Editorial

DOI: 10.5582/bst.2022.01062

More effective vaccines and oral antivirals: Keys for the battle against Omicron

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SUMMARY With the rapid roll out of vaccination programs and extraordinary non-pharmaceutical interventions (NPIs) by the government, China has maintained a "dynamic zero-COVID-19" policy over the last two years. However, the global pandemic and immune evasion of Omicron variant poses a huge challenge to China. Currently, about 87.69% of the Chinese population has been vaccinated, most with inactivated vaccines. Although seroepidemiological data on the vaccinated are lacking, published data suggested that even a homologous booster of an inactivated vaccine displayed very limited neutralizing activity against the Omicron variant and that neutralizing activity was significantly lower than that of a heterologous booster or mRNA vaccine alone. A great concern is whether the neutralizing antibodies induced by inactivated vaccines can provide sufficient protection against the Omicron variant since local transmission of the Omicron variant is now occurring in China. The era of extraordinary NPIs by governments and countries to control the transmission of SARS-CoV-2 is going to change. Omicron's immune evasion of neutralizing antibodies induced by current vaccines and the majority of existing therapeutic SARS-CoV-2 monoclonal antibodies (mAbs) suggest an urgent need for more effective vaccines and highly effective oral antivirals, which will be the keys for the battle against Omicron in the future.

Keywords Omicron, vaccine, oral antivirals

Due to its strong tropism in the upper respiratory tract and its considerable evasion of antibody neutralization, the Omicron variant has spread rapidly and efficiently around the world (*1,2*). Currently, more than 2 million newly confirmed COVID-19 cases are reported to the WHO around the world every day (*https://covid19.who.int/*), and over 90% of the SAS-CoV-2 sequences recently uploaded to the GISAID database (*https://www.gisaid.org/*) were the Omicron variant. Despite the obvious increase in transmissibility, the disease burden of the Omicron variant has been found to be lower than that of the Delta variant. Real-world studies conducted in South Africa revealed a decrease in severity and mortality for the Omicron variant in comparison to other variants (*3-5*). For children under the age of 5 with an initial SARS-CoV-2 infection, the risk of a visit to the emergency department (ED), hospitalization, intensive care unit (ICU) admission, or placement on mechanical ventilation within 3 days of infection is significantly lower in the Omicron cohort than in the matching Delta cohort (*6*). Based on the high transmissibility and low pathogenicity of the Omicron variant, several countries have rescinded policies to control the spread of Omicron variant and instead placed their hopes on infection-acquired immunity, though this obviously ignores the increase in fatalities among the huge infected population, the long-term health consequences of COVID-19, and the accompanying social issues related to the commitment of medical resources (*7,8*). In addition, naive infection with the Omicron variant induces limited cross-variant immunity (*9*), and an mRNA-Omicron vaccine boost may not provide greater immunity or protection compared to a boost with the current mRNA-1273 vaccine (*10*).

With the rapid roll out of vaccination programs and extraordinary non-pharmaceutical interventions (NPIs) by the government, China has maintained a "dynamic zero-COVID-19" policy over the last two years (*11*). However, the "dynamic zero-COVID-19" policy is now facing huge challenges due to the global pandemic caused by the Omicron variant. Currently, about 87.69% of the Chinese population has been vaccinated, mostly with inactivated vaccines (*https://ourworldindata.org/coronavirus*). Although seroepidemiological data on the vaccinated are lacking, published data suggested that even a homologous booster of an inactivated vaccine

displayed very limited neutralizing activity against the Omicron variant (*12-14*) and that neutralizing activity was significantly lower than that of a heterologous booster or mRNA vaccine alone (*15-20*). Moreover, breakthrough infections with the Omicron variant have also been found in individuals who received a homologous booster with an mRNA vaccine (*21*). A great concern is whether the neutralizing antibodies induced by inactivated vaccines can provide sufficient protection against the Omicron variant since local transmission of the Omicron variant is now occurring in China. Several oral antivirals have been authorized for emergency use in the treatment of mild-to-moderate COVID-19 by the US Food and Drug Administration (FDA), including Molnupiravir and Paxlovid. In clinical trials, these oral antivirals significantly reduced hospital admissions and deaths among people with COVID-19 who are at high risk of severe illness in comparison to a placebo (*22,23*). Until recently, there were no such oral antivirals in China, although several remdesivir derivatives that were designed and modified by Chinese researchers were found to be safe and highly effective in preclinical studies (*24,25*).

Currently, there are three theories on the origins of the Omicron variant (*26*). Although determining which of the three is true is difficult, more variants are sure to appear with unpredictable mutations. The era of extraordinary NPIs by governments and countries to control the transmission of SARS-CoV-2 is going to change. Omicron's immune evasion of neutralizing antibodies induced by current vaccines and the majority of existing therapeutic SARS-CoV-2 monoclonal antibodies (mAbs) suggest an urgent need for more effective vaccines and highly effective oral antivirals, which will be the keys for the battle against Omicron in the future.

Acknowledgements

The author wishes to thank Dr. Yang Yang and Dr. Yang Hangzhou for assisting with this manuscript.

Funding: None.

Conflict of Interest: The author has no conflicts of interest to disclose.

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Received February 10, 2022; Revised February 15, 2022; Accepted February 16, 2022.

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Released online in J-STAGE as advance publication February 17, 2022.