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Mini Review

Update On The Latest Sars-Cov-2 Variants In Immunocompromised Patients With Comorbilities: Clinical Outcomes, Viral Persistence, Intra – Host Evolution And Implications For New Combination Therapies. A Narrative Review And Clinical Experience.

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Running title: Persistent SARS-CoV-2 Infection in Immunocompromised Patients.

Abstract

Background: Despite the transition of Coronavirus Disease 2019 (COVID-19) from a pandemic to an endemic phase, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to pose a major threat to immunocompromised patients. Individuals with impaired immune function—including recipients of solid organ or hematopoietic stem-cell transplantation, patients with hematologic malignancies, individuals receiving B-cell-depleting therapies, those with advanced HIV infection, and patients undergoing prolonged immunosuppressive treatment—remain at substantially increased risk of severe disease, prolonged viral replication, persistent infection, and poor clinical outcomes. Persistent SARS-CoV-2 infection in these populations has emerged as an important clinical challenge and may also contribute to intra-host viral evolution and the emergence of variants with immune escape or antiviral resistance.
Methods: A narrative review of the literature was performed through a structured search of PubMed, Embase, and Scopus databases covering publications from January 2020 to June 2026. Current international guidelines, observational studies, randomized clinical trials, systematic reviews, and relevant case reports focusing on immunocompromised adults with SARS-CoV-2 infection were critically reviewed.
Results: Current evidence demonstrates that impaired humoral and cellular immunity significantly delay viral clearance, favour prolonged viral shedding, and increase the likelihood of persistent infection. Immunocompromised patients experience higher rates of hospitalization, intensive care admission, opportunistic infections, and mortality compared with immunocompetent individuals. Persistent viral replication provides favourable conditions for intra-host viral evolution, facilitating the accumulation of mutations associated with immune escape and antiviral resistance. Recent advances in antiviral therapy, including remdesivir, nirmatrelvir/ritonavir, molnupiravir, and emerging long-acting monoclonal antibodies, have improved patient outcomes, although therapeutic failures and drug resistance remain important concerns. These findings highlight the growing importance of individualized antiviral stewardship strategies in this vulnerable population.
Conclusions: Persistent SARS-CoV-2 infection in immunocompromised patients represents a distinct clinical entity requiring early diagnosis, individualized therapeutic approaches, careful virological monitoring, and multidisciplinary management. Future research should focus on optimizing antiviral strategies, understanding mechanisms of viral evolution, and developing novel therapeutic interventions capable of preventing prolonged infection and limiting the emergence of new viral variants.

Keywords: SARS-CoV-2; Immunocompromised patients ; Viral persistence ; Intra-host evolution; Antiviral therapy ; Monoclonal antibodies; Antiviral stewardship.

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INTRODUCTION

The global epidemiology of Coronavirus Disease 2019 (COVID-19) has changed substantially since the beginning of the pandemic. Although widespread vaccination, naturally acquired immunity, and the availability of effective antiviral therapies have markedly reduced mortality in the general population, SARS-CoV-2 continues to represent a significant cause of morbidity and mortality among immunocompromised patients. Unlike immunocompetent individuals, who generally achieve viral clearance within a few days or weeks, immunocompromised patients frequently experience prolonged viral replication, delayed immune responses, recurrent clinical relapses, and persistent detection of replication-competent virus. These characteristics have transformed persistent SARS-CoV-2 infection into an increasingly recognized clinical syndrome requiring dedicated diagnostic and therapeutic strategies.

Accumulating evidence indicates that prolonged infection is not simply associated with worse clinical outcomes but also creates a unique biological environment that promotes continuous viral evolution. Inadequate humoral and cellular immune responses allow sustained viral replication, while selective pressure exerted by antiviral agents and neutralizing antibodies may facilitate the emergence of escape mutations. Several reports have documented the appearance of spike protein mutations during chronic infection, many of which resemble those subsequently identified in circulating variants of concern. Consequently, immunocompromised hosts are increasingly regarded not only as patients at high risk of severe COVID-19 but also as potential reservoirs for intra-host viral evolution.

The spectrum of immunocompromising conditions[1,2] associated with persistent SARS-CoV-2 infection is broad and includes recipients of solid organ or hematopoietic stem-cell transplantation, patients with hematological malignancies, individuals receiving anti-CD20 monoclonal antibodies or other B-cell-depleting therapies, subjects undergoing chemotherapy or prolonged corticosteroid treatment, patients with primary immunodeficiencies, and individuals with advanced HIV infection.[4,5,6] Each of these conditions is characterized by distinct defects in innate or adaptive immunity, leading to variable susceptibility to severe disease and prolonged viral persistence.

Recent therapeutic advances have considerably modified the management of COVID-19 in these populations. Direct-acting antiviral agents, including remdesivir and nirmatrelvir/ritonavir, together with newer antiviral compounds and long-acting monoclonal antibodies, have improved clinical outcomes. Nevertheless, optimal treatment duration, the management of antiviral resistance, drug–drug interactions, and the role of combination therapies remain incompletely defined, particularly in patients with persistent infection. These challenges emphasize the growing importance of antiviral stewardship, integrating timely diagnosis, individualized treatment, virological monitoring, and rational use of antiviral agents to maximize therapeutic efficacy while minimizing the emergence of resistance.

In this narrative review, we critically examine the current evidence regarding the epidemiology, immunopathogenesis, clinical outcomes, mechanisms of viral persistence, intra-host evolution, and therapeutic management of SARS-CoV-2 infection in immunocompromised patients. Particular attention is devoted to recent advances in antiviral therapy, monoclonal antibodies, and antiviral stewardship, highlighting current knowledge gaps and future research priorities. [3]

CLINICAL OUTCOMES

SARS-CoV-2 infection in immunocompromised patients is associated with significantly worse clinical outcomes compared with the general population. Multiple studies have demonstrated higher rates of hospitalization, intensive care unit (ICU) admission, and mortality among patients with impaired immune function, particularly those with hematologic malignancies, solid organ transplants, or receiving immunosuppressive therapies [4,5].

Patients with hematologic malignancies represent one of the highest-risk groups, with reported mortality rates exceeding 30% in early pandemic cohorts, although outcomes have improved with vaccination and antiviral therapies [6,7]. Similarly, solid organ transplant recipients exhibit increased risk of severe disease due to chronic immunosuppression and reduced capacity to mount effective antiviral immune responses [8,9].

Clinical presentation in immunocompromised individuals may differ from that of immunocompetent patients. Symptoms can be atypical, attenuated, or prolonged, and inflammatory markers may be less elevated, potentially delaying diagnosis and appropriate management [10]. Furthermore, these patients are more likely to experience prolonged viral shedding and persistent infection, which can last for weeks or even months, contributing to ongoing symptoms and increased risk of complications [11].

Elderly patients with comorbidities, although not always classified as immunocompromised, frequently share similar clinical trajectories due to immunosenescence and reduced physiological reserve. Advanced age, cardiovascular disease, diabetes, chronic kidney disease, and chronic lung disease are well-established risk factors for severe COVID-19 outcomes, including several respiratory failure and death [12].

Another important aspect is the increased risk of secondary infections. Immunocompromised patients are more susceptible to bacterial and fungal superinfections,

particularly during prolonged hospitalization or ICU stay. However, despite this risk, the actual prevalence of confirmed bacterial co-infection at presentation remains relatively low, while empirical antibiotic use is disproportionately high, highlighting a gap in antimicrobial stewardship

Vaccination has significantly improved outcomes in immunocompromised populations, reducing the risk of severe disease and mortality. Nevertheless, vaccine effectiveness may be reduced in these patients, particularly in those receiving B-cell depleting therapies, underscoring the continued vulnerability of this group and the need for additional preventive strategies [13].

Overall, SARS-CoV-2 infection in immunocompromised and high-risk elderly populations is characterized by increased severity, atypical clinical features, prolonged disease course.

These findings support the need for tailored clinical management and targeted public health interventions.

VIRAL PERSISTENCE AND VARIANTS OF CONCERN IN IMMUNOCOMPROMISED PATIENTS

Infections caused by SARS-CoV-2 in patients with weakened immune systems are often marked by extended periods of viral replication and slow clearance, creating an environment that fosters viral evolution within the host. Unlike those with healthy immune systems, who generally eliminate the virus in a few weeks, immunocompromised individuals can test positive for the virus through PCR for much longer durations, sometimes lasting several months [14,15].

Continuous infection in these individuals has been linked to ongoing viral replication rather than leftover non-infectious RNA, as shown by viral culture and genomic sequencing analyses. This sustained viral presence heightens the risk for mutations to accumulate in the viral genome, especially in the spike protein region, which could impact the virus's fitness, ability to spread, and capacity to evade the immune system [16].

Numerous case reports and studies have highlighted the evolution of SARS-CoV-2 within immunocompromised patients, noting the rise of mutations similar to those found in variants of concern. These observations lend credence to the idea that patients with compromised immune systems might act as breeding grounds for new variants due to the selective pressures posed by incomplete immune responses or antiviral medications.

The influence of antiviral treatments and monoclonal antibody therapies may also play a significant role in viral evolution in these cases. Insufficient or extended exposure to antiviral drugs has been linked to the emergence of mutations associated with resistance, particularly among patients experiencing persistent infections. This underscores the necessity for judicious use of antiviral medications and vigilant monitoring within immunocompromised groups.

Variants of concern that exhibit enhanced transmissibility or the ability to escape immunity present additional challenges for immunocompromised patients. Weakened immunity from vaccines and diminished neutralizing antibody responses can result in a greater vulnerability to reinfection or a prolonged illness.

From both a clinical and public health standpoint, the issue of prolonged viral shedding presents significant challenges concerning infection control and isolation guidelines. Typical isolation durations may not be adequate for individuals with weakened immune systems, necessitating more extended precautions to prevent transmission within healthcare settings.

In summary, the persistence of the virus and its evolution within hosts are vital considerations in understanding SARS-CoV-2 infections in immunocompromised patients, impacting clinical management, antiviral approaches, and global monitoring of new variants [17,18].

SARS-COV-2 VARIANTS OF CONCERN AS OF 26 JUNE 2026

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 29 June 2026 is available here.

Description of the tables

The tables 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)

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

All sub-lineages of the listed lineages are also included in the variant. For the full list of lineages, please look at the table here.

Variants under monitoring

WHO label	Lineage + ad ditional muta tions	Country first detected (community)	Spike muta tions of interest	Year and month first detected	Impact on transmissibility	Impact on im munity	Impact on se verity	Transmission in EU/EEA
Omicron	NB.1.8.1	n/a	G184S, A435S, K478I	n/a	No evidence	No evidence	No evidence	Community
Omicron	XFG	n/a	S31P, K182R, K444R, N487D, T572I	n/a	No evidence	No evidence	No evidence	Dominant
Omicron	BA.3.2	South Africa	(r)	November 2024	No evidence	No evidence	No evidence	Community

r: I326V, G339Y, A348P, S371F, S373P, S375F, R403K, D405N, R408S, K417N, A435S, N440R, V445A, G446D, L452W, N460K, S477N, T478N, E484K, G496S, Q498R, N501Y, K529N, E554D, E583D, D614G, H625R, N641K, V642G, E654K, H655Y, N679R, P681R, A688D, S704L

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 + ad ditional muta tions	Country first detected (community)	Spike muta tions of inter est	Year and month first detected	Impact on transmissibil ity	Impact on im munity	Impact on se verity	Rationale for de-escalation
Alpha	B.1.1.7	United King- dom	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 im pact on vaccine in duced immunity
n/a	B.1.1.7+E484K	United King dom	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 ex tremely low levels in the EU/EEA and available data indi cating 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)
Eta	B.1.525	Nigeria	E484K, D614G, Q677H	December 2020	No evidence	Increased (m) (12, 17)	No evidence	No longer detected or detected at ex tremely 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 ex tremely 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 ex tremely 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 ex tremely 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 ex tremely 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 ex tremely low levels in the EU/EEA
n/a	A.23.1+E484K	United Kingdom	V367F, E484K, Q613H	December 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at ex tremely 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 ex tremely 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 ex tremely 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 ex tremely 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 ex tremely 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 ex tremely 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 ex tremely 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 ex tremely low levels in the EU/EEA
n/a	B.1.526	USA	E484K, D614G, A701V	December 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at ex tremely 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
n/a	P.2	Brazil	E484K, D614G	January 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at ex tremely 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 ex tremely 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 EU/EEA
n/a	AT.1	Russian Federation	E484K, D614G, N679K, ins-679GIAL	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
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
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
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
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 Delta
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 King dom	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 ex tremely 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 ex tremely low levels in the EU/EEA
Omicron	BA.3	South Africa	(z)	November 2021	No evidence	No evidence	No evidence	Detected at ex tremely low levels in the EU/EEA
Omicron	BA.2 + L452X	n/a	L452X	n/a	No evidence	Increased (50)	No evidence	Detected at ex tremely 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 mutation-al 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 mutation-al 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 mutation-al 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 ex-tremely low levels in the EU/EEA
Omicron	BF.7	n/a	R346T, F486V	n/a	No evidence	No evidence	No evidence	Detected at ex tremely low levels in the EU/EEA
Omicron	BA.2	South Africa	(y)	November 2021	Increased (v) (42, 52)	Increased (v) (46)	Reduced (v) (53, 54)	Parental lineages are no longer circu-lating, ECDC moni-toring 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 circu-lating, ECDC moni-toring 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 circu-lating, ECDC moni-toring 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 ex tremely low levels in the EU/EEA
Omicron	XBB (z)	n/a	N460K, F490S	n/a	Increased (1)	In - creased(57-61)	Unclear(62)	Detected at ex tremely low levels in the EU/EEA
Omicron	CH.1.1	n/a	K444T, L452R	n/a	Increased (1, 63)	Increased (v) (57, 58, 60, 64)	No evidence	Detected at ex tremely 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
Omicron	BA.2.86 + F456L	n/a	F456L		No evidence	No evidence	No evidence	Mutation present in the majority of circulating descendants
Omicron	KP.3	n/a	F456L, Q493E		No evidence	No evidence	No evidence	Decreased to low proportions in EU/EEA
Omicron	XEC	n/a	T22N, F59S, F456L, Q493E, V1104L		No evidence	No evidence	No evidence	Decreased to low proportions in EU/EEA
Omicron	LP.8.1	n/a	H445R, Q493E, F186L, R190S		No evidence	No evidence	No evidence	Decreased to low proportions in EU/EEA

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.

Variant classification functions as a key means of communication to notify EU/EEA nations regarding the development of SARS-CoV-2 variants that pose significant concerns and may influence the public health situation within the EU/EEA [19].

The ECDC Strategic Analysis of Variants in Europe (SAVE) Working Group is an interdisciplinary group consisting of ECDC . At present, these meetings occur monthly to evaluate both the actual and anticipated effects of existing and newly identified SARS-CoV-2 variants within the EU/EEA and on a global scale.

ECDC employs three classifications for variants to convey escalating levels of concern regarding new or emerging SARS-CoV-2 variants: variant under monitoring (VUM), variant of interest (VOI), and variant of concern (VOC). The criteria for classification and suggested actions for member states can be found here: ECDC variant classification criteria.

Ongoing evaluation of new evidence related to variants is conducted based on information gathered from epidemic intelligence, genomic horizon scanning, or various scientific resources. When a determination is made to categorize a variant differently, whether it be adding, removing, or changing its status, the tables are adjusted to show this modification. These tables are regularly reviewed and shared with ECDC stakeholders, including the European Commission and the WHO Regional Office for Europe's collaborative virus characterization working group.

Data on variant surveillance, which encompasses the distribution of VOC and VOI proportions within the EU/EEA, as well as detailed epidemiological updates for specific countries concerning COVID-19, is accessible through 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 13 April 2026 is available here.

Description of the tables

The tables 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:
   - o Transmissibility
   - o Immunity
   - o 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.

ANTIVIRALS AND MONOCLONAL ANTIBODIES STEWARDSHIP IN IMMUNOCOMPROMISED PATIENTS AND ELDERLY PATIENTS WITH COMOEBILITIES

Handling SARS-CoV-2 infections in individuals who are immunocompromised, older, or have multiple health issues necessitates a customized strategy that combines antiviral treatments and monoclonal antibodies in a well-organized

stewardship plan. These groups face a higher likelihood of experiencing severe illness, extended periods of viral replication, and less effective immune reactions, highlighting the importance of prompt and suitable treatment measures [19,20].

- **Antiviral Therapy Stewardship**

Direct-acting antivirals such as remdesivir and nirmatrelvir/ritonavir are essential for the prompt treatment of COVID-19 in individuals at high risk. Research shows that starting antiviral treatment early can greatly lower the chances of developing severe illness, being hospitalized, and dying [21]. Nevertheless, for those who are immunocompromised, typical treatment lengths might not suffice due to extended viral replication, and in certain situations, longer or repeated treatments may be necessary[22].

Principles of stewardship are vital to guarantee proper use of antivirals. These principles include:

- quickly identifying patients who qualify
- starting treatment promptly (within 5 to 7 days after symptoms begin)
- taking into account interactions between medications, especially for transplant patients and those on complicated drug regimens
- steering clear of unnecessary or extended treatment without a virological reason

Insufficient antiviral exposure might lead to inadequate viral control and promote the development of mutations linked to resistance, especially in individuals with ongoing infections [23].

- **Monoclonal Antibodies Stewardship**

Monoclonal antibodies (mAbs) that target the SARS-CoV-2 spike protein have been crucial in halting disease progression among high-risk individuals. Nonetheless, their efficacy has been substantially affected by the rise of viral variants capable of evading the immune response[24].

In individuals with compromised immune systems, monoclonal antibodies may hold particular significance because their natural antibody production is diminished. However, careful management is necessary to:

- identify mAbs effective against prevalent variants
- refrain from usage when resistance is probable
- combine mAbs with antiviral treatment when suitable

The ongoing development of variants posing a threat has resulted in decreased effectiveness or the discontinuation of several monoclonal antibodies, highlighting the necessity for ongoing monitoring and updates to guidelines. [25, 26, 27].

- **Integrated Stewardship Approach**

A comprehensive stewardship strategy for antivirals and monoclonal antibodies should include:

- risk stratification of patients
- rapid diagnostic pathways
- multidisciplinary decision-making (infectious disease specialists, pharmacists)
- monitoring for treatment response and resistance
- alignment with updated clinical guidelines

Such an approach is essential to optimize outcomes, reduce inappropriate use, and limit the development of antiviral resistance.

Antiviral and monoclonal antibody stewardship is a critical component of COVID-19 management in immunocompromised, elderly, and comorbid patients. Optimizing the timing, selection, and duration of therapies, while adapting to evolving variants, is essential to improve clinical outcomes and ensure sustainable use of therapeutic resources.

LATEST THERAPEUTIC STRATEGIES: MONOCLONAL ANTIBODIES IN SARS-COV-2 INFECTION

Monoclonal antibodies (mAbs) targeting the SARS-CoV-2 spike protein have represented a key therapeutic and preventive strategy, particularly for immunocompromised, elderly, and high-risk patients. These agents provide passive immunity by neutralizing viral entry into host cells, thereby reducing disease progression and hospitalization in early phases of infection [28].

- **Evolution of Monoclonal Antibody Therapies**

Early monoclonal antibodies, including bamlanivimab/etesevimab and casirivimab/imdevimab, demonstrated efficacy in reducing hospitalization and death in high-risk outpatients . However, the rapid emergence of variants of concern (VOCs), particularly Omicron and its sublineages, has significantly reduced the neutralizing activity of many first-generation mAbs, leading to withdrawal or reduced clinical use [29,30].

This dynamic landscape highlights a critical limitation of monoclonal antibodies: their efficacy is highly dependent on the antigenic profile of circulating variants. Indeed, several studies have shown that mAbs developed against earlier strains may lose effectiveness against newer variants due to spike protein mutations [31].

- **Next-Generation Monoclonal Antibodies**

Recent efforts have focused on developing next-generation monoclonal antibodies with broader neutralizing activity and resistance to viral escape. Agents such as Sipavibart, approved in 2025 for pre-exposure prophylaxis in immunocompromised patients, represent a new class of long-acting antibodies designed to maintain efficacy across multiple variants [32].

As of 26 June 2026, the only “next generation” anti–SARS CoV 2 monoclonal antibody with guideline support for immunocompromised patients is pemivibart for pre exposure prophylaxis

(PrEP), contingent on local variant susceptibility; sipavibart has RCT efficacy only when non F456L variants predominate and is not reliable when F456L lineages circulate. [33].

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- **What "next generation mAbs" mean in June 2026 (actionable options)**

1) Pemivibart (VYD222/PEMGARDA) — PrEP (most clinically relevant)

- **Use case:** immunocompromised patients (including with comorbidities) who are unlikely to mount adequate vaccine responses; PrEP only (not treatment). IDSA recommendation is conditional and hinges on variant susceptibility.

- **Evidence supporting use in immunocompromised hosts:**
- CANOPY phase 3 interim RCT data support preventive benefit and an immunobridging pathway for evolving variants [34].
- Mechanistic support in immunocompromised and non immunocompromised cohorts shows **>55 fold increase in measured neutralizing titers against XBB.1.5 at day 28 [35]**, strengthening plausibility against contemporary Omicron-lineage variants when in vitro activity is retained. [36, 37]
- **Key limitation (critical in June 2026):** real world effectiveness will track **in vitro neutralization vs currently circulating variants**; the guideline explicitly conditions use on susceptibility. [**TABLE 1**]

2) Sipavibart (AZD3152) — PrEP but variant-limited (F456L problem)

- SUPERNOVA phase 3 RCT in immunocompromised patients (Lancet Infect Dis 2025) showed prevention of symptomatic COVID 19 over 181 days:
- Any variant: 7.4% vs 10.9% symptomatic COVID 19 (sipavibart vs comparator), RRR 34.9% (p=0.0006).
- Non F456L variants: 3.3% vs 5.5%, RRR 42.9% (p=0.0012).
- F456L-containing variants: 2.9% vs 3.9%, RRR 30.4% with CI crossing 0 (no clear efficacy).
- Practical June 2026 implication: if your region's dominant lineages carry Spike F456L (or functionally resistant phenotypes), sipavibart should generally not be relied upon for protection. This is explicitly highlighted in the RCT interpretation (resistant variants dominating by Nov 2024).

How to choose in an immunocompromised patient with comorbidities (June 2026) [**TABLE 1**]

1. Confirm local susceptibility (genomic surveillance / up-to-date in vitro neutralization reports) before giving any anti spike mAb PrEP, because variant escape is the dominant failure mode.
2. If susceptible: pemivibart is the leading next gen PrEP option with IDSA support and 2025–2026 clinical/immunobridging evidence in immunocompromised populations.
3. If resistant to available mAbs: do not substitute another mAb empirically; consider non mAb strategies (antivirals/other approaches) per local protocols—this dataset does not provide June 2026 treatment-mAb options with proven activity.

ROLE IN IMMUNOCOMPROMISED PATIENTS

Immunocompromised individuals benefit particularly from monoclonal antibodies due to their impaired ability to mount effective humoral responses. In this population, mAbs can be used both for:

- pre-exposure prophylaxis, to prevent infection
- early treatment, to reduce viral load and disease severity

Clinical trials have demonstrated that monoclonal antibodies can significantly reduce symptomatic infection and severe outcomes in immunocompromised patients when administered early.

However, persistent infection in these patients may promote viral evolution under selective pressure, potentially reducing mAb effectiveness and necessitating combination strategies with antivirals.

Table 1. Next-generation mAbs relevant to immunocompromised patients (June 2026).

Agent	Intended role	Variant dependency (key point)	Best supporting clinical evidence	Clinical Evidence
Pemivibart	Pre-exposure prophylaxis in moderately/severely immunocompromised	Use only if predominant regional variants are susceptible	IDSA 2025 focused update supports use aligned to FDA EUA; CANOPY phase 3 interim and immunobridging support	IDSA guideline update (CID 2025) [34]; CANOPY interim phase 3 (CID 2025) [35]; neutralization-titer analysis including immunocompromised cohort (JID 2026) [36]
Sipavibart	Pre-exposure prophylaxis in immunocompromised (investigational/availability dependent)	Loss of efficacy vs F456L lineages (e.g., KP.2/KP.3*)	SUPERNOVA phase 3 RCT prevention benefit when susceptible variants dominated; no clear benefit vs F456L	Phase 3 RCT, immunocompromised cohort (Lancet Infect Dis 2025) [37]

COMBINATION STRATEGIES AND FUTURE DIRECTIONS

Emerging research endorses the implementation of integrated therapeutic strategies that combine monoclonal antibodies with direct-acting antivirals, especially in patients exhibiting prolonged infections or elevated viral loads. This approach has the potential to enhance viral clearance and mitigate the likelihood of resistance emergence[38].

Future avenues in monoclonal antibody therapy encompass:

- the creation of broadly neutralizing antibodies aimed at conserved viral epitopes
- the employment of antibody cocktails to thwart escape mutations
- the incorporation of real-time genomic monitoring and diagnosis information.

Despite these advancements, the swift evolution of SARS-CoV-2 poses a significant obstacle, necessitating ongoing modifications to monoclonal antibody frameworks [39].

Monoclonal antibodies continue to play a crucial role in the management of SARS-CoV-2 among immunocompromised individuals, the elderly and persons with comorbility. Nevertheless, their clinical effectiveness is increasingly shaped by viral evolution. Next-generation antibodies and combination therapy strategies appear to offer promising solutions to address existing challenges and enhance clinical outcomes in at-risk populations.

DISCUSSION

This review emphasizes the intricate relationship between the immune status of the host and SARS-CoV-2 infection among patients with compromised immune systems. In contrast to immunocompetent patients, these individuals often show extended viral replication, delayed clearance of the virus, and uncommon clinical paths. The ongoing presence of SARS-CoV-2 infection carries significant consequences not only for how individual patients are managed but also for controlling infections and the evolution of the virus.

A key discovery highlighted in the literature is the possibility of viral evolution within the host during lengthy infections. Numerous studies have indicated the build-up of mutations in immunocompromised patients, raising concerns about the potential emergence of variants with changed transmissibility or abilities to evade the immune response. This highlights the necessity for prompt antiviral treatment and vigilant virological monitoring in this demographic.

From a clinical standpoint, confirming active infection poses significant challenges. Continued positive PCR results may indicate either ongoing viral replication or merely residual non-infectious viral RNA, complicating the decisions surrounding isolation and treatment. Advanced diagnostic approaches, such as viral culture and genomic sequencing, could offer further clarity but are generally not available in many clinical environments.

A major concern highlighted in this review is the prevalent use of empirical antibiotics among immunocompromised COVID-19 patients. Even though the rates of confirmed bacterial co-infections are relatively low, the prescription of antibiotics remains elevated, motivated by diagnostic ambiguity and the perceived susceptibility of these patients. This habit fosters antimicrobial resistance and underscores the pressing need for enhanced antimicrobial stewardship programs specifically designed for immunocompromised groups.

Management strategies for SARS-CoV-2 infection in individuals with weakened immune systems must be tailored to the individual. Antiviral medications, like remdesivir and nirmatrelvir/ritonavir, are crucial, especially when administered early. Nonetheless, occurrences of treatment failures and relapses have been noted, indicating that prolonged or merged antiviral therapies could be vital in numerous situations. The significance of monoclonal antibodies has changed with the rise of new variants, and their effectiveness may differ based on the strains circulating.

In conclusion, SARS-CoV-2 infection in patients with compromised immune systems constitutes a unique clinical scenario that necessitates specialized diagnostic, therapeutic, and stewardship approaches.

Future studies should concentrate on discovering dependable biomarkers for active infection, refining antiviral treatment protocols, and formulating evidence-based guidelines

to enhance clinical results and diminish the inappropriate use of antivirals and antibiotics for comorbilities.

CONCLUSION

The swift progression of SARS-CoV-2 has significantly reduced the efficacy of numerous monoclonal antibodies, highlighting the necessity for ongoing adjustments in therapeutic methodologies and immediate genomic monitoring. Within this framework, next-generation broadly neutralizing antibodies along with combination therapies that include antivirals represent promising pathways to enhance viral elimination and improve clinical results.

A crucial objective is the establishment of integrated stewardship initiatives that encompass antivirals, monoclonal antibodies, and antibiotics. These initiatives should concentrate on the prompt identification of high-risk individuals, the timely commencement of suitable treatments, the reduction of unnecessary use of antimicrobials, and the continuous surveillance for resistance and therapeutic failures.

Subsequent investigations should emphasize the discovery of dependable biomarkers for active infection, the refinement of treatment duration for persistent conditions, and the formulation of evidence-based protocols specifically designed for immunocompromised and elderly populations. Strengthening global monitoring systems and guaranteeing equitable access to effective treatments will be vital in alleviating the ongoing consequences of COVID-19 among at-risk populations.

Conflicts of interest

The authors do not have a commercial or other association that might pose a conflict of interest.

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