghai outbreak provided a cogent test the effectiveness of the vaccines being used to build population immunity in the mainland of China. In

this 650,000-person outbreak, there were 588 COVID-19 deaths, and only 5% of these fatal COVID-19 cases were vaccinated. An elegant, matched case-control study by Shanghai CDC and Fudan University scientists, led by Dr. Huang and colleagues, showed that boosted primary-series vaccine effectiveness was 93% against severe COVID-19 and 96% against fatal COVID-19 – results that are nearly identical to those of McMenamin and colleagues in Hong Kong, furthering our confidence in the vaccines being used in China and emphasizing the importance of the booster dose (16).

Population immunity created by the vaccination campaign is paying off by keeping the severity of illness low in the domestic importation outbreaks (17). In difficult-to-control large outbreaks, unvaccinated people with comorbidities and the elderly are at risk of serious or fatal COVID-19. Gaps in population immunity from gaps in vaccination coverage expose people to risk — vaccines only work when given (18).

Sustaining optimized protection for a safe, long-term exit of the pandemic will almost certainly require well-timed second booster doses. The design of second booster dose strategy will be based on emerging evidence of duration of protection afforded by the vaccines.

The pathway forward is clear. Vaccinate with confidence and finish strong! Every person vaccinated and every person boosted receives clinically meaningful direct protection from serious/critical/fatal COVID-19. Medical practitioners need to ensure that their patients are vaccinated, especially their patients with comorbidities — it is safe and effective to do so. Families need to ensure that parents, grandparents, and great-grandparents are vaccinated in addition to their children. Immunization programs need to work to reach everyone not yet vaccinated, not yet boosted and confidently protect them with the vaccines we have. Regulatory authorities and manufacturers should work to remove the contraindication to vaccinating during pregnancy so pregnant women can join the vaccination campaign and be protected from COVID-19. There is no evidence to support a pregnancy contraindication, and over two-thirds of countries recommend vaccinating pregnant women, including with China-produced inactivated vaccines (19–20).

Everyone wants to return to normal life. Vaccination is the key, and time will run out for the vaccination campaign. Although the campaign has been marvelously successful to date, protecting the vast majority of people, the campaign is not completed yet.

China-produced vaccines are up to the task of protection, and although the last 10% will be the most difficult to reach, the results of success will be well worth the effort and are essential for a smooth exit from the pandemic.

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