Towards SARS-CoV-2 serotypes?

Etienne Simon-Loriere[1] ✉ *and Olivier Schwartz*[2,3] ✉

The magnitude of immune evasion of Omicron raises the question whether it should be considered as a distinct SARS-CoV-2 serotype. Here, we discuss lines of evidence in support or against the concept of SARS-CoV-2 serotypes, and the implications of this classification.

A serotype is defined as a variation within a microbial species, distinguished by the humoral immune response. The serotype classification of bacteria or viruses is based on their surface antigens and was established before the availability of other techniques, such as genome sequencing or mass spectrometry. Antibodies generated to one serotype do not usually efficiently protect against another serotype. Serotypes have been described in many viral species and generally correspond to genotypes. A classification by serotype is not unprecedented in the family *Coronaviridae*, for example, feline coronavirus (FCoV) has two serotypes.

Omicron's extensive set of mutations is associated with substantial functional and structural differences (fitness and tropism) compared with previous variants[1]. The Omicron spike trimer has a more compact organization that improves stability and enhances attachment but reduces fusion[2,3]. These differences likely contribute to the 50–90% reduction in risk of hospitalization and mortality of Omicron relative to Delta and suggest that continued SARS-CoV-2 evolution may produce variants with different biological properties.

Phylogenetic analysis

A phylogenetic analysis of SARS-CoV-2 evolution in humans distinguishes two types of variant. Most viral evolution represents the steady accumulation of substitutions in the main circulating lineages over time. In parallel, variants with a cluster of changes have emerged, akin to an evolutionary jump. Five such unexpected variants were termed variants of concern (VOCs) because of their extensive genomic changes and spread (Alpha, Beta, Gamma, Delta and Omicron). Omicron is the most striking and recent example of a divergent (and diverse) lineage that quickly spread after its detection. Non-mutually exclusive hypotheses have been proposed for VOC emergence, including circulation in regions with limited genomic surveillance, long-term evolution in immunocompromised individuals and replication in an animal reservoir.

The initial Omicron variant (BA.1), first identified in Botswana and South Africa in November 2021, has 54 mutations and 7 indels compared with the ancestral sequence, with more than half of those in spike. The lineage does not derive from recently circulating variants, and comprises sublineages (BA.1, BA.2 and BA.3). While BA.2 and BA.3 share many of the signature changes of BA.1, they carry unique mutations[4], and their evolution might have included recombination.

Among the 34 amino acid changes in the BA.1 spike, 15 are in the receptor-binding domain (RBD), representing ~7% of changes. BA.2 and BA.3 share 14 of the 15 RBD changes of BA.1. Previous VOCs had only 8–12 changes in spike, 1–3 of which are in the RBD. This produces spike phylogenies compared with those based on complete genomes, with a similar topology but stretched Omicron branch (FIG. 1; Supplementary Fig. 1). Phylogenies using amino acid sequences for spike and the RBD also show a distinction of Omicron sublineages (Supplementary Fig. 1). Combined with the biological differences, Omicron could be considered a distinct SARS-CoV-2 strain. We thus propose to include the ancestral virus and main variants (Alpha, Beta, Gamma and Delta) in a serotype 1, and Omicron BA.1, BA.2 and BA.3 as a distinct serotype 2 (FIG. 1).

Limited antibody cross-reactivity

Classifying Omicron lineages in a novel serotype implies that the antibodies generated against the previous variants do not efficiently cross-react against these lineages, and vice versa. Is this the case? Omicron displays considerable escape to neutralization by antibodies generated by vaccination or previous infection. A third-dose booster, vaccination of previously infected individuals or SARS-CoV-2 breakthrough infection elicits potent and broad neutralizing antibody responses. Therefore, the evolution and recall of the memory B cell population enable the generation of affinity-matured improved versions of the antibodies.

Less is known about the reciprocal situation; the neutralization breadth of antibodies generated to Omicron has only started to be characterized. In a study of few individuals, neutralization of Delta was 2.5-fold lower than Omicron[5]. Similarly, in mice, an Omicron RBD-based mRNA vaccine induced potent neutralizing antibodies to Omicron but not against other variants[6]. Infections with the ancestral or Alpha variant induced the broadest immunity[7], while other VOCs elicited more

[1]*Institut Pasteur, Université de Paris, G5 Evolutionary Genomics of RNA viruses, Paris, France.*

[2]*Institut Pasteur, Université de Paris, CNRS UMR3569, Virus and Immunity Unit, Paris, France.*

[3]*Vaccine Research Institute, Créteil, France.*

✉*e-mail: etienne.simon-loriere@pasteur.fr; olivier.schwartz@pasteur.fr*

https://doi.org/10.1038/s41579-022-00708-x

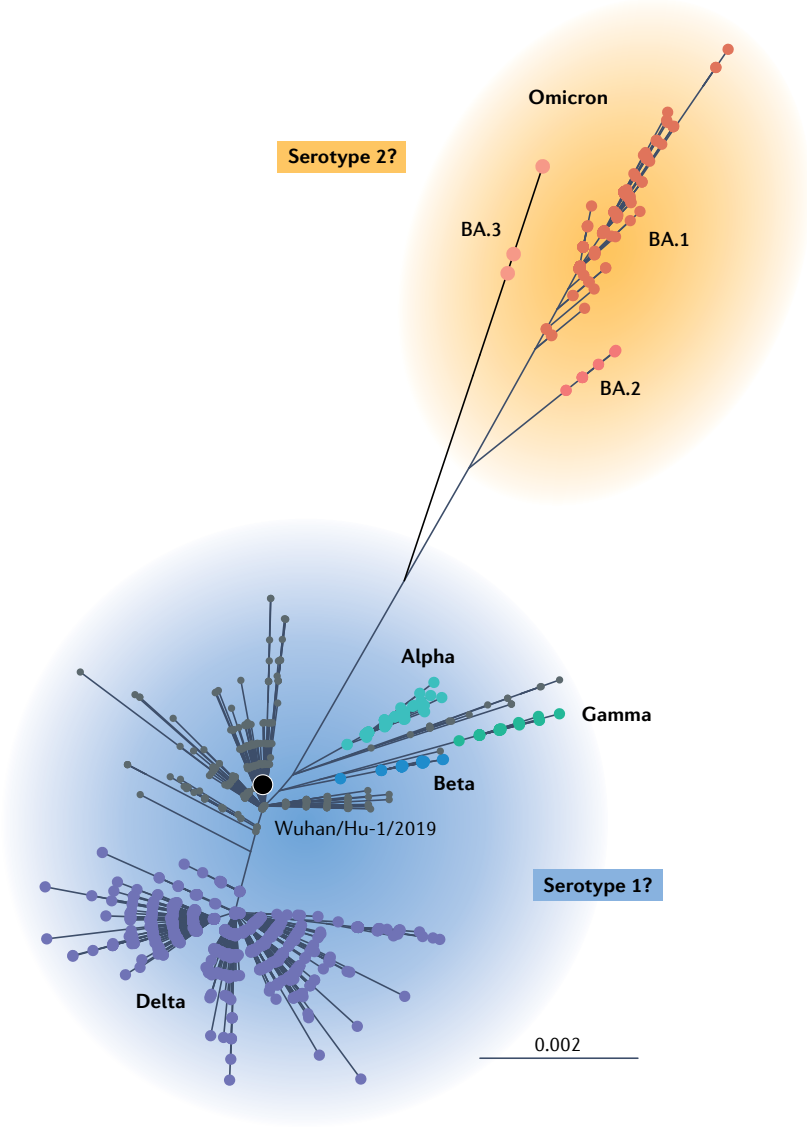

Fig. 1 | **SARS-CoV-2 global evolution and Omicron divergence.** Maximum likelihood phylogenies inferred from spike nucleotide sequences; scale corresponding to number of substitutions per site.

lineage-specific responses, with some cross-reactivity. Antigenic cartography analyses indicated that all VOCs except Omicron belong to one large antigenic cluster, whereas Omicron forms a new cluster, escaping vaccine or convalescent sera[7,8].

Omicron is thus particularly unsensitive to antibodies elicited against prior variants. Future work is warranted to confirm whether Omicron-elicited antibodies are also poorly cross-reactive against preceding variants and to determine whether all Omicron sublineages may be included in the same serotype. Recent results indeed indicate that Omicron sublineages are antigenically equidistant from the ancestral SARS-CoV-2 (REF.[9]).

Boundaries of each serotype may be difficult to establish, owing to the generally high rate of change, combined with recurrent or convergent changes in various lineages. Within each serotype, different antigenic clusters may be present, indicating a continuum of immune escape and immunodominance patterns[8], and boundaries will likely evolve when new variants appear. In parallel, repeated exposure to the virus or vaccinal antigens will increase the breadth and potency of the humoral response, limiting serotype specificity.

Implications

Classifying SARS-CoV-2 into serotypes may help to better understand differences or solve issues observed in the diagnosis, treatment and vaccination of COVID-19. Some rapid antigenic tests are less sensitive against Omicron[10], probably because of the choice of the antibodies used for detection. Spike-based serology tests use antigens derived from the ancestral sequence and may also be less accurate for Omicron-elicited antibodies. PCR tests need to be continuously adapted to cover and possibly identify variants or serotypes, as a fast complement to genomic surveillance that can be leveraged for patient care. Treatments with monoclonal antibodies have been strongly affected by Omicron, highlighting the need for molecules with broad anti-coronavirus activity. Vaccine manufacturers are testing updated vaccines to enhance the breadth of the elicited antibodies, although this strategy remains under debate.

Omicron displays pathological, genetic, structural and antigenic features that clearly distinguish it from prior SARS-CoV-2 variants. Grouping the ancestral virus and variants as members of the original serotype 1 while considering Omicron BA.1, and probably BA.2 and BA.3, as a distinct serotype 2 should facilitate surveying the evolution of the SARS-CoV-2 pandemic and tailoring of diagnostic, treatment and prevention tools.

1. Peacock, T. P. et al. The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry. Preprint at *bioRxiv* https://doi.org/10.1101/2021.12.31.474653 (2022).
2. Cui, Z. et al. Structural and functional characterizations of infectivity and immune evasion of SARS-CoV-2 Omicron. *Cell* https://doi.org/10.1016/j.cell.2022.01.019 (2022).
3. Planas, D. et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature* https://doi.org/10.1038/d41586-021-03827-2 (2021).
4. Viana, R. et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. *Nature* https://doi.org/10.1038/s41586-022-04411-y (2022).
5. Khan, K. et al. Omicron infection of vaccinated individuals enhances neutralizing immunity against the Delta variant. Preprint at *medRxiv* https://doi.org/10.1101/2021.12.27.21268439 (2022).
6. Lee, I.-J. et al. Omicron-specific mRNA vaccine induced potent neutralizing antibody against Omicron but not other SARS-CoV-2 variants. Preprint at *bioRxiv* https://doi.org/10.1101/2022.01.31.478406 (2022).
7. van der Straten, K. et al. Mapping the antigenic diversification of SARS-CoV-2. Preprint at *medRxiv* https://doi.org/10.1101/2022.01.03.21268582 (2022).
8. Wilks, S. H. et al. Mapping SARS-CoV-2 antigenic relationships and serological responses. Preprint at *bioRxiv* https://doi.org/10.1101/2022.01.28.477987 (2022).
9. Iketani, S. et al. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. Preprint at *bioRxiv* https://doi.org/10.1101/2022.02.07.479306 (2022).
10. Bekliz, M. et al. Sensitivity of SARS-CoV-2 antigen-detecting rapid tests for Omicron variant. Preprint at *medRxiv* https://doi.org/10.1101/2021.12.18.21268018 (2022).

Acknowledgements
The authors thank D. Planas, T. Bruel, H. Mouquet and A. Fontanet for critical reading and contributing and originating laboratories for sequences.

Competing interests
The authors declare no competing interests.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1038/s41579-022-00708-x.