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Omicron variant of SARS-CoV-2 imposes a new challenge for the global public health

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ABSTRACT

Since its first discovery, the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evoked another wave of infection and caused global concern and panic. Moreover, although the data are still limited, Omicron showed highly concerning characteristics, including higher transmissibility, extensive immune escape and potentially altered host range. We interpreted these characteristics based on currently available data and outlined some urgent questions, calling for a more comprehensive investigation.

1. Omicron spread around the world

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) keeps evolving into new variants, consequently, the pandemic control turns out to be an extensive "arms race" between SARS-CoV-2 and humankind. Variants with evidence of heightened transmissibility, increased pathogenicity, immune evasion and a higher risk of eluding testing are classified as variants of concern (VOCs). By far, five VOCs have been announced by the World Health Organization (WHO), namely Alpha, Beta, Gamma, Delta and the recently reported Omicron. Omicron variant (B.1.1.529) was first reported to WHO on 24 November 2021, and has spread to 149 countries across all six WHO regions as of 6 January 2022 [1]. The emergence of Omicron variant has evoked global panic and concern, and multiple countries closed their border. Regardless of the quick response, the emergence of Omicron has evoked another wave of infection. Studies of household and contact of the UK demonstrated a higher risk of transmission in contacts from an Omicron index case than Delta index cases, with the adjusted odds ratio of 2.9 [1].

Alarmingly, the Omicron variant carries an unusual number of mutations, particularly on the spike (S) protein including the receptor-binding domain (RBD), which might lead to altered transmissibility and immune escapes [2]. Population-level evidence showed an association between the emergence of Omicron and a higher risk of reinfection, indicating its ability to evade immunity from prior infection [1]. Consistently, experiments of pseudovirus infection showed that serum samples from convalescent patients had decreased neutralization ability against pseudotyped Omicron [3]. Comprehensive studies in the laboratory and on a population level are urgently needed to assess the transmissibility, infectivity and immune escape of the Omicron variant to advise reformulation of pandemic control policies.

2. Omicron escapes many commercially available neutralizing antibodies

Some of the substitutions observed on Omicron RBD are associated with immune escape. The Omicron variant has shown extensive escape from commercially available neutralizing antibodies (Nabs) [4] and sera from convalescent patients [3], consistent with a higher risk of reinfection indicating immune escape [1]. In particular, substitutions on site 484 and 493 strongly affect binding by polyclonal antibodies in human convalescent plasma [5]. Other substitutions affecting antibody neutralization include K417N and G447N.

Multiple substitutions have been observed on E484, among which changes to K, Q and P reduced neutralization titers by more than an order of magnitude. Particularly, E484K was also observed in Beta and Gamma variants and found to emerge as an escape mutation from mAb C121 and C144 [5]. Additionally, E484K is shown to reduce the neutralizing ability of clinically available mAb cocktail REGN10989/REGN10934. Three more substitutions, namely E484A (found in Omi-

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cron), E484D and E484G also confer virus resistance to convalescent plasma. Q493 of prototype SARS-CoV-2 is critical for binding to Class 2 and 3 antibodies [5]. Notably, Q493R was reported to emerge during bamlanivimab/etesevimab cocktail treatment, suggesting its essential role in immune evasion [6].

According to previous studies, S477N ranked prominently among MAb escape mutations [7] but was not found to be crucial in deep mutational scanning (DMS) with convalescent plasma. K417N tends to affect the binding of Class 1 antibodies and is less important for polyclonal antibodies targeting RBD, which mainly relate to Class 2 antibodies [7]. Moreover, a recent study demonstrated that K417N mutation led to reduced cellular immune responses [8]. However, structural analysis showed that K417N might moderately decrease binding affinity of human ACE2 [2], indicating an evolutionary trade-off between infectivity and immune escape.

3. The protective effects of the approved vaccines are significantly reduced

Although a saturated strategy has been applied to vaccine development and implementation, breakthrough infections have been reported worldwide. Omicron strain has further worsened the situation. A large proportion of Omicron infectants in UK have received two vaccination doses, indicating compromised protection efficacy by currently approved vaccines. Laboratory pseudovirus infection also showed extensive escape from neutralization by plasma from mRNA, inactivated or protein subunit vaccinees [3,9].

Booster doses have been indicated to compensate for the immune evasion. Pfizer and BioNTech claimed that booster dose induces virus neutralization comparable with the protection provided by two doses against the prototype virus. Additionally, Anhui Zhifei Longcom announced that after booster dose, the recombinant vaccine ZF2001 demonstrated a moderate 3-fold decrease in neutralizing titer against Omicron variant compared with the prototype SARS-CoV-2 [3]. At the time of the publication of this editorial, China and a number of developed countries have started to promote the implementation of booster dose, which might help containing Omicron spread. On the other hand, novel vaccines targeting the Omicron strain need to be developed. Pfizer and BioNTech aim to put forward a vaccine specifically targeting the Omicron by March 2022, while Moderna planned to create Omicron variant vaccine by early 2022.

4. The interspecies transmission of Omicron needs to be evaluated

Humans are not the only victim of SARS-CoV-2. Spillover events of SARS-CoV-2 from human to several mammal species have been confirmed based on epidemiological investigation and serological evidences. These species include companion animals (cats, dogs and ferrets), animals in zoos (lions, tigers, gorillas and otters) and minks in farms [10]. Among them, minks are of particular interest, as there is evidence of animal to human transmission. Animals in the wild could also have been exposed to SARS-CoV-2. For example, serosurveillance of wild white-tailed deers in the USA showed that antibodies to SARS-CoV-2 were detected in 40% of samples collected during 2021. Besides, snow leopards and pumas are infected with SARS-CoV-2 in nature. Furthermore, several wildlife species have been demonstrated to be susceptible to SARS-CoV-2 via experimental infection experiments, such as Egyptian fruit bats, marmosets, macaques, bank voles, and North American deer mice [10].

Mutations at hotspots of spike protein can largely determine the host range and lead to cross-species transmission [11], while host-adapting mutations may cause new effects. Structural and functional studies revealed several critical binding sites on SARS-CoV-2 RBD, including residues 493, 498 and 501, at which mutations are closely associated with the transmission to mice [10]. SARS-CoV-2 mutants with N501Y mutation could break the interspecies barrier and infect mice. Subsequently, mouse-adapted strains emerged, with Q498H, Q493K or Q493H mutations, which increased the binding affinity to hACE2 [2]. Besides, Q493Y and Q498Y influenced the host range [12]. The RBD of Omicron strain carries mutations on all the three sites, which causes concerns for altered host range. Additionally, Y453F, F486L or N501T mutations were somehow introduced to the S protein of mink-adapted strains. Y453F and N501T also has been demonstrated to enhance the interaction with hACE2.

It remains to be proved whether the rarely reported mutations of Omicron were accumulated in a chronically infected immunocompromised individual or a non-human host and spilled back into people. No matter how they appeared, the risk of cross-species transmission and expansion of infectious tropism should be further researched. Although the potential host range of SARS-CoV-2 had been preliminarily revealed [10], the susceptibility of most wild terrestrial animals has not been deeply investigated yet. The widely distributing rodents and bats, for example, experience different evolutionary pressures due to their unique niches and habits, which might result in unpredictable mutations in viruses harboring in these animals. Moreover, their ability to migrate distantly may assist the spreading of SARS-COV-2 to human habitats or depopulated zones. The molecular mechanism of potential host adaptation of SARS-CoV-2 and its close relative has been unveiled and residues on site 41 and 42 of ACE2 were identified as important determinants for RBD recognition [13]. In addition, aquatic animals, especially marine mammals, should also be closely monitored. Due to frequent maritime production activities, SARS-CoV-2 could transmit to susceptible marine mammals and spread in the marine ecosystem, which may lead to unexpected variants and threats. The susceptibility studies need to be conducted systematically now that rodents, bats and whales have been proved to be the host of specific coronaviruses, for example, mouse hepatitis virus (MHV), SARS and SW1 [11,14,15]

Therefore, it is urgent to evaluate the interspecies transmission risk of this strain. The question of whether Omicron will break interspecies barriers and expand the infectious tropism range needs an urgent answer by carrying out large-scale screening of wildlife, in order to formulate strategies for prevention and control [10]. Only then can we rationally reduce the possibility of cross-species transmission and spillback events as much as possible.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Zepeng Xu: Investigation, Writing – Original Draft. **Kefang Liu:** Conceptualization, Writing – Review & Editing. **George F. Gao:** Supervision, Writing – Review & Editing.

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