The new UK SARS-CoV-2 variant and lockdown – causes and consequences

Introduction: emergence of SARS-CoV-2 variants of concern

In December 2020, a new variant of SARS-CoV-2 was discovered by the COVID-19 Genomics United Kingdom Consortium (COG-UK), called B.1.1.7 or variant of concern (VOC) 202012/01. On sequencing analysis, 17 mutation sites were characterised in the new variant, compared to its most recent ancestor. Many of these mutations were in nucleotides encoding the spike (S) protein on the surface of SARS-CoV-2, through which the virus binds to and enters human cells. The concomitant increase in COVID-19 incidence due to VOC in the UK suggests that this new variant will quickly become the most dominant.

SARS-CoV-2 previously accumulated mutations at a relatively consistent rate, equating to approximately 1–2 mutations per month. Over the course of infection, the major SARS-CoV-2 population remains identical in most patients. The sudden appearance of a large cluster of non-synonymous substitutions of immunologic significance is therefore unusual. The prevailing theory is that VOC arose from prolonged SARS-CoV-2 shedding in immunocompromised patients. Although live viruses have not been cultured in the majority of those infected after day 9 of symptom onset or initial PCR positivity on nasopharyngeal swab, those who are immunocompromised can exhibit prolonged viral replication, lasting up to 119 days. The addition of therapies which exert specific selection pressure on the virus in the context of an immunocompromised host may combine to accelerate SARS-CoV-2 genomic evolution. Emergence of new dominant mutations in immunocompromised patients who receive corticosteroids, intravenous immunoglobulins, monoclonal antibodies and convalescent plasma are being increasingly reported – although it remains unclear whether the enhanced diversity in these patients is due to uninhibited replication or specific selection pressures from treatment.

Will the new variant increase transmission?

It is important to investigate whether changes in virus phenotype would lead to meaningful increases in transmission between humans. Epidemiological analyses have suggested this to be the case for VOC. For example, whole genome sequence data collected from community-based diagnostic testing showed an increase in prevalence of VOC over September to December 2020 at an...
exponential rate. Estimated reproduction numbers for VOC are substantially higher than for non-VOC lineages, with an estimated overall difference of 0.4–0.7. Independent two-strain mathematical models of SARS-CoV-2 transmission fitted to the prevalence of SARS-CoV-2, the relative frequency of VOC, observed COVID-19 hospital admissions, hospital, intensive care unit (ICU) bed occupancy and deaths from COVID-19 in the most heavily affected regions in the UK also suggest a 56% increase in transmission (95% credible interval 50–74%) compared to other variants. These estimates are of particular concern because they were calculated during periods when many regions of the UK were in the highest social distancing restrictions (Tier 4, Table 1). The previous UK tiered system is therefore insufficient to contain VOC. Despite the virus having infected over 4 million and killed over 120 thousand people in the UK, the majority of the population are not immune to SARS-CoV-2. The new variant poses a major risk of rapid spread to vulnerable populations, such as those with cardiovascular comorbidities, ethnic minority groups or the elderly. The implementation of a third national lockdown on 5 January 2021 aimed to address the same problem that all countries faced this time last year, at the start of the pandemic – to prevent excess deaths that would result when all reasonable capacity in hospital is exceeded. However, all levels of measures implemented over the past year in the UK still allowed a degree of social mixing and close contact indoors, for example in key worker groups such as bus drivers, educational settings and places of worship (highlighted in bold in Table 1). Clusters of positive cases arising from these settings are a key characteristic of SARS-CoV-2 transmission. For instance, an outbreak investigation from China identified that 24 out of 67 passengers were infected during a 50-minute return bus journey, which was linked to an index case who was symptomatic the day before the trip. In Washington State, a mildly symptomatic index case attended a choir practice lasting 2.5 hours: out of 61 persons, 32 confirmed and 20 probably secondary COVID-19 cases occured, with an attack rate of 53.5% to 86.7%. In November and December 2020, educational settings were among the largest institutions in the UK linked to SARS-CoV-2 infections, which remained open during Tier 4 measures and is most implicated in viral transmission (a significantly larger proportion of VOC cases has been reported in under 20 year olds than non-VOC cases). The only way to prevent viral transmission is to stop its ongoing replication in a susceptible population; this must be communicated effectively to the public in the current lockdown, and is likely to be the major reason why the draconian measures undertaken in East Asia (where the population had been primed by previous experiences with SARS) were effective at suppressing subsequent waves of infection. Any population mixing will mean ongoing viral replication, with likely ongoing implications on those with long-term health conditions and the national economy.

Ongoing consequences of the variant

The rise of new variants in the community also poses significant challenges to the contact tracing efforts that will be needed to effectively maintain control of the virus locally once lockdown measures end, until population-level immunity is achieved. In this regard, the current national Track and Trace system, which places emphasis on a centralised contact tracing platform and does not take into account the local needs of the community, has proved to be insufficient. Increased efforts must be made to work with local public health authorities and health services, who are best placed to understand the needs of their areas of jurisdiction, and to implement both context- and area-specific interventions. Within Leicester, for example, where there is a diverse ethnic population, this would mean establishing relationships with community leaders to create a bespoke, culturally appropriate interventions that these high-risk communities can easily access. VOC also has consequences for the UK vaccination programme. A more transmissible virus will require greater vaccine uptake for population-level control. Recently, the Joint Committee on Vaccination and Immunisation (JCVI) recommended prolongation of the second dose of both the Pfizer BioNTech and Oxford AstraZeneca vaccines to 12 weeks, to increase vaccine uptake amongst the most vulnerable. Vaccines are typically given in more than one dose to increase the quantity, quality and longevity of antibody responses. The Oxford/AstraZeneca vaccine demonstrated efficacy at a range of dose intervals, with antibody responses after the boost being significantly stronger with longer intervals. For the Pfizer BioNTech vaccine, efficacy in the period from 14 days after first dose to 21 days is high. Although there is no direct evidence of efficacy beyond a 3-week interval, there is also no evidence in existing vaccines for a stronger immunological response having been exerted at 3 weeks compared to longer intervals. It is therefore a pragmatic intervention recommended based on first principles and experience from previous vaccines, in the absence of high-quality evidence, with the aim of maximising protection in the population. Finally, the presence of VOC is already global. Other highly transmissible variants, such as one identified in South Africa, have appeared. There is now an urgent need to determine whether these lineages could affect the efficacy of vaccines, since all current approved vaccines aim to construct the S protein. Theoretically the impact should be minimal, as the S protein will have many epitopes as immunological targets. However, should the mutation affect protein folding in the new variant, this may affect binding of antibodies induced by the vaccine to older variants. There is also the possibility that novel variants may escape vaccine control, particularly in the context of a partially immunised population, which may in turn exert a strong selection pressure on the SARS-CoV-2. Vaccine developers will need to consider experimenting with variant sequences and powering post-licensing studies to detect differences in transmission and efficacy between preexisting and new variants. Licensing authorities may also need to clarify abbreviated pathways to marketing for vaccines that involve altering strain formulation, without any other changes to their composition – similar to what is in place for the annually updated seasonal influenza vaccine.

Conclusion

The arrival of VOC marks a new chapter in the global fight against COVID-19, and with it, new challenges that must be addressed. It is likely that, at least for now, we will have to learn to live with the virus.

References

<table>
<thead>
<tr>
<th>Tier</th>
<th>Mixing</th>
<th>Bars, pubs and restaurants</th>
<th>Retail, indoor leisure, accommodation, personal care, entertainment, places of worship</th>
<th>Education</th>
<th>Travel</th>
<th>Weddings and funerals</th>
<th>Exercise</th>
<th>Residential home visits</th>
<th>Large sporting events, live performances and business meetings</th>
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<tbody>
<tr>
<td>Tier 1</td>
<td>Maximum of six indoors or outdoors, apart from with members of a single household or support bubble</td>
<td>Bars, pubs and restaurants must be table service only, stop taking orders at 10pm, close by 11pm</td>
<td>Schools and universities open</td>
<td>Travelling possible but avoid going to Tier 3 areas</td>
<td>15 guests for weddings and 30 for funerals</td>
<td>Permitted but maximum of six indoors</td>
<td>Indoor visits limited to two people from a Tier 1 area with social distancing, no physical contact, PPE use and good hand hygiene</td>
<td>Limited to 50% capacity of 4,000 people outdoors (whichever is lower) and 50% capacity or 1,000 people indoors (whichever is lower)</td>
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<tr>
<td>Tier 2</td>
<td>No mixing of households indoors, apart from support bubbles. Maximum of six outdoors</td>
<td>Pubs and bars must close. Restaurants can only serve alcohol with meals. Venues must stop taking orders at 10pm, close by 11pm</td>
<td>Schools and universities open</td>
<td>Reduce travelling if possible. Avoid entering a Tier 3 area</td>
<td>15 guests for weddings and 30 for funerals</td>
<td>Classes and organised sport can take place outdoors, but not indoors</td>
<td>Outdoor/airtight visits only</td>
<td>Limited to 50% capacity or 2000 people outdoors (whichever is lower) and 40% capacity or 1000 people indoors (whoever is lower)</td>
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<td>Tier 3</td>
<td>No mixing of households indoors, apart from support bubbles. Maximum of six outdoors</td>
<td>Hospitality is closed, with exception of sales by takeaway, drive-through or delivery</td>
<td>Retail, indoor leisure, personal care and places of worship open. Entertainment venues, accommodation closed</td>
<td>Overnight stays advised to be avoided. Avoid travelling outside own area if possible</td>
<td>15 guests for weddings and 30 for funerals</td>
<td>Classes and organised adult sport can date place outdoors only</td>
<td>Outdoor/airtight visits only</td>
<td>Events should not take place; drive-in events permitted</td>
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<td>Tier 4</td>
<td>No household mixing, apart from support bubbles. Maximum of two people mixing outdoors</td>
<td>Hospitality is closed, with exception of sales by takeaway, drive-through or delivery</td>
<td>Essential shops open only; all other venues closed. Places of worship open for private prayer and communal worship</td>
<td>Schools and universities open</td>
<td>Overnight stays must be avoided. Travel is only permitted for work or education. Must not leave a Tier 4 area</td>
<td>Selected funerals of up to 30 people permitted only</td>
<td>Exercise is permitted on an individual basis only, with household or support bubble or with one person from another household</td>
<td>Outdoor/airight visits only. Clinically extremely vulnerable advised to stay home as much as possible, except to go outdoors for exercise or to attend health appointments</td>
<td>Events should not take place</td>
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<td>Lockdown Regulations in March 2020 – July 2020</td>
<td>No mixing of household until 13 June 2020, when support bubbles were instigated</td>
<td>All closed</td>
<td>All closed apart from essential shops. Outdoor non-food markets can reopen</td>
<td>All closed</td>
<td>Overnight stays not permitted</td>
<td>Only certain funerals permitted</td>
<td>Outdoor exercise alone or with other members of the household permitted only</td>
<td>Not permitted; 13 June rules were relaxed to allow some to visit care homes</td>
<td>Events should not take place</td>
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<tr>
<td>Lockdown Regulations in January 2021</td>
<td>No mixing of households, apart from support bubbles</td>
<td>Hospitality is closed, with exception of sales by takeaway, drive-through or delivery</td>
<td>All closed apart from essential shops. Places of worship open for private prayer and communal worship</td>
<td>Schools open for vulnerable children and children of critical workers. Universities open for students in medicine/dentistry/health/social work/veterinary science/education</td>
<td>Overnight stays must be avoided. Travel is only permitted for work or education</td>
<td>Funerals allowed, maximum of 30 people. Weddings allowed for 6 people</td>
<td>Outdoor exercise alone or with other members of the household permitted only</td>
<td>Care home visits can take place with arrangements such as substantial screens, visiting pods or behind windows</td>
<td>Events should not take place</td>
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