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THREAT ASSESSMENT BRIEF

Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom

20 December 2020

Summary

Over the last few weeks, the United Kingdom (UK) has faced a rapid increase in COVID-19 cases in South East England, leading to enhanced epidemiological and virological investigations. Analysis of viral genome sequence data identified a large proportion of cases belonged to a new single phylogenetic cluster. The new variant is defined by multiple spike protein mutations (deletion 69-70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H) present as well as mutations in other genomic regions. While it is known and expected that viruses constantly change through mutation leading to the emergence of new variants, preliminary analysis in the UK suggests that this variant is significantly more transmissible than previously circulating variants, with an estimated potential to increase the reproductive number (R) by 0.4 or greater with an estimated increased transmissibility of up to 70%. This new variant has emerged at a time of the year when there has traditionally been increased family and social mixing. There is no indication at this point of increased infection severity associated with the new variant. A few cases with the new variant have to date been reported by Denmark and the Netherlands and, according to media reports, in Belgium.

Given that there is currently a lack of evidence to indicate the extent to which the new virus variant is spread outside the UK, timely efforts to prevent and control its spread are needed, and include the following:

- Public health authorities and laboratories are urged to analyse and sequence virus isolates in a timely manner to identify cases of the new variant. People with an epidemiological link to cases with the new variant or travel history to areas known to be affected should be identified immediately to test, isolate and follow up their contacts in order to stop the spread of the new variant.
- If cases infected with this new SARS-CoV-2 variant or other new SARS-CoV-2 variants of potential concern are identified, countries should notify through the Early Warning and Response System of the European Union.
- The importance of strict adherence to non-pharmaceutical interventions according to national policies needs to be communicated to the public, and in particular guidance on the avoidance of non-essential travel and social activities should be stressed.
- Laboratories should review the PCR performance and drop-out of the S-gene. PCR could be used as an indicator for cases with the new variant for further sequencing and investigation.
- Suspected cases of COVID-19 reinfection should be followed up, closely accompanied by sequencing respective virus isolates from these cases. Similarly, cases with treatment failures using convalescent plasma or monoclonal antibodies should be further studied.
- With the implementation of vaccination, close monitoring of COVID-19-vaccinated individuals needs to be ensured to identify possible vaccination failure and breakthrough infections. Virus isolates from these cases should be sequenced and characterised genetically and antigenically.

Suggested citation: European Centre for Disease Prevention and Control. Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom – 20 December 2020. ECDC: Stockholm; 2020.

Introduction

A SARS-CoV-2 variant, referred to as SARS-CoV-2 VUI 202012/01 (Variant Under Investigation, year 2020, month 12, variant 01), has been identified through viral genomic sequencing in the United Kingdom (UK). It is defined by multiple spike protein mutations (deletion 69-70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H) present.

The aim of this Threat Assessment Brief is to summarise the findings, assess potential public health implications of this new variant, provide options for response and point out limitations, unknowns and needs for further studies and investigations. The following possible implications for human health have been considered:

- The probability of a wider spread of the new virus variant across the European Union (EU) and European Economic Area (EEA);
- The potential impact on SARS-CoV-2 diagnostics;
- The potential impact on severity of disease in a population orgroup;
- The potential impact on the occurrence of variant viruses to increase frequency of reinfections;
- The potential impact on vaccine match and effectiveness.

Event background

Over the last few weeks, the UK has faced a rapid increase in COVID-19 cases (Figures 1 and 2, Annex Figures 5 and 6). This increase was pronounced in South East England, with an increase in the 14-day case notification rate from 100 cases per 100 000 population in week 41/2020 to over 400 per 100 000 in week 50/2020 (Fig. 1 and Annex Fig. 6).

This increase led to an enhanced epidemiological and virological investigation. Analysis using viral genome sequence data identified a large proportion (>50%) of cases belonged to a new single phylogenetic cluster [1]. This variant is referred to in the UK as SARS-CoV-2 VUI 202012/01 (Variant Under Investigation, year 2020, month 12, variant 01). Overall, around 5 to 10% of all COVID-19 cases are regularly sequenced in the UK, with a sequencing coverage in Kent, the part of South East England that was most affected, of around 4%. As of 13 December 2020, 1 108 individuals had been identified with this virus variant in England, with the earliest case identified from 20 September 2020. The observed rapid increase in COVID-19 cases overall was temporally associated with the emergence of the new variant in this area in November 2020. The reported COVID-19 cases related to the VUI 202012/01 variant are concentrated in Kent and wider South East England, including the regions of London and the East of England, but there are indications of a more widespread occurrence of cases across the UK as well as small numbers of cases detected in other countries. In Wales, as of 14 December 2020, 20 individuals had been identified with this virus variant of 4 733 sequenced samples collected since 1 November. Additionally, Denmark has reported nine cases [2], the Netherlands reported one case [3], and one case from Australia was identified through the GISAID EpiCov database. Media report that four cases have been identified in Belgium in recent months [4].

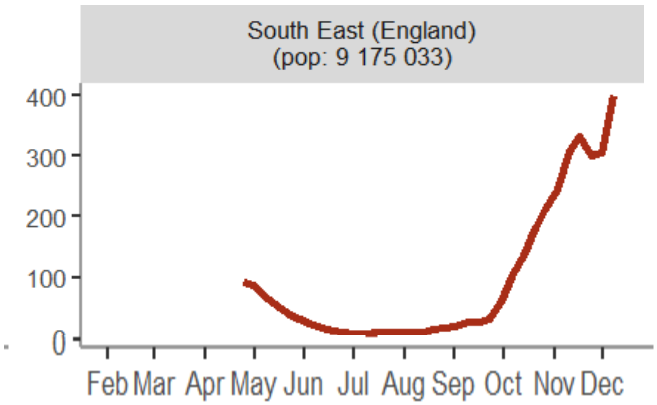
On 19 December 2020, in response to the increase of this variant, the countries of the UK have announced stricter measures to be applied from 20 December and over the coming weeks, with affected areas going into a 'Tier 4' level with movement restrictions within and between more and less heavily affected areas [5,6]. These measures include recommendations for residents of the most affected areas to restrict movements and travel, including international travel, outside of these areas. The government of Scotland announced a travel ban between Scotland and rest of UK from 26 December.

In addition, the Netherlands issued a travel ban from the UK effective from 6:00 a.m. on 20 December 2020 until 1 January 2021 [3] and Belgium halted flight and train travel to the UK for a 24-hour period as of midnight on 20 December 2020 [7].

Epidemiology

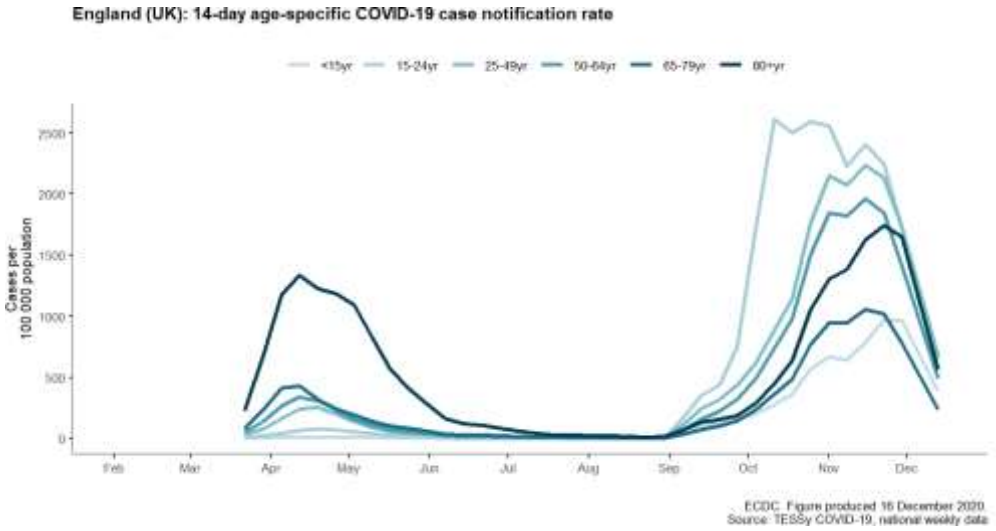
The investigations into the properties of this new variant are ongoing, and poorer clinical outcomes, higher mortality or particularly affected groups have not been reported to date. The cases with the VUI 202012/01 variant are predominantly identified in people younger than 60 years, but the increase of overall COVID-19 cases in England is similarly driven by this age group (Figure 2). Preliminary modelling results show a strong association between the presence of the new variant in the Kent/South East England region and increasing incidence of COVID-19. Among the 20 VUI 202012/01 cases identified in Wales, cases have a median age of 41 years (range 11-71 years), and are mainly located in South Wales, where incidences are also rising. The increasing proportion of cases with the VUI 202012/01 variant among all sequenced isolates uploaded to the GISAID database is shown in Figure 3.

Figure 1. Fourteen-day COVID-19 case notification rates per 100 000 population in South East England, UK, by reporting date as of 16 December 2020



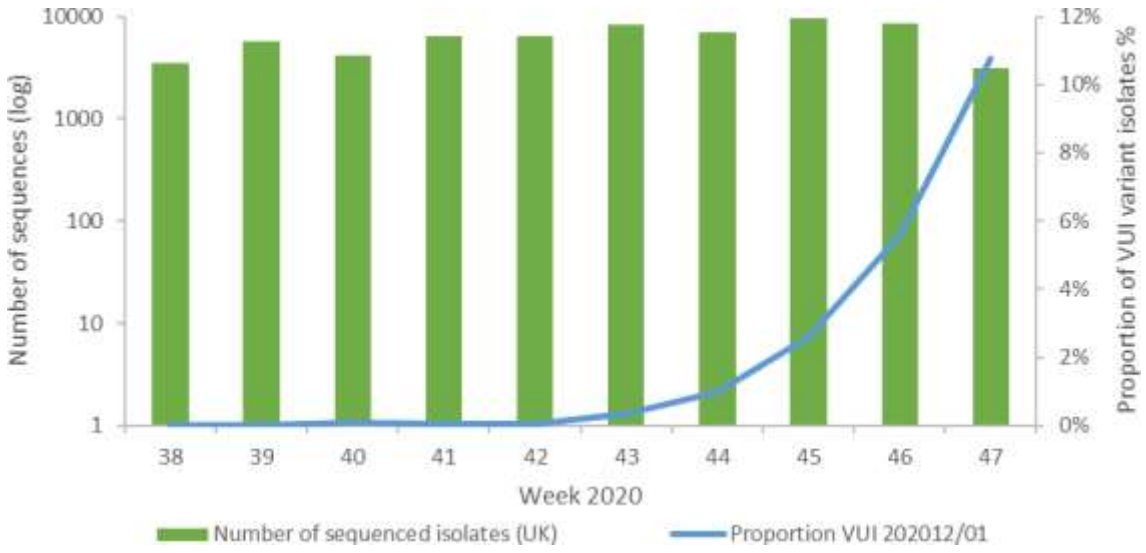
Source: The European Surveillance System (TESSy), COVID-19 national weekly data (http://covid19-country-overviews.ecdc.europa.eu/#34_United_Kingdom)

Figure 2. England (UK) 14-day age-specific COVID-19 case notification rate with cases per 100 000 population by reporting date as of 16 December 2020



Source: TESSy, COVID-19 national weekly data (http://covid19-country-overviews.ecdc.europa.eu/#34_United_Kingdom)

Figure 3. Total number of SARS-CoV-2 sequences from the UK and proportion of VUI 202012/01 variant sequences among all UK sequences in the GISAID EpiCoV database (as of 20 December 2020) by week of sampling, 2020



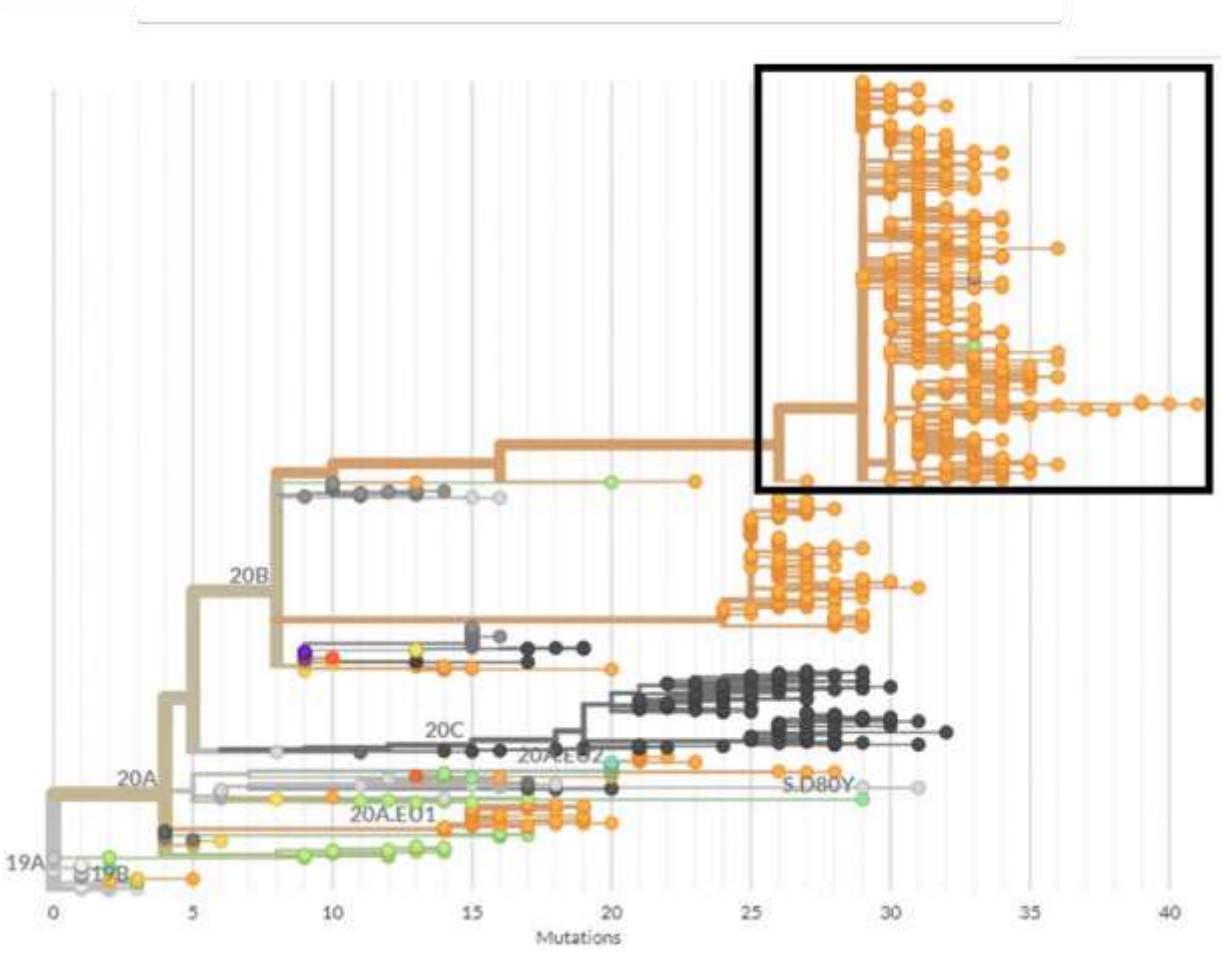
Source: GISAID EpiCoV database

Genomic properties of the new SARS-CoV-2 variant

This new SARS-CoV-2 virus variant is referred to in the UK as SARS-CoV-2 VUI 202012/01. It is defined by multiple spike protein mutations (deletion 69-70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H) present as well as mutations in other genomic regions [8]. One of the mutations (N501Y) is located within the receptor binding domain. The variant belongs to Nextstrain clade 20B [9,10], GISAID clade GR [11,12], lineage B.1.1.7 [13,14]. Phylogenetic analysis (Figure 4) reveals that there are very few intermediary forms between this variant and other circulating virus reported to GISAID. The cluster differs by 29 nucleotide substitutions from the original Wuhan strain, which is higher than current molecular clock estimates of around two substitutions per genome per month [10]. The fraction of non-synonymous mutations in the spike protein for the variant is much higher than expected from random mutations (27% of the 22 substitutions acquired since the Nextstrain clade 20B common ancestor are located in the S-gene, which comprises 13% of the viral genome, and all of these substitutions are non-synonymous). Three sequences from Denmark and one from Australia, from samples collected in November 2020, cluster with the UK variant, most likely indicating that international spread has occurred, although the extent remains unknown.

The UK has an established SARS-CoV-2 genome sequencing consortium called COG-UK. It consists of the national public health institutes, National Health Service organisations, academic institutions and the Wellcome Sanger Institute [15]. They are working to keep sequencing coverage high and geographically representative and to keep turnaround times low. The consortium is by far the largest contributor to the GISAID EpiCov database in the world, with more than 120 000 of around 270 000 genomes published so far. This initiative increases the likelihood that emerging variants are identified and can be assessed in a timely fashion.

Figure 4. Phylogenetic tree, subsampled dataset focused on N501Y-variants of SARS-CoV-2 from Nextstrain [16]



Nodes within the cluster formed by the new SARS-CoV-2 VUI 202012/01 variant (black box) are coloured by country: United Kingdom (orange), Australia (grey), and Denmark (green). Other colours indicate countries not involved in the cluster.

Possible sources of SARS-CoV-2 virus variants with a high number of mutations in the spike protein

The unusually high number of spike protein mutations, other genomic properties of the variant, and the high sequencing coverage in the UK suggest that the variant has not emerged through gradual accumulation of mutations in the UK. It is also unlikely that the variant could have arisen through selection pressure from ongoing vaccination programmes as the observed increase does not match the timing of such activities.

One possible explanation for the emergence of the variant is prolonged SARS-CoV-2 infection in a single patient, potentially with reduced immunocompetence, similar to what has previously been described [17,18]. Such prolonged infection can lead to accumulation of immune escape mutations at an elevated rate.

Another possible explanation could be adaptation processes in a virus that occur in a different susceptible animal species and is then transmitted back to humans from the animal hosts. This led to the emergence of a variant with multiple spike protein mutations (including RBD mutation Y453F and deletion 69-70) in Denmark during transmission among mink [19]. Several different spike protein mutations associated with mink have also been described in the Netherlands [20]. The UK has reported to ECDC and the WHO Regional Office for Europe that there is no clear epidemiological link to animals for VUI 202012/01, so this explanation is less likely for this variant [1].

Lastly, it is also possible that the variant has emerged through circulation in countries with no or very low sequencing coverage. This hypothesis is less plausible, however, as random mutations acquired during circulation of the virus would not explain the unusually high proportion of spike protein mutations, and undetected circulation for a long enough time for the high number of mutations to accumulate (around 10 months according to current molecular clock estimates) is also not very likely due to global travel patterns.

South Africa reports through the GISAID EpiCoV database [11] and a public press release [21,22] a similar rapid increase since October of a variant with the spike protein mutation N501Y, two additional RBD mutations and multiple additional spike protein mutations. This variant has no close evolutionary relation to VUI 202012/01 but demonstrates that the emergence of successful variants with similar properties may not be rare.

Ongoing investigations in the UK

Investigations are ongoing to understand the spread of the new virus variant across the UK and EU/EEA. In the UK, investigations include evaluation of clinical severity, transmissibility and antigenic change, including neutralisation by sera from convalescent and immunised patients. Fitness studies in primary human airway cultures are also being undertaken. Reinfection and infections in vaccinated patients are monitored as part of standard UK surveillance. The performance of diagnostic assays, including lateral flow devices, is being reviewed.

Epidemiological and phylodynamic analyses are also being undertaken to assess if there is evidence of increased transmissibility of the new variant with respect to other co-circulating viral variants. Work is ongoing to improve availability of samples from the community for genetic characterisation. Ongoing virological analyses also include the use of a cell culture infectivity assay, which could provide a biological explanation for any observed increase in transmissibility.

Possible implications for human health

Viruses constantly change through mutation and the emergence of a new variant is an expected occurrence and not in itself a cause for concern. A diversification of SARS-CoV-2 due to evolution and adaptation processes has been observed globally and is expected to occur with ongoing transmission of viruses in general and particularly for RNA viruses [23].

Most mutations that emerge will not provide selective advantage to the virus. However, some mutations or combinations of mutations may provide the virus with a selective advantage, such as increased transmissibility through an increase in receptor binding or the ability to evade the host immune response by altering the surface structures recognised by antibodies. Previous investigation of the D614G variant identified that while the 614G variant provided a selective advantage, through increased cellular infectivity, there was no identifiable effect on infection severity or outcome [24].

The considerations below are based on very limited information and the assessment will be updated should more data become available.

Probability of a wider spread of the new virus variant across the EU/EEA

Preliminary modelling results communicated by the UK on 19 December suggest that the variant is significantly more transmissible than previously circulating variants, with an estimated increase in reproductive number (R) by 0.4 or greater with an estimated increased transmissibility of up to 70% [25]. Further epidemiological and virological investigations are needed to further quantify the increase in transmissibility and to understand the biological mechanism behind the increase. Any increased transmissibility would increase the likelihood of spread, particularly if increased family and social mixing that is traditional at this time of the year is not reduced, and further spread outside the UK, especially if non-essential travel is not reduced or avoided altogether, could eventually lead to the variant replacing currently circulating variants in much of the EU/EEA.

Small numbers of isolates with the variant VUI 202012/01 have been reported from Belgium, Denmark and the Netherlands. However, most EU/EEA countries sequence much smaller proportions of virus isolates than the UK, so ongoing circulation of this variant outside of the UK cannot be excluded.

Potential impact on SARS-CoV-2 diagnostics

The UK reports that the deletion 69-70 in the spike protein of the variant causes a negative result from S-gene RT-PCR assays applied in some laboratories in the UK [26]. This specific mutation has occurred many times in different countries and is geographically widespread. Assays targeting the S-gene are not widely used for primary detection and only one assay targeting the S-gene is on the list of published in-house assays listed by the WHO [27]. Relying only on the S-gene for primary detection of SARS-CoV-2 infection using RT-PCR is not recommended because mutations are more likely to occur in this gene [28].

Potential impact on severity of disease in a population or group

The available information regarding severity of the new virus variant is limited. To date, there is no indication of increased infection severity observed related to the variant, but the assessment is challenged by the fact that the majority of cases were reported in people under 60 years old, who are less likely to develop severe symptoms [29].

None of the previously described SARS-CoV-2 variants have been shown to cause increased infection severity; on the contrary, a clade 19B variant with lower severity was detected in Singapore in the spring and then disappeared [30].

Potential impact on occurrence of variant viruses to increase frequency of reinfections

The mutations observed in the new variant are related to the receptor binding site and other surface structures, which may alter the antigenic properties of the virus. Based on the number and location of spike protein mutations, it seems likely that some reduction in neutralisation by antibodies will be seen, but there is as yet no evidence that there is a resulting impact on increased risk for reinfection or lower vaccine effectiveness. Some level of reduction in neutralisation by convalescent sera and monoclonal antibodies has been observed to date for a wide range of variants with unclear clinical impact [17,18,31,32]. No information is currently available on whether there is any increased frequency of reinfections associated with VUI 202012/01 or observed impact on the ongoing vaccination.

Possible impact on vaccine match and effectiveness

No phenotypic data are available for the new variant and no data are available with respect to the ability of antibodies elicited by vaccines under development to neutralise this variant. As mentioned above, the new virus variant displays several mutations in the spike protein, including in the receptor binding site. Most of the new candidate vaccines are based upon the spike protein sequence. It is therefore essential to monitor changes in the spike protein among the circulating SARS-CoV-2 strains and assess possible antigenic changes. The antigenic characterisation of the new variant is ongoing, and results are expected in the coming weeks. It will be important to carry out surveillance of field effectiveness of COVID-19 vaccines in use, if possible including variant-virus-specific estimates. Surveillance of primary vaccine failures using variant-virus-specific outcomes may also help in understanding if there is an impact on vaccine effectiveness.

It should be remembered that T-cell immunity plays a role in protection against and clearance of COVID-19 virus infections. Although T-cell immunity is being assessed both following SARS-CoV-2 infection and following vaccination, it is still unknown what role it could have for correlates of protection.

Options for response and considerations to support public health action

The four nations of the UK have announced stricter measures to be applied from 20 December and over the coming weeks. These measures include recommendations for residents of the most affected areas to restrict movements and travel, including international travel, outside of these areas. The government of Scotland has announced a travel ban between Scotland and rest of UK from 26 December. In addition, the Netherlands and Belgium issued an immediate travel ban for flights carrying passengers from the UK.

Given that there is currently a lack of evidence to indicate that the new virus variant is widely spread and the occurrence is limited to a few countries or local areas, timely efforts to prevent and control the spread of the variant should mirror those effective in an early epidemic phase, including avoidance of non-essential travel to and from the affected areas as well as increased testing efforts, contact tracing and isolation of confirmed cases with epidemiological link to affected areas. Efforts to carry out sequencing of cases in a timely manner, including cases who have recently been to or are in contact with people from affected areas, is important to understand the spread of the variant. ECDC will, in collaboration with the EU/EEA Member States, continue to monitor and report on new affected areas.

ECDC has previously recommended reducing non-essential travel and social activities [33].

SARS-CoV-2 genetic evolution has the potential to impact on the antigenic properties, transmissibility or severity of the virus. It is therefore important to monitor the evolution through sequencing of virus isolates and to assess whether there is a need for EU/EEA Member States to adjust their response to COVID-19. The following suggestions should be considered for public health response.

National public health authorities should:

- Immediately identify people with an epidemiological link to cases with the new variant or travel history to areas known to be affected in order to test, isolate and follow up their contacts so as to stop the spread of the new variant. Virus isolates from such cases should be sequenced in a timely manner to identify cases of the new variant.
- Continue to advise the population on the need for non-pharmaceutical interventions according to their national policies, and consider in particular guidance on the avoidance of travel and avoidance of non-essential social activities.

- Continue to monitor for abrupt changes in rates of transmission or disease severity as part of the process of identifying and assessing the impact of variants.
- Notify cases of the new variant as well as new SARS-CoV-2 variants of potential concern through the Early Warning and Response System of the European Union.
- Follow up reports of suspected cases of COVID-19 reinfection and initiate sequence analysis of virus isolates from these cases.
- Follow up reports of cases with treatment failures using convalescent plasma or monoclonal antibodies as recently described [17] and initiate sequence analysis of virus isolates from these cases.
- Ensure that close monitoring of COVID-19-vaccinated individuals regarding vaccination failure and breakthrough infections is in place and initiate sequence analysis of virus isolates from these cases, and then conduct antigenic characterisation to confirm or exclude vaccine escape mutants.
- Develop standardised mechanisms, in partnership with global stakeholders, including triggers to investigate and assess newly emerging variants of SARS-CoV-2 in terms of animal reservoir, antigenic characteristics, transmissibility, infection severity, cross-protection and also with regard to adapting vaccine strain recommendations. If needed, establish systems for reassessing vaccine composition and strategy.

National public health laboratories should:

- Sequence virus isolates from cases with an epidemiological link to countries where the variant is present, currently the UK, Denmark, and the Netherlands according to official reports, and possibly also Belgium.
- Increase the number of sequenced SARS-CoV-2 virus isolates to identify new variants similar to the UK variants in EU/EEA Member States. Laboratories can refer to the upcoming technical note *Sequencing of SARS-CoV-2* which is in preparation by ECDC and the WHO Regional Office for Europe for guidance about technologies and sample selection. ECDC can offer sequencing services to countries with limited national capacity in this area.
- Increase representativeness of isolates selected for sequencing based on population and geographic location of infections to identify emerging variants and assess spread.
- Assess the implications of the drop out of the S-gene target RT-PCR in use for diagnostic purposes and adapt the gene target regions for SARS-CoV-2 PCR diagnostics. If sequencing capacity is limited, multi-target RT-PCR assays that include a S-gene target that is affected by the deletions present in the variant can be used for identifying isolates that show a S-gene drop out as signal for further investigation. Note that the deletion at positions 69-70 of the spike protein is not exclusive to this variant. Confirmation using sequencing is recommended.
- Increase capacities to perform in-depth virus characterisation analyses genetically and antigenically or share isolates with SARS-CoV-2 reference laboratories for further genetic and antigenic investigations.

Limitations identified

- This assessment is based on data available to ECDC as of 19 December 2020. There are still very limited antigenic and phenotypic data and epidemiological follow-up data on most affected population groups, transmissibility, and potential impact on infection severity is still being gathered.
- Not all people with COVID-19-like symptoms or contacts of confirmed cases are being tested for SARS-CoV-2, so the notified cases are an underestimation of the true numbers unless population-wide testing approaches are performed.
- Sequence data are not generated for all confirmed COVID-19 cases and sequence information therefore might not be representative of all circulating SARS-CoV-2 viruses across a country.
- Sequence data generation and analysis both require time to be performed. This, together with the time needed to upload to the GISAID database and public sharing means that there may be a substantial lag in the data available to fully assess the occurrence and/or spread of this mutation (Figure 3).

Source and date of request

ECDC internal decision, 16 December 2020.

Consulted experts

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All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

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Disclaimer

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This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

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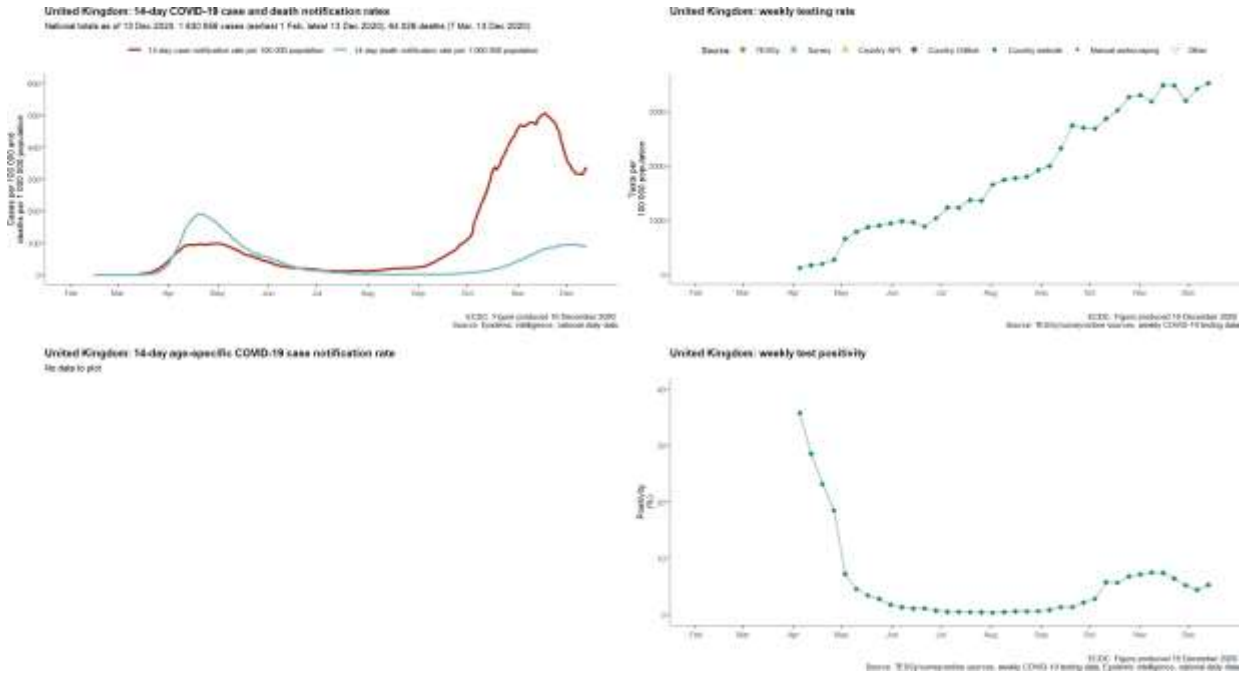
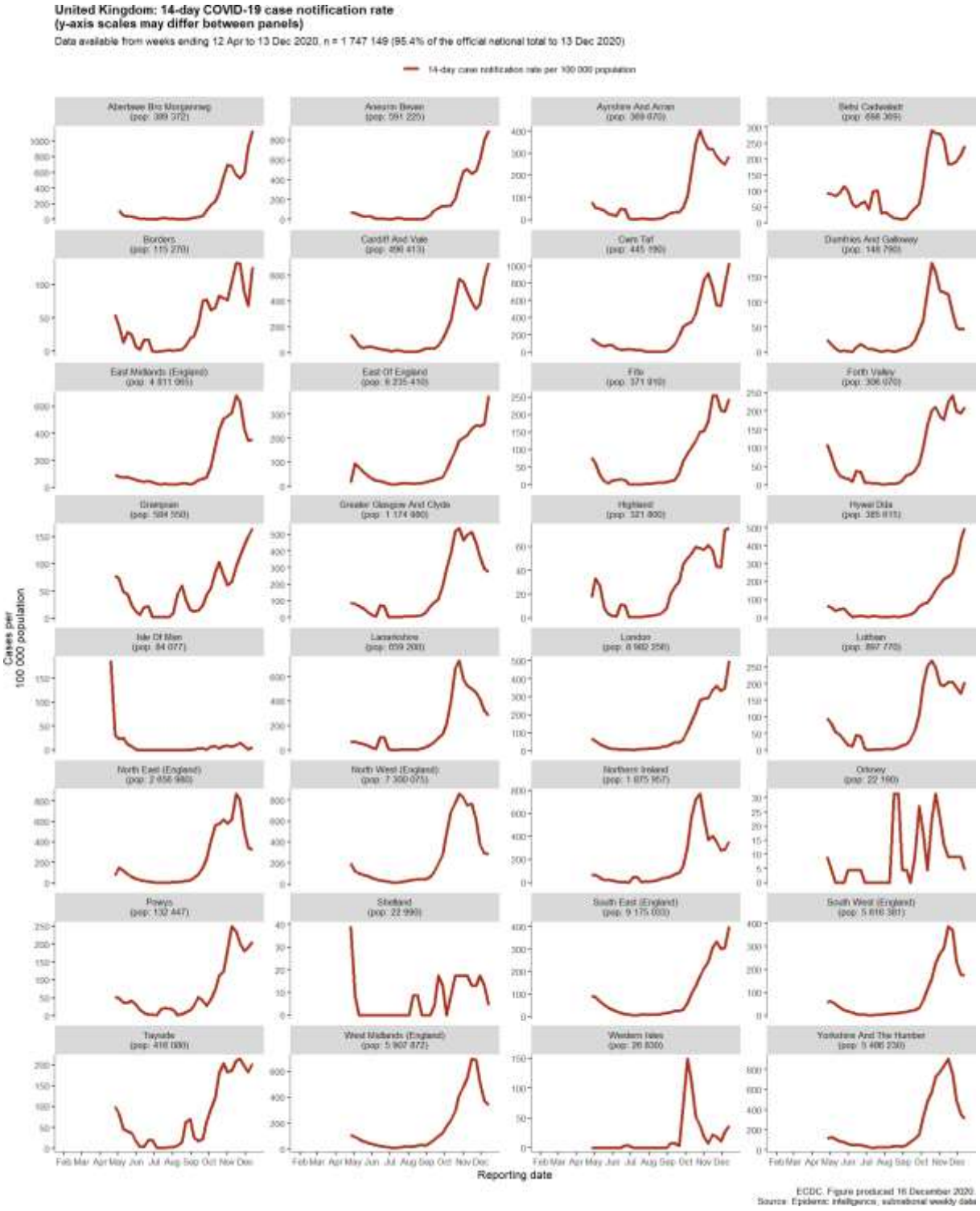
Annex

Figure 5. Cumulative number of COVID-19 cases and deaths per 100 000 population over a 14-day period, weekly testing rate and test positivity, the United Kingdom, by reporting date as of 16 December 2020



Source: TESSy, COVID-19 national weekly data (http://covid19-country-overviews.ecdc.europa.eu/#34_United_Kingdom)

Figure 6. 14-day COVID-19 case notification rate displayed by cases per 100 000 population in the United Kingdom by subnational regions and reporting date as of 16 December 2020



Source: TESSy, COVID-19 national weekly data (http://covid19-country-overviews.ecdc.europa.eu/#34_United_Kingdom)