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# An updated framework for SARS-CoV-2 variants reflects the unpredictability of viral evolution

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The World Health Organization framework for tracking SARS-CoV-2 variants has been updated to reflect the continued evolution of the virus; this framework could be adapted for other emerging respiratory diseases with epidemic and pandemic potential.

Throughout the COVID-19 pandemic, SARS-CoV-2 variants have been designated as variants of concern (VOCs) and variants of interest (VOIs) on the basis of their potential to replace previously circulating variants and cause new waves of increased transmission globally; such variants may require adjustments in public health responses. During the first two years of the pandemic, four VOCs and eight VOIs were designated by the World Health Organization (WHO), and these were overall closely related to the index virus.

## Omicron descendants

The B.1.1.529 lineage was reported to the WHO from South Africa on 24 November 2021 and, on the advice of the WHO Technical Advisory Group on Virus Evolution (TAG-VE), was classified as a VOC and named Omicron on 26 November 2021. This decision was based on the large number of amino acid substitutions (Fig. 1), including some in key antigenic sites of the spike protein, as well as preliminary evidence suggesting an increased risk of reinfection and data suggesting a growth advantage in multiple provinces of South Africa, compared with other VOCs[1].

Within months after its emergence, Omicron became the globally predominant lineage. The combined evidence from its distinct genetic profile, comparison of antigenic cross-reactivity using animal sera[2], replication studies in experimental models of the human respiratory tract[3] and clinical and epidemiological data in humans[4] showed that Omicron was an immune escape variant and had increased affinity for upper respiratory tract cells, explaining its advantage over previously circulating variants despite high vaccination coverage. Since then, Omicron has continued to evolve genetically and antigenically, creating an expanding range of descendant lineages. So far, Omicron's descendant lineages have all been characterized by the properties of evasion from existing population immunity and a preference for infecting the upper rather than the lower respiratory tract[5].

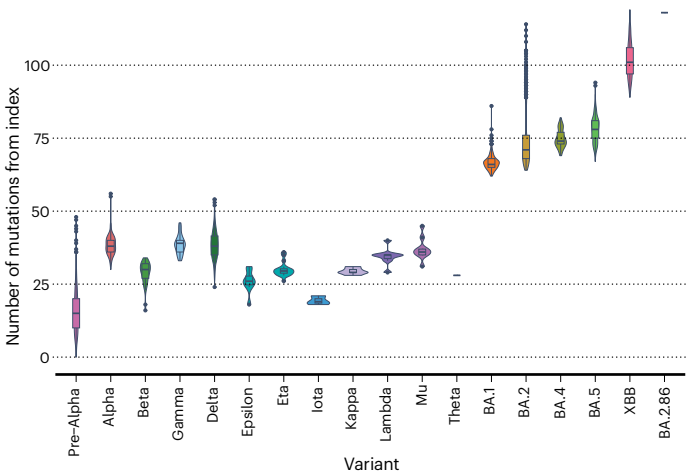


**Fig. 1 | Number of amino acid substitutions from the index virus in SARS-CoV-2 variants of interest and variants of concern.** A curated phylogenetic tree and associated metadata were downloaded from nextstrain, which uses data from the Global Initiative for Sharing All Influenza Data (GISAID) database. The number of amino acid substitutions from the index for each taxon refers to the full genome and was extracted from the phylogenetic tree branch lengths and plotted in R (v4.3.0).

The original WHO variant tracking system was designed to identify and label variants of interest or concern with Greek alphabet letters according to their associated risk[6]. In line with the original VOC definition, all Omicron descendant lineages were considered part of the Omicron VOC. However, the emergence of Omicron, changes in the clinical and epidemiological landscape from increased population-level immunity from past infection and/or increasing vaccination coverage into the fourth year of the pandemic, and the improved availability of diagnostics and therapeutics required the WHO's classification system to be revised. On 15 March 2023, the WHO updated its working definitions of variants under monitoring (VUMs), VOI and VOCs so that Omicron descendant lineages could be independently characterized and classified as VUMs, VOIs or VOCs as needed. The aim was to refine the definition of VOC to encompass new SARS-CoV-2 variants that are substantially genotypically and phenotypically different from pre-Omicron and Omicron variants. This implied that the use of a VOC assignment would clearly indicate that a variant poses a greater threat to public health than the Omicron descendant lineages already in circulation — for example, that it shows a clear change in disease severity or tropism.

During the pandemic, the WHO established two COVID-19 technical advisory groups. The mandate for designating a VOC based on the associated public health risk lies with the TAG-VE. The WHO TAG on COVID-19 Vaccine Composition (TAG-CO-VAC) considers the genetic and antigenic characteristics of SARS-CoV-2 variants and the implications for COVID-19 vaccines. The mandate of the TAG-CO-VAC is to formulate advice to the WHO on when to update the COVID-19 vaccine antigen composition[7]. Whereas the TAG-VE's mandate focuses on severe disease and impact on health systems, the TAG-CO-VAC focuses on advice to enhance vaccine-induced immune responses to circulating SARS-CoV-2 variants.

## New variants of interest

Pre-Omicron variants, including the index virus, VOCs Alpha, Beta, Gamma and Delta, and VOIs Epsilon, Zeta, Eta, Theta, Iota, Kappa, Lambda and Mu (as well as their respective descendant lineages), represent a distinct set of genotypic and phenotypic variants compared with Omicron and its descendants. The immunity induced by infection with pre-Omicron variants or from pre-Omicron vaccines provides higher protection against infection caused by pre-Omicron variants than against infections caused by Omicron and its descendant lineages[8,9]. Some Omicron descendant lineages, such as BA.1, BA.2 and BA.5, have caused large surges in incidence rates, especially in geographic regions without immunity from Omicron variants, irrespective of vaccination coverage[4]. This can partly be explained by the divergent antigenic evolution of Omicron and its descendant lineages[7].

In October 2022, XBB, a recombinant between two Omicron BA.2 descendant lineages, increased in circulation. XBB and its descendant lineages reached >90% of the sequences submitted to repositories globally in April 2023. The spread of XBB descendant lineages such as XBB.1.5, XBB.1.16 and EG.5 (a descendant lineage of XBB.1.9.2), all designated as VOIs, was characterized by a pronounced growth advantage over other circulating variants, which is likely driven by the immune escape potential of these VOIs; this includes escape in individuals with recent history of BA.2 and/or BA.5 infection[10]. The observed reduction in neutralizing antibody titers against XBB.1 descendant lineages in individuals who had received two, three or four doses of index virus–based vaccines, or a booster dose of a bivalent (BA.1- or BA.4/5-containing) mRNA vaccine, compared with titers specific for the antigens included in the vaccine[11], contributed to the recommendation by the WHO in May 2023, on advice from TAG-CO-VAC, to update vaccine antigen composition to a monovalent XBB.1 descendant lineage.

## Reduced impact of variants

The increasing levels of population immunity globally since the emergence of Omicron have provided substantial long-term protection against severe disease. This makes it challenging to distinguish a clear signature of higher severity for any newly emerging lineage based on clinical and epidemiological data in humans. Existing immunity, alongside the use of diagnostics and therapeutics and advances in clinical care, has probably had a critical role in mitigating the potential impact of emerging SARS-CoV-2 variants.

Despite this pattern of continuous lineage replacement, none of the XBB descendant lineages have met the WHO's updated definition of a VOC. Given the relatively poor cross-neutralization of early Omicron lineages, however, XBB variants may represent a different antigenic cluster within the Omicron family[11]. Quantitative thresholds to determine new antigenic clusters using neutralization assays need to be agreed upon by the scientific community. The ability to establish meaningful thresholds depends greatly on the reproducibility and repeatability of estimates characterizing antigenicity across laboratories. The WHO has established the Coronavirus Network (CoViNet), through which harmonization of antigenic characterization across laboratories in different geographic regions will be coordinated. The results of this initiative may inform the feasibility of defining such thresholds.

## A risk-evaluation framework

The WHO SARS-CoV-2 variant risk-evaluation framework[12] is designed to assist in evaluating the risk posed by emerging SARS-CoV-2 variants based on the evidence available and the level of confidence in the gathered information. Although the framework is focused on the risk posed by new SARS-CoV-2 variants and lineages to the human population, it also provides a relevant risk-assessment framework that can be adapted for the evaluation of any newly emerging coronavirus or other respiratory pathogen that demonstrates human-to-human transmission. The framework is designed to address the challenges of summarizing and evaluating existing evidence to inform timely decision-making for public health response. Guidance is provided by proposing a list of relevant risk indicators along with a set of studies that can be conducted to support prompt and balanced weighting of information for an overall risk evaluation of a newly detected variant of potential concern.

As part of the 2022 Strategic Preparedness, Readiness and Response Plan[13], the WHO presents case scenarios to consider the different directions that SARS-CoV-2 could take in its evolution. Although the weighting of the various components of the assessment may change, for example as a function of how an emerging virus evolves, clinical severity is currently given more weight than growth advantage and antibody escape (which includes considerations related to vaccines) because of its potential greater impact on healthcare systems and population health. Treatability (impact on therapeutics) and detectability (impact on diagnostics) are also assessed.

A variant associated with high clinical severity could lead to higher morbidity and increased hospitalizations and deaths. In contrast, a variant with high growth advantage or antibody escape may be more transmissible but may not result in greater number of severe illnesses requiring hospitalization. However, a substantial rise in total infections within a short time could create a substantial strain on health systems,

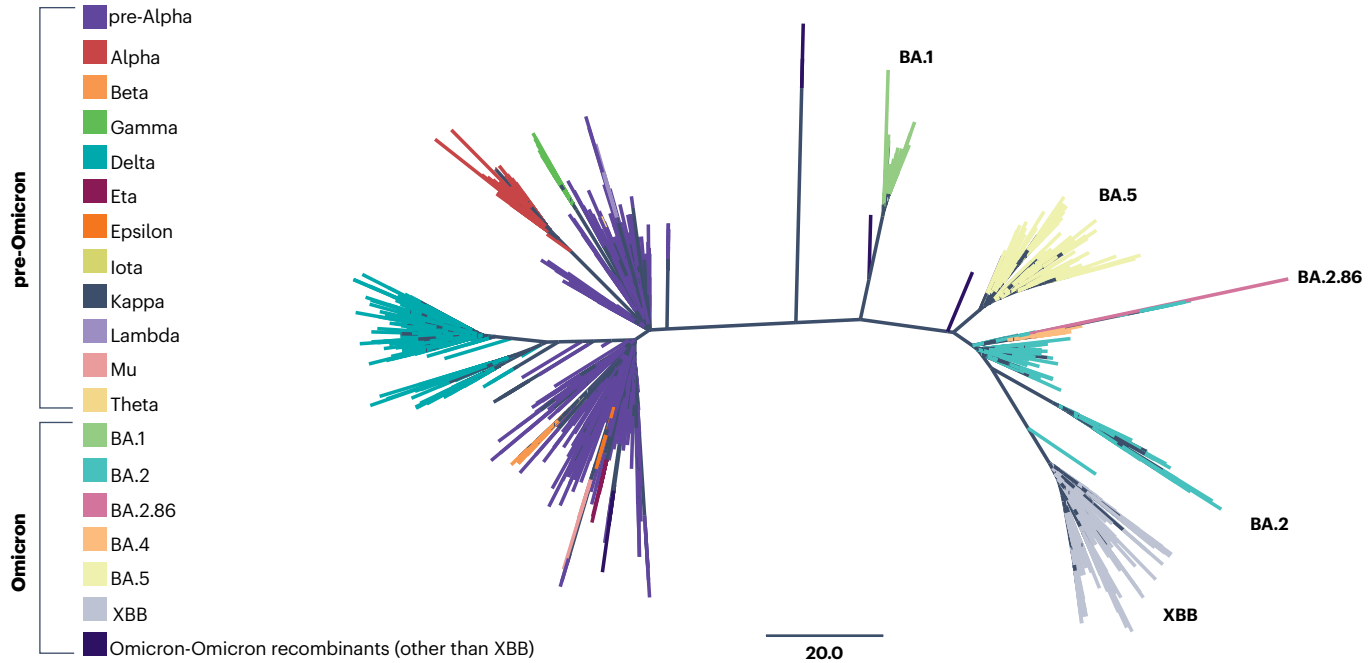


**Fig. 2 | Spike-based phylogenetic tree with variants of interest and variants of concern.** The curated unrooted phylogenetic tree was downloaded from nextstrain (nextstrain.org), which uses data from the GISAID database. The taxon names were used to extract respective metadata from the GISAID database. The phylogenetic tree and associated metadata were visualized in FigTree (v1.4.4).

and therefore the public health risk posed by a new variant or lineage could be high even if the severity of associated clinical illness was unaffected (as with the emergence of Omicron). The risk evaluation considers levels of immunity to specific variants in a population and encompasses the available data regarding cross-protection with other previously circulating variants.

The WHO risk-evaluation framework should rigorously and comprehensively examine quantitative and qualitative information from multiple sources, which should be triangulated to provide an additional reality check on the assessed situational level. The context assessment, including local capacities and vulnerabilities, may result in an upward or downward adjustment of the calculated situational level.

The framework[12] describes actions to be taken for each public health risk level. For example, variants assessed as posing very high risk require urgent reporting and action, including increased sequencing and investigation, targeted public health measures and changes to pharmaceutical interventions. As this is a rapidly evolving landscape, consultation with the experts from the WHO TAG-VE remains necessary for the determination of risk.

## Unpredictability of SARS-CoV-2 evolution

SARS-CoV-2 evolution remains unpredictable, but the data collected during its 4 years of circulation have informed planning for future scenarios of virus evolution. Population immunity acquired from vaccines and prior infection has reached very high levels in most settings.

This genetic diversity, illustrated in Fig. 2, could be acquired by various means. For example, the circulation of viruses in animals generates very high genetic diversity[14], resulting in variants whose potential to spill over into humans and spread in the human population remains undetermined. Gradual yet undetected viral circulation in the human population for extended periods of time can occur, especially if such circulation remains geographically restricted in an heavily under sampled (and under-sequenced) region; this would build immunity in that limited region, but not in the rest of the world[15]. Alternatively, genetic diversification might be enhanced in persistent or chronic infections, which can cause viral shedding for months to years, resulting in the emergence of divergent viruses[16].

Knowledge of SARS-CoV-2 is only 4 years old, as indicated by the recent example of the emergence of BA.2.86. The number and nature of amino acid substitutions carried by BA.2.86 alerted the WHO, the TAG-VE and other scientists that this variant could evade current population immunity and spread globally. However, live virus-neutralization studies have shown no substantial differences in this variant's ability to be neutralized by antibodies from vaccinated individuals who have also experienced infection with an Omicron variant, compared with that of XBB.1.5 (ref. 17). A BA.2.86 descendant lineage (JN.1, which carries the additional spike mutation L455S) has become dominant, and as of March 2024, it represented 96% of publicly available sequences. It remains unclear to date what genetic and phenotypic features have made JN.1 so successful relative to its parent lineage.

New variants can be identified faster by robust monitoring of virus evolution in susceptible animal species; efforts to provide more visibility of genomic surveillance blind spots; and enhanced genomic surveillance among high-risk populations, such as immunosuppressed individuals. Surveillance mechanisms, such as early warning systems for clinical severity caused by respiratory pathogens, genomics data with associated metadata, wastewater monitoring programs, and comprehensive monitoring of the effectiveness of countermeasures, including therapeutics, vaccines and diagnostics, will continue to have a pivotal role going forward in guiding public health interventions.

In order for us to be prepared to future variants of concern, it is essential that genomics surveillance strategies within integrated respiratory virus surveillance systems remain active and that further laboratory and epidemiological studies be rapidly performed to ensure a fast risk assessment of novel emerging variants.

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## Competing interests

The authors declare no competing interests.