Clinical challenges of SARS-CoV-2 variants (Review)

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Abstract. Since the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, there have been challenges recognizing the clinical features of SARS-CoV-2 and identifying therapeutic options. This has been compounded by viral mutations that affect clinical response and primary epidemiological indicators. Multiple variants of SARS-CoV-2 have been identified and classified on the basis of nomenclature implemented by scientific organizations and the World Health Organisation (WHO). A total of five variants of concern (VOCs) have been identified to date. The present study aimed to analyse clinical and epidemiological features of each variant. Based on these characteristics, predictions were made about potential future evolution. Considering the time and location of SARS-CoV-2 VOC emergence, it was hypothesised that mutations were not due to pressure caused by the vaccines introduced in December 2020 but were dependent on natural characteristics of the virus. In the process of adapting to the human body, SARS-CoV-2 is expected to undergo evolution to become more contagious but less deadly. SARS-CoV-2 was hypothesized to continue spread through isolated epidemic outbreaks due to the unimmunized population, mostly unvaccinated children and adults, and for coronaviruses to continue to present a public health problem.

Contents

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1. Introduction

Coronaviruses are a large virus family that cause a number of diseases in mammals and birds, such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). Phylogenetic evidence suggests that RNA-dependent RNA polymerase sequence divergence occurred 7,000-8,000 years ago in mammals, showing that this type of virus is prone to interspecies transmission and pathogenicity (1).

There are currently seven types of coronavirus with human tropism: Human coronavirus (HCoV)-HKU1, HCoV-OC43, HCoV-229E, HCoV-NL63 (2003), MERS-CoV, SARS-CoV and SARS-CoV-2 (2). Among the Coronaviridae family, the β-coronavirus genus (which includes SARS-CoV and SARS-CoV-2) has the highest human pathogenic potential.

Coronaviruses are named for the crown pattern formed by surface spikes. Their genomes are large RNA-type structures, 26-32 kb in length, with single-stranded positive-sense RNA (3). Viruses such as SARS-CoV-2 acquire mutations due to rapid replication and error-prone viral polymerase (4).

The open reading frame (ORF)1a/b region of coronaviruses encodes 16 non-structural proteins, while ORFs region encodes structural proteins such as spike (S), envelope, membrane and nucleocapsid (N) protein. Surface antigenic structures are specific and mutations result in viral variants with unique features (5).

Viruses such as SARS-CoV-2 adapt to the immune response in different species various tissues, leading to mutation. Most mutations, however, do not lead to a change in phenotype or infectivity (6).

All seven types of coronavirus in humans have different genetic mutations. MERS-CoV exhibits mutant S, ORF4b and ORF3 genes, while SARS-CoV exhibits mutant S and ORF8 genes (4). The primary genetic anomalies in SARS-CoV-2 are located in the S gene (4). Natural selection produces variants that promote virus survival via more efficient inter-human transmissibility, replication or intracellular penetration

capacity. Additionally, the frequency of random events serves a key role in the creation of novel variants; evolution of more transmissible forms is more likely than evolution of more pathogenic variants (4).

A nomenclature to define novel emerging viruses was developed to facilitate surveillance of epidemiological events. Variant refers to changes in genomic structures; strain denotes changes in terms of virulence or transmissibility (7).

Viral genotype changes are classified as follows: Mutation, single viral genomic mutation; lineage, a group of associated viruses with common origin and variant, viral genomes that contain one or more mutations. To guide implementation of measures to protect the population, public health organizations introduced the terms variant of concern (VOC), variant of interest (VOI) and variant under monitoring based on the impact on the population (disease severity and transmissibility). The United States also uses the terms variant being monitored and variant of high consequence, although no variant of SARS-CoV-2 has been included in the latter category so far.

The Global Initiative on Sharing All Influenza Data, Nextstrain, and Pango systems have specified SARS-CoV-2 lineage nomenclature. Furthermore, the World Health Organisation (WHO) founded the Technical Advisory Group on Virus Evolution to define key genetic lines emerging from SARS-CoV-2 mutations and classified these as VOC or VOI. VOCs include Alpha, Beta, Delta, Gama and Omicron and VOIs include Mu and Lambda variants (Table I) (8).

The present review investigated SARS-CoV-2 variants and their clinical features. The present study aimed to support healthcare practitioners and public health policymakers in treating patients and minimizing the outbreaks.

2. SARS-CoV-2 variant gene mutations and impact of clinical features on disease evolution

Numerous mutations, including five VOCs have been identified as a result of the global effort to detect mutations in the SARS-CoV-2 genome (Table I).

Alpha variant (Lineage B.1.1.7). The first notable variant, Alpha, was detected in southeast England in September 2020 and caused concern due to its increased transmissibility and number of viral replications compared with its predecessors. SARS-CoV-2 Alpha variant was reported to have a transmissibility of 1.3-1.5 times that of the original strain (9).

The Alpha variant has 10 mutations in the S protein that led to structural changes. The N501Y mutation appears in the S glycoprotein receptor-binding domain (RBD) at position 501 and results in amino acid asparagine (N) being replaced with tyrosine (Y). The N501Y mutation increases the binding affinity via an additional binding site for angiotensin-converting enzyme (ACE)2 SARS-CoV-2 entry receptor (10,11). H69del/V70del mutation is potentially associated with immune evasion and is not detected by S-gene PCR assays, resulting in S gene target failure. The P681H mutation near the S1/S2 furin cleavage site facilitates epithelial cell entry (10,12). As a result of these mutations, there has been an increase in the percentage of hospitalizations and mortality. The D614G mutation (also registered in all subsequent VOCs) is hypothesized to enhance viral replication (10).

A model was created to evaluate the relative change in transmissibility and level of immune evasion for distinct SARS-CoV-2 variants while accounting for false negatives, reporting delays, disease seasonality, non-pharmaceutical intervention (such as self-isolation and social distancing) and vaccination (13). The study estimated that Alpha variant exhibits a 46.6% increase in transmissibility but no immunological escape from protection conferred by previous wild-type infection.

Monel *et al* (14) analysed 426 nasopharyngeal swabs from patients who had microbiologically confirmed SARS-CoV-2 infection in a retrospective study: 200 samples were from the pre-Alpha dominance period (before September 2020) and 226 were from the dominant Alpha surge. The aforementioned study found a strong correlation between viral antigen detection and viable viral shedding, as well as an association between infectious titre and rapid diagnostic test positivity, low cycle threshold (Cq) value, early symptom onset and the absence of nasopharyngeal IgG or IgA. Alpha variant exhibits higher nasopharyngeal viral load and longer viral shedding, as well as a stronger affinity for ACE2 receptor binding and higher fusogenicity (15,16).

A study of 381,773 participants used the national Covid-19 Infection Survey, a representative, longitudinal household sample, to investigate the spread of Alpha variant in the United Kingdom (17). A total of 9,032 (50.3%) positive results were triple-gene-positive, indicating detection of all three regions of the SARS-CoV-2 genome tested (ORF1ab region and N and S gene); 5,258 (29.3%) had S gene target failure (indicative of Alpha variant) and 3,673 (20.4%) exhibited other gene combinations. Although infection with S gene target failure was more common than triple-gene-positive infection in symptomatic infection, absolute increases in confirmed diagnosis were similar regardless of whether people reported symptoms, suggesting that asymptomatic infection may serve a key role in the spread of Alpha variant. No notable change was observed in the efficacy of natural or vaccine-induced antibodies, potentially due to the lack of pressure induced by introduction of large-scale vaccination at that time (December 2020-August 2021) (18).

According to Vassallo *et al* (19), patients infected with the Alpha variant of SARS-CoV-2 exhibit a more unfavourable evolution than those infected with previous strains. A total of 65 patients infected with Alpha variant participated in the aforementioned study, which compared patients who had never been immunized against COVID-19 with a control group of patients infected with a previous strain. The non-immunized mortality rate was 15.4 compared with 12.9% in the control group. There were also significant differences in the percentage of patients admitted to intensive care unit: 27.7 in the study group vs. 8.6% for control group. The severity of pneumonia was associated with intensive care admission and mortality rate. In patients with Alpha infection, the severity of the disease was also associated with increased viral load, as assessed by Cq value in reverse transcription-quantitative PCR diagnostic testing in the aforementioned study. By contrast, mortality was lower during the second wave of disease (March-May 2020), which was characterised by the spread of Alpha infection, according to a retrospective investigation in the United Kingdom (20).

Table I. Variants of concern.

WHO nomenclature	Pango lineage	GISAID clade	Nextstrain clade	Emergence
Alpha	B.1.1.7.	GRY	20I (V1)	United Kingdom, Sep 2020
Beta	B.1.351	GH/501Y.V2	20H (V2)	South Africa, May 2020
Delta	B.1.617.2	G/478K.V1	21A, 21I, 21J	India, Oct 2020
Gamma	P.1	GR/501Y.V3	20J (V3)	Brazil, Nov 2020
Omicron	B.1.1.529	GRA	21K, 21L, 21M	South Africa, 24 Nov 2021

WHO, World Health Organisation; GISAID, Global Initiative on Sharing All Influenza Data.

SARS-CoV-2 PCR positivity was predicted by seven symptoms in a study of >1 million people in England: Loss or change of smell, loss or change of taste, fever, new persistent cough, chills, appetite loss and muscle ache (21).

Beta variant (B.1.351). In December 2020, South Africa announced the discovery of a novel variant with an E484K mutation. Three subgroups of this variant with a total of 12 mutations and one depletion were discovered: K417N, E484K and N501Y mutations led to an increase in S protein affinity for ACE2 (7).

Certain evidence suggests that one S protein mutation, E484K, may suppress the efficacy of neutralizing antibodies (22,23).

Studies have investigated the effect of three amino acid changes found in numerous VOCs (including Alpha, Beta and Gamma) on the structure and function of SARS-CoV-2 S glycoprotein RBD (24,25). The aforementioned studies discovered that these alterations change the structure, stability and ability of the RBD to bind to ACE2 in an unpredictable manner. Thus, RBD VOC substitutions change the structure and stability of the RBD, with K417N and N501Y increasing stability and E484K decreasing stability. These substitutions result in stability similar to the wild-type/Wuhan strain RBD, but with a more open conformation and higher ACE2 binding affinity.

The aforementioned mutations caused contagiousness of the novel variants to increase by up to 52% (7). The E484K mutation causes conformational changes that put pressure on immunological evasion (7). These RBD substitutions in Beta S protein decrease the binding and neutralization of both mRNA vaccine-induced antibodies and potent human monoclonal antibodies (24).

According to one study, Beta exhibits increased rates of transmissibility (32.4%) and immune escape (61.3%) (13).

To the best of our knowledge, there are few studies on Beta variant and with most reports focus on increased viral load and immune response evasion (7,26). A study evaluating the impact of Beta variant in South Africa during the second wave of infection found an increase in hospitalization rate and in-hospital mortality (26). The increased mortality was due to a higher percentage of elderly people being admitted to hospitals, as well greater demand on the healthcare system.

Gamma variant (P.1. or 20J/501Y.V3, Lineage B.1.1.28). Due to three changes in the RBD domain (K417T, E484K and N501Y), the WHO included Gamma variant in the VOC group simultaneously with Beta variant. This novel variant has 17 mutations, 11 of which are in the S protein. These mutations have consequences in terms of infectivity, risk of reinfection and immune evasion: Compared with wild-type, Gamma variant exhibits a 161% increase in infection rate and 50% increase in mortality (7).

A model simulation indicated that Gamma variant has a 43.3% increase in transmissibility rate and 52.5% increase in immune escape (13). Gamma variant shows an improved ability to resist the immune response acquired during infection with previous variants (13).

The most common symptoms identified in 423 people infected with Gamma variant of SARS-CoV-2 who worked in the health system in Sao Paulo, Brazil, were coryza, headache, cough, sore throat, myalgia, and asthenia (27).

SARS-CoV-2 caused by Gamma variant is more likely than wild-type to cause cold-like symptoms. Hyposmia/anosmia and dysgeusia are more common in younger and female patients according to one study (7). Coryza (73%) and headache (72%) are among the most common symptoms (27).

Delta variant (1.2.7., Lineage B.1.617. or B.1.617.2). In October 2020, India announced the discovery of a novel variant including three key S protein mutations (L452R, E484Q and P681R) that increased rate of transmission (8). This variant caused concern due to increased household transmissibility (+64%) and doubled risk of hospitalization compared with Alpha (28). Because the genomic changes discovered in this variant include mutations found in both Alpha and Beta variants, it was considered to be an epidemic variant with significant risk (29). The strain subsequently became dominant in multiple countries (including Denmark, Germany and the Netherlands), suggesting that it had a competitive advantage over previously identified strains (30). A Delta variant outbreak was discovered in Guangzhou, China, in May 2021, with rapid spread (four transmission generations within 10 days) (31).

To understand the links between viral variants, disease severity and viral shedding kinetics, a retrospective study evaluated the outcomes of individuals infected with Alpha, Beta and Delta variant (32). Compared with wild-type, Delta was associated with greater risk of ventilation, intensive care unit admission or mortality and the OR odds ratio for pneumonia was 1.88 (95% CI, 0.95-3.76). Alpha and Beta did not display these associations. Vaccination status was linked to decreased severity. Delta was associated with lower PCR

Cq values and increased duration of Cq value ≤30 (median duration, 18 days for Delta, 13 days for wild-type). The aforementioned study revealed a potential link between infection with Delta variant and risk of pneumonia or severe COVID-19. In respiratory samples, Delta was associated with higher viral load and longer viral shedding (32).

Twohig *et al* (33) found that patients infected with Delta variant had more than double the risk of hospital admission and increased risk of hospital attendance (emergency care attendance or hospital admission) compared with those infected with Alpha variant. The aforementioned study also discovered that non-vaccinated patients infected with Delta were more than twice as likely to be admitted to hospital as those infected with Alpha variant. Compared with wild-type and Alpha variant, Delta variant causes more severe illness and poorer clinical outcomes (33).

In a study comparing Delta and Alpha infection traits in southern Italy, researchers discovered a decrease in the proportion of subjects under the age of 36 years with Delta infection, as well as a higher risk of hospitalization; for the two groups, risk of death was similar (34).

A study involving 1,915 patients in South Korea found that individuals diagnosed during community-based spread of Delta were more likely to exhibit symptomatic and severe SARS-CoV-2 (35). Symptoms such as fever, chills, fatigue, cough, sputum production and dyspnea were more common in the Delta-dominant group compared with the Delta-minor group. Moreover, compared with the incidence of asymptomatic cases during the isolation period, pneumonia was more common in the Delta-dominant group. Delta-dominant infection was an independent risk factor for all severity factors (oxygen saturation <95%, progression of dyspnoea, increased pneumonic infiltration) as well as for the probability of hospital transfer in multivariate analysis (35).

The clinical characteristics of the Delta variant include a shorter incubation time, shorter period of evolution towards critical forms of the disease (associated with increase mortality and intensive care admission rate) and a higher frequency of critical forms (31).

A national cohort study in Qatar compared patients infected with Beta with those infected with Delta variant (36). The study revealed that patients with Beta variant were more likely to be hospitalized (27.3 vs. 20.0%) and exhibit mild-moderate or severe-critical disease (27.9 vs. 20.2%). There were no significant differences in the need for supplemental or high-flow oxygen, mechanical ventilation or death between the two groups (36). Old age and comorbidities in patients infected with the Delta variant were associated with higher risk of poor outcomes compared with patients infected with Beta variant (36).

Following infection with Delta, double-vaccinated patients exhibit a considerably decreased risk of intermediate or severe outcomes. Vaccination is associated with decreased peak levels of systemic inflammation, fewer symptoms, fewer instances of asymptomatic infection and improved clinical outcomes (37).

Omicron variant (B.1.1.529). Omicron variant emerged in South Africa and Botswana ~12 months after the previous VOC. This variant contains >60 substitutions, deletions and insertions, including 39 on S protein, of which 15 occur in the RBD and confer a considerable increase in morbidity (10,38,39). Multiple Omicron mutations reported to be identical in the Alpha and Delta variants result in increased transmissibility rate of +105% compared with Delta variant (40). Omicron variant has the ability to avoid infection-blocking antibodies and causes less severe symptoms, exerting less impact on the lungs (39). Tropism for the upper respiratory tract is associated with milder clinical manifestation and decreased mortality. However, the increased presence of the virus in the upper respiratory tract may result in easier spread (39).

One Omicron variant mutation is associated with S gene target failure (or S gene dropout), which means that one region of the gene targeted by PCR testing will result in a false negative (39).

The aforementioned studies indicated that Omicron variant has unique characteristics, such as altered transmissibility and severity of disease, as a result of its dozens of mutations, resulting in altered rates of infection dissemination, morbidity and mortality.

According to preliminary data from South Africa, there are no unique symptoms associated with Omicron variant infection, although more patients are asymptomatic compared with other variants (10).

A study showed that the Omicron-driven fourth wave had a lower severity of disease, with fewer deaths, ICU admissions and length of hospital stay in its first global epicentre in South Africa. This clinical profile is also likely to have been influenced by younger patient age as this age group was less affected by previous variants of the virus (41).

The wave grew faster than preceding waves, replacing the Delta variant within weeks and starting to diminish in both cases and hospital admissions in the fifth week since its start (41).

Mild symptoms were commonly observed in Omicron variant infection. Mild cough, fever, generalized myalgia, malaise, scratchy but not painful throat, headache, body discomfort and moderate to severe fatigue are among symptoms reported by patients (39).

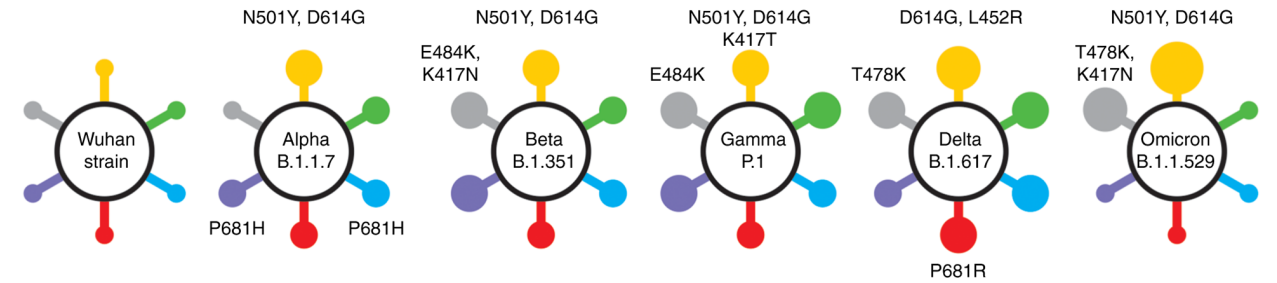
3. Discussion

The proportion of individuals with asymptomatic disease did not significantly change as the incidence of Alpha increased (42). A study of 165 people found that those infected with Alpha (50%) and Beta (90%) variants are mostly asymptomatic, but those infected with Delta (17%) variant exhibit severe clinical symptoms (43). It is important to identify the asymptomatic cases in order to decrease virus transmission, however this is difficult to do in practice and consumes a lot of resources.

With the emergence of multiple variants of SARS-CoV-2, identifying infected patients may become difficult. Identification is accomplished using viral whole-genome sequencing, which is not globally available and has a high cost in terms of both material and human resources (44). Although a number of cheaper tests have been proposed (such as detection of multiple variant lineages with >20 key SARS-CoV-2 S mutations), efforts to adapt diagnostic techniques to rapid viral evolution are ongoing (45). Rapid antigen tests are a less expensive alternative to molecular assay for diagnosis and

Table II. Number of severe acute respiratory syndrome coronavirus 2 tests in different countries.

Country, publication date	Mean number of tests (7-day average)	Number of positive tests (7-day average)	Proportion of positive tests, %	Population, 100,000	Number of tests/100,000 inhabitants
France, 07.01.2022	1,371.513	272.931	19.9	673.9	2,035.2
Germany, 09.01.2022	212.644	48.483	22.8	841.9	252.5
Italy, 07.01.2022	829.723	136.904	16.5	603.2	1,375.5
Spain, 06.01.2022	295.479	89.678	30.3	467.8	631.6
UK, 07.01.2022	1,800.852	180.085	10.0	684.3	2,631.6
US, 07.01.2022	2,304.498	665.539	28.9	3,324.0	693.2
Canada, 07.01.2022	166.253	40.133	24.1	382.5	434.6



Characteristic	Alpha variant B.1.1.7	Beta variant B.1.351	Gamma variant P.1	Delta variant B.1.617	Omicron variant B.1.1.529
Transmissibility	++	++	++	+++	++++
Symptoms	+	+	++	++	–
Hospitalization rate	+	+	+	++	–
Intensive care unit	+	+	+	++	–
Mortality	+	++	++	+	–
Immunology escape	–	++	++	++	+++

+, ++, +++, ++++ : Semiquantitative scale (boost of the effect)
– : Semiquantitative scale (decrease of the effect)

Figure 1. Mutations and clinical characteristics of severe acute respiratory syndrome coronavirus 2 variants of concern. The size of each spike glycoprotein signifies the magnitude of the effect associated with a specific gene mutation. +, increase; -, decrease.

are sensitive to Alpha, Beta and Gamma variants (46,47). Serological tests determine prior infection based on the detection of antibodies but there is no data on the ability to discriminate between different viral strains (48).

SARS-CoV-2 has a range of clinical features and undergoes continuous evolution (Fig. 1).

Although respiratory symptoms (assessed by lung damage) are the most common, the mechanisms triggered by infection are various and dynamic; these include cytokine storm, coagulation disorders, as evaluated by the appearance of thrombosis, oxidative stress that causes ferroptosis, changes in immune cells and neurological impairment (49-53). Typical clinical manifestations in the first reports of SARS-CoV-2 (including fever, fatigue, loss of smell, myalgia, headache, cough and shortness of breath), have either become less significant or associated with specific variants (49-53). During SARS-CoV-2 infection, interferon pathways become impaired, causing higher mortality and longer disease course (54).

Alpha, Beta, Gamma, and Delta variants were discovered in 2020. All of these variants were isolated before SARS-CoV-2 vaccination became widely available (8,55). As a result, their emergence was more likely due to spontaneous mutations arising during gene transcription instead of the vaccine or convalescent plasma treatment. Omicron variant emerged following immunisation efforts, especially in developed countries. However, only ~25% of the population in South Africa (in which Omicron emerged) was vaccinated at the end of November 2021, which suggests that there was not enough pressure from immunological escape to lead to novel variants (8). Based on these findings, it was hypothesized that the occurrence of mutations in SARS-CoV-2 is the result of natural processes rather than human intervention.

From the perspective of the impact of each variant on public health, as assessed by indicators such as mortality, hospitalization risk, and admission in intensive care units, variations may arise from differences between national health systems. On the other hand, concerns about the severity of variants were not always realised, based on data from retrospective studies. The better preparation of health systems from one wave to the next and early introduction of antiviral therapy (such as remdesivir), thromboprophylaxis, high flow oxygen therapy or non-pharmacological treatments (placing patients in a prone position) had a considerable impact (56-59).

Changes in clinical features such as anosmia or dysgenesis occurred during the emergence of Gamma infection and were notable following emergence of the Omicron variant. Clinical signs have changed, suggesting a progression towards a cold-like character with a self-limiting evolution (39).

Given the large number of symptomatic people and increased demand for SARS-CoV-2 infection tests, it is unclear whether extensive testing is still feasible and necessary (Cojocaru *et al*, unpublished data). Analysis of the average number of tests reported by certain European countries, the United States and Canada in the first 7 days of 2022 revealed significant variation in the number of diagnostic tests performed for SARS-CoV-2 infection (Table II) (60). The positive rate is higher where the number of tests is lower, suggesting a large number of undiagnosed positive cases. In these cases, it seems logical to change the approach to symptomatic infections by focusing resources on cases with a high risk of adverse effects and expanding hotline networks to assist these patients (Cojocaru *et al*, unpublished data).

A study has revealed an average of 7.23 mutations per sample and a significant frequency of single nucleotide transitions (61). Shen *et al* (62) found SARS-CoV-2 genetic variation in certain infected patients, indicating rapid viral evolution. Although the appearance of novel variants is directly associated with the number of existing viral units, the emergence of novel mutations with negative effects is possible even in areas where viral transmission is low. However, it is predicted that mutations will be promote an increase in contagiousness rather than severity. Therefore, an increasing number of people will develop immune responses following vaccination or infection. SARS-CoV-2 infection is predicted to form a pattern of influenza-like outbreaks of varying magnitude. However, reproduction of the seasonal pattern of the infections is less likely as SARS-CoV-2 is not associated with periodicity in viral transmission and outbreaks (Cojocaru *et al*, unpublished data).

Immune evasion as a way of avoiding the host immune response creates a risk of emergence of a novel variant (Cojocaru *et al*, unpublished data). An *in vitro* study has shown that substitution of the E484K gene, which is found in Beta and Gamma variants, is responsible for immune escape from convalescent serum or vaccine-induced antibodies (22). A high degree of immune escape has also been reported for the Delta and Omicron variants and may be associated with mutation on T478K gene (63).

Another approach that may be considered is based on the spread of infection in unimmunized people, which is supported by the fact that partial protection generated by vaccinations that only protect against severe forms of disease. SARS-CoV-2 infection may be more common among young children, especially since vaccination for children aged 5-12 years has been introduced in few countries (Cojocaru *et al*, unpublished data).

As SARS-CoV-2 is expanding faster than previously known seasonal coronaviruses or influenza viruses, an epidemiological model predicts that risk of infection will persist for a long period (6). This will have an impact on travel, event participation and public health. Although the general principles of combating the spread have been known since the sixteenth century, based on quarantine and virus transmission prevention, these measures are difficult to implement in the modern era due to high population mobility, urban sprawl and the easy spread of misinformation through communication channels (64). The international rapid response in creating vaccines and treatments that lower viral replication and risk of multisystem impairment is unprecedented. Societal attitudes do not fully keep up with rapid progress of medical research and pose a barrier to current challenges.

The incidence of cancer in post-COVID patients is not yet known. Currently, it is only known that COVID-19 pandemic delayed cancer screening and late therapy resulted in more aggressive cancer behaviour. This may be due to difficulties in scheduling physician visits and delayed cancer diagnosis.

The emergence of SARS-CoV-2 variants has raised issues about vaccination efficacy. Multiple studies have been performed to identify mutations that may be responsible for the decline in vaccine effectiveness (65,66). Current data suggest that protection for the Alpha variant induced by Pfizer-BioNTech vaccine is similar to that for wild-type SARS-CoV-2 virus, but is significantly lower for Beta, Gamma and Delta variants (65,66). Preliminary data on Pfizer-BioNTech vaccine indicated that a third dose is required for adequate protection against Omicron variant infection (67).

Inequalities in the ability to respond to viral spread remain primarily due to global social, economic, and cultural differences; this may provide a viral reservoir that will trigger outbreaks. SARS-CoV-2 will continue to be a major challenge spread of viral infection is controlled (68). In the past two years, SARS-CoV-2 has resulted in >313 million cases and 5.5 million deaths, as well as a global economic crisis, which has affected the $90 trillion global economy (69).

4. Limitations

Although the present systematic review adds to knowledge of SARS-CoV-2 variants and their associated clinical symptomatology, it has certain limitations. The present review analysed only SARS-CoV-2 VOC mutations and clinical signs. The number of reports which describe SARS-CoV-2 symptoms is still limited. The knowledge of various strains and variants, as well as their effect on symptoms, is incomplete. Researchers may also struggle to discover new mutations and describe new symptoms given the capacity of the virus to develop new variants.

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Authors' contributions

CC and EC conceptualized the study. EC designed the methodology. CC, EC, DZ and AMT performed the literature review. AMT constructed the figure. DZ edited the manuscript. EC wrote the manuscript and supervised the project. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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