Adapted vaccine strategy: facing the persistent challenges of COVID-19

On May 5, 2023, WHO announced that COVID-19 would be an ongoing health issue and was no longer meeting the criteria for a public health emergency of international concern.[1] Although vaccinations and natural infections have provided hybrid population immunity against SARS-CoV-2, there are still waves of SARS-CoV-2 infections due to the waning nature of the immunity and the emergence of omicron subvariants with strong immune evasion. Additionally, immune imprinting caused by exposure to the original SARS-CoV-2 spike and pre-omicron variants might result in inefficient production of omicron-specific antibodies.[2] In the context of the transition of COVID-19 from an emerging concern to an enduring health challenge, it is especially important to establish an optimal strategy to tackle its long-term threats.

In *The Lancet Infectious Diseases*, Ivan T Lee and colleagues[3] present the interim results of a phase 2 and 3 randomised, observer-blind, active-controlled clinical trial, which provide immunogenicity and safety data comparing the omicron BA.1 monovalent vaccine (50 µg omicron BA.1 spike mRNA; trial part 1) and omicron BA.1 bivalent vaccine (25 µg ancestral SARS-CoV-2 spike plus 25 µg omicron-BA.1 spike mRNAs; trial part 2) with the original mRNA-1273 vaccine (50 µg ancestral SARS-CoV-2 spike mRNA) as the second booster dose (fourth overall dose). At day 29 following vaccination, compared with the mRNA-1273 vaccine, the omicron BA.1 monovalent and bivalent vaccines both induced superior neutralising antibody responses against omicron BA.1 (geometric mean concentration ratios 1·68 [99% CI 1·45–1·95] for monovalent *vs* original and 1·53 [1·41–1·67] for bivalent *vs* original) and non-inferior neutralising antibody responses against ancestral SARS-CoV-2 (Asp614Gly) (geometric mean concentration ratios 0·82 [95% CI 0·74–0·91] for monovalent *vs* original and 1·05 [99% CI 0·96–1·15] for bivalent *vs* original). These findings were observed regardless of age group. Additionally, both the omicron BA.1 monovalent (27·0% [95% CI 19·4–34·3]) and bivalent (13·9% [10·2–17·7]) vaccines showed a higher seroresponse rate against the BA.1 strain. In spike binding antibody analyses for five strains, the omicron BA.1 bivalent vaccine elicited higher binding antibodies for omicron BA.1 and several other non-omicron strains, whereas the omicron BA.1 monovalent vaccine induced higher binding antibodies for omicron BA.1 only. The trial did not identify any new safety signal in either the omicron BA.1-containing monovalent or bivalent vaccine.

The highly contagious omicron variant and its subvariants have distinct receptor-binding domain mutations that improve binding affinity and immune evasion ability.[4] Adapted vaccines containing omicron antigens have the potential to mitigate the immune gaps and trigger antibodies that are more omicron-specific, thus providing more profound immune protection. In the trial by Lee and colleagues,[3] both the bivalent and monovalent omicron BA.1-containing vaccines elicit more omicron BA.1 antibodies than the original mRNA-1273 vaccine, and the BA.1 bivalent vaccine elicits a wider range of antibodies against other strains than did omicron BA.1 monovalent vaccines. It is hard to draw solid inference regarding the superiority of the bivalent or the monovalent omicron BA.1 vaccine because the comparison between them is not head-to-head, and the sample size of part 1 (724) is roughly a quarter of the size of that in part 2 (2824). As for clinical effectiveness, both the omicron BA.1 monovalent and bivalent vaccine groups had numerically lower COVID-19 incidence rates. The exploratory analysis of relative vaccine effectiveness did not identify a significant difference in overall COVID-19 cases between the omicron-containing vaccine groups and the original vaccine group (relative vaccine effectiveness 13·5% [95% CI −17·8 to 36·5] in molovalent *vs* original and 11·4% [−10·2 to 28·7] in bivalent *vs* original). Due to the low event rate, the vaccine effectiveness estimates were imprecise and the confidence intervals were wide. Bivalent vaccines have been used in booster schemes, as such several large observational studies have provided vaccine effectiveness data relative to not receiving bivalent vaccines. A population-based observational study in Nordic countries showed that administering the omicron BA.1 bivalent vaccine as a fourth dose decreased hospitalisations by 74·0% (95% CI 68·6–79·4) and deaths

Flickr - Jernej Furman

Lancet Infect Dis 2023

Published Online
June 19, 2023
https://doi.org/10.1016/S1473-3099(23)00370-5

See Online/Articles
https://doi.org/10.1016/S1473-3099(23)00295-5

by 80·1% (72·0–88·2) compared with only administering three doses of vaccines.[5] Omicron BA.5-containing bivalent vaccines also showed clinical benefits in preventing symptomatic infection and hospitalisation.[6,7]

The rapid evolution of omicron variants poses great challenges to vaccine development. For example, while clinical trials for omicron BA.1-containing vaccines were underway, BA.1 was rapidly replaced by BA.2 after several months, which was subsequently replaced by BA.4/BA.5 and other more immune-evasive subvariants. In light of the public health urgency of using omicron-containing vaccines, the US Food and Drug Administration issued emergency use authorisations for Moderna and Pfizer–BioNTech BA.5 bivalent mRNA vaccines based on the effectiveness and safety data of the original mRNA vaccines, immunogenicity and safety data of BA.1 bivalent vaccines, and non-clinical data of BA.5 bivalent vaccines.[8] In the face of the persistent challenge of rapidly evolving SARS-CoV-2 variants, COVID-19 vaccines need to be regularly adapted in the future. Given the convergent evolutionary trend of omicron variants, the antigenic epitopes of future strains could potentially be predictable.[2] Although there is consensus that emerging omicron antigens need to be integrated into adapted vaccines, the role of the ancestral strain antigen is controversial. In a trial in which adults older than 55 years were randomly assigned to receive either 30 μg or 60 μg of the BNT162b2 vaccine, omicron BA.1 monovalent vaccine, or omicron BA.1 bivalent vaccine (six groups in total), participants who received the BA.1 monovalent vaccine showed a greater increase in neutralising antibodies against omicron BA.1 than recipients of the BA.1 bivalent vaccine.[9] Moreover, several other studies have shown that omicron-containing bivalent vaccines might not induce substantially higher neutralising or binding antibodies against emerging variants, such as BA.5, XBB, and BQ.1.1, than the original vaccines, and repeated exposure to ancestral SARS-CoV-2 antigens might exacerbate the immune imprinting.[10–12] Monovalent ancestral vaccines are no longer used for booster shots in places where omicron bivalent vaccines have been introduced. Therefore, there is a deficiency of large-scale population-based effectiveness data on head-to-head comparison of omicron-containing vaccines and ancestral monovalent vaccines, which warrants research. In addition to the composition of the vaccines, the time required for vaccine development and the speed of clinical availability are also crucial when facing the rapidly mutating omicron variants. The method of predicting circulating strains and updating components of vaccines annually without repeating clinical trials has been successful in influenza vaccines. Regulating agencies need to formulate an approval framework that harmonises safety, effectiveness, and speed.

We declare no competing interests.

*Lianhan Shang, *Bin Cao*
caobin_ben@163.com

Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, National Center for Respiratory Medicine, China–Japan Friendship Hospital, Beijing, China (LS, BC); Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, China (LS, BC); Tsinghua University–Peking University Joint Center for Life Sciences, Beijing, China (BC)

1 WHO. Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic. 2023. https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic (accessed May 8, 2023).

2 Cao Y, Jian F, Wang J, et al. Imprinted SARS-CoV-2 humoral immunity induces convergent omicron RBD evolution. *Nature* 2023; **614:** 521–29.

3 Lee IT, Cosgrove CA, Moore P, et al. Omicron BA.1-containing mRNA-1273 boosters compared with the original COVID-19 vaccine in the UK: a randomised, observer-blind, active-controlled trial. *Lancet Infect Dis* 2023; published online June 19. https://doi.org/10.1016/S1473-3099(23)00295-5.

4 Cui Z, Liu P, Wang N, et al. Structural and functional characterizations of infectivity and immune evasion of SARS-CoV-2 omicron. *Cell* 2022; **185:** 860–71.

5 Niklas Worm A, Emilia Myrup T, Ulrike B, et al. Comparative effectiveness of the bivalent BA.4–5 and BA.1 mRNA-booster vaccines in the Nordic countries. *medRxiv* 2023; published Jan 19. https://doi.org/10.1101/2023.01.19.23284764 (preprint).

6 Link-Gelles R, Ciesla AA, Roper LE, et al. Early estimates of bivalent mRNA booster dose vaccine effectiveness in preventing symptomatic SARS-CoV-2 infection attributable to omicron BA.5- and XBB/XBB.1.5-related sublineages among immunocompetent adults—increasing community access to testing program, United States, December 2022–January 2023. *MMWR Morb Mortal Wkly Rep* 2023; **72:** 119–24.

7 Surie D, DeCuir J, Zhu Y, et al. Early estimates of bivalent mRNA vaccine effectiveness in preventing COVID-19-associated hospitalization among immunocompetent adults aged ≥65 years—IVY Network, 18 states, September 8–November 30, 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 1625–30.

8 US Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes Moderna, Pfizer–BioNTech bivalent COVID-19 vaccines for use as a booster dose. 2022. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-moderna-pfizer-biontech-bivalent-covid-19-vaccines-use (accessed May 8, 2023).

9 Winokur P, Gayed J, Fitz-Patrick D, et al. Bivalent omicron BA.1-adapted BNT162b2 booster in adults older than 55 years. *N Engl J Med* 2023; **388:** 214–27.

10 Ayijiang Y, Weiliang S, Jing W, et al. Repeated omicron infection alleviates SARS-CoV-2 immune imprinting. *bioRxiv* 2023; published May 1. https://doi.org/10.1101/2023.05.01.538516 (preprint).

11 Qian W, Yicheng G, Anthony RT, et al. Deep immunological imprinting due to the ancestral spike in the current bivalent COVID-19 vaccine. *bioRxiv* 2023; published May 3. https://doi.org/10.1101/2023.05.03.539268 (preprint).

12 Wang Q, Bowen A, Tam AR, et al. SARS-CoV-2 neutralising antibodies after bivalent versus monovalent booster. *Lancet Infect Dis* 2023; **23:** 527–28.