EDITORIALS

Effectiveness of an Inactivated SARS-CoV-2 Vaccine

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The world needs more vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19), in order to mitigate the tragic health and socioeconomic consequences of the pandemic. Even vaccines with lower effectiveness may have a substantial effect on public health. Six Covid-19 vaccines have obtained Emergency Use Listing by the World Health Organization (WHO). Each vaccine has different attributes, advantages, and disadvantages, and multiple factors must be considered in guiding policy decisions. Point estimates of vaccine efficacy from phase 3 trials, often with relatively wide and overlapping confidence intervals, vary considerably among vaccine products. However, such point estimates cannot be compared directly, because efficacy trials were done in different epidemiologic settings and used different case definitions, clinical end points, and protocols for the ascertainment of such end points.

The Covid-19 vaccine CoronaVac, developed by the Chinese company Sinovac, was one of the first vaccines to be deployed globally. To date, more than 750 million doses have been administered in more than 40 countries. CoronaVac is an aluminum hydroxide–adjuvanted, inactivated whole-virus vaccine. The vaccine can be transported and stored at refrigerator temperatures of 2 to 8°C. Safety data from postauthorization passive surveillance data from China (35.8 million vaccine doses distributed at the time of the WHO evaluation for Emergency Use Listing) and from Brazil, Indonesia, and Chile (approximately 20 million doses) have indicated no unexpected safety signals.[1] Three randomized, placebo-controlled, phase 3 clinical trials, in Brazil, Indonesia, and Turkey, have been conducted. According to interim analyses, the point estimates of efficacy against symptomatic illness have varied — 50.65% in Brazil, 65.30% in Indonesia, and 83.50% in Turkey — with a median observation time of 2 months.[1] Efficacy against hospitalization and death was substantially higher, reaching 100%, but with wide confidence intervals. The number of participants older than 60 years of age in the clinical trials was insufficient to determine efficacy in this age group. Furthermore, the trials were conducted at a time when variants of concern had not yet emerged. Post-introduction vaccine effectiveness studies are therefore needed to address remaining knowledge gaps.

Chile was one of the first countries to implement use of the CoronaVac vaccine in its national program on a large scale. Approved for emergency use in a two-dose schedule on January 20, 2021, the mass campaign started 2 weeks later, with an initial focus on achieving high coverage rates among older persons and health workers according to the WHO Prioritization Roadmap. The researchers in Chile report in this issue of the *Journal* on their prospective national cohort study,[2] which was conducted early in the rollout and included 10.2 million persons 16 years of age or older. The authors estimated hazard ratios, accounting for time-varying vaccination status, participant age, and outcomes (symptomatic illness, hospitalization, intensive care unit [ICU] admission, and death). The adjusted vaccine ef-

fectiveness of full immunization (receipt of two doses, assessed ≥14 days after the second dose, with a 4-week interval between the doses) was 65.9% (95% confidence interval [CI], 65.2 to 66.6) against Covid-19 and was 87.4% (95% CI, 86.7 to 88.2) against hospitalization, 90.3% (95% CI, 89.1 to 91.4) against ICU admission, and 86.3% (95% CI, 84.5 to 87.9) against Covid-19–related death, thereby confirming the phase 3 trial results.

The study in Chile also addressed vaccine effectiveness in older persons, which had not been adequately investigated in the phase 3 trials. The adjusted vaccine effectiveness in the fully immunized group of persons 60 years of age or older was 66.6% (95% CI, 65.4 to 67.8) against Covid-19 and was 85.3% (95% CI, 84.3 to 86.3) against hospitalization, 89.2% (95% CI, 87.6 to 90.6) against ICU admission, and 86.5% (95% CI, 84.6 to 88.1) against Covid-19–related death, findings that underpin the benefit of this vaccine in this priority age group.

The findings from the Chilean national cohort are further corroborated by a smaller population-based study, Project S, which was conducted in the municipality of Serrana, Brazil, and showed similar interim results regarding vaccine effectiveness against symptomatic illness, hospitalization, and death.[3] The data from Chile and Brazil underscore the finding that, despite the effectiveness of the vaccine against symptomatic illness being lower than that observed with the messenger RNA (mRNA) vaccines, the effectiveness of the CoronaVac vaccine against hospitalizations and deaths may still be substantial. These findings are encouraging. Reducing deaths and protecting health care systems are the primary public health goals during the acute phase of the pandemic.

Of note, the vaccine effectiveness as assessed 14 days after the receipt of only one dose of vaccine was considerably lower: 15.5% (95% CI, 14.2 to 16.8) against Covid-19 and 37.4% (95% CI, 34.9 to 39.9) against hospitalization, 44.7% (95% CI, 40.9 to 48.3) against ICU admission, and 45.7% (95% CI, 40.9 to 50.2) against Covid-19–related death. These findings are in contrast to those observed with the mRNA vaccines developed by Pfizer–BioNTech and Moderna, as well as with the Oxford–AstraZeneca vaccine, in which substantial vaccine effectiveness was also documented after the first dose.[4] Much lower levels of neutralizing antibodies after a single dose of the CoronaVac vaccine than after a single dose of the Pfizer–BioNTech mRNA vaccine were also documented; the level of neutralizing antibodies increased after the second dose but remained lower than that observed with the mRNA vaccine.[5]

Chile has achieved one of the highest vaccination coverage rates in the world, close to rates in Bahrain, Israel, Malta, and Mongolia, which are among the countries with the highest vaccine coverage rates.[6] In Israel, the almost-exclusive use of mRNA vaccines has had a dramatic effect on reducing the incidence of Covid-19,[7] and similar results have been seen in Malta. In contrast, Bahrain, Chile, and Mongolia, in which inactivated virus vaccines have mainly been used, have not yet seen the expected substantial effect. In Indonesia, there have been breakthrough infections, including severe disease and deaths, in health care workers who were fully vaccinated with the CoronaVac vaccine.[8,9]

There are various explanations for the lower effect of vaccination that has been observed in Chile. The easing of nonpharmaceutical interventions probably occurred too early in Chile and led to an initial resurgence of cases.[10] Evidence that mRNA vaccines can reduce transmission and provide indirect protection to the unvaccinated is increasing[11,12] but has yet to be documented for the CoronaVac vaccine. Lower vaccine effectiveness against mild infection will lead to breakthrough infections that could sustain transmission, thus requiring a higher vaccine coverage to achieve herd immunity. Furthermore, all studies that have been conducted to date involved a very short follow-up; data on the duration of efficacy of the CoronaVac vaccine are lacking. Immune persistence evaluation of the CoronaVac vaccine has shown that, after 6 months, the prevalence of seropositivity decreased to 17%, which suggests that clinical protection may decrease rapidly, thus indicating the potential need for a third dose.[1]

Thus, country-level experience with inactivated virus vaccines may be explained in part by a combination of poor effectiveness against mild or asymptomatic infection and waning effectiveness. Countries using these vaccines are now looking for options. Given the higher neutralizing antibody titers that have been achieved by

means of heterologous priming for other SARS-CoV-2 vaccines,[13] mix-and-match studies are urgently needed for the CoronaVac vaccine and the other inactivated virus vaccines.

The national cohort study from Chile should serve as a useful model for other countries to follow, but longer follow-up time is needed to monitor vaccine effectiveness over time, against variants, and in various subpopulations and settings. The WHO has published guidance on how best to conduct and evaluate post-introduction vaccine effectiveness studies.[14] The global health community needs to work together to resolve remaining knowledge gaps regarding Covid-19 vaccine effectiveness, with timely sharing of evolving data in order to support prompt policy decisions.

Dr. Wilder-Smith serves as a consultant to the World Health Organization (WHO), and Dr. Mulholland as a member of the WHO Strategic Advisory Group of Experts on Immunization. The views presented here are those of the authors and do not reflect the position of the WHO.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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Immune Thrombocytopenia Treatment

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Idiopathic thrombocytopenia (ITP) has a long history. In 1025, Avicenna described in the *Canon of Medicine* a patient with characteristics of ITP, which became known as "idiopathic thrombocytopenic purpura." Splenectomy was the first effective treatment, beginning in 1916, achieving a complete response without recurrence in most patients.[1] Glucocorticoids were introduced as therapy for the disease in 1949, and the term "idiopathic" became obsolete in 1950 when William Harrington, then a hematology fellow at Washington University in St. Louis, transfused blood into himself from a woman with the disease whose platelet count had not increased after splenectomy. Within hours, Harrington's platelet count went from 250,000 to 3000 with