SARS-COV-2 VARIANTS
UPDATE 28/12/20

1. Background

A first risk assessment concerning the mutation of the SARS-CoV-2 virus detected in the United Kingdom VOC 202012/01, was done on **20/12/20**.

As of 26 December, more than 3 000 cases of this new variant have been reported in the UK, mainly from the South East, East and London area with increasing proportion but also with a wider geographic spread across the country (ECDC, Rapid Risk Assessment, confidential draft). Few VOC 202012/01 cases have also been reported from other EU/EEA countries (Belgium, Denmark, France, Germany, Iceland, Ireland, Italy, and the Netherlands) and globally (Japan, Switzerland, Singapore, Hong Kong SAR) (ECDC, Rapid Risk Assessment, confidential draft). Modelling evidence is consistent with increased transmissibility for the new variant (1). A key mutation in this new variant is the N501Y in the receptor-binding domain. Previous research (deep mutation scanning and a mouse-model) did indeed show that the N501Y mutation strengthens the binding of the spike-protein to the human ACE2-receptor (2,3), which might translate into increased transmissibility.

In addition to VOC 202012/01, South Africa reported on 18 December 2020 about the emergence and rapid increase of another SARS-CoV-2 variant of potential concern, designated 501.V2. Like VOC 202012/01, 501.V2 has multiple mutations in the spike protein. In addition to the N501Y mutation, it has two more mutations in the receptor-binding domain. The previously mentioned deep mutation scanning, suggested E484K might modestly increase binding-capacity to the receptor whilst K417N is thought to have no or very limited impact on receptor-binding capacity (2,4). The variant was first observed in samples from October, and since then more than 300 cases with the 501.V2 variant have been confirmed in South Africa. Phylogenetic analysis indicate that the variant likely emerged early August (4). Preliminary results indicate that this variant too is associated with increased transmissibility and faster spread. There are currently no indications that the variant is associated with higher infection severity. On 22 December 2020, two contact cases to returning travelers from South Africa were tested positive for this 501.V2 variant in the UK.

A first threat analysis on the emergence of the UK variant was done by ECDC and is available here. A new risk assessment presenting the latest available information on the two variants of potential concern, and assessing the risk of the introduction and spread of these variants in the EU/EEA as well as the increased impact of on health systems was done by ECDC, sent out as a confidential report to member states for feedback and will be publicly available soon.

2. Specific risk factor

There continues to exist concern about the possible **spread** in Belgium of these or other new variants with selective advantages such as higher transmissibility or infection severity, especially **with return of travelers after the Christmas holidays**.

According to data from the Passenger Locator Forms, in the month of December, about 400 travelers reached Belgium from South Africa and about 12.000 from UK.

3. Actions taken since risk assessment of 20/12/20

- Borders with UK have been briefly closed The border is now open for returning Belgian residents and some exceptions (https://diplomatie.belgium.be/nl/Diensten/Op_reis_in_het_buitenland/reisadviezen/verenigd_koninkrijk). For persons who do not have their main residence in Belgium, the ban on entering Belgium from the UK by air, rail and sea will be maintained until 31 December 2020.
- A negative RT-PCR test result is asked for non-residents >12yr entering Belgium from red zones (including most parts of UK and South Africa). The test should be taken within the 72 hrs prior to entering Belgium. (Antigen tests are only accepted for truckers blocked at the UK border).
- The RIZIV/INAMI agrees to more comprehensive whole genome sequencing (WGS), a surveillance plan will be completed.
- For Belgium, a combined RAG/GEMS advice was already given on 20/12 to quarantine and test all travelers returning from red zones, independently of the score on the self-assessment-tool (SAT). So far this has not been implemented, but the threshold of the SAT to induce quarantine has been lowered.

4. Risk assessment and elements to consider

4.1. TRANSMISSIBILITY

- Although there remain many uncertainties regarding biological implications of certain mutations, the emergence and subsequent dominance of VUI-202012/01 in a period of relatively high prevalence suggests VUI-202012/01 does have a selective advantage over other variants, as was noted by the English expert committee NERVTAG (5). Davies et al estimate that VOC 202012/01 is 56% more transmissible (95% credible interval 50-74%) than preexisting variants of SARS-CoV-2 (5). The overall proportion of VOC 2020/12/01 among all virus sequences in the UK increased substantially, particularly from week 48/2020 (1) to reach about 30% of the sequenced strains end December. The higher transmissibility could possibly be linked to higher viral loads(6).

- Nevertheless if UK is facing an increase of the number of cases which is occurring simultaneously with the circulation of an increased proportion of the variant strain, this observation is not conclusive to establish a link between both events. The current overall virus transmission in the UK seems e.g. less intense than the one during the peak of the epidemic in Belgium in October.

  Evolution of the seven-day incidence rate by 100.000 inhabitants during a 3 weeks delay, in Belgium (week 40-41) in UK (week 49-50)

Belgium		UK	
Week	*7 days incidence*	*Week*	*7 days incidence*
40	164	49	162
41	337	50	227
42	618	51	344

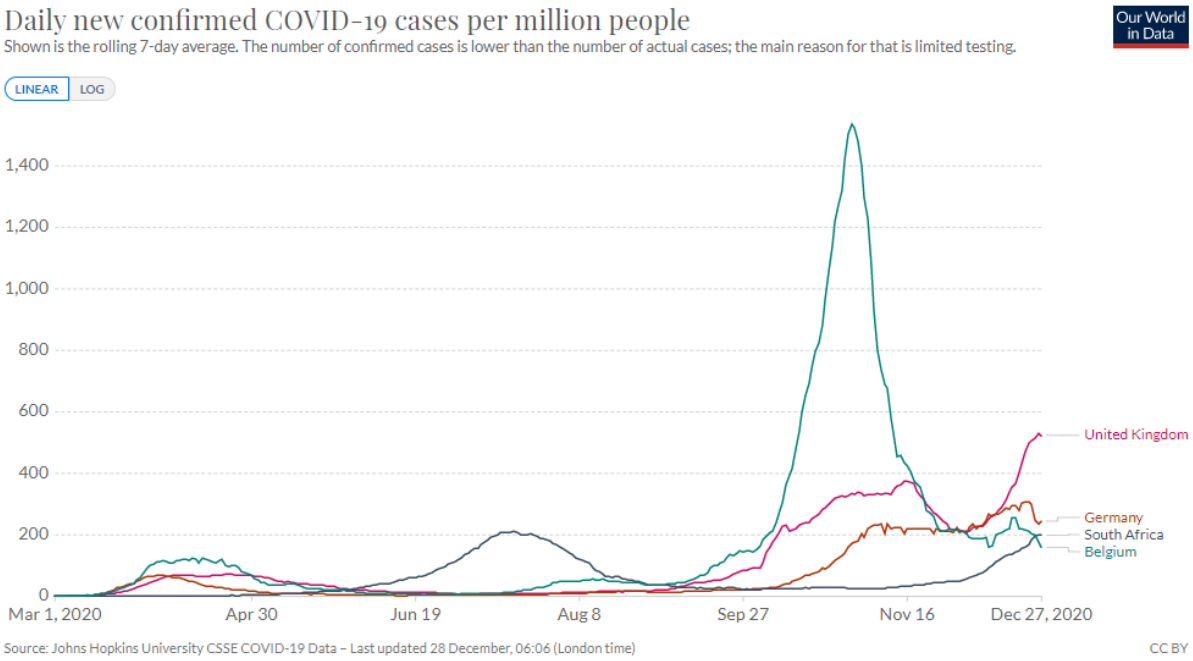
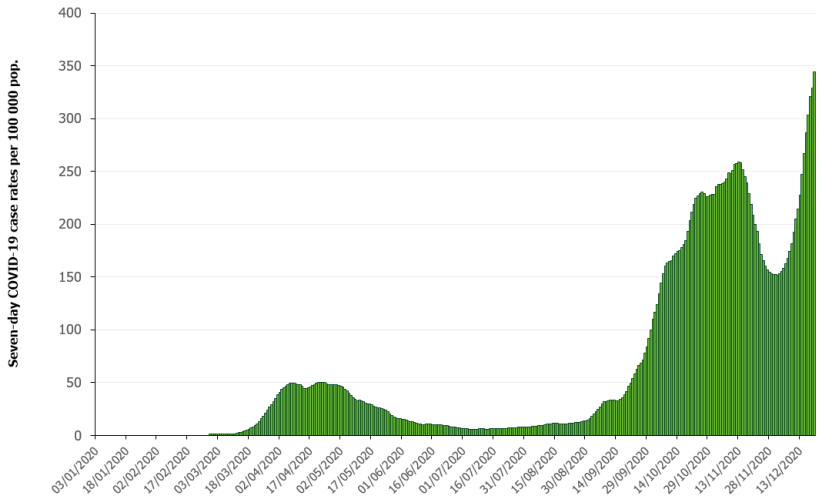


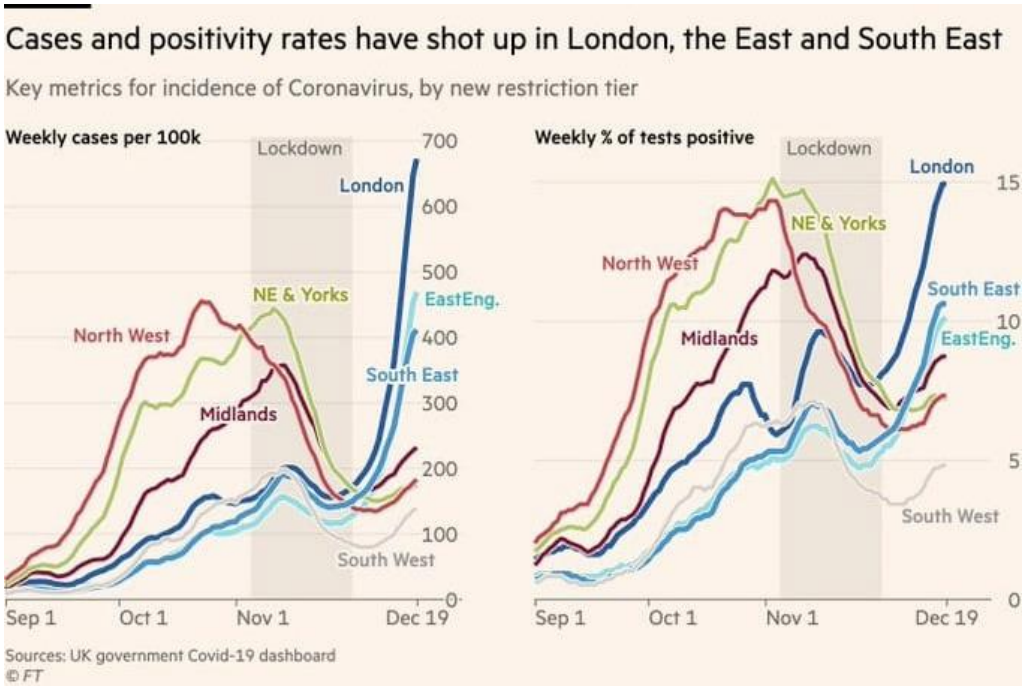
Figure 1: Seven-day COVID-19 case rates per 100 000 population in the United Kingdom, by specimen date, as of 25 December 2020. *(Source ECDC)*



This increase is more visible in the areas where circulation of the variant virus has been reported (London and South East Region) as can be seen from the table and figure below. The increase observed could be driven by the observed increased transmissibility of the variant. (See also https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea).

	Incidence Dec 22	Incidence Dec 29

East of England		
East Anglia	297,3	415,8
Bedfordshire and Hertfordshire	786,6	1195,6
Essex	1.260,1	1880,1
London		
Inner London — West	1.055,2	1776,9
Inner London — East	1.512,0	2445,4
Outer London — East and North East	2.237,2	3210,5
Outer London — South	1.516,3	2340,7
Outer London — West and North West	1.243,9	2044,1
South East (UK)		
Berkshire, Buckinghamshire and Oxfordshire	337,1	1187,7
Surrey, East and West Sussex	184,6	722,5
Hampshire and Isle of Wight	353,4	617,0
Kent	1.333,3	1539,8



Regional variations can also be observed even without circulation of this strain as it was observed during the peak in October, in Belgium, where the incidence was much higher in Brussels and Wallonia than in Flanders.

7 days incidence by 100.000 inhabitants, by regions, Belgium, weeks 40-44

	40	41	42	43	44
Brussels	205	335	558	869	2086
Flanders	71	95	191	357	1128
Wallonia	105	218	513	987	1400

- A rapid evolving incidence can be due to different factors.
  Data can be difficult to interpret since viral spread is not only influenced by characteristics of the virus, but also by human behavior. For example, bars and restaurants are still opened in South Africa and in many parts of the UK. "Founder effects" can importantly skew the data.

4.2. SEVERITY

- Although there is no information that the variant strains lead to more severe infection, an important increase in case numbers will cause an additional strain on the healthcare system.

4.3. SPREAD IN EU AND BELGIUM

The spread of these strains in Belgium and different other European countries is not exactly known, due to limited whole genome sequencing until now. Small numbers of cases have been reported by multiple other countries, sometimes without a travel history to the UK (cf. Belgium). Since cases of VOC 202012/01 have been reported already from October, and 501V2 is thought to have emerged already in August, more widespread circulation in Europe, and Belgium in particular, cannot be excluded.

Table 1: Places reporting VOC 202012/01 cases, as of 25 December 2020. *(Source ECDC and contacts with colleagues)*

Places	Number of cases	Epidemiological information
England	3 316	
Wales	20	
Scotland	18	
Northern Ireland	1	Unknown travel history
Denmark	46	Twelve are contacts of previous cases; Twelve cases are from Northern Jutland, 19 from the Capital region, 1 from the Zealand region and 1 from South Denmark; Phylogenetic analysis indicates that all nine cases with a sequence published before 25 December 2020 could originate from a single introduction [8].
Ireland	7	
Japan	5	Travel history to United Kingdom; Four cases were asymptomatic.
Israel	5	Travel history to United Kingdom (three cases), England (one case) and no travel history (one case).
Belgium	4 possible cases	Definitive sequencing ongoing.
Australia	4	Travel history to United Kingdom; Two in New South Wales and two in Victoria.
The Netherlands	11	.Further investigations are ongoing with contact tracing and intensified genome sequence surveillance
Iceland	13	Travel history to England.
Hong Kong SAR	2	Travel history to United Kingdom.
Switzerland	2	
Germany	1	Travel history to England; Three asymptomatic close contacts under investigation.
Italy	1	Travel history to United Kingdom.
France	1	Travel history to England.
Singapore	1	Travel history to United Kingdom.

It is certainly possible that *more variants* exist in other countries, without having been detected so far, because of lack of WGS. The fact that two different strains emerged around the same time, which both have several (and in part similar) mutations in the S-protein, highlights the future potential for mutations and the importance of a) maintaining low levels of virus circulation and b) adequate surveillance system.

The ECDC advises that countries should respond with enhanced surveillance, testing and detection including increased follow-up and testing of people with an epidemiological link to the affected areas, and sequencing of such isolates, as well as strengthening timely and representative sequencing overall. National public health authorities should notify cases of new variants as well as new SARS-CoV-2 variants of potential concern (ECDC, Rapid Risk Assessment, confidential draft).

Transmissibility seems increased, but there is no reason to expect that the type of effective non-pharmaceutical interventions would change (i.e. reduction of close contacts, isolation, quarantine, respiratory hygiene…).

4.4. IMPACT ON TEST QUALITY

- The deletion at genomic positions 21765-21770, corresponding to residues 69-70 in the spike protein in variant VOC 202012/01 and other variants carrying this mutation, such as mink-related variants from Denmark, may cause some RT-PCR assays to produce an "S-gene drop-out". The tri-target (ORF1ab, N, S) COVID-19 TaqPath assay from Thermo Fischer has been reported by the UK to have S-gene dropout for this deletion. As PCR-tests have multiple targets for amplification, this drop-out is unlikely to cause a false-negative result.
- Until now, there has not been any report that the new variant viruses would negatively impact Rapid Antigen Detection Tests (RADT). Since most of the commercially available RADT are based on the detection of the SARS-CoV-2 nucleoprotein protein, their performance should not be affected by changes in the spike protein.

4.5. CHILDREN

- The scientific consensus thus far is that younger children are less susceptible to SARS-CoV-2 (although this is debated by some). Several mechanisms have been proposed to explain this relative resistance, from immune imprinting by other viruses (7) to distribution, maturation, and functioning of viral receptors (8). It is not unlikely that a higher affinity of the virus for the receptor would also affect susceptibility of children for the virus, as it does in adults. A mathematical model that assumed an increased susceptibility in children only, was far less able to explain the observed increase in cases in the UK than a model assuming increased transmissibility in all age groups and lower susceptibility for children (<19 y) compared to other age groups (5). In the UK, cases in <15-year olds rose both in regions with and without the new strain.

4.6. VACCINE

- There is currently insufficient evidence to assess the effectiveness of vaccination against the new strains. Serum containing neutralizing antibodies from individuals that were vaccinated with the Pfizer/BioNTech vaccine is being used to assess efficacy against the new strains. It is hoped that results will be available shortly.

5. Risk characterization

Viruses constantly change through mutation but **the emergence of this new variants is a cause for concern** because both new variants have important changes in the spike protein. This could offer a selective advantage, meaning an increasing transmissibility, an impact on reinfection, vaccine efficacy and diagnostic tests (cf. previous RAG 20-12-2020).

The current epidemiological situation in the UK might nevertheless theoretically also be explained (partially) by other factors than this mutation.

Despite only few countries having a thorough genomic surveillance, some countries have already reported cases with the same strain.

The risk to human health is double:

- Considering current travel disposition in EU, the probability of introduction and further spread of the SARS-CoV-2 VOC 202012/01 and other variants in Belgium is currently high.
- If higher transmission should be confirmed, even if an increase in infection severity has not so far been identified, the spread of this strain in Belgium could facilitate the increase of cases leading to higher demand on health systems in the coming weeks while our system has still a high level of new cases and hospitalizations.

6. Advice

The RAG assesses that

- Uncertainties related to this finding invite applying principle of precaution until more evidences on the public health impact will be available.
- Existing measures have to be maintained
    - The focus should be on a thorough surveillance by whole genome sequencing rather than only focus on samples with a link to the UK. A comprehensive surveillance plan is being elaborated in collaboration with the NRC.
    - All non-essential cross-border travel should continue to be strongly discouraged. Such a measure can have maximum effect only if taken at European level.
    - Contact-tracing is in place and should continue to be done thoroughly, especially around positive cases with a link to UK/South-Africa or with confirmed infection with a variant strain. Classification into low or high risk and consequent measures should be done as for other cases, allowing for a case by case approach.

The RAG experts reiterate the advice to reinforce measures for all travelers. And for example, to make quarantine and test on day 7 mandatory for all travelers from red zones (as little is known about possible other mutant variants in other countries), independently of the SAT. In addition, and consistent with the advice for testing of high-risk contacts, a test as soon as possible after arrival for all returning travelers is recommended. A clear and repeated communication about these measures to the public is key for understanding and adherence.

Finally, quarantine and testing for all high risk contacts (not only travelers) is stressed by RAG members, as little is known about the eventual current spread of new variants.

More detailed and specific advices, were made by the GEMS group on 28/12/2020.

Literature

1. Public Health England. Investigation of novel SARS-COV-2 variant: Variant of Concern 202012/01 [Internet]. GOV.UK. [cited 2020 Dec 28]. Available from: https://www.gov.uk/government/publications/investigation-of-novel-sars-cov-2-variant-variant-of-concern-20201201

2. Starr TN, Greaney AJ, Hilton SK, Ellis D, Crawford KHD, Dingens AS, et al. Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. Cell. 2020 Sep 3;182(5):1295-1310.e20.

3. Gu H, Chen Q, Yang G, He L, Fan H, Deng Y-Q, et al. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science. 2020 Sep 25;369(6511):1603–7.

4. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. medRxiv. 2020 Dec 22;2020.12.21.20248640.

5. Davies, Nicholas G. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England.

6. BDI-pathogens/covid-19_instant_tracing [Internet]. GitHub. [cited 2020 Dec 29]. Available from: https://github.com/BDI-pathogens/covid-19_instant_tracing

7. Mizumoto K, Omori R, Nishiura H. Age specificity of cases and attack rate of novel coronavirus disease (COVID-19) [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Mar [cited 2020 Mar 31]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.03.09.20033142

8. Lee P-I, Hu Y-L, Chen P-Y, Huang Y-C, Hsueh P-R. Are children less susceptible to COVID-19? Journal of Microbiology, Immunology and Infection [Internet]. 2020 Feb 25 [cited 2020 Mar 11]; Available from: http://www.sciencedirect.com/science/article/pii/S1684118220300396