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Review Article

New COVID-19 Variant NB.1.8.1: Symptoms, Spread and The Latest Combination Therapies for Vulnerable and Immunocompromised Persons: A Literature Review and Clinical Experience in June 2025

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Abstract

Despite the end of the pandemic, COVID-19 continues to pose a serious health threat. As of May 2025, the most notable COVID-19 variant is NB.1.8.1, informally known as "Nimbus." This Omicron subvariant has been rapidly spreading across Asia, Europe and North America. It has been linked to a particularly severe sore throat, described by patients as feeling like "razor blades," along with other flu-like symptoms such as fatigue, cough, fever, congestion and muscle aches. The World Health Organization (WHO) has designated NB.1.8.1 as a "Variant Under Monitoring" due to its increased immune evasion capabilities. Despite its rapid transmission, current data suggest that it does not lead to more severe disease compared to earlier strains. In addition to NB.1.8.1, other Omicron subvariants such as XEC and LP.8.1 continue to circulate. XEC, a recombinant variant fiint identified in Germany in June 2024, has been increasing in prevalence globally. It has been detected in several countries, including South Africa and is currently the most common SARS-CoV-2 subvariant reported. Health authorities continue to monitor these variants closely. Preventive measures such as vaccination, mask-wearing and good hygiene remain essential in reducing the spread of COVID-19. The challenges of outpatient administration and associated costs, monoclonal antibodies were a mainstay of the COVID-19 armamentarium from November 2020, when bamlanivimab first received US Food and Drug Administration Emergency Use Authorization (EUA), through November 2022. Ideal qualities of treatments include effectiveness in preventing hospitalization and death, safety and tolerability for patients, easy administration in the outpatient environment and cost-effectiveness. Monoclonal antibodies (mAbs) that neutralize SARS-CoV-2 fit the safety and efficacy profile in randomized clinical trials. This minireview of clinical experience explain the latest variant of concerns, the symptoms and the importance of early combination therapies for NB 1.8.1 to treat quickly immunocompromised and elderly persons.

Keywords: Monoclonal Antibodies; Early Treatment; NB 1.8.1

Introduction

Since its emergence in late 2019, the COVID-19 virus has continued to evolve through constant mutation, giving rise to new variants with varying levels of transmissibility and severity.

From Alpha to Omicron and its numerous sub-lineages, the virus has consistently demonstrated its ability to adapt and persist. In 2025, the recent surge in cases is being attributed to a new sub-variant of Omicron, informally known as "Omicron XBB 2.3-like," the lastest NB1.8.1 which is now drawing the attention of medicins, virologists and public health authorities worldwide [1,2]. Unlike earlier strains, this current sub-variant appears to cause milder symptoms in most people, especially those who are vaccinated or have had prior infections. However, its high transmissibility is of concern, particularly for high-density urban areas

and immune-compromised individuals and ederly persons. Preliminary data suggests that the virus has now become better at escaping some of the body's existing defenses, making it harder to stop with previous immunity alone [3].

Early research data from multiple labs are reassuring and show that existing antibodies work against the new variants. These data are also encouraging because of what it may mean for the effectiveness of the 2023-2024 COVID-19 vaccine [4,5].

Monoclonal antibodies targeting the anti-SARS-CoV-2 spike (S) protein are prescribed in high-income countries to prevent severe disease in at-risk patients. Although studies report efficacy as between 50-85%, global access is currently largely inequitable [6]. Multivariant omicron (B.1.1.529) and subvariant (BA.2 followed by BA.4 and BA.5) dominance has challenged the treatment landscape for mild-to-moderate disease, introducing considerable certainty on the efficacy of monoclonal antibodies and leading to changes to initial recommendations for some of them [7,8]. Contemporaneously, oral, direct-acting antivirals with a reported efficacy ranging from 30% (molnupiravir) to 89-90% (nirmatrelvir/ritonavir) have recently received conditional or emergency approval in some countries and been recommended in international guidelines such as the World Health Organization guidelines. S-217622, also known as ensitrelvir, a 3CL protease inhibitor that has been shown to significantly reduce the infectious viral load, is currently in phase 3 trials and waiting for emergency approval in Japan and should be submitted soon in China. The main purpose of this opinion paper is to highlight the possible strategies to optimize and protect current and future therapeutic options to treat the most vulnerable patients.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Characteristics and Initial Risk Assessment of NB.1.8.1, 23 May 2025

NB.1.8.1 is a variant of SARS-CoV-2 that originates from the recombinant variant XDV.1.5.1, with the first sample documented on 22 January 2025.

The World Health Organization (WHO) monitors NB.1.8.1 as one of six Variants Under Monitoring (VUMs) since it was classified as such on 23 May 2025 [9,10]. In contrast to the leading SARS-CoV-2 variant, LP.8.1, NB.1.8.1 exhibits several additional Spike mutations, specifically: T22N, F59S, G184S, A435S, V445H and T478I. When assessed against the JN.1 variant, NB.1.8.1 presents the following mutations: T22N, F59S, G184S, A435S, F456L, T478I and Q493E. The Spike mutation at position 445 is known to improve the binding affinity to hACE2, potentially raising the variant's transmissibility. Additionally, mutations at position 435 have been shown to diminish the neutralizing effectiveness of class 1 and class 1/4 antibodies, while alterations at position 478 are associated with improved evasion of Class 1/2 antibodies [11,12]. In studies using pseudoviruses and plasma from individuals with BA.5 breakthrough infections linked to JN.1 or XDV+F456L, NB.1.8.1 exhibited a reduction of 1.5 to 1.6 times in neutralization efficiency compared to LP.8.1.1. Mice that had previously been vaccinated with various SARS-CoV-2 variants demonstrated comparable or slightly lower neutralizing antibody levels against NB.1.8.1 after receiving further immunization with monovalent KP.2 or monovalent LP.8.1 mRNA vaccines, in comparison to the immunization with KP.2 or LP.8.1 antigens [13].

As of 18 May 2025, a total of 518 sequences of NB.1.8.1 have been reported to GISAID [14,15] across 22 countries, representing 10.7% of the global sequences available during epidemiological week 17 of 2025 (from 21 to 27 April 2025).

Although these numbers remain relatively modest, there has been a notable increase in prevalence from 2.5% four weeks earlier, during epidemiological week 14 of 2025 (31 March to 6 April 2025), as illustrated in Table 1.

Between epidemiological weeks 14 and 17 of 2025, NB.1.8.1's prevalence rose across all three WHO regions that consistently report SARS-CoV-2 sequences, with an increase from 8.9% to 11.7% in the Western Pacific Region (WPR), from 1.6% to 4.9% in the Region of the Americas (AMR) and from 1.0% to 6.0% in the European Region (EUR).

Only five sequences of NB.1.8.1 have been identified in the South East Asia Region (SEAR), with no sequences reported from the African Region (AFR) or the East Mediterranean Region (EMR).

Lineage*	Countries§	Sequences§	2025-14	2025-15	2025-16	2025-17
VOIs						
JN.1	143	339570	12.0	12.1	11.5	9.7
VUMs						
KP.3	85	61526	2.7	2.2	0.8	1.5
KP.3.1.1	89	117331	9.5	10.8	10.2	8.5
LB.1	99	25457	2.4	2.5	1.7	0.9
XEC	73	52366	22.3	20.0	18.8	17.8
LP.8.1	51	15993	42.0	41.4	40.9	39.0
NB.1.8.1	22	518	2.5	4.1	7.1	10.7
Recombinant	144	513365	6.6	6.9	8.9	11.8
Others	111	35263	0.1	0.1	-	0.1

Table 1: Global proportions of SARS-CoV-2 Variants, epidemiological week 14 to 17 of 2025.

Figures by WHO, Data from Global Initiative on Sharing All Influenza Data (GISAID), extracted on 18 May 2025
§Number of countries and sequences are since the emergence of the variants.
*The variants listed include descendant lineages, except those individually specified elsewhere in the table.
The VOI and the VUMs that have shown increasing trends are highlighted in yellow, those that have remained stable are highlighted in blue, while those with decreasing trends are highlighted in green.

Emergence and Spread of NB.1.8.1
Origin and Detection: The variant NB.1.8.1 was initially recognized as a major factor contributing to the surge of COVID-19 infections in China. By the end of May 2025, the U. S. Centers for Disease Control and Prevention (CDC) validated its occurrence within the United States.

Global Spread: The World Health Organization (WHO) along with various health organizations have observed that NB.1.8.1 is currently circulating globally, with instances recorded in numerous nations. The swift spread of this variant has raised alarms regarding the possibility of heightened COVID-19 case numbers in different areas [16].

Variant Characteristics
- Genetic Profile: NB.1.8.1 is a subvariant of the Omicron lineage, featuring several mutations in the spike protein. These mutations may enhance its ability to evade immune responses, although current evidence suggests it does not cause more severe illness compared to previous Omicron subvariants [17]
- Transmission: Early data indicate that NB.1.8.1 is highly transmissible, contributing to spikes in case numbers where it becomes dominant
- Compared to the currently dominant variant in the U.S. (LP.8.1), NB.1.8.1 has a handful of new mutations on the spike protein that may enhance its ability to bind to our cells, according to the World Health Organization (WHO). NB.1.8.1 retains "high ACE2 affinity and humoral immune evasion, supporting its potential for future dominance," Dr. James Lawler of the University of Nebraska Medical Center's Global Center for Health Security in Omaha told MedPage Today, citing research reports coming out of China
- It is actually a recombinant mutant strain, which means it is a mixture of two or more mutant Omicron strains. The researchers don't have a clear understanding, after this hybrid recombination, what kind of mutation will it undergo and what kind of aftereffects will it have [18]

Symptoms Now and Then: What's Different?
Unlike earlier strains, this current sub-variant appears to cause milder symptoms in most people, especially those who are vaccinated or have had prior infections. However, its high transmissibility is of concern, particularly for high-density urban areas and immune-compromised individuals.

As summer brings another rise in COVID-19 infections, patients across Asia, Europe and North America are reporting a searing sore throat so intense it has earned a dramatic nickname: “razor blade throat”. Though not a new symptom, the phenomenon has gained fresh attention amid the spread of a fast-moving Omicron subvariant, formally known as NB.1.8.1 and colloquially as “Nimbus”.

Patients in China and elsewhere describe the pain as akin to “swallowing shattered glass,” with some saying they’ve been left unable to speak, eat or even stay hydrated.

Preliminary data suggests that the virus has now become better at escaping some of the body’s existing defenses, making it harder to stop with previous immunity alone.
One of the striking changes in 2025 is the symptom profile. While fever, cough and breathlessness were hallmark symptoms in 2020 and 2021, newer cases tend to exhibit more subtle signs as a pronounced, persistent Sore throat “as razor blade throat”, Nasal congestion, Headaches, Fatigue, Occasionally, gastrointestinal issues like diarrhea.

Severe complications like Acute Respiratory Distress Syndrome (ARDS) and cytokine storms have drastically declined, thanks to early detection, better clinical protocols and immunity buildup through vaccination and previous infections [19].

The CDC outlines the following as common COVID-19 symptoms:
- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Sore throat
- Congestion or a runny nose
- New loss of taste or smell
- Fatigue
- Muscle or body aches
- Headache
- Nausea or vomiting

The CDC advises seeking medical care if you experience any of the following symptoms:
- Trouble breathing
- Persistent pain or pressure in the chest
- New confusion
- Inability to wake or stay awake
- Depending on skin tone, lips, nail beds and skin may appear pale, gray or blue

SARS-CoV-2 Variants of Concern as of 28 May 2025
European Centre for Disease Prevention and Control.An agency of the European Union. Surveillance and Monitoring Comunicable Disease Threats Reports, 26 April-3 May 2025, week 18 [20]. Variant classification serves as an important communication tool for alerting EU/EEA countries about the emergence of SARS-CoV-2 variants with concerning properties likely to impact the epidemiological situation in the EU/EEA.

The ECDC Strategic Analysis of Variants in Europe (SAVE) Working Group is a multidisciplinary team comprising of ECDC Experts working in Respiratory Viruses, Microbiology, Bioinformatics, Mathematical Modelling, Epidemic Intelligence, Emergency Preparedness and Response and Vaccine-Preventable Diseases and Immunisation. Currently meetings are held once per month to assess the observed or predicted impact of currently circulating and newly emerging SARS-CoV-2 variants in the EU/EEA and globally.

ECDC utilises three categories of variant classification to communicate increasing levels of concern about a new or emerging SARS-CoV-2 variant: Variant Under Monitoring (VUM), Variant Of Interest (VOI) and Variant Of Concern (VOC). Classification

criteria and recommended Member state actions are available here:
ECDC variant classification criteria and recommended Member State actions

New evidence is regularly assessed on variants detected through epidemic intelligence, genomic horizon scanning or other scientific sources. If a decision is made to add, remove or change the category for any variant, the tables are updated to reflect this change. The tables are regularly sent for consultation to ECDC stakeholders, such as the European Commission and WHO Regional Office for Europe's joint virus characterisation working group.

Variant surveillance data, including the distribution of VOC and VOI variant proportions in the EU/EEA and detailed country-specific COVID-19 epidemiological updates are available as part of the European Respiratory Virus Surveillance Summary (ERVISS).

Useful Links: Slides from the most recent SAVE WG meeting are available in EpiPulse, with SARS-CoV-2 variant classification updates also published in ECDC's Communicable Disease Threats Reports. To review a timeline of variant classification decisions, visit our change log.

Following classification of a VOC, VOI or VUM, multiple closely related sub-lineages may emerge. To facilitate reporting of variant detections by countries to TESSy, a table listing sub-lineages for monitored variants as of 6 May 2025 is available here.

Description of the Tables

The Table 1-3 include:

Category: Variant of Concern (VOC), Variant of Interest (VOI) or Variant Under Monitoring (VUM).

1. WHO label: As of 31st May 2021, WHO proposed labels for global SARS-CoV-2 variants of concern and variants of interest to be used alongside the scientific nomenclature in communications about variants to the public. This list includes variants on WHO's global list of VOC and VOI and is updated as WHO's list changes.
2. Lineage and additional mutations: the variant designation specified by one or more Pango lineages and any additional characteristic spike protein changes. An alternate description may be used if the variant is not easy to describe using this nomenclature. For updated information on Pango lineages and definition of lineages and for instructions on how to suggest new lineages, visit the Pango lineages website. Each lineage in then table is linked to the respective lineage page on the Pango lineages website.
3. Country first detected: only present if there is moderate confidence in the evidence relating to the first country of detection.
4. Spike mutations of interest: not all spike protein amino acid changes are included - this is not a full reference for assignment of the variants. It includes changes to spike protein residues 319-541 (receptor binding domain) and 613-705 (the S1 part of the S1/S2 junction and a small stretch on the S2 side) and any additional unusual changes specific to the variant.
5. Year and month first detected: as reported in the GISAID EpiCoV database. This can be adjusted backwards in time if new retrospective detections are made.
6. Evidence concerning properties in three different categories:

- Transmissibility
- Immunity
- Infection severity

Each category is annotated as increased, reduced, similar, unclear or no evidence depending on the currently available evidence. Increased or reduced means that there is evidence demonstrating that the property is different enough for the variant compared to previously circulating variants that it is likely to have an impact on the epidemiological situation in the EU/EEA. Similar means that there is evidence that demonstrates that the property is not different enough for this variant compared to previously circulating variants that it is unlikely to have an impact. Unclear means that the current evidence is preliminary or contradictory enough to make the assessment uncertain. No evidence means that no evidence has yet been evaluated for this category. The evidence is further annotated with v or m to indicate whether the evidence is available for the variant itself (v) or for mutations associated with the variant (m).

7. Transmission in the EU/EEA: categorised as dominant, community, outbreak(s) and sporadic/travel. The categories are qualitative and the assessment is based on surveillance data collected in TESSy, GISAID EpiCoV data, epidemic intelligence

data and direct communications with the affected countries.

Variants of Concern (VOC) at 28 May 2025

As of 3 March 2023, ECDC has de-escalated BA.2, BA.4 and BA.5 from its list of SARS-CoV-2 Variants Of Concern (VOC), as these parental lineages are no longer circulating. ECDC will continue to categorise and report on specific SARS-CoV-2 sub-lineages in circulation that are relevant to the epidemiological situation.

There are currently no SARS-CoV-2 variants meeting the VOC criteria.

Variants of Interest (VOI)

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Omicron	BA.2.86	n/a	I332V, D339H, R403K, V445H, G446S, N450D, L452W, N481K, 483del, E484K, F486P	n/a	Baseline (6)	Baseline (6-8)	Baseline	Community
Omicron	KP.3	n/a	Q493E, F456L	n/a	No evidence	No evidence	No evidence	Dominant

Table 1: Variants of Interest (VOI).

Variants Under Monitoring at 28 May 2025.

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Omicron	XEC	n/a	T22N, F59S, F456L, Q493E, V1104L	n/a	No evidence	No evidence	No evidence	Community
Omicron	LP.8.1	n/a	H445R, Q493E, F186L, R190S	n/a	No evidence	No evidence	No evidence	Community
Omicron	NB.1.8.1	n/a	G184S, A435S, K478I	n/a	No evidence	No evidence	No evidence	Community

Table 2: Variants Under Monitoring (VUM).

De-Escalated Variants

These additional variants of SARS-CoV-2 have been de-escalated based on at least one the following criteria: (1) the variant is no longer circulating, (2) the variant has been circulating for a long time without any impact on the overall epidemiological situation, (3) scientific evidence demonstrates that the variant is not associated with any concerning properties.

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Alpha	B.1.1.7	United Kingdom	N501Y, D614G, P681H	September 2020	Increased (v) (9)	Similar	Increased (v) (10, 11)	Drastically reduced circulation in the EU/EEA following the emergence of Delta; little evidence of impact on vaccine induced immunity
n/a	B.1.1.7+E484K	United Kingdom	E484K, N501Y, D614G, P681H	December 2020	Increased (v) (9)	Increased (v) (12, 13)	Increased (v) (10)	Very low levels of circulation in the EU/EEA
Epsilon	B.1.427/B.1.429	USA	L452R, D614G	September 2020	Unclear (14)	Increased (v) (14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA and available data indicating that vaccines and treatments are effective against such variant
n/a	B.1.616*(c)*	France	V483A, D614G, H655Y, G669S	February 2021	Detection (c) (15)	No evidence	No evidence	Not detected since 2021-04-23 (16)

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Eta	B.1.525	Nigeria	E484K, D614G, Q677H	December 2020	No evidence	Increased (m) (12, 17)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
Theta	P.3	The Philippines	E484K, N501Y, D614G, P681H	January 2021	Increased (m) (9)	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
Kappa	B.1.617.1	India	L452R, E484Q, D614G, P681R	December 2020	Increased (v) (18)	Increased (v) (19-22)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.620	Unclear (b)	S477N, E484K, D614G, P681H	February 2021	No evidence	Increased (m) (12, 23)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.617.3	India	L452R, E484Q, D614G, P681R	February 2021	Increased (m) ((9)1)	Increased (m) (12, 14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.214.2	Unclear2	Q414K, N450K, ins214TDR, D614G	December 2020	No evidence	No evidence	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	A.23.1+E484K	United Kingdom	V367F, E484K,	December 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
			Q613H					detected at extremely low levels in the EU/EEA
n/a	A.27	Unclear (b)	L452R, N501Y, A653V, H655Y	December 2020	Increased (m) (9)	Increased (m) (14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	A.28	Unclear (b)	E484K, N501T, H655Y	December 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	C.16	Unclear (b)	L452R, D614G	October 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.351+P384L	South Africa	P384L, K417N, E484K, N501Y, D614G, A701V	December 2020	Increased (v) (24)	Increased (v) (25, 26)	Unclear (27)	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.351+E516Q	Unclear (b)	K417N, E484K, N501Y, E516Q, D614G, A701V	January 2021	Increased (v) (24)	Increased (v) (25, 26)	Unclear (27)	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.1.7+L452R	United Kingdom	L452R, N501Y, D614G, P681H	January 2021	Increased (v) (9)	Increased (m) (14)	Increased (v) (10)	No longer detected or detected at extremely

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								low levels in the EU/EEA
n/a	B.1.1.7+S494P	United Kingdom	S494P, N501Y, D614G, P681H	January 2021	Increased (v) (9)	Increased (m) (28)	Increased (v) (10)	No longer detected or detected at extremely low levels in the EU/EEA
Iota	B.1.526	USA	E484K, D614G, A701V	December 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.526.1	USA	L452R, D614G	October 2020	No evidence	Increased (m) (14)	No evidence	Lineage withdrawn from Pango
n/a	B.1.526.2	USA	S477N, D614G	December 2020	No evidence	No evidence	No evidence	Lineage withdrawn from Pango
Zeta	P.2	Brazil	E484K, D614G	January 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.1.519	Mexico	T478K, D614G	November 2020	No evidence	Increased (m) (14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	AV.1	United Kingdom	N439K, E484K, D614G, P681H	March 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								EU/EEA
n/a	AT.1	Russian Federation	E484K, D614G, N679K, ins679GIAL	January 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	C.36+L452R	Egypt	L452R, D614G, Q677H	December 2020	No evidence	Increased (m) (14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	P.1+P681H	Italy	D614G, E484K, H655Y, K417T, N501Y, P681H	February 2021	No evidence	Unclear (29, 30)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
Mu	B.1.621	Colombia	R346K, E484K, N501Y, D614G, P681H	January 2021	Increased (m) (9)	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
Lambda	C.37	Peru	L452Q, F490S, D614G	December 2020	No evidence	Increased (v) (31, 32)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	AY.4.2	United Kingdom	L452R, T478K, D614G, P681R, A222V, Y145H	June 2021	Increased (v) (33)	Similar (v) (33, 34)	Similar (v) (33)	Delta sub-lineages will continue to be monitored within Delta VOC

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
n/a	B.1.1.318	Unclear (b)	E484K, D614G, P681H	January 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.617.2 + K417N	United Kingdom	L452R, T478K, D614G, P681R, K417N	June 2021	No evidence	No evidence	No evidence	Delta sub-lineages will continue to be monitored within Delta VOC
n/a	C.1.2	South Africa	D614G, E484K, H655Y, N501Y, N679K, Y449H	June 2021	Increased (m) (9)	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.617.2 + E484X (d)	India	L452R, T478K, D614G, P681R, E484X (d)	April 2021	No evidence	No evidence	No evidence	Delta sub-lineages will continue to be monitored within Delta VOC
n/a	B.1.617.2 + Q613H	India	L452R, T478K, D614G, P681R, Q613H	April 2021	No evidence	No evidence	No evidence	Delta sub-lineages will continue to be monitored within Delta VOC
n/a	B.1.617.2 + Q677H	India	L452R, T478K, D614G, P681R, Q677H	April 2021	No evidence	No evidence	No evidence	Delta sub-lineages will continue to be monitored within

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								Delta VOC
Beta	B.1.351	South Africa	K417N, E484K, N501Y, D614G, A701V	September 2020	Increased (v) (24)	Increased (v) (25, 26)	Increased (v) (11, 27)	No longer detected or detected at extremely low levels in the EU/EEA
Gamma	P.1	Brazil	K417T, E484K, N501Y, D614G, H655Y	December 2020	Increased (v) (35)	Increased (v) (36)	Increased (v) (11)	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.640	The Republic of Congo	D614G, F490R, N394S, N501Y, P681H, R346S, Y449N, 137−145de	September 2021	No evidence	No evidence	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	XF	United Kingdom	Omicron-like	January 2022	No evidence	No evidence	No evidence	No longer detected.
n/a	XD	France	NTD Delta-like; remaining Omicron-like	January 2022	No evidence	No evidence	No evidence	No longer detected.
Delta	B.1.617.2	India	L452R, T478K, D614G, P681R	December 2020	Increased (v) (37)	Increased (v) (38-40)	Increased (v) (39, 41)	Detected at extremely low levels in the EU/EEA
Omicron	BA.1	South Africa and Botswana	(x)	November 2021	Increased (v) (42, 43)	Increased (v)(44-46)	Reduced (v) (47-49)	Detected at extremely low levels in the EU/EEA
Omicron	BA.3	South Africa	(z)	November 2021	No evidence	No evidence	No evidence	Detected at extremely low levels

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								in the EU/EEA
Omicron	BA.2 + L452X	n/a	L452X	n/a	No evidence	Increased (50)	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	XAK	Germany		June 2022	No evidence	No evidence	No evidence	No longer detected.
Omicron	B.1.1.529 + R346X	n/a	R346X	n/a	No evidence	No evidence	No evidence	Instead of mutational proxies, tracking by lineages (majorly BQ.1 and BF.7)
Omicron	B.1.1.529 + K444X, N460X	n/a	K444X, N460X	n/a	No evidence	Increased (m)(51)	No evidence	Instead of mutational proxies, tracking by lineages (majorly BQ.1)
Omicron	B.1.1.529 + N460X, F490X	n/a	N460X, F490X	n/a	No evidence	Increased (m)(51)	No evidence	Instead of mutational proxies, tracking by lineages (majorly BA.2.75 and XBB)
Omicron	BA.2.3.20	n/a	K444R, L452M, N460K	n/a	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	BF.7	n/a	R346T, F486V	n/a	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Omicron	BA.2	South Africa	(y)	November 2021	Increased (v)(42, 52)	Increased (v) (46)	Reduced (v)(53, 54)	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation
Omicron	BA.4	South Africa	L452R, F486V, R493Q	January 2022	No evidence	Increased(50, 55)	No evidence	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation
Omicron	BA.5	South Africa	L452R, F486V, R493Q	February 2022	No evidence	Increased(50, 55)	Unclear (56)	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation
Omicron	XBC (x)	n/a	N440K, F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	BN.1	n/a	R346T, K356T, F490S,	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	XAY	n/a	F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	BQ.1	n/a	K444T, N460K	n/a	Increased (5)	Increased (2, 3, 61-63)	Unclear (64)	Detected at extremely low levels in the EU/EEA
Omicron	XBB (z)	n/a	N460K, F490S	n/a	Increased (1)	Increased(57-61)	Unclear(62)	Detected at extremely low levels in the EU/EEA

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Omicron	CH.1.1	n/a	K444T, L452R	n/a	Increased (1, 63)	Increased (v) (57, 58, 60, 64)	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	XBB.1.16	n/a	E180V, T478R, F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	BA.2.75	India	W152R, F157L, I210V, G257S, D339H, G446S, N460K, Q493 (reversion)	May 2022	Unclear (65)	Similar to Baseline (57, 58, 66)	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	DV.7.1	n/a	K444T, L452R, L455F	n/a	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	XBB.1.5-like + L455F + F456L	n/a	**L455F**, **F456L**, N460K, S486P, F490S	n/a	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	BA.2.87.1	South Africa	(q) (e)	2023 September	No evidence	No evidence	No evidence	Not detected in EU/EEA
Omicron	XBB.1.5-like	United States	N460K, S486P, F490S	n/a	Similar to Baseline (1, 2)	Reduced (v) (1, 3, 5)	Similar to Baseline (4)	No longer detected or detected at extremely low levels in the EU/EEA
Omicron	BA.2.86 + R346T + F456L	n/a	R346T, F456L		No evidence	No evidence	No evidence	Decreased to low proportions in EU/EEA
Omicron	BA.2.86 + R346T	n/a	R346T		No evidence	No evidence	No evidence	Decreased to low proportions in EU/EEA

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Omicron	BA.2.86 + F456L	n/a	F456L		No evidence	No evidence	No evidence	Mutation present in the majority of circulating descendants

x: A67V, Δ69-70, T95I, G142D, Δ143-145, N211I, Δ212, ins215EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F
y: G142D, N211I, Δ212, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K
z: A67V, Δ69-70, Δ143-145, N211I, Δ212, G339D, S371F, S373P, S375F, D405N, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, D796Y, Q954H, N969K
q: G75D,S98F,V126A,W152L,R190S,K417T,K444N,V445G,L452M,N481K,V642G,K679R,S691P,T791I,Y796H,D936G
n/a: not applicable, no WHO label has been assigned to this variant at this time
All sub-lineages of the listed lineages are also included in the variant, e.g., B.1.429.1 is included in B.1.427/B.1.429 as it is a sub-lineage of B.1.429.
(a) No assessment of transmission is given for variants in the monitoring category, only detected/not detected.
(b) The earliest detections from several different countries are close in time and there is no clearly demonstrated travel link to a specific country that explains the detections.
(c) The property of concern for this variant was the fact that there are reports of difficulties associated with detecting it in upper respiratory tract samples. These difficulties were not caused by primer-template mismatch but rather by the virus not being present in sufficient quantities in the upper respiratory tract.
(d) Any amino acid substitution
(e) Preliminary mutations based on a limited number of genomes

Table 3: De-escalated variants**.**

Vaccines and Latest Monoclonal Antibodies and Their Efficacy Against New Variants at June 2025

CDC Recommendations: The World Health Organization states that currently approved COVID-19 vaccines are expected to remain effective against the NB.1.8.1 variant.

The CDC advises that everyone over the age of six months get the 2024-2025 COVID-19 vaccine, specifically the 2024-2025 Moderna COVID-19 Vaccine. People who have never received a COVID-19 vaccine, are age 65 and older, are immunocompromised, live at a long-term care facility, are pregnant, breastfeeding, trying to get pregnant, and/or want to avoid getting long COVID, should get the vaccine, especially.

Recent developments in monoclonal antibody therapies have focused on targeting newer variants of SARS-CoV-2. Here are some of the most promising monoclonal antibodies currently under investigation or authorized for use:

1. Bebtelovimab

- *Target:* The spike protein, specifically the Receptor-Binding Domain (RBD)
- *Efficacy:* Bebtelovimab has shown activity against several Omicron subvariants, including BA.2 and BA.4/BA.5

However, its efficacy has been reduced against some more recent Omicron sublineages, leading to evolving recommendations for its use.

- *Indication:* It has been authorized for use in patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease, including those who are immunocompromised or elderly

2. Evusheld (AstraZeneca's tixagevimab and cilgavimab)

- *Target:* The spike protein

- *Efficacy:* This combination has been shown to be effective against many variants, including Omicron and is currently used both for pre-exposure prophylaxis and post-exposure treatment in high-risk individuals. However, recent studies indicate that its efficacy against newer Omicron subvariants (e.g., XBB) may be reduced
- *Indication:* Recommended for immunocompromised individuals who may not respond well to vaccination or who are at increased risk of exposure

3. *Casirivimab and Imdevimab (REGEN-COV)*

- *Target:* The spike protein, blocking the virus from entering human cells
- *Efficacy:* This combination has demonstrated variable effectiveness against the Omicron variants, with significant reductions in neutralization against some subvariants. As a result, the FDA withdrew its Emergency Use Authorization (EUA) for this mAb for treatment of COVID-19 in certain regions
- *Indication:* Previously used for mild to moderate cases in high-risk patients, but less relevant with the emergence of resistant variants

4. Sotrovimab

- *Target:* The spike protein
- *Efficacy:* Sotrovimab was initially effective against several VOCs, but its efficacy against Omicron and its subvariants (particularly BA.4/BA.5) is now limited. The monoclonal antibody is no longer authorized in regions where Omicron subvariants predominate
- *Indication:* Earlier used for mild to moderate COVID-19 treatment in high-risk patients, but replaced by more effective alternatives in most settings

5. Arctivimab and Cilgavimab (Bamlanivimab, Etesevimab)

- *Target:* Spike protein
- *Efficacy:* This combination showed reduced efficacy against Omicron and its subvariants. However, they remain relevant for earlier strains like Delta
- *Indication:* Previously used in high-risk populations, but largely superseded by newer agents due to reduced effectiveness against current VOCs

Use in Immunocompromised and Elderly Populations

Immunocompromised and elderly patients are at a heightened risk of severe COVID-19 outcomes and many do not respond adequately to vaccines. Monoclonal antibodies provide an important therapeutic option for these groups, particularly in preventing disease progression and reducing hospitalization rates.

1. Immunocompromised Patients

- Individuals with conditions such as cancer, HIV/AIDS or those undergoing immunosuppressive treatments (e.g., organ transplant recipients) may not mount an adequate immune response to vaccination. For these patients, monoclonal antibodies can serve as a critical bridge to protection
- Monoclonal antibody treatments, such as Evusheld, have been used for pre-exposure prophylaxis in these individuals, offering protection against infection and severe disease. However, as new variants emerge, updated monoclonal antibody therapies that can effectively neutralize these strains are critical

2. Elderly Patients

- Elderly individuals, particularly those over the age of 65, are at higher risk of severe disease due to age-related decline in immune function and the presence of comorbidities such as diabetes, hypertension and cardiovascular disease
- Monoclonal antibodies have shown a role in both treatment and prevention in this group, providing significant benefits when administered early in the course of infection
- As with immunocompromised patients, it is important that monoclonal antibody treatments are updated to address the evolving viral landscape, particularly in the face of more immune-evasive variants

Challenges and Limitations

- *Resistance to New Variants:* One of the main challenges is the growing resistance of newer variants to existing monoclonal antibodies. As the virus continues to evolve, there is an ongoing need for the development of monoclonal antibodies that can

target conserved regions of the spike protein or other viral components

- *Distribution and Accessibility:* The availability of monoclonal antibodies varies by region and distribution to high-risk populations, especially in low-resource settings, remains a challenge
- *Side Effects and Safety:* While monoclonal antibodies generally have a favorable safety profile, some side effects, such as allergic reactions, are possible. Careful monitoring is required, particularly for immunocompromised and elderly patients who may have other health conditions

WHO Recommendations

The World Health Organization (WHO) alongside its Technical Advisory Group on Virus Evolution (TAG-VE) maintains its guidance that Member States should focus on particular actions to effectively manage uncertainties concerning antibody escape and the severity associated with NB.1.8.1:

- Implement neutralization assays utilizing human sera that is representative of the impacted community or communities, as well as sera from unexposed animal models infected with live virus isolates of NB.1.8.1
- Carry out a comparative assessment to identify alterations in ongoing or incidental indicators of severity

The WHO, along with its Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC), routinely evaluates the influence of variants on the efficacy of COVID-19 vaccines to provide guidance for potential updates to vaccine formulations. In its most recent recommendation, dated 15 May 2025, the WHO TAG-CO-VAC indicated that monovalent JN.1 or KP.2 continue to be suitable antigens for COVID-19 vaccines, while monovalent LP.8.1 is also deemed a viable alternative vaccine antigen [21. The following risk evaluation adheres to the WHO's published framework for assessing the risks related to SARS-CoV-2 variants and is grounded in the evidence currently accessible. This risk assessment will be updated regularly as additional evidence and data emerge from various countries. With the decreasing incidence of Variants of Interest (VOIs) and the growing inability of Variants Under Monitoring (VUMs) to satisfy the definitions for VOIs, the WHO commenced risk evaluations for VUM designations alongside VOI designations on 29 November 2024.

Conclusion

In light of the changing global epidemiological landscape regarding COVID-19 and to assist member states in managing the persistent threat posed by COVID-19 as they transition from addressing it as a public health emergency of international concern to its incorporation into broader disease prevention and control strategies, the Standing Recommendations for COVID-19 under the International Health Regulations issued by the Director General of the World Health Organization, which were originally set to end on 30 April 2025, have been prolonged for another year, maintaining the same guidelines, until 30 April 2026 [22]. The ongoing mutations of SARS-CoV-2 variants require continual advancement in the development of monoclonal Antibodies (mAbs) aimed at neutralizing new and evolving strains. For patients with compromised immune systems, monoclonal antibodies such as Evusheld, Bebtelovimab and newer combination treatment options provide essential preventive and therapeutic measures, particularly for those at elevated risk of experiencing severe illness. As the virus keeps mutating, persistent research, which includes the creation of new bispecific monoclonal antibodies and long-lasting therapies, will be crucial in enhancing health outcomes for these susceptible populations. Future studies focused on emerging variants and enhancements in vaccine strategies will be vital to thwarting potential future outbreaks and reducing the repercussions of SARS-CoV-2 on worldwide health.

Conflict of Interest

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Author's Contribution

All authors contributed equally in this paper.

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