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Narrative review

Novel SARS-CoV-2 variants: the pandemics within the pandemic

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ABSTRACT

Background: Many new variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been termed *variants of concern/interest* (VOC/I) because of the greater risk they pose due to possible enhanced transmissibility and/or severity, immune escape, diagnostic and/or treatment failure, and reduced vaccine efficacy.
Aims: We sought to review the current knowledge of emerging SARS-CoV-2 variants, particularly those deemed VOC/Is: B.1.351, B.1.1.7, and P.1.
Sources: MEDLINE and BioRxiv databases, as well as the grey literature, were searched for reports of SARS-CoV-2 variants since November 2020. Relevant articles and their references were screened.
Content: Mutations on the spike protein in particular may affect both affinity for the SARS-CoV-2 cell receptor ACEII and antibody binding. These VOC/Is often share similar mutation sets. The N501Y mutation is shared by the three main VOCs: B.1.1.7, first identified in the United Kingdom, P.1, originating from Brazil, and B.1.351, first described in South Africa. This mutation likely increases transmissibility by increasing affinity for ACEII. The B.1.351 and P.1 variants also display the E484K mutation which decreases binding of neutralizing antibodies, leading to partial immune escape; this favours reinfections, and decreases the *in vitro* efficacy of some antibody therapies or vaccines. Those mutations may also have phenotypical repercussions of greater severity. Furthermore, the accumulation of mutations poses a diagnostic risk (lowered when using multiplex assays), as seen for some assays targeting the *S* gene. With ongoing surveillance, many new VOC/Is have been identified. The emergence of the E484K mutation independently in different parts of the globe may reflect the adaptation of SARS-CoV-2 to humans against a background of increasing immunity.
Implications: These VOC/Is are increasing in frequency globally and pose challenges to any herd immunity approach to managing the pandemic. While vaccination is ongoing, vaccine updates may be prudent. The virus continues to adapt to transmission in humans, and further divergence from the initial Wuhan sequences is expected. **Erik Boehm, Clin Microbiol Infect 2021;27:1109**

Introduction

The evolutionary rate of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is low (approximately 1×10^{-3} substitutions/site/year) thanks to its proof-reading RNA polymerase. This represents a fixation of 1 or 2 nucleotide changes per month per lineage in the 30,000 base pairs of the virus [1]. These deletions, insertions or substitutions of nucleotides may be either synonymous, with few or no repercussions to the virus, or non-synonymous, leading to a change in the amino-acid sequence. The huge number of infected individuals and the high viral load produced during each infection offer many opportunities for SARS-CoV-2 mutations to arise and undergo selection, especially during increasing population immunity. Those mutations, especially when arising on the S-gene coding for the spike (S) protein, may affect

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both viral entry into targeted cells—mediated by the binding of S to its ACEII receptor—and the efficacy of antibodies. Because the receptor binding domain (RBD) of S is the main target of neutralizing antibodies [2], and all approved vaccines express a form of S, mutations to S and its RBD in particular pose a concern for vaccine effectiveness and transmissibility of SARS-CoV-2. Mutations at the N-terminus are also potentially problematic, as a number of highly potent neutralizing antibodies target this domain [3]. The impact of the mutations occurring in other regions of the genome is less well characterized.

Early in the pandemic, the D614G mutation of S arose and is now found in nearly every sequence worldwide, likely due to epidemiological factors and a transmission advantage. In the summer of 2020, a variant spreading in minks accumulated numerous mutations while retaining the potential to infect humans, which led to the slaughtering of Danish mink populations [4].

By the end of December 2020, new variants have emerged that have accumulated multiple mutations, called 'variants of interest' (VOIs) because they lead to phenotypic modifications, or have genomic mutations suspected to lead to such modifications, and have been identified in multiple transmission events or in multiple countries. 'Variants of concern' (VOCs) have additionally been demonstrated to be associated with increased transmissibility, increased virulence, or changes in clinical disease presentation, or decreased effectiveness of public health and social measures or available diagnostics, vaccines, and therapeutics [5].

Here we describe variants meeting the definition of VOC and VOI as of March 2021, and discuss their known characteristics.

Sources

We searched the MEDLINE and BioRxiv databases for reports of SARS-CoV-2 variants since November 2020. The grey literature, including Google database and Twitter, was surveyed using the same keywords. Search terms used in various combinations were as follows: "SARS-CoV-2", "variants", "variants of concern", "VOC", "variants of interest", "VOI", "mutations", "evolution", "B.1.1.7", "B.1.351", "P.1", "B.1.148", "B.1.1.28", "N501Y", "E484K", and "L452R". We screened all articles identified and relevant references cited in those articles.

Overview of new variants

An overview of the new VOCs and VOIs is given in Table 1. Lineage names, as determined by Pango (https://cov-lineages.org/descriptions.html) and characterized by a combination of genetic and epidemiological supports, are commonly used, as are names given upon first identification [6].

The number of new mutations accumulated by many of these VOCs and VOIs before detection is rather high. For some, the apparent lack of intermediates suggests a long period of undetected replication and evolution, which may be explainable by intra-host evolution during a long chronic infection, poor monitoring, evolutionary pressure due to high exposure rates, or evolution within an intermediate animal host such as mink [4]. Notably, some mutations have arisen independently multiple times.

Common features of the VOCs include multiple mutations in S compared to the Wuhan reference sequence, and at least one mutation in the RBD of S. They are associated with a surge or rebound of the pandemic in countries where they have been identified, particularly in the UK, South Africa and some cities of Brazil. The B.1.1.7, B.1.351, and P.1 variants are now known to have variously established clusters in all continents except Antarctica [7].

Mink variants and animal reservoirs

Some of divergent sequences were identified in humans who had been in contact with mink [8], and attributed to adaptation of the virus to mink hosts, suggesting that the role of human-to-animal-to-human transmission chains need to be carefully considered. Notably, some mink-associated variants achieved partial escape from neutralizing antibodies [9], emphasizing that the emergence of immune escape mutations does not necessarily mean that emergence of these variants is due to selection pressure from human population-level immunity. Transmission of these variants have been contained [10], likely due to efforts in culling mink populations. Nonetheless, there remains a risk of further outbreaks from mink and other farmed or domestic animals. It must be kept in mind that novel variants may be concerning not just for their effects in humans and human-to-human transmissibility, but also

Table 1
Naming conventions and number of mutations of the main three variants of concern (VOCs) identified in late 2020

Location of first identification	Pangolin name	Nextstrain name	Other names	Mutations
Britain	B.1.1.7	20I/501Y.V1	-VOC 202012/01 VOC 202102/02: also carries the E484K mutation	14 aa mutations (10 in S) 6 aa deletions, VOC 202102/02: +1 S mutation
South Africa	B.1.351	20H/501Y.V2		18 aa mutations (7 in S) 3 aa deletions (3 in S)
Brazil	P.1	20J/501Y.V3		21 aa mutations (12 in S) 3 aa deletions
Brazil	P.2			14 aa mutations (3 in S)
Philippines	P.3			7 lineage defining S mutations
USA, California	B.1.427/B.1.429			15-20 aa mutations (4-6 in S), 0-1 deletions,
USA, New York	B.1.526			15 aa mutations (6 in S), 3 deletions
Multiple	B.1.525		Sub-variant G/484K.V3: also carries the E484K mutation	16 aa mutations (6 in S) 3 deletions (3 in S), G/484K.V3: +1aa S mutation
Uganda			Ugandan A.23.1	12-17 aa mutations (4-7 in S)
Colombia			B.1.111-E484K	10 non-synonymous coding
Tanzania			A.VOI.V2	31 aa mutations (11 in S), 3 deletions (3 in S)
India	B.1.617		'double mutant'	At least 2 RBD mutations in S
Wales	AP.1		B.1.1.70.1	17-21 aa mutations, (2-5 in S)
France, Brittany	B.1.616		'Brittany Variant'	10 S mutations
France, Paris			HMN.19B/'Henri Mondor'	18 aa substitutions, 8 in S

Aa, amino acid; S, spike protein; RBD, receptor binding domain.

their ability to establish animal reservoirs of SARS-CoV-2 and the potentially elevated transmission due to a human–animal–human route [11].

Notable mutations

Several combined mutations define each new lineage (Table 2). When occurring in S, and especially in its RBD, these mutations may affect receptor or antibody binding. The following mutations are particularly noteworthy.

The *N501Y mutation*, within the RBD of S, results in greater affinity for human ACEII receptor [12], which may increase transmissibility.

The *E484K mutation*, also in the RBD of S, is associated with immune escape [13] and increased ACEII affinity [14]. Notably, a similar mutation, E484Q, is also associated with immune escape [13].

The *K417N* and *K417T mutations* of the S protein are involved in conformational change and in antibody escape [13,14]. K417N was found to attenuate affinity for ACEII, but this is compensated for by the presence of N510Y, as affinity is still higher than when both mutations are absent [15].

The *L452R mutation* is within the RBD, and thus may be relevant to transmissibility or immune escape [16]; indeed, the L452R mutation has been shown to result in binding-escape from the therapeutic mAb bamlanivimab (LY-CoV555) [17].

The *Δ69-70 mutations* of the S protein are associated with increased infectivity and decreased sera neutralization [18,19], as well as an S-gene target failure (SGTF) in some multiplex RT-PCR tests [20]. Most tests have built-in redundancy by targeting multiple genes, and thus will still detect SARS-CoV-2 if it harbours this mutation.

Notably, mAbs in development that target conserved epitopes with SARS-CoV-1 are thought to retain their activity against all S mutants.

Mutations in the nucleocapsid (N) protein may pose a potential diagnostic risk, as commercially available antigenic rapid diagnostic tests (Ag-RDTs) detect the presence of N protein [21].

General antibody neutralization and immune escape remarks

Studies testing specific monoclonal antibodies often report severe reductions or complete escape following mutations in S. Thus VOCs and VOIs with mutations in S are a concern for various antibody-mediated therapies such as etesivimab (LY-CoV016), bamlanivimab, and casirivimab (REGN10933) [17,22]. Resistance to specific monoclonal antibodies or resistance due to a single mutation are unlikely to significantly affect neutralizing activity of polyclonal sera, while multiple mutations may have more substantial effects; this is supported by studies using vaccine sera and pseudovirus (PsV) [23]. No single mutation identified so far would be sufficient to abolish neutralizing activity, so we can expect that current vaccines and exposure to other variants will still provide some degree of protection. Notably, neutralization studies give no indication on the effectiveness of cell-mediated immunity elicited after vaccination, which also contributes to protection against coronavirus disease 2019 (COVID-19). Indeed, the vast majority of SARS-CoV-2 T-cell epitopes are not affected by the mutations characterizing the current VOCs [24].

Characteristics of WHO-designated VOCs

B.1.1.7 or 501Y.V1 or VOC 202012/01

Transmissibility/viral load and duration

This VOC is reportedly 43–82% more transmissible [25], with conflicting data suggesting elevated viral loads that persist longer [26], or no significant differences in viral load [27]. Notably, implementation of strict public health and social measures have successfully reduced transmission. As of March 2021, it accounted for nearly 80% of sequenced cases in Europe; up-to-date frequencies can be found at https://cov-lineages.org/global_report_B.1.1.7.html.

Symptom presentation and disease severity

B.1.1.7 was initially reported to not result in increased severity, and it contains a loss-of-function mutation in Orf8 that is linked to milder disease [28]. Later reports indicated that it was associated with an increased risk of severe disease and death, but more controlled studies have shown that not to be the case [29,30]. Preliminary results from a self-reported symptom survey reveal that, relative to infections by previous variants, B.1.1.7 infection more frequently causes cough, sore throat, fatigue and myalgia, while anosmia is less common [31].

Host changes

A small increase in the number of infections in the under-20 age group has been suggested [32], but no conclusions should be drawn given the limited data and multiple risks of bias. *In vitro* data suggest that this variant may be able to establish infections in rats and mice [33], but this does not appear to be the case *in vivo* [34].

Immune escape concerns

This variant contains a few mutations linked with potential immune escape (Table 2), and convalescent plasma or vaccine sera show reductions in neutralizing antibody titres, although neutralization generally remains robust (Supplementary Material Table S1). There is no evidence of elevated reinfection rates [30], and current vaccines largely retain their effectiveness against this variant (Table 3). To date, *in vitro* data suggest escape from the therapeutic mAb etesevimab, while casirivimab, bamlanivimab, and imdevimab retain their activity [33]. Recently, the E484K mutation has been identified in multiple B.1.1.7 sequences (designated VOC202102/02). No relevant data are available for this sub-variant yet, but other E484K-bearing variants have been linked to reduced vaccine efficacy and escape from some therapeutic mAbs. Interestingly, it has been reported that antibodies generated following an infection with B.1.1.7 demonstrated poor cross-reactivity against other strains (parental or B.1.351), indicating some degree of asymmetric heterotypic immunity [35]. This raises the possibility that a VOC demonstrating escape from the immune response raised against other strains may also result in those other strains demonstrating escape from the immune response raised against the VOC.

Diagnostic impact

This variant results in SGTF in some multiplex RT-PCR tests, but Ag-RDTs are apparently unaffected [36]; no other diagnostic issues are known.

B.1.351

Transmissibility/viral load and duration

B.1.351—which emerged in a background of high HIV prevalence and high rates of population exposure—quickly spread to become the dominant lineage in South Africa [37]. There is currently very little data outside of South Africa on B.1.351, and transmission is reportedly 1.5x higher for this variant [38]. In February 2021 it reached nearly 80% of sequenced cases in Africa; up-to-date frequencies can be found at https://cov-lineages.org/global_report_B.1.351.html.

Table 2

Mutations of selected new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants (only S mutations shown) compared to the Wuhan reference sequence.[a] Multiple mutations are associated with immune escape or increased ACEII affinity [3,12–14,17–19,58,60–65]

Description of mutation (mutations: effects/features)	B.1.1.7	B.1.351	P.1	P.2	P.3	A.23.1	B.1.525	B.1.429	B.1.526	B.1.111-E484K	A.VOI.V2	B.1.616	HMN.19B	AP.1	B.1.617
D614G: already dominant worldwide [60]	+	+	+	+	+	–	–	+	+	+	–	+	–	+	+
N501Y: increased affinity for the hACEII receptor [12]	+	+	+	–	+	–	–	–	–	–	–	–	+	+	–
E484K: K and Q reduced sera neutralization [13], increased affinity for hACEII receptor [14]	K	K	K	K	K	K	K	–	K	K	K	–	–	–	Q
L452R: loss of mAb[17,61,62], decreased sera neutralization [63]	–	–	–	–	–	–	–	+	–	–	–	–	+	–	+
S13I, **W152C**: Escape from mAbs against the N-terminus [64]	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–
L18F: Immune escape from NAbs against N-terminus [3]	+/–	+/–	+	–	–	–	–	–	–	–	–	–	+	–	–
Δ69, **Δ70:** infectivity increase [19], reduced sera neutralization [18]	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–
Δ 141-143: mAB escape [18]	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–
Δ144: resistance to 4A8 monoclonal antibody [18]	+	–	–	–	–	–	+	–	–	–	+	+	–	–	–
R246I/M: Unk E, may aid nAb resistance? [65]	–	I	–	–	–	–	–	–	–	–	M	–	–	–	–
L249S: May aid resistance to neutralizing Abs	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–
D253G: May aid resistance to neutralizing Abs [65]	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–
V367F: Modest infectivity increase, higher ACEII affinity [61]	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–
K417N/T: conformational change, escapes some nAbs[13,14]	–	N	T	–	–	–	–	–	–	–	–	–	–	–	–
S477N: Result in escape from some mAbs [62]	–	–	–	–	–	–	–	–	+/–	–	–	–	–	–	–
T478R: Within the receptor binding domain	–	–	–	–	–	–	–	–	–	–	R	–	–	–	K
V483: Escape from some mAbs[61]	–	–	–	–	–	–	–	–	–	–	–	A	–	–	–
Q613H: Similar consequences to the D614G mutation?	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–
H655Y: mAb escape, linked to feline propagation [58]	–	–	+	–	–	–	–	–	–	–	+	+	+	–	–
Q677H: near furin cleavage site, may affect transmissibility	–	–	–	–	–	–	+	+/–	–	–	–	–	+/–	–	–
P681H/R: near furin cleavage site, may affect transmissibility	H	–	–	–	H	R	–	–	–	–	H	–	–	–	R
L5F: Unknown effects (Unk E)	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–
T19R, **G142D**, **E154K**, **E156G**, **Δ157-158**, **V382L**, **N440T**, **950N**, **Q1071H**, **H1101D**, **D1153Y**: Unk E	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+/–
T20N, **P26S**, **D138Y**, **R190S**, **T1027I**: Unk E	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
S31F, **S50L**, **P384L**, **A1070S**: Unk E	–	–	–	–	–	–	–	–	–	–	–	–	–	+/–	–
Q52R, **F888L**: Unk E	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–
H66D, **G142V**, **G669S**, **Q949R**, **N1187D**: Unk E	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–
D80A, Δ242-244: Unk E	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–
D80Y, **I210N**, **Δ211**, **Δ247-249**, **W258L**, **R346K**, **Q957H**: Unk E	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–
T95I: Unk E	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+/–
R102I, **F157L**,: Unk E	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–
D215G: Unk E	–	+	–	–	–	–	–	–	–	–	+	+	–	–	–
E1092K, **H1101Y**: Unk E	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–
A570D, **T716I**, **S982A**, **D1118H**: Unknown effects	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
A653V, **D796Y**, **G1219V**: Unk E	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–
A701V: Unk E	–	+	–	–	–	–	–	–	+	–	–	–	–	–	–
V1176F: Unk E	–	–	+	+	+	–	–	–	–	–	–	–	–	–	–
F1121L: Unk E	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–

[a] Green indicates the mutation is present, red that it is not, and grey that it is sometimes present.

Table 3
Clinical observations for new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants

Variants	B.1.1.7	B1.351	P.1	B.1. 427/429	B.1.526	Others
Transmissibility	Rate of transmission 43–82% higher (16)	1.5x higher [38]	2.6-fold higher [47]	18–24% higher [51]	Elevated, no precise data	No published data
Severity	No change [29,30];	Possibly increased fatality rate [38]	Elevated mortality rate, but may be due only to healthcare system overload [48]	No published data	No published data	No published data
Symptoms	Cough, sore throat, fatigue and myalgia more frequent, while anosmia is less common [31]	No published data	No published data	No published data	No published data	No published data
Age distribution of cases	Small, statistically significant shift towards higher youth infection rates; may be an artefact [32]	Anecdotally, more young people being infected	No published data	No published data	Anecdotally, more old people being infected	No published data
Re-infection rate	No significant difference [30]	One study: reinfection independent of serostatus [44]	No precise data, transmission in high seroprevalence environment	No published data	No published data	No published data
Detection by current RT-PCR	S-gene dropout	Unaffected	Unaffected	Unaffected	Unaffected	B.1.525: S-gene dropout, others unaffected
Viral load	Not significantly different [27]	Reportedly higher	No published data	1 Ct-value higher	No published data	No published data
Detection by Ag-RDT	No significant differences [36]	Similar sensitivity [46]	No published data	No data	No published data	No published data

Ag-RDT, antigenic rapid diagnostic test.

Symptom presentation and disease severity

The mortality rate of the second wave was noted to be higher, suggesting the possibility of an increased severity, although differing demographics and overloading of the hospitals are confounding factors [38]. No other data are found in terms of clinical characteristics.

Host changes

In vitro data suggest that this variant may be able to establish infections in rats and mice [33], which seems to have been confirmed *in vivo* [34].

Immune escape concerns

Convalescent plasma or vaccine sera generally show reductions in neutralizing antibody titres, with substantially greater reductions than for B.1.1.7 (Supplementary Material Table S1). This effect is due mostly to the E484K mutation [39]. Notably, efficacy of mAbs approved for COVID-19 treatment—such as etesevimab [17], bamlanivimab, and REGN10989—may be abolished or reduced [22].

Convalescent sera from patients infected with B.1.351 contain highly cross-reactive antibodies able to neutralize other variants, even though antibodies raised against parental viruses are not highly cross-reactive with B.1.351 [40]. A Moderna press release suggests that antibody neutralization titres are above levels expected to be protective [41], while a Pfizer press release showed effectiveness with six cases of B.1.351 in the control group and 0 in the vaccinated group [42]. In contrast, a study in Israel found that infections in vaccinated individuals were eight times more likely to be caused by B.1.351 than in unvaccinated individuals, suggesting reduced vaccine efficacy against B.1.351 [43]. Vaccine studies have generally found decreased efficacy in South Africa, where >90% of the cases were B.1.351, relative to that in the USA (Table 4). Furthermore, serology and epidemiological studies indicated that one third of the population had previously been exposed to earlier SARS-CoV-2 variants (and were excluded from the analysis), suggesting a strong selection pressure for immune escape. A study conducted in South Africa found a >5% reinfection rate that did not differ between seropositive and seronegative people, suggesting a lack of protection in response to previous infections [44].

Concerningly, AstraZeneca's ChAdOx1-nCoV19 vaccine showed only minimal protection against mild or moderate SARS-CoV-2 infection in South Africa, with no data concerning severe disease [45].

Diagnostic impact

The Panbio Ag-RDT sensitivity is apparently unaffected [46]. No diagnostic issues are known.

P.1

Transmissibility/viral load and duration

The P.1 variant is estimated to be 2.6 times more transmissible [47]. Notably, the cases due to the P.1 variant in January in Manaus, a city with high exposure rates, represented 85.4% (41/48) of the identified SARS-CoV-2 sequences [48]. In February 2021, it reached nearly 40% of sequenced cases in South America. Up-to-date frequencies can be found at https://cov-lineages.org/global_report_P.1.html.

Symptom presentation and disease severity

No data are available.

Table 4
Effects of the different variants on therapeutics and vaccines

Vaccines	B.1.1.7	B1.351	P.1	Other VOC/Is
mRNA Vaccine Pfizer/BioNTech BNT162b2	90–95% efficacy in a setting of 81.5% B.1.1.7 prevalence, estimated by SGTF [66]	100% effective (53–100% CI), based on six cases in placebo group versus none in vaccine group [42]	No published data	No published data
Protein subunit vaccine Novavax NVX-CoV2373	85.6% efficacy against B.1.1.7 95.6% efficacy against non-B.1.1.7 Only one severe case [67]	60% efficacy in HIV(−) subjects in South Africa (92.7% of sequences were B.1.351), 51% against B.1.351 specifically No severe cases, too few events to conclude [67]	No published data	No published data
Adenovirus vaccine Janssen (J&J) Ad26.COV2.S	No published data	52% efficacy against moderate disease and 72% against severe/critical disease in South Africa (>95% of sequences were B.1.351), versus 72% efficacy in USA 100% protection against death [68]	No published data	Insufficient data for P.2, No data for others
Adenovirus vaccine AstraZeneca AZD1222	70% efficacy versus B.1.1.7 versus 81% against non-B.1.1.7 [69]	10% efficacy against mild and moderate disease in young people, no data against severe disease [45]	No published data	No published data
mAb therapies:				
LY-CoV555 (Bamlanivimab)	Susceptible	Resistant [22,55]	Resistant [22,55]	B.1.429: Resistant [64]
Etesevimab	Resistant [33]	Resistant [33]	Resistant [33]	No data
REGN10933 and REGN10987 (Casirivimab + Imdevimab)	Susceptible	Partially resistant to Casirimivab, but Imdevimab is effective [33,55]	Partially resistant to Casirivimab but Imdevimab is effective [33,55]	B.1.526 with E484k is resists Casirivimab [70]

Vaccine efficacy is given as efficacy against symptomatic infection unless otherwise specified).
SGTF, S-gene target failure.

Host changes

In vitro data suggest that this variant may be able to establish infections in rats and mice [33], which seems to have been confirmed *in vivo* [34].

Immune escape concerns

Similar to the results reported for B.1.351, the efficacy of therapeutic mAbs—including bamlanivimab, casirivimab, and etesivimab [17,23,33], as well as REGN10989—may be abolished/reduced [22]. The pervasiveness may be due to immune escape in the context of a high level of population immunity [49]. Indeed, modelling suggests up to 28% of the cases in Manaus between December 2020 and February 2021 may have been reinfections [47]. Convalescent plasma or vaccine sera generally show reductions in neutralizing antibody titres, with substantially greater reductions than for B.1.1.7, but less than for B.1.351 (Supplementary Material Table S1). Preliminary data showed a complete escape from neutralization by CoronaVax sera, but neutralization titres were low even against non-VOI strains [50]. While reports of reinfection have been reported for P.1, the time frame is not outside the range of intervals seen with earlier variants.

Diagnostic impact

There are no data on diagnostic impact, but notably P.1 has four mutations in the N gene, suggesting a need for evaluation of Ag-RDT effectiveness.

Characteristics of disputed VOCs considered to be VOIs by the WHO

B.1.429/427/Cal20-C

This variant has been classified as a VOC by the CDC, but has not received that designation from the WHO.

Transmissibility/viral load and duration

These variants are estimated to be 18–24% more transmissible [51], and secondary household attack rate is elevated [52]. Viral load was reported to be approximately two-fold higher. These variants are increasing in prevalence in southern California, and now account for over 50% of the identified sequences there [16].

Symptom presentation and disease severity

No data are available.

Host changes

No data are available.

Immune escape concerns

Serum neutralization is reportedly decreased (Supplementary Material Table S1), and the L452R mutation has been reported to escape neutralization by bamlanivimab.

Diagnostic impact

No data are available, but no issues are expected.

B.1.526

Transmissibility/viral load and duration

This variant has dramatically increased in prevalence in the North-East USA at the present time, and its detection rate has been steadily increasing [7,53].

Symptom presentation and disease severity

Patients with this lineage were on average more frequently hospitalized [53], but this may be due to patient age.

Host changes

Notably, patients with this lineage were on average older [53].

Immune escape concerns

Sub-variants carrying the E484K mutation raise concerns for immune escape. The D253G mutation is also notable, and believed to play a role in immune escape.

Diagnostic impact

No data are available, but no issues are expected.

Other remarks

This variant contains multiple mutations, notably S477N or E484K near the RBD, but not both at the same time. Researchers referred to it as a VOC, although it has not received this designation from the WHO.

B.1.617 variant identified in India

The Indian SARS-CoV-2 Consortium on Genomics has reported detection of a variant with the L452R and the E484Q mutations, but very few data are available at this time. Initially reported as a 'double mutant' for the presence of two prominent RBD mutations (E484Q and L452R), sequences of this lineage lacking E484Q have been found. Preliminary data suggest a reduction in neutralization titres of approximately 2x (Supplementary Material Table S1). The Indian government considers this variant a VOC, but it has not received that designation from the WHO. There are now three recognized sub-variants of B.1.617: B.1.617.1 (all with E484Q), B.1.617.2 (all with Δ157,158), and B.1.617.3, although E484Q and Δ157,158 can also be found in B.1.617 and B.1.617.3. The mutation V382L has also been reported, although its effect is unknown.

Transmissibility/viral load and duration

Detection of this variant temporally corresponds with a surge in cases, and this variant reportedly represented 15–20% of the samples as of March 2021 [54].

Symptom presentation and disease severity

No data are available.

Host changes

No data are available.

Immune escape concerns

Both the E484Q and L452R mutations are a cause for concern for immune escape.

Diagnostic impact

No data are available, but diagnostic impact is unlikely.

Characteristics of other E484 mutation-containing VOIs

The presence of the E484K mutation by itself should be enough to qualify a variant for VOI status. The known instances of variants with the E484K are too numerous to list here, but include: P.2, P.3, and some isolates of A.23.1 and B.1.111, B.1.525, B.1.619, N.9, N.10, and A.VOI.V2. Data on these variants are scarce, but the presence of the E484K mutation raises concerns for immune escape. Many of these variants are temporally linked to a surge in cases, but their emergence may be an effect rather than a cause of such surges.

P.3 is also notable for containing the N501Y mutation that is found in the three variants classified as VOCs by the WHO, which has been linked to increased ACEII affinity/transmissibility, ability to use the ACEII in rats and mice, as well as decreased effectiveness of etesevimab [33,55].

P.2 is linked to reductions in neutralizing antibody titres of convalescent plasma or vaccine sera for P.2 (Supplementary Material Table S1), and there are reports of reinfection for P.2, but the time frame is not outside the range of intervals seen with earlier variants.

A.23.1 is notable for its lack of the D614G mutation, with a Q613H mutation instead that may be functionally similar. A Ugandan variant replaced previously circulating viruses in Uganda within 2 months, suggesting higher transmissibility, and it has already been detected multiple times outside of that country [56].

B.1.621 has been identified in Columbia as having a similar mutation profile (E484K and N501Y) as the VOCs B.1.351 and P.1, but is from a distinct lineage. No further information is available at this time.

In Brazil, a new lineage, provisionally named 'MG' (with a suggested designation of P.4, but the designation is still pending) has been identified with N501T and E484Q mutations in Minas Gerais [57]. No further information is available at this time.

Other VOIs of note

B.1.616, 20C variant identified in Brittany, France

This variant was first identified during a nosocomial outbreak in a geriatric ward. While many cases were severe, this is not unexpected given the age of the patients. This variant has been reported to yield weaker RT-PCR positives, and to have a lower detection rate from nasopharyngeal samples. The current working hypothesis is that this is due to an altered tropism requiring sampling of the lower respiratory tract. Only one case has been detected outside of Brittany, and that case had a confirmed link to the Brittany cluster. Transmission beyond Brittany therefore seems limited, but notably it does possess a mutation linked to transmission in felines [58].

HMN.19B—Henri Mondor 19B variant identified in France

Very little information is available about this variant, but it contains the L452R and N501Y mutations, both of which have been linked to increases in transmissibility. Notably, it belongs to clade 19B, which had become rare from early 2020 and lacks the common D614G mutation; thus its resurgence in this variant may indicate that its mutations confer increased transmissibility [59,60]. No severe cases were reported, and two cases of reinfections were reported, but the subjects had become seronegative prior to infection. One subject had received the first dose of BNT162b2 11 days prior.

Conclusion

New variants, sharing some common mutations, have emerged independently across the world against a background of increasing population immunity, and they have spread rapidly in the areas where they were identified. In many ways this mirrors the early independent emergence and spread of D614G mutations. Their mutations likely render them more transmissible (e.g. N501Y), with some ability to escape previous immunity (e.g. E484K), and they may be able to effectively establish infections in animals that are routinely in close proximity to humans. This was to be expected given the number of infections across the world, and that the virus has only been adapting to human transmission for a short time. While vaccination strategies aim to reduce the burden of COVID-19, the efficacy of the vaccines may be reduced by the emergence of these new mutations; nevertheless, two doses may still protect against severe COVID-19.

With the increase in worldwide genome sequencing surveillance, the number of newly identified variants is expected to increase. Surveillance of all newly identified variants must be closely monitored in order to be able to take necessary countermeasures as early as possible.

Author contributions

EB, IK, PV, IE and LK wrote the first draft of the manuscript and conducted the literature research. All authors critically reviewed the manuscript and accepted the final version.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.05.022.

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