



The image shows a modern, multi-story building with a glass facade and a grid-like structure on top. Several flags are flying from poles in front of the building, including the European Union flag and the ECDC logo flag. The building is set against a clear blue sky.



The logo for the European Centre for Disease Prevention and Control (ECDC). It features a stylized globe icon above the lowercase letters 'ecdc'. Below this, the full name 'EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL' is written in a smaller font, with a small European Union flag icon to the left.

Risk related to spread of new SARS-CoV-2 variants of concern in the EU/EEA and update to sequencing guidance

ECOVID-LabNet, 20 January 2021

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Background – Increased detection of SARS-CoV-2 variant viruses

B.1.1.7 - VOC 202012/01



- The United Kingdom (UK) has faced a rapid increase in COVID-19 case rates, which is associated with the emergence of a new SARS-CoV-2 variant, VOC 202012/01, which has led to increased pressure to the healthcare system.
- More than 16 800 cases of this new variant have been reported from the UK.
- The new variant shows increased (app. 50% higher) transmissibility compared to previously circulating variants, but no other changes in characteristics have been observed so far.
- VOC 202012/01 is defined by multiple spike protein changes (**deletion 69-70**, deletion 144, **N501Y**, A570D, D614G, P681H, T716I, S982A, D1118H) as well as by mutations in other genomic regions
- It is also referred to as clade 20B variant following classification by Nextstrain, GISAID clade GR or Pangolin nomenclature lineage **B.1.1.7**

Proportion of UK SARS-CoV-2 sequences classified as VOC 202012/01 per week, and total sequences per week from the UK.

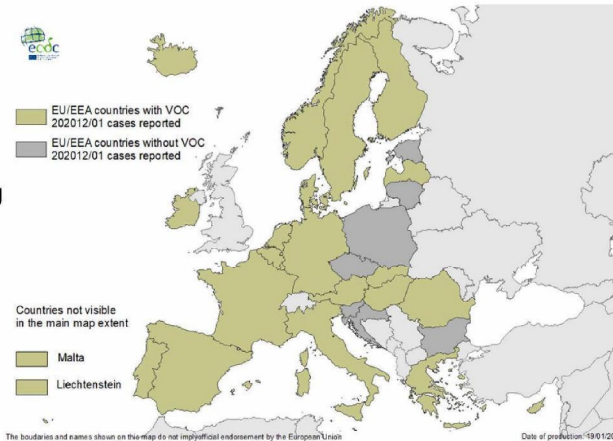


Weeks 1 and 2 of 2021 are omitted due to very few sequences being available.
Source: GISAID EpiCov database. More detailed national analysis of sequences from the UK can be found at the COVID-19 Genomics UK Consortium

EU/EEA countries reporting B.1.1.7 - VOC 202012/01 cases

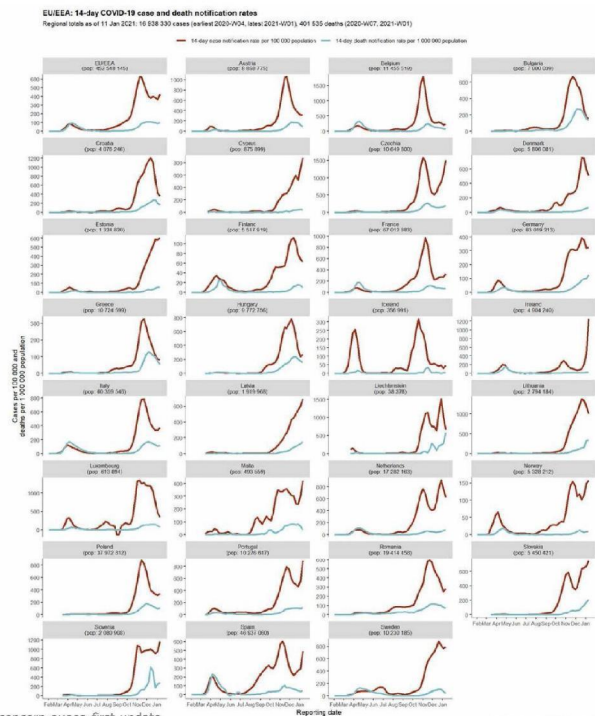


- VOC 202012/01 has been identified in most EU/EEA countries, both in returning travellers (mainly from the UK) and from the community (non-travel-associated).
- Community spread in EU/EEA countries is likely ongoing but the extent is unclear
- Sampling strategy varies a lot between countries, comparing case numbers is currently difficult
- Many countries have implemented detection of cases through targeted testing of travellers from UK or contacts of confirmed cases



In the EU/EEA, about 1 300 cases have been identified in 23 countries: Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Luxembourg, Malta, Netherlands, Norway, Portugal, Romania, Slovakia, Spain and Sweden.

Epidemiological situation

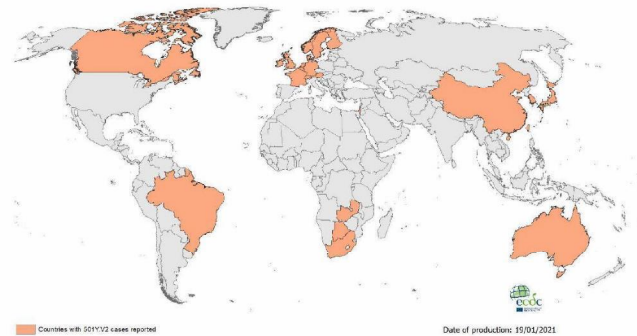


<https://www.ecdc.europa.eu/en/publications-data/covid-19-risk-assessment-spread-new-variants-concern-eueea-first-update>

Countries reporting B.1.351 - 501Y.V2 cases



- Variant 501Y.V2, first identified in South Africa, is also referred to as Nextstrain clade 20C, GISAID clade GH, Pangolin lineage **B.1.351**.
- 501Y.V2 is defined by multiple spike protein changes present in all viruses (D80A, D215G, **E484K**, **N501Y** and A701V), and more recently collected viruses have additional changes (L18F, R246I, K417N, and deletion 242-244).
- Three of the changes (K417N, E484K, and N501Y) are located within the receptor-binding domain (RBD).
- This lineage exhibits complete escape from three classes of therapeutically relevant monoclonal antibodies¹
- 501Y.V2 shows substantial or complete escape from neutralizing antibodies in COVID-19 convalescent plasma¹



- Approximately 570 cases of 501Y.V2 have been identified in 23 countries.
- In the EU/EEA, 30 cases have been identified in 10 countries: Germany (6), France (5), Belgium (4), Ireland (3), the Netherlands (3), Denmark (2), Finland (2), Austria (1), Norway (1) and Sweden (1)
- Outside the EU/EEA, approximately 540 cases have been identified in 13 countries: South Africa (447), United Kingdom (54), Australia (6), Botswana (6), Canada (2), China (2), Switzerland (2), Brazil (1), Japan (1), South Korea (1) and Taiwan (1) and Zambia (1)

¹ <https://www.biorxiv.org/content/10.1101/2021.01.18.427166v1.full.pdf>
<https://www.ecdc.europa.eu/en/publications-data/covid-19-risk-assessment-spread-new-variants-concern-eueea-first-update>

New SARS-CoV-2 variant P.1



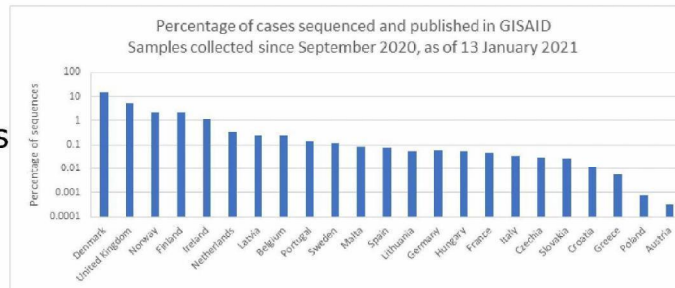
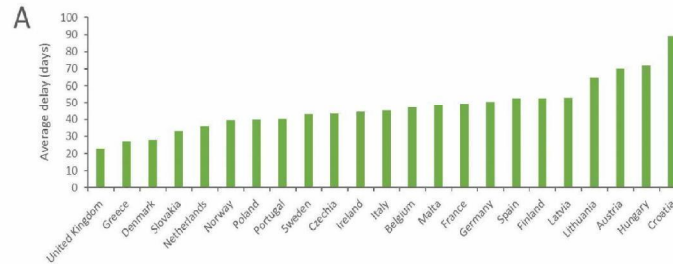
- Variant P.1, described in Brazil, belongs to Nextstrain clade 20B, GISAID clade GR and Pangolin lineage **P.1** (formerly part of B.1.1.28).
- The variant is not closely related to VOC 202012/01 nor to 501Y.V2
- 11 amino acid changes in the spike protein compared to its ancestral lineage B.1.1.28, of which three are located in the RBD. It has been assigned to the **novel lineage P.1** as it is divergent from its ancestral lineage, and no more levels of classification are available in the naming scheme.
- The full set of spike protein changes for the variant are L18F, T20N, P26S, D138Y, R190S, K417T, **E484K**, **N501Y**, H655Y, T1027I, and V1176F.
- On 10 January 2021, Japan reported four cases of COVID-19 associated with a novel variant of SARS-CoV-2 in returning travellers from Brazil.
- On 12 January 2021, a preprint article¹ describing a variant detected in Manaus, Brazil, identical to the one detected in Japan was published.
- The variant seems to have spread rapidly in Manaus, with 13 out of 31 genomes (31%) generated from 37 samples collected from patients seeking private healthcare in mid/late-December being identified as this variant. Very little information is currently available about the epidemiology of this variant, ECDC is monitoring the situation through Epidemic Intelligence and global sequence databases.
- No EU/EEA countries have reported identifying this variant so far.
- In addition to the P.1 variant, there is also another variant within lineage B.1.1.28, denoted **B.1.1.28(E484K)**, circulating in Brazil with the E484K change, but with none of the other mutations defining lineage P.1. The two variants share a common ancestor within the B.1.1.28 lineage but both variants have diverged from it and the mutations leading to the spike protein E484K change have likely occurred independently.

¹Faria NR, Claro IM, Candido D, Franco LA, Andrade PS, Coletti TM, et al. Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings. [cited 14 January 2021]. Available from: <https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586>

Variant detection capability in the EU/EEA



- Sequencing of the viral genome, or at least the S-gene, is required for samples with a positive test for SARS-CoV-2
- Very few countries have sequenced and published more than 1% of cases* since September 2020
- Sequencing efforts are now targeted to find specific variants, which reduces the representativeness of sequences from many countries



Source: GISAID EpicoV database, *Iceland has reported to ECDC that all cases in the country are reported within 48 hours, although these have not been uploaded to GISAID recently.



Risk assessment (1)



- ECDC assesses the probability of the introduction and community spread of variants of concern in the EU/EEA as **high/very high** due to its increased transmissibility. :
 - The probability of variant viruses being introduced and further spread in the EU/EEA currently being **high**.
 - The increased transmissibility is likely to lead to an **increased number** of cases and thus to **higher hospitalisation and death rates**, particularly for those in older age groups or with co-morbidities.



Options for response (1)



- Member States need to **increase** the level of **surveillance** and **sequencing** of a representative selection of samples from community COVID-19 cases to identify local community spread and monitor trends over time;
- Consider implementing RT-PCR pre-screening for N501Y or deletion 69-70;
- Perform timely, targeted and representative sequencing of community cases to detect variant viruses early and monitor the incidence;
- Enhance targeted follow-up, testing, contact tracing and isolation of suspected and confirmed cases of the variant virus;
- Monitor local, regional and national situation to identify areas with abrupt changes in rates of transmission or disease severity;
- Notify cases of the new variant, as well as any other new SARS-CoV-2 variants of potential concern, through EWRS and TESSy.



Options for response (2)



Member states should prepare **laboratories** for a **higher demand** of testing. Laboratories should:

- Ensure **human and material resources** to manage an increasing number of requests for detection and characterisation of COVID-19 samples;
- Increase sequencing capacity by involving **all possible sequencing capacity** in the Member States from clinical, diagnostic, academic and commercial laboratories;
- Prevent laboratory **consumable shortages** by keeping a stock of reagents, plastic ware and personal protective equipment, and anticipating orders.



Update to ECDC sequencing guidance

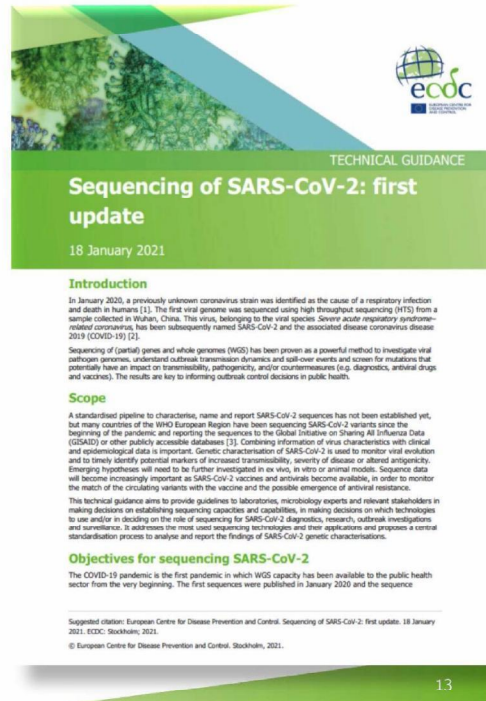
Updated sequencing guidance

Updated

1. Sampling strategy
 - Community-based random sampling
 - Targeted monitoring of e.g. outbreaks

2. Sample size calculations

<https://www.ecdc.europa.eu/en/publications-data/sequencing-sars-cov-2>



TECHNICAL GUIDANCE

Sequencing of SARS-CoV-2: first update

18 January 2021

Introduction

In January 2020, a previously unknown coronavirus strain was identified as the cause of a respiratory infection and death in humans [1]. The first viral genome was sequenced using high throughput sequencing (HTS) from a sample collected in Wuhan, China. This virus, belonging to the viral species Severe acute respiratory syndrome-related coronavirus, has been subsequently named SARS-CoV-2 and the associated disease coronavirus disease 2019 (COVID-19) [2].

Sequencing of (partial) genes and whole genomes (WGS) has been proven as a powerful method to investigate viral pathogen genomes, understand outbreak transmission dynamics and spill-over events and screen for mutations that potentially have an impact on transmissibility, pathogenicity, and/or countermeasures (e.g. diagnostics, antiviral drugs, and vaccines). The results are key to informing outbreak control decisions in public health.

Scope

A standardised pipeline to characterise, name and report SARS-CoV-2 sequences has not been established yet, but many countries of the WHO European Region have been sequencing SARS-CoV-2 variants since the beginning of the pandemic and reporting the sequences to the Global Initiative on Sharing All Influenza Data (GISAID) or other publicly accessible databases [3]. Combining information of virus characteristics with clinical and epidemiological data is important. Genetic characterisation of SARS-CoV-2 is used to monitor viral evolution and to timely identify potential markers of increased transmissibility, severity of disease or altered antigenicity. Emerging hypotheses will need to be further investigated in *ex vivo*, *in vitro* or animal models. Sequence data will become increasingly important as SARS-CoV-2 vaccines and antivirals become available, in order to monitor the match of the circulating variants with the vaccine and the possible emergence of antiviral resistance.

This technical guidance aims to provide guidelines to laboratories, microbiology experts and relevant stakeholders in making decisions on establishing sequencing capacities and capabilities, in making decisions on which technologies to use and/or in deciding on the role of sequencing for SARS-CoV-2 diagnostics, research, outbreak investigations and surveillance. It addresses the most used sequencing technologies, and their applications and proposes a central standardisation process to analyse and report the findings of SARS-CoV-2 genetic characterisations.

Objectives for sequencing SARS-CoV-2

The COVID-19 pandemic is the first pandemic in which WGS capacity has been available to the public health sector from the very beginning. The first sequences were published in January 2020 and the sequence

Suggested citation: European Centre for Disease Prevention and Control. Sequencing of SARS-CoV-2: first update. 18 January 2021. ECDC, Stockholm, 2021.
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Community-based sampling



For surveillance purposes, and for early detection and prevalence calculation of variant virus circulation

- **representative** viruses from **different geographic locations and time points**, as well as from patients of varied **demographics** and across the disease **severity** spectrum should be selected for sequencing.
- continue with surveillance of SARS-CoV-2 viruses in community and hospital settings and use **random sampling** of COVID-19 cases for virus characterisation

Targeted monitoring



For monitoring of virus evolution and changes in the virus genome, include a selection of SARS-CoV-2

- vaccine escape variants
- viruses causing reinfections
- variants emerging in animal populations or in human-animal interaction
- viruses that may alter diagnostic performance
- variants with increased transmission, especially if they are not explained by other epidemiological factors
- cases with an epidemiological link to areas of variant circulation or other evidence suggesting exposure to such a variant

Sample size



A minimum ability to roughly quantify the proportion of a variant present at a prevalence of 2.5% of the total circulating variants:

- each country to sequence **at least approximately 500 randomly selected samples each week.**

Number of sequences required, 50 000 total number of cases per time unit and geographic unit

Expected prevalence of variant among all circulating viruses	Number of sequences required per time unit and geographic unit of desired resolution			
	Only detect presence of variant viruses with 95% confidence (no precision)	Determination of proportion of variant		
		Low precision (95% relative CI $\pm 50\%$)	Medium precision (95% relative CI $\pm 25\%$)	High precision (95% relative CI $\pm 10\%$)
25.00%	12	46	183	1 114
10.00%	30	138	544	3 133
5.00%	60	289	1 128	5 988
2.50%	119	589	2 236	10 336
1.00%	297	1 455	5 146	17 764
0.50%	588	2 801	8 948	23 212
0.25%	1 156	5 179	14 129	27 379
0.10%	2 748	10 511	21 605	30 669

<https://www.ecdc.europa.eu/en/publications-data/sequencing-sars-cov-2>

ECDC sequencing service (under discussion)



- Technical capacity: 2000 isolates per week, likely 3000/day mid February
- cDNA or RNA (CT<30) can be used as material for sequencing
- Turn-around-time around 5 days if shipping is optimised
- Shipping services under negotiation
- Initial bioinformatic analysis can likely be offered

Work in progress to define details and make contractual arrangements

Individual countries who have expressed the need for support or have too low capacity for virus characterisation will be contacted

Please contact 5.1.2e ecdc.europa.eu if you need such support

Technical support for neutralisation assay



Contract between ECDC and RIVM signed for supporting the EU/EEA Member states with neutralisation assays

1. To perform confirmatory virus neutralisation testing for EU/EEA Member States public health laboratories that do not have the capacity to do so themselves.
2. To offer technical support to laboratories that are currently performing virus neutralisation testing themselves.

Please contact 5.1.2e ecdc.europa.eu if you need such support



TESSy reporting of variant virus detections

Current new variant data collection



NCOV case-based reporting:

Variable: VirusVariant

- WILD_TYPE
- VOC_202012_01
- S_GENE_DELETION (only after sequencing)
- 501_V2
- CLUSTER_5
- Y453F
- VARIANT_OTHER
- UNK

Variable: VirusVariantOther

Also: WgsSequenceId

NCOVAGGR aggregated reporting:

- Variant501V2
- VariantCluster5
- VariantSGeneDelete (only after sequencing)
- VariantVOC_202012_01
- VariantY453F
- NumberSequencedViruses (denominator)



Reporting as of 19 January



NCOVAGGR:

- 6 countries reported number of sequenced viruses
- 7 countries reported data on variants

NCOV:

- 3 countries reported data on variants (none on wild-type)

Limited reporting – specific challenges?