

COMMENTARY

Glancing back at SARS-CoV-2: Serological classification

Xin Sun^{1,2,3} and Jun Liu^{2,3*}¹Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, China²National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases (NITFID), National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China³NHC Key Laboratory of Biosafety, Research Unit of Adaptive Evolution and Control of Emerging Viruses, Chinese Academy of Medical Sciences, National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China

Abstract

Coronavirus disease 2019 (COVID-19) has exerted a profound influence on the global community over the past few years. As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to mutate, the ongoing COVID-19 pandemic presents significant challenges to public health. The serotype is defined as a distinct variant within a microbial species, characterized by specific immune reactions. It has previously been used to study various pathogens, such as human papillomavirus and dengue virus. SARS-CoV-2 serotype classification has been proposed by different groups recently. At present, the main prevalent variants of the SARS-CoV-2 have been classified into six distinct serotypes. SARS-CoV-2 serotype classification has been applied in areas such as surveillance, early warning, and vaccination, etc. Consequently, we reviewed previous studies and propose further perspectives for future applications of SARS-CoV-2 serotypes classification.

Keywords: Severe acute respiratory syndrome coronavirus 2; Serotype; Classification***Corresponding author:**Jun Liu
(liujun@ivdc.chinacdc.cn)**Citation:** Sun X, Liu J. Glancing back at SARS-CoV-2: Serological classification. *Microbes & Immunity*. 2026;3(2):7681. doi: 10.36922/mi.7681**Received:** December 16, 2024**Revised:** February 17, 2025**Accepted:** February 24, 2025**Published online:** March 13, 2025**Copyright:** © 2025 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.**Publisher's Note:** AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Conception

The past 5 years have seen uninterrupted mutation events of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – the virus that resulted in one of the biggest pandemics in recent history – and continuous emergence of diverse virus variant strains such as BA.2.86, JN.1, KP.2, JN.1.18, and LB.1, with distinct characteristics. Actually, as early as June 2020, the World Health Organization (WHO) has established a Virus Evolution Working Group, focusing on the emerging SARS-CoV-2 variants, their phenotypes, impacts, and corresponding response measures. At the end of 2020, some of the variants which posed an increased risk to global public health were classified by the WHO as variants of interest (VOIs) or variants of concern (VOCs), to prioritize global monitoring and research efforts. In March 2023, to better identify the additional or new threats posed by the Omicron variant strain, the WHO updated the tracking system and working definitions, which modified VOCs and VOIs, to deal with the difficulties of tracking Omicron sub-lineages, independently.¹

This classification system of SARS-CoV-2 variants facilitates timely-understanding of the situation regarding variant strains for countries and research institutions, enabling them to implement corresponding measures to address potential risks, and to perform responding activities. Different variants emerge at varying times and exhibit diverse levels of prevalence in each country, resulting in the emergence of a “multi-peak wave” where multiple variants coexist within specific regions. Consequently, developing comprehensive and effective prevention and control measures targeting individual variants alone proves arduous. Simply applying a similar monitoring “grading” approach for SARS-CoV-2 variants is not applicable within the current epidemic context. Moreover, the immune evasion characteristics exhibited by the Omicron variants need to be investigated in laboratory one by one and the forthcoming wave of infections are also challenging. With the introduction of the serotype classification concept of SARS-CoV-2 variants and the further laboratory investigation, recently, new insights were brought forth for the SARS-CoV-2 classification.^{2,3}

2. The serotypes of SARS-CoV-2 variants

The Omicron variants of SARS-CoV-2 exhibit distinct pathological, transmission, and antigenic features compared to each other and also to the variants (including prototype) before Omicron, laying the foundation for classification of SARS-CoV-2 serotypes. In early 2022, Simon-Loriere and Schwartz⁴ proposed the hypothesis of distinct serotypes of the SARS-CoV-2 based on evolutionary analysis. They classified the prototype strain and other major variant strains, for example, Alpha, Beta, Gamma, and Delta as Serotype 1, while considering categorizing the three main members of the Omicron family (BA.1, BA.2, BA.3) as Serotype 2.

Afterward, Tan *et al.*² conducted serotype analysis based on serum samples from unvaccinated individuals who had recovered from initial infection. The results showed no significant cross-neutralization activity among the three tests targeting SARS-CoV-1, SARS-CoV-2 prototype, and SARS-CoV-2 Omicron variant. This finding supports the classification of currently known human-infecting SARS-related coronaviruses into three distinct serotypes.

At present, an increasing number of Omicron variants are being identified and designated. Hu *et al.*³ employed mRNA vaccines for spike (S) protein receptor-binding domain (RBD) of 23 representative variants. Through comprehensive assessment of mouse sera's cross-neutralization levels against pseudo-viruses, these 23

representative mutant strains were categorized into five serotypes.³ Serotype I encompasses all pre-Omicron variants, while the remaining four serotypes represent distinct evolutionary stages of the Omicron variant, namely, Serotype II (e.g., BA.1 and BA.1.1); Serotype III (e.g., BA.2, BA.3, BA.2.75, and BA.2.12.1); Serotype IV (e.g., BA.5, BF.7, BQ.1, and BQ.1.1); and Serotype V (e.g., XBB and XBB.1.5). Afterward, the same research team used the same investigation strategy to further classify four newly emerged variants, namely, XBB.1.16, EG.5, FL.1.5.1, and BA.2.86. Among them, BA.2.86 showed significantly reduced bidirectional cross-reactivity with other serotypes and was thus classified as a new serotype called Serotype VI.⁵ At present, the main prevalent variants of the SARS-CoV-2 have been classified into six distinct serotypes (Figure 1).

Recently, Ruan *et al.*⁶ concentrated on the serotyping and antigenicity analysis of SARS-CoV-2 variants using the S protein as the immunogen, and their findings align with those obtained from RBD-based serotyping.⁶

3. Significance of serotype classification

Serotype classification is a more “broad-spectrum” classification methodology, which relies on and also summarizes the serological cross-reactivities of different variants of the same virus; therefore, it can propose more applicable strategies for infectious disease prevention and control. From the perspective of monitoring mutant strains, conducting systematic research on the serotyping of SARS-CoV-2 is of great significance for quickly classifying newly emerging variant strains and evaluating their immune escape risks or capabilities. This can promptly determine whether a newly mutated strain has become a serological type to evade recognition by immune system, providing important scientific evidence to inform public health response strategies.

In the field of vaccine development, serotype classification can provide reference for the timely updating of vaccine design and experimental plans and predict the coverage of new vaccines for SARS-CoV-2 variants. This methodology may also be helpful for the development of broad-spectrum coronavirus vaccines targeting current and even future potential variants.

In addition, the significantly different serological features between variants, to some extent, have driven our understanding of pre-existing immunity. The relationship between serotypes and pre-existing immunity can uncover key information about immune memory and vaccine efficacy, providing scientific basis for the development of next-generation vaccines. At the same time, in combination with investigations on SARS-CoV-2 variants and immune

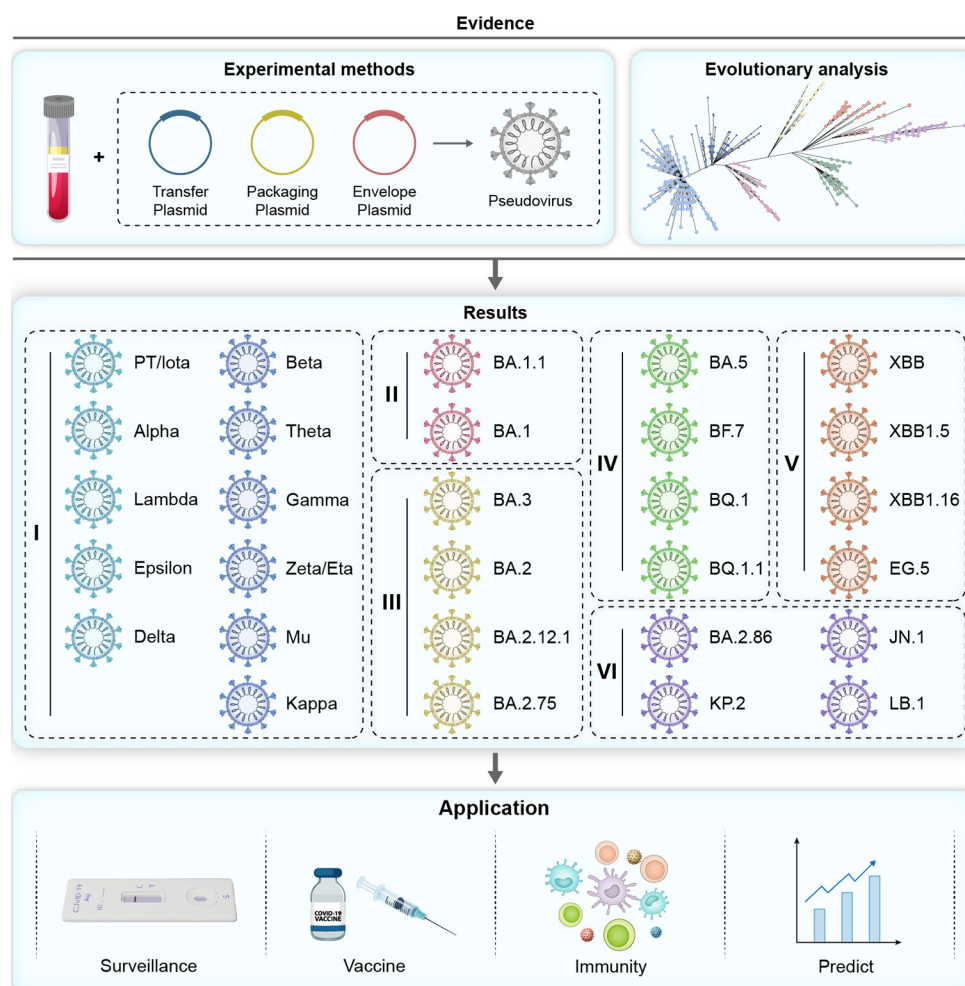


Figure 1. Classification and application of SARS-CoV-2 serotypes. Different strains of SARS-CoV-2 have been classified into serotypes using neutralization assays with serum samples and pseudo-viruses, together with the utilization of evolutionary analysis methods. At present, the main variant strains of SARS-CoV-2 can be divided into six serotypes, including the recently prevalent variants JN.1, KP.2, and LB.1, which would also fall under Serotype VI. The application of SARS-CoV-2 serotype classification mainly includes disease monitoring, vaccine development, human immune evaluation, and prediction of variant strains.

Abbreviation: SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

escape mechanisms, serotype typing provides new insights into predicting future potential directions of variation. This will help enhance global capabilities in responding to variants of SARS-CoV-2, preventing potential impacts on public health from emerging serotypes or antigenic drifts.

4. Perspective on serotype classification

In previous studies, researchers have conducted serotyping for viruses such as dengue viruses, human papillomavirus, and influenza viruses. This serotyping methodology has extensive applications in various fields including clinical classification, population immunity evaluation, and vaccine development. The serotype is defined as a distinct variant within a microbial species,

characterized by specific immune reactions. Serotyping of bacteria or viruses relies on the identification of surface antigens, and antibodies generated against one serotype typically exhibit limited efficacy against other serotypes.⁴ Although researchers have conducted relevant explorations and experimental verifications on the serotypes of the SARS-CoV-2, there are still certain challenges in this field from both immunological theory and practical perspectives.

First, it may be necessary to comprehensively examine other regions of the S protein in different variants and also other proteins for their impact on serotype classification. The current research on SARS-CoV-2 serotypes is mostly concentrated on animal experiments, but the immune background of humans presents higher complexities. In

addition, given the challenges in obtaining human sera after certain SARS-CoV-2 variant infections, investigation of the serotype concepts among humans proves to be pivotal.

Second, there is no internationally recognized standard to determine the serotype of SARS-CoV-2 nowadays; therefore, it is necessary to establish an acknowledged serotype classification standard to promote the in-depth advancements of this research domain in the right direction. With the continuous emergence of SARS-CoV-2 variants and the sharp increase in the types of variant strains, it is difficult to achieve instant classification of SARS-CoV-2 serotypes only through the existing laboratory research methods. Therefore, bioinformatics research methods can be incorporated to identify mutation sites in RBD of the S protein, ensuring the timely and effective discovery of new variant situations in the future. This will be conducive to promoting the application of serotype classification.

Finally, based on the principle of serotype classification, there is still a need to establish and continuously improve standards for monitoring epidemiological trends, and combine the concept of serotype with relevant epidemiological studies to explore the epidemic patterns of different serotypes. This will provide the basis for vaccine use strategies and enable the prediction of outbreak development and the assessment of the population's immune barrier. More specifically, these efforts will give rise to strategies for guiding the time interval of vaccination and vaccines updates, predicting the possible outbreak time and epidemic intensity of a new round of epidemic, as well as further exploring the humoral and cellular immune response mechanisms of the population, for achieving more widespread uptake of vaccines.

Serotype classification is a crucial tool for comprehending the complex variants of SARS-CoV-2. Through experimental investigations and evolutionary analysis of diverse variants of COVID-19, a comprehensive serotype classification system has been established. Nevertheless, there are still further works associated with accurately categorizing the serotypes of SARS-CoV-2. In future research endeavors, refining and leveraging the outcomes of serotype classification for SARS-CoV-2 will undoubtedly augment our understanding and safeguard public health.

Acknowledgments

We thank members of the team of Xin Zhao from the Institute of Microbiology of the Chinese Academy of Sciences, Beijing, China, for their thoughtful discussions.

Funding

This work was supported by the National Key Research and Development Program of China (2022YFC2604100) and the National Natural Science Foundation of China (92269203).

Conflict of interest

Jun Liu is an Editorial Board Member of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, the authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Jun Liu

Writing—original draft: All authors

Writing—review & editing: Jun Liu

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. WHO. *Tracking SARS-CoV-2 Variants*. Available from: <https://www.who.int/activities/tracking-SARS-CoV-2-variants> [Last accessed on 2024 Jul 19].
2. Tan CW, Zhu F, Chia WN, *et al.* Distinctive serotypes of SARS-related coronaviruses defined by convalescent sera from unvaccinated individuals. *Hlife*. 2023;1:26-34. doi: 10.1016/j.hlife.2023.07.002
3. Hu S, Wu C, Wu X, *et al.* Classification of five SARS-CoV-2 serotypes based on RBD antigenicities. *Sci Bull (Beijing)*. 2023;68(23):3003-3012. doi: 10.1016/j.scib.2023.09.048
4. Simon-Loriere E, Schwartz O. Towards SARS-CoV-2 serotypes? *Nat Rev Microbiol*. 2022;20(4):187-188. doi: 10.1038/s41579-022-00708-x
5. Du P, Wu C, Hu S, Fan R, Gao GF, Wang Q. The omicron BA.2.86 subvariant as a new serotype of SARS-CoV-2. *Lancet Microbe*. 2024;5(6):e516. doi: 10.1016/S2666-5247(23)00411-1
6. Ruan W, Gao P, Qu X, *et al.* SARS-CoV-2 serotyping based on spike antigenicity and its implications for host immune evasion. *eBioMedicine*. 2025;114:105634.