

When is Covid, Covid?

September 11, 2020

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We are constantly following the tally of Covid-19 cases. But one question won't go away: when is Covid-19 actually Covid-19?

Covid-19 was [first identified](https://linkinghub.elsevier.com/retrieve/pii/S0140673620301835) [https://linkinghub.elsevier.com/retrieve/pii/S0140673620301835], as a severe disease-causing atypical pneumonia, accompanied by fever, cough and sometimes a range of other symptoms. The clinical features of the 41 patients infected with 2019 novel coronavirus in Wuhan included pneumonia with abnormal findings on chest CT. The agent was identified as SARS-CoV-2.

Testing by RT-PCR has been globally implemented to identify RNA sequences thought to be unique to SARS-CoV-2. Worldwide case numbers are based on the reporting of the presence or absence of small RNA sequences of the SARS-CoV-2 genome.

Some diseases can be diagnosed based on a test alone; most diseases, however, are defined by the cluster of symptoms and signs, in addition to test results. A [recent review](https://www.cochrane.org/news/featured-review-can-symptoms-and-medical-examination-accurately-diagnose-covid-19-disease) [https://www.cochrane.org/news/featured-review-can-symptoms-and-medical-examination-accurately-diagnose-covid-19-disease] found that a single symptom or sign could not accurately diagnose COVID-19.

A highly cited [rapid review](https://pubmed.ncbi.nlm.nih.gov/32029004/) [https://pubmed.ncbi.nlm.nih.gov/32029004/], guideline defined a suspected case as a patient with any of two of the following clinical features: fever, imaging features of pneumonia, normal or reduced white blood cell count, or reduced lymphocyte count in the early stages of the disease onset. A confirmed case was defined as positive for the 2019-nCoV by the real-time PCR test for nucleic acid in respiratory or blood samples.

Disease control agencies and the World Health Organisation have produced guidance for diagnosing Covid-19. We looked up case definitions*, and copied them into a table ([Table 1. Case definitions](https://docs.google.com/spreadsheets/d/1PEzYQhFQAuInde01HUvvueZgO9gUojUMoH-hz523FSw/edit#gid=0) [https://docs.google.com/spreadsheets/d/1PEzYQhFQAuInde01HUvvueZgO9gUojUMoH-hz523FSw/edit#gid=0].) to compare them.

WHO

- A suspect case has clinical symptoms of respiratory disease, perhaps with other associated presentations.
- A probable case is a suspect case for whom laboratory testing was inconclusive or not possible.
- A confirmed case is “A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.”

Thus, a positive laboratory test – type of test not specified here – trumps all else. We were not able to find WHO guidance on how PCR tests should be interpreted, specifically in relation to [cycle count or viral load](#)

[\[https://docs.google.com/document/d/11QlCxf6WLVDPyeGi-Y5gN7YeP9zyncac8f6lazzSP_FfM/edit\]](https://docs.google.com/document/d/11QlCxf6WLVDPyeGi-Y5gN7YeP9zyncac8f6lazzSP_FfM/edit).

European Union

For the [European Centers for Disease Control](#) [\[https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition\]](https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition) (ECDC), a case may be defined from clinical symptoms, or from radiology, or from “detection of SARS-CoV-2 nucleic acid in a clinical specimen” alone.

- Possible cases if diagnosed from clinical criteria,
- Probable if diagnosed from clinical and epidemiological criteria,
- Confirmed in “any person meeting the laboratory criteria”.

So, again, a positive laboratory test is more important than clinical diagnoses, and again, we were unable to find guidance on how laboratory tests should be applied and interpreted, particularly in PCR in relation to cycle count and viral load.

USA

The [US Centers for Disease Control](#) [\[https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/\]](https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/) (CDC) states

- Probable case meets clinical criteria and epidemiological evidence, or has presumptive laboratory evidence with either clinical or epidemiological evidence, or has Covid-19 or SARS-CoV-2 on the death certificate as a cause or significant contributor to death.
- Confirmed case “Meets confirmatory laboratory evidence”.

No information is given on interpreting PCR tests in relation to cycle count thresholds or viral load. Again, it looks as though a PCR test trumps clinical diagnoses.

China

Case definitions in China have changed over time, possibly affecting our [understanding of transmission](#) [\[https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667\(20\)30089-X/fulltext\]](https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30089-X/fulltext) (this change may also be happening in other world regions).

- Suspect cases the clinical manifestations include fever and/or respiratory symptoms; aforementioned imaging characteristics of novel coronavirus pneumonia; normal or decreased WBC count, normal or decreased lymphocyte count in the early stage of onset.

The latest [case definition](#)

[\[https://www.chinadaily.com.cn/pdf/2020/1.Clinical.Protocols.for.the.Diagnosis.and.Treatment.of.COVID-19.V7.pdf\]](https://www.chinadaily.com.cn/pdf/2020/1.Clinical.Protocols.for.the.Diagnosis.and.Treatment.of.COVID-19.V7.pdf) WE

identified states:

- Confirmed cases can be via RT-PCR, or if the genome sequence is highly homologous, or antibodies are detected via serology.

UK

The [UK government guidance on diagnosis](https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection) [https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection] is based on clinical symptoms. Testing (not specified) is recommended for cases who are well enough to remain in the community. No guidance is given as to how to interpret such a test or any actions that should be taken consequent to the test results. Thus, new cases in the UK could reasonably be thought to mean cases diagnosed by clinical symptoms.

Public Health England describes the [four pillars of testing](https://www.gov.uk/government/publications/coronavirus-covid-19-testing-data-methodology/covid-19-testing-data-methodology-note) [https://www.gov.uk/government/publications/coronavirus-covid-19-testing-data-methodology/covid-19-testing-data-methodology-note] to include swab testing and additionally serology testing for certain groups. The [methodology](https://www.gov.uk/government/publications/coronavirus-covid-19-testing-data-methodology/covid-19-testing-data-methodology-note) [https://www.gov.uk/government/publications/coronavirus-covid-19-testing-data-methodology/covid-19-testing-data-methodology-note] for counting cases states the following:

“If a person has both a negative and a positive test, then only their positive test will be counted. If a person is tested as positive under both pillar 1 and pillar 2, then only the first positive case is counted.”

An asymptomatic person who tested positive could have two confirmatory negative tests, but would still count as a confirmed case. In Wales, data is deduplicated on 42-day episodes; if someone is tested twice, 43 days apart, they will be included in the case count measure twice.

The UK government updates its guidance and [recently posted on assurances](https://www.gov.uk/government/publications/sars-cov-2-rna-testing-assurance-of-positive-results-during-periods-of-low-prevalence) [https://www.gov.uk/government/publications/sars-cov-2-rna-testing-assurance-of-positive-results-during-periods-of-low-prevalence] of positive results during periods of low prevalence.

The latest guidance states that ‘positive test results at the limit of detection that occur early in the cycle of infection are important as these represent individuals who may go on to transmit infection.’ The guidance asks laboratories to ‘determine the threshold for a positive result at the limit of detection based on the in-use assay,’ without stating what the threshold should be. If necessary, the laboratory should request a repeat sample; again this advice is given without a threshold to guide when to do the repeat test.

What is the case definition being used for clusters of UK cases being reported currently?

We deduce that a reported “case” is most probably simply the result of a positive PCR test. The new guidance is meaningless unless it provides a clear threshold for the limits of detection. For many whose test turns up positive, there may be nothing recorded about any clinical symptoms.

Italy

The Italian government [defines](https://snlg.iss.it/wp-content/uploads/2020/03/CircolareMinSal_DefinizioneCasoCOVID19.pdf) [\[https://snlg.iss.it/wp-content/uploads/2020/03/CircolareMinSal_DefinizioneCasoCOVID19.pdf\]](https://snlg.iss.it/wp-content/uploads/2020/03/CircolareMinSal_DefinizioneCasoCOVID19.pdf) a Probable Case as a suspected case in whom results of test for SARS-CoV-2 is unclear or inconclusive on the basis of specific protocols for Real Time PCR of SARS-CoV-2 in the designated regional reference laboratories or is positive to a pan-coronavirus test.

A confirmed case is a case with laboratory confirmation of SARS-CoV-2, carried out either in the national reference laboratories of the Istituto Superiore di Sanità (ISS, e.g. Italian NIH) or in the designated regional reference laboratories fulfilling the criteria at Annex 3 of the policy letter, independently from clinical symptoms or signs. Annex 3 was updated from 9 March to [3 april](http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2020&codLeg=73799&parte=1%20&serie=null). [\[http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2020&codLeg=73799&parte=1%20&serie=null\]](http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2020&codLeg=73799&parte=1%20&serie=null)

Annexe 3 lists accredited sub-regional laboratories authorised to carry out PCR testing for SARS CoV 2. Accreditation with the dedicated regional laboratory is based on the concordance of the first five positive and 10 negative specimens

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Another complexity is there may be a difference between a clinical case definition – applied to an individual presenting for health care – and a surveillance definition used to collect information for public health use. Many more case definitions may be published globally, but these were enough to confuse us.

The definition of suspected cases resembles what we would normally expect for making a diagnosis based on a set of clinical criteria. This is, however, discarded when it comes to a confirmatory diagnosis and replaced by a single PCR test result. However, there is no guidance providing details on the specific RNA sequences required by testing, a threshold for the test result and the need for confirmatory testing. It is therefore not clear to us what constitutes a positive result.

Currently, any person meeting the laboratory criteria is a confirmed case. Yet, a case definition should be a set of standard criteria for classifying whether a person has a certain disease, syndrome, or other health condition ([Centers for Disease Control and Prevention](https://www.cdc.gov/csels/dsepd/ss1978/lesson1/section5.html) [\[https://www.cdc.gov/csels/dsepd/ss1978/lesson1/section5.html\]](https://www.cdc.gov/csels/dsepd/ss1978/lesson1/section5.html).)

The PCR test positivity counts should include a standardized threshold level of detection, and at a minimum, the recording of the presence or absence of symptoms. As a disease, the COVID-19 case definition should constitute a disorder that produces a specific set of symptoms and signs. The in-hospital case definition should, therefore, record the CT lung findings and associated blood tests.

Only when an international standard is agreed upon will we be able to make comparisons, and answer the question of when is Covid, Covid?.

Disclaimer: The article has not been peer-reviewed; it should not replace individual clinical judgement and the sources cited should be checked. The views expressed in this commentary represent the views of the authors and not necessarily those of the host institution, the NHS, the NIHR, or the Department of Health and Social Care.

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The logo for Trip Database, featuring the word "Trip" in a large, stylized purple font. The letters have small colored accents: a red dot on the top of the 'i', a green bar on the bottom of the 'T', a blue bar on the bottom of the 'r', and a yellow bar on the bottom of the 'p'.

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