



# Methods for the detection and identification of SARS-CoV-2 variants

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## Summary

Whole Genome Sequencing, or at least complete or partial S-gene, should be performed to confirm infection with a specific variant. For early detection and prevalence calculation of variants of concern (e.g. B.1.1.7/501Y.V1, B.1.351/501Y.V2, P.1/501Y.V3), alternative methods have been developed, such as diagnostic screening PCR-based assays. While testing strategies should be flexible and rapidly adaptable to change, depending on the local epidemiology, population dynamics and resources, sample and method selection are key and will depend on the objectives. Specific objectives include the assessment of the circulation of the different SARS-CoV-2 variants in the community selecting representative samples, genetic characterisation to monitor the virus evolution and inform vaccine composition decisions or outbreak analyses. When PCR-based assays are used, confirmatory sequencing of at least a subset of viruses should be performed to be able to use these assay results as indicators of community circulation of the variants of concern. Before introducing a new testing method or a new assay, a validation and verification exercise should be carried out to ensure that the laboratory testing system is performing adequately for the circulating viruses. Reporting the results to The European Surveillance System (TESSy) and the sequences to GISAID or other public databases should be done in a timely manner (ideally weekly).

This document was developed by technical experts from ECDC and WHO Regional Office for Europe with review by experts of the SARS-CoV-2 Characterisation Working Group.

## Introduction

Several SARS-CoV-2 variants of concern (VOC) have emerged in the past months and monitoring them in all countries is key. To be able to confirm infection with a specific variant, sequencing of the whole SARS-CoV-2 genome, or at least whole or partial S-gene for the current variants is required. The only way to identify and characterise new variants and unambiguously type existing variants is with genomics. Guidance on sequencing of SARS-CoV-2 can be found in ECDC's technical guidance [Sequencing of SARS-CoV-2](#) and the [WHO's Genomic sequencing of SARS-CoV-2: a guide to implementation for maximum impact on public health](#) [1,2].

While countries are building or up-scaling their high throughput sequencing capacities, results are made available with a time delay that makes Whole genome sequencing (WGS) insufficient for timely detection of variants for public health response (e.g. contact tracing) and calculation of prevalence of VOCs in the community. Despite a significant drop of costs, WGS is still a relatively expensive method in comparison with some of the screening approaches based on PCR. It also requires an investment in equipment as well as training in equipment and bioinformatics analysis. Therefore, at the moment, WGS cannot be implemented in all diagnostic laboratories. Sanger sequencing of the S-gene, can in some settings be more feasible and timely than WGS.

For early detection and prevalence calculation of VOCs (i.e. B.1.1.7/501Y.V1, B.1.351/501Y.V2, P.1/501Y.V3), alternative methods, such as using diagnostic screening PCR-based assays that generate results in a few hours, with subsequent verification/confirmation by sequencing, can be valuable. Several groups have already developed or are currently developing and evaluating such techniques.

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Erratum: 19 March 2021: Additions to the text were made in the Summary and Results section to highlight that data should be submitted to GISAID or other public databases.

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## Scope and objective

This technical guidance provides guidance to laboratories, microbiology experts and relevant stakeholders in making decisions on establishing or scaling up capability and capacity to detect and identify circulating SARS-CoV-2 variants, and in making decisions on which technologies to use and for which objective.

The objective of this document is to present the available methods (screening and sequencing) for detection and identification of circulating SARS-CoV-2 VOCs. The document also outlines quality assessment issues, as well as considerations on sample and method selection and results reporting based on the different objectives of testing.

## Sequencing

### Whole genome sequencing

Whole genome sequencing is an important method to characterise viruses genetically. Using either a tiled amplicon approach or shotgun sequencing, the entire genome of the virus will be sequenced and can be compared with other circulating strains [1]. Whole genome sequencing can be used efficiently to detect VOCs as it represents an unbiased approach without the need for prior knowledge on the presence of certain mutations in the viral genome. It is a resource-intensive method that can take several days for generation of results, depending on the protocol. Data storage issues and bioinformatics support need to be considered. Guidance on the implementation of WGS can be found in ECDC's technical guidance [Sequencing of SARS-CoV-2](#), and the [WHO's Genomic sequencing of SARS-CoV-2: a guide to implementation for maximum impact on public health](#) [1,2].

### Sanger or partial next generation sequencing amplicon-based sequencing

Sanger or next generation sequencing (NGS) amplicon-based sequencing of selected parts of the viral genome are alternative methods for the identification of VOCs. With these techniques, targeted whole or partial S-gene sequencing can be performed using a genetic analyser. The NGS method comes with the same challenges as WGS regarding equipment and bioinformatics analysis. Protocols for specific RT-PCRs for marker regions of the S-gene region indicative of the B.1.1.7/501Y.V1 and B.1.351/501Y.V2 VOCs, followed by sequencing have been developed [3]. The region to be sequenced should cover at least the entire N-terminal and receptor binding domain (RBD) (amino acid 1-541, 1623 bp) to reliably differentiate between the circulating variants. Signature mutations for the variant in the sequenced region should be present. Ideally S-gene amino acids 1-800 (2 400 bp) or the entire S-gene should be sequenced to also monitor the S1/S2 cleavage site and other regions of interest. The B.1.351/501Y.V2 variant has variable reported mutation profiles, so it is recommended to use the minimum set: D80A, D215G, E484K, N501Y, A701V.

ECDC can support countries with WGS and bioinformatics analyses. Please contact [PHE.Support.Microbiology@ecdc.europa.eu](mailto:PHE.Support.Microbiology@ecdc.europa.eu) for more information.

## Diagnostic screening assays of known VOCs

### S-gene drop out or target failure

For the B.1.1.7/501Y.V1 (also called VOC 202012/01), a negative or significantly weaker positive S-gene result in multiplex RT-PCR assays, with positive results for the other targets, has been used as an indicator or screening method to identify this particular variant. The weaker signal or complete failure of the S-gene target is caused by a deletion at nt207-212 in the respective gene. The S-gene target failure occurs for some assays that include a S-gene target, but not all [2]. By coincidence, the pattern of detection of B.1.1.7/501Y.V1 with a specific commercial assay, can be used to detect those currently circulating variants of concern [4,5]. Variant B.1.1.7/501Y.V1 gives a positive signal in ORF1 and N-gene targeted RT-PCRs, but not in S-based RT-PCR, and is therefore called S-gene target failure or target failure; this pattern can be used as an indicator of potential circulation of the B.1.1.7/501Y.V1 variant.

It needs to be noted that this target failure (S-gene target failure) is not exclusive to B.1.1.7/501Y.V1 and will also identify other variants (non-VOC) and cannot differentiate between them, while it will also fail to detect some other VOC. It is worth mentioning that prior to the emergence of the B.1.17 VOC in the United Kingdom

(UK), 1-5% of sequenced samples already had the deletion/target failure (drop out). The S-gene target failure does not occur for 501Y.V2 and most probably not for lineage P.1. This strategy should preferably be used when there is already high prevalence of the VOC in the setting. Confirmation of the presence of the deletion at nucleotides 207-212 by sequencing is recommended at least for a subset of samples, especially in a low prevalence setting; this will be needed to increase the confidence of the results and should be closely monitored. In regions where other variant(s) with the same deletion but not VOC circulate, sequencing of all S-gene target failures is necessary.

Increasing the numbers of sequenced samples screened by S-gene target failure can be considered to assess the regional correlation between S-gene target failure and B.1.1.7/501Y.V1, as this varies with the regionally circulating variants [6]. If the correlation is very high, S-gene target failure can be used to approximate the frequency of B.1.1.7/501Y.V1.

## Multiplex RT-PCR, including S-gene target failure

With a multiple channel real time RT-PCR device, the normal E and/or N and/or ORF-1 target assays may be combined with the S-gene target, so the VOC screening could be integrated with the normal routine, in a single run [7].

Another method has been developed based on the ORF1a gene (ORF1a  $\Delta$ 3675-3677) that exists in all three variants, which has not yet been widely detected in other SARS-CoV-2 lineages. Using ORF1a  $\Delta$ 3675-3677 as the primary target and spike  $\Delta$ 69-70 to differentiate, an open source PCR assay was designed to detect SARS-CoV-2 variants of concern (preprint) [8].

It is important to emphasise that results should not be over-interpreted and must be checked/continuously validated through the use of genomics.

## Screening SNP assays

Screening for VOC specific amino acid substitutions can be done using a specific RT-PCR assays targeting single nucleotide polymorphisms (SNP) to screen e.g. spike N501Y and HV69-70del mutations (e.g. present in B.1.1.7/501Y.V1 VOC) [7]. Appropriate positive controls will be needed. This method allows quick (this is a <1h assay) estimation of the prevalence of the specific mutation-positive variants in the community.

Of note, there are N501Y lineages that are not VOCs, which currently circulate, and therefore verification of at least a subset of samples should be done using sequencing.

## Screening SNP by specific real time RT-PCR melting curve analysis

Some real time PCR platforms allow for melting curve analysis. Commercial assays have been developed to use this genotyping method to identify specific amino acid substitutions, e.g. HV69-70del, K417N, N439K, Y453F, E484K, N501Y, A570D, D614G, P681H or V1176F.

## Reverse transcription loop-mediated and transcription-mediated amplification isothermal amplification

Reverse transcription loop-mediated isothermal amplification (RT-LAMP) and transcription-mediated amplification (TMA) on Panther Hologic machines techniques have emerged as an alternative molecular detection method for the detection of SARS-CoV-2. RT-LAMP technique has some advantages such as faster test results and need of fewer resources, while maintaining high sensitivity and specificity, although currently available protocols will not differentiate between specific VOCs [9]. Some protocols however, e.g. LamPORE, provide a possible pathway through to sequencing.

Proper clinical validation studies are needed to evaluate the new techniques and assess the potential role they could play in the different settings.

## Rapid antigen detection tests

Rapid antigen tests can contribute to overall COVID-19 testing capacity, offering advantages in terms of shorter turnaround times and reduced costs, especially in situations in which RT-PCR testing capacity is limited, although their sensitivity is generally lower than for RT-PCR [10]. Rapid antigen tests may detect the presence of SARS-CoV-2 (including variant viruses) but cannot identify/differentiate the type of VOC; they can help to reduce further transmission through early detection of highly infectious cases, enabling a rapid start of contact tracing.

So far, the UK has evaluated five rapid antigen tests (targeting the nucleocapsid protein) and they were all found to detect the new variant B.1.1.7/501Y.V1 [11]. Further validation of the tests is needed to ensure that they detect the emerging variants.

## Neutralisation assays and antigenic characterisation

To decide if a variant of interest is a variant of concern, the particular variant would need to be assessed more broadly through a risk assessment process looking into various risk elements (e.g. increase transmissibility, morbidity/mortality or vaccine escape). For laboratories to assess at least the antigenic distance to the currently available vaccine antigen and to main circulating viruses, it would be important to perform antigenic characterisation through neutralisation assay with convalescent sera and standards. Multiple laboratory methods to perform virus neutralisation test have been developed. Some examples are microneutralisation assay [12], pseudovirus neutralisation assay [13], surrogate virus neutralisation test [14]. Assays with replication competent SARS-CoV-2 isolates are normally either plaque reduction/focus forming assays or TCID50 (Median Tissue Culture Infectious Dose)-based assays. However, they have the disadvantage that they require biosafety level (BSL)-3 laboratories and are often labour intense. On the other hand, assays using replication-defective pseudotyped viral particles can be performed under BSL-1 or BSL-2 conditions. As all neutralisation assays require living cells, they are more difficult to standardise than ELISAs and, therefore, testing the robustness of these assays is a crucial step [15]. A comparison of four different types of neutralisation assays has shown that these SARS-CoV-2 neutralisation assays were robust, results were comparable and produced highly reproducible neutralisation titres [15].

## Considerations for sample and method selection

Testing strategies should be flexible and rapidly adaptable to change, depending on the local epidemiology, population dynamics and resources. Sample and method selection are key and will depend on the objectives:

- Timely testing of people with symptoms, fostered through improving access to testing and encouraging people to seek testing as soon as possible after symptom onset, remains important to enable rapid initiation of infection prevention and control measures. Targeted (e.g. from outbreaks) or convenience sampling for VOC identification is important for early detection and response activities. Sequencing or screening for early detection of circulating VOCs can be done using one of the aforementioned methods. All or a selection of positive samples can be screened for VOCs and a subset of those can be selected for further confirmatory sequencing. Sequencing of viruses from areas with overall higher increase may be necessary, for the initial identification of novel VOCs.
- Currently, a priority should be to assess the level of circulation of known variants of concern in the community and therefore a representative sample needs to be collected regularly from each country to accurately estimate and monitor prevalence of the VOCs. There is a risk of bias in the sequencing results if the sample selection is not representative, e.g. when the selection of samples for sequencing is based on samples for confirmation of targeted screening. For testing representative samples, sequencing should be the preferred method, however screening methods can also be useful, as fast result turn-around time is important to inform public health interventions. Sequencing can be used to assess the fraction of S-gene target failure or other screening method that is VOC, to be able to use the screening method as an indicator of the overall situation. The [ECDC sequencing guidance](#) recommends testing at least 500 random/representative samples per country per week.
- In parallel, WGS should be done for virus genetic characterisation to monitor the virus evolution and inform vaccine composition decisions. For this purpose, samples should be collected from vaccine breakthrough infections, reinfections, prolonged/chronic infections, severe infections and across the disease spectrum and different demographics, zoonotic infections, and outbreaks [1].
- Depending on the available resources, WGS sequencing can be done for additional objectives, like outbreak analyses, phylodynamic analyses and other research studies.

Guidance on sample selection and how to calculate the minimum number of viruses to be sequenced for surveillance purposes can be found in the first update of ECDC's technical guidance Sequencing of SARS-CoV-2 [1].

## Quality assessment

Before introducing a new testing method or a new assay, or when a new PCR technician is introduced at the laboratory, a validation and verification exercise should be carried out, to ensure that the laboratory testing system is performing adequately for the circulating viruses [16]. In general, laboratories should have a quality assurance system in place and are encouraged to participate in external quality assessment (EQA) schemes or perform result comparison between laboratories, of a subset of samples [16]. ECDC is planning a molecular External Quality Assessment for national COVID19 reference laboratories in the near future. Please contact [PHE.Support.Microbiology@ecdc.europa.eu](mailto:PHE.Support.Microbiology@ecdc.europa.eu) for more information.

As SARS-CoV-2 is an RNA virus and mutates with intermediate frequency, it is expected that more VOCs will emerge. Genomics is the best tool for identification of new variants. The diagnostic laboratories need to remain vigilant to detect any mismatches of RT-PCR assay primers and probes in comparison to circulating virus genomes and detection capability of other assays such as rapid antigen tests, and to adapt Sanger sequencing protocols. The vast majority of primer/probe binding sites of commercial assays are not publicly known. It is important to note that it was coincidental that detection assays targeting the S-gene enable the identification of B.1.1.7 lineage variants. For all assays, it is vital to keep track of possible incidents of suboptimal performance and to inform the manufacturer of a commercial assay and international SARS-CoV-2 public health networks of any concerns you may experience with a specific assay.

## Results reporting

Detections of SARS-CoV-2 should be reported on a weekly basis to [The European Surveillance System \(TESSy\)](#). Detection of novel VOCs or outbreaks of currently circulating VOCs should be reported immediately through the Early Warning and Response System (EWRS), while VOC detections should be reported to TESSy weekly.

SARS-CoV-2 sequences should be submitted to [GISAID or other public databases](#) in a timely manner, i.e. ideally within one to two weeks from sample collection. Raw data can be deposited in the COVID-19 data portal ([www.covid19dataportal.org](http://www.covid19dataportal.org)).

It is the responsibility of reporting Member State to assess whether the virus is a variant included in the variant list, irrespective of the method used for detection/identification. Variables for reporting of VOCs (VirusVariant) have been implemented within the aggregated (NCOVaggr) and case-based (NCOV) ESSy record types, where sequence ID numbers (GISAID identifiers) should be reported as well. Raw sequencing data, ENA/SRA accession numbers, can also be submitted to TESSy. Any epidemiological data available, including the setting from where the sample was obtained and probable country of infection, should be reported if data are submitted using the case-based record type (NCOV). This will enable the data analysis and interpretation by identifying those representative cases that reflect the prevalence of VOCs in the community.

Please contact [tessy@ecdc.europa.eu](mailto:tessy@ecdc.europa.eu) for assistance with TESSy uploading. Please contact [PHE.Support.Microbiology@ecdc.europa.eu](mailto:PHE.Support.Microbiology@ecdc.europa.eu) if you need assistance with the interpretation/reporting of the sequencing results.

## Laboratory support

ECDC and WHO/Europe coordinate their support to countries in the WHO European Region. ECDC is supporting scaling up of sequencing and neutralisation assay capacity in EU/EEA Member States. Please contact [PHE.Support.Microbiology@ecdc.europa.eu](mailto:PHE.Support.Microbiology@ecdc.europa.eu) for more information. Countries wishing to receive support from WHO/Europe may contact [euinfluenza@who.int](mailto:euinfluenza@who.int)

## Protocol and information sharing

WHO Regional Office for Europe jointly with ECDC has set up a protocol/information sharing platform EZCollab for 'COVID-19 protocol sharing'. Registration can be done in: [https://ezcollab.who.int/euroflu/flulab/covid19\\_protocols](https://ezcollab.who.int/euroflu/flulab/covid19_protocols)

## Key messages

- Whole SARS-CoV-2 genome sequencing, or at least whole or partial S-gene, should be used to confirm infection with a specific variant.
- For the early detection and prevalence calculation of VOCs (i.e. B.1.1.7/501Y.V1, B.1.351/501Y.V2, P.1/501Y.V3), alternative methods, such as diagnostic screening PCR-based assays can also be used.
- Sequencing should be used to confirm at least a subset of the viruses, when PCR-based methods are used.
- Sample and method selection are key and will depend on the objectives, e.g. for assessing the circulation of the different SARS-CoV-2 variants using representative samples from the community, genetic characterisation to monitor the virus evolution, and informing vaccine composition decisions or outbreak analyses.
- Assay validation should be carried out to ensure that the laboratory testing system is performing adequately for the circulating viruses.
- SARS-CoV-2 consensus sequences are strongly recommended to be submitted to GISAID or other public databases.
- Detection of novel VOCs or outbreaks of currently circulating VOCs should be reported immediately through the EWRS, while VOC detections should be reported to TESSy weekly.

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