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COVID-19 caseness: An epidemiologic perspective

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ABSTRACT

The concept of caseness in the COVID-19 virus is important for early case finding and reporting. These are essential steps for prevention and control. This review defines and differentiates between types of cases and specifies the elements of each case definition in general with their application to COVID-19, where appropriate. These terms and their application are useful for the surveillance team, epidemiologists, clinicians, policy makers as well as the public in general.

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The emergence and worldwide spread of COVID-19 is a new public health crisis. The virus was believed to be originated in bats and its mode of transmission to humans is definitely unknown. The disease is transmitted by droplets of respiratory discharges or contact with contaminated surfaces. It presents with fatigue, malaise, fever, cough, sore throat and difficult breathing. Many people are asymptomatic, most of cases are mild and some progress to pneumonia and multi-organ dysfunction. The case fatality rate varies from 0.13% to 4.34% according to patients' registries of different countries [1,2].

Detection of the virus in respiratory secretions by PCR confirms the diagnosis. There is no specific treatment and treatment is essentially supportive. Severe cases need intensive care with artificial ventilation. Prevention entails social distancing, isolation of both suspected and symptomatic cases as well as infection control practices at health facilities [3]. Case definitions are important for

surveillance purposes; however it does not replace epidemiologic or clinical assessment and management of individual patient [4].

Caseness (also called case definition, clinical definition, or clinical case definition) in epidemiology is a set of diagnostic features used to make decision as to whether the subject is diseased or not. This can be based on clinical, laboratory and/or epidemiological criteria with the consideration of place, time and person [5–7]. In epidemiology the case definition is broader than the clinical definition as a variety of criteria can be used to define cases in epidemiology [8].

Standard case definition is applying a standardized set of criteria to identify a particular disease [6]. This standardization ensures that all cases are diagnosed in the same way, irrespective of time, place and person. This should not rely on laboratory detection of the organism alone, as some organisms may be present without disease [9–11].

Case is a person who has the particular disease which meets the case definition for surveillance and epidemic investigation purposes. This can differ from the ordinary clinical definition [5].

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Patient is a person who receives health care according to his/her needs. Most patients are classified as having a disease, illness or sickness. Sometimes patients are not diseased e.g. seeking vaccination, family planning or routine periodic health check-up [12,13].

Disease is the pathological changes or deviation from the normal biology, most often physical and sometimes psychiatric. It is an objective term diagnosed by health care personnel and includes a specific diagnosis based on systematic and standardized codes [12].

Illness is a subjective experience of a disease or illness based on subjective feelings and symptoms, sometimes no disease can be diagnosed. It is entirely personal and is not related to a stage of infectiousness [12]. It is an absence of wellness as perceived by the subject or others [14].

Sickness is the external aspect of ill-health. It is the social function an ill or sick person takes or is given in community, in different life situations [15,16].

Case classification Gradients of being a case (suspected, probable or confirmed). This is used where early case reporting is important and where definite diagnoses is difficult (e.g. laboratory confirmation) [5] such as in COVID-19 in poor countries that lack diagnostic facilities.

Modifying case definitions Case definitions can be refined or changed over time as more information becomes available. For new communicable diseases such as COVID-19, it is preferred to use sensitive case definition to identify every possible case. These changes include a adding new laboratory criteria, suspected and probable case definition as two different levels (rather than a single level), and a new epidemiological criterion. A major issue of changing case definition has a tremendous impact on case numbers and case ascertainment. It causes confusion in classifying cases and increases the burden of managing non-cases. Optimal case definition can vary from locality to another depending on the diagnostic facilities [16–18].

Characteristics of ideal case definition

Ideally case definition should be simple, clear, appropriate, concise, sensitive, specific and easy to apply to whole population of concern. Patients fulfilling the definition can be categorized as suspected, probable or confirmed [7].

Balancing sensitivity and specificity is crucial in case definition. A broad or loose definition is a sensitive one so as to catch all or most of the true cases as it focuses on clinical criteria. This is associated with high both true positive and false negative rates. On the other hand, specific definition is a strict one to be sure that any subject identified really had the disease as it relies on laboratory confirmation. This minimize both the false positive and the true positive rates [9,10,19,20].

Importance of case definition

The benefits and limitations of case definition in practice depend on their purpose, the skills of the user and the context in which they are used. Case definition is used for [7,9,21–24]:

- 1) surveillance as it forms the basis for any efforts at case search and is an essential epidemiologic surveillance, consistency and comparability in reporting, tracking the presence and distribution of cases in a given locality;
- 2) clinical care: early case finding and isolation of those with extremely infectious diseases are important for timely initiation treatment and control of further transmission of the infection.
- 3) research: all research on the diseases depends on the selecting a reliable and valid definitions in order to measure morbidity and mortality rates accurately and to detect biological markers.

Case definition is important in all types of epidemiological and clinical studies. Ideal case definition is problematic with the lack of a valid gold standard test [17].

- 4) service provision: development of a lucid case definition is crucial to effective investigation of epidemics. The use of a common case definition helps in standardization of the cases both within a current epidemic investigation and perhaps between outbreaks that differ over time or place.
- 5) Standardized case definitions will improve the quality of data reported in any the national infectious diseases notification [25].

Case definitions in infectious diseases

Cases of disease can be classified into overlapping and non-mutually exclusive types and each type has utility in different settings [26]. This is applicable to COVID-19. The following is a brief description of each type of case definition:

1-Index (primary, zero) case

There is confusion between the three terms and often used synonymously. Actually they have different definitions.

-Patient (case) zero is a term used to describe the first human infected by a disease, it may be diagnosed or not. Finding the patient zero will allow medics to determine where it came from. While, index case (patient) is defined as the first reported case of the disease that is diagnosed by clinician or epidemiologist. On the other hand the primary case is a person who gets the disease from an exposure and is the first case in the population. It is not always the index case [8,27–29]. Tracing back to the index case it is very difficult particularly if it had a mild disease. Knowing the patient Zero in an outbreak like coronavirus is paramount to trace the origin and exact initial genetic structure of the virus and identify the exact lineage of transmission. Also it helps to find if there has been a change in the genetic structure of the virus [30]. Earlier cases may be found and are labeled primary, secondary, tertiary, etc. Many epidemics of the emerging infectious diseases begin with a single case contracting an infection. It is notable that knowing the origin of an epidemic (i.e. zero/primary case) does not elucidate their cause [31]. Identifying patient zero is important both epidemiologically and politically [32]. The origin of COVID-19 has already caused a diplomatic spat between the US and China.

2-Secondary case

Is a person who gets a disease from exposure to a diseased person, or primary case, rather than the epidemic source itself (e.g. home contacts who get infected) [29].

3-Missed (hidden, undiagnosed) case

Missed case is a subject having an infectious disease with minimal symptoms and signs and does not seek medical advice or the health care provider fails to diagnosis it [33].

4-Clinically compatible case

A clinically compatible case has the medical history, signs and/or symptoms that agree with the clinical description of the disease [33], and its specific clinical criteria are included in the case classification [34]. It is a general clinical impression that this is a case of disease [26].

5-Epidemiologically linked case

This is a case in contact with a diseased person or exposed to environmental source together with possibility of acquiring infection by the known methods of spread [26,33–36].

6-Latent case

In latent diseases the causal pathogens remain dormant for extended periods of time with no active replication. Herpes simplex viruses, varicella-zoster virus can reactivate to become active infections during stress and immunosuppression [37]. It is not clear whether COVID-19 remains latent then reactivates.

7-Asymptomatic case

It is possible that a large proportion of the population will have COVID-19 yet have no symptoms at all, especially in the children and young age groups. Figures up to 80% have been reported [38–40]. Some asymptomatic cases will become symptomatic over the next week (known as pre-symptomatic) [39]. Asymptomatic spread of the COVID-19 is of concern. Many researchers believe that asymptomatic cases of COVID-19 could be an important source of spread [40–42]. Asymptomatic infections are to be regarded as cases, if the infection has public health or therapeutic implications [35].

8-Recurrent case (re-infection)

It is not clear if patients recovered from COVID-19 can be re-infected. Some recovered patients fulfilling the discharge criteria may become positive again for COVID-19 RNA [43]. There are few case reports of individual confirmed cases whose oropharyngeal swab test turned positive in convalescence and they recommended active surveillance of COVID-19 RNA for infectivity assessment [43,44]. There are several possible explanations. The remaining viruses in patients reactivate due to lack of sufficient immunity or the immune weakened after recovery or the virus stayed dormant before reactivating. Another possibility is the reinfection through another virus [45]. However, there is no current evidence of reinfection with the virus after recovery. Viral RNA shedding declines with symptoms resolution, and may continue for few weeks [46]. However, clinical recovery has been associated with the detection of IgM and IgG antibodies, a signal of immunity [47,48].

9-Under investigation case

Person Under Investigation (PUI) is any asymptomatic person or suspect case under investigation for the COVID-19 virus where information is not yet available to classify it as confirmed, probable or not a case [49,50].

10-Suspected (possible) case

It is an individual (or a group of individuals) who have signs and symptoms of the disease yet has not been diagnosed as having the disease [51]. This is a case with lower certainty and is classified as suspected for surveillance purposes. It has the clinical criteria mentioned in the case definition but lacks epidemiological or laboratory evidence of the disease. This definition has high sensitivity and low specificity. This allows for finding of most cases however, some false positives cases will be included [25,26,29,33,35].

The suspected case of COVID-19 is defined as “a patient with acute respiratory illness (fever and at least one sign/symptom of cough, shortness of breath) AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR a patient with any acute respiratory illness AND having been in *contact* with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset; OR a patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation” [50]. Suspected cases that are not tested should be isolated either at home or isolation institution till 48 h after resolving symptoms for at least 10 days after onset [50,51].

11-Probable case

Probable case is a suspected case plus supportive laboratory results or epidemiologic link [29] and is classified as probable for surveillance purposes [25,26,33,35,50].

Presumptive or supportive laboratory results: Specified laboratory findings that are consistent with the diagnosis but do not fulfill the criteria of laboratory confirmation [33].

In the probable case of COVID-19 laboratory testing is not conclusive or was not done for any reason.

A subject with fever (>38 C) and/or cough plus one of the following within two weeks before the onset of illness: travel to an

infected area or contact with a probable or confirmed case or contact with a person with acute respiratory symptoms who has been in an infected area with unavailable, negative or inclusive laboratory testing of COVID-19 [4,25,51].

12-Confirmed (definitive) case

A case that is classified as definitive for surveillance purposes and is laboratory confirmed by one or more tests and may fulfill the described clinical case definition or not. This definition should have high specificity and less sensitivity; so that most of the cases will be true positive and some will be missed [25,26,34,35].

A confirmed case of COVID-19 is a case with laboratory confirmation of infection using a real-time PCR or nucleic acid sequencing on at least one specific target genome performed at a reference laboratory (Canada MOH, 2020) irrespective of clinical signs and symptoms. If testing is unavailable or limited, confirmed case counts will not reflect the true burden of disease [51,52].

Laboratory definitive evidence requires detection of COVID-19 from a clinical specimen using a validated PCR, and/or significant rise in IgG antibody level to COVID-19 between paired sera (if serological testing is available) [50]. Although other laboratory methods can be used in clinical diagnosis, only tests approved in the standard definition are accepted for national surveillance system [26,33]. Based on the evolving situation with COVID-19 there is no longer a Presumptive Confirmed Case definition for surveillance purposes [49,53].

13-Discarded case (Not a case)

An ‘under investigation’ case that has a negative test and has been failed to fulfill the criteria for a possible, suspect, probable or confirmed case. A summary of diagnoses for discarded cases should be made routinely [10,34,50].

14-Recovered (cured) case

In the early phase of COVID-19 spread with little number of cases and little burden on health facilities and maximum capacity of laboratory testing patients may be discharged to home based on clinical improvement and laboratory tests. The clinical criteria include absence of fever for more than three days, disappearance of respiratory symptoms and resolution of pulmonary inflammation as evidenced by imaging with no need for hospital care of other morbidities. The laboratory evidences of recovery include viral clearance in respiratory specimens; 2–4 negative PCR tests for nasopharyngeal swabs with ≥ 24 h apart; as well as appearance of specific IgG when serological test is available. When deciding on criteria for hospital discharge of COVID-19 cases consider the epidemiological situation, the existing capacity of the healthcare facilities and the diagnostic laboratory resources [54]. The WHO defined the criteria for release from isolation for symptomatic patients as 10 days after symptom onset, plus at least 3 days without symptoms (without fever and respiratory symptoms) and for asymptomatic patients as 10 days after test positive [55].

15- Severe and critical case: The WHO [55] defined **severe COVID-19** as cases with severe pneumonia. However Zhang et al. [56] defined severe cases as having at least one of the following: respiratory rate ≥ 30 /min; oxygen saturation $\leq 93\%$ at rest; and oxygenation index (PaO₂/FiO₂) ≤ 300 mmHg. The WHO [55] defined **critical cases** as having acute respiratory distress syndrome, sepsis, and or septic shock. While Zhang et al. [56] defined critical cases as having septic shock, respiratory failure, and/or multi-organ dysfunction or failure.

Evolutionary process and variability in COVID-19 case definitions and diagnosis

There is a continuous and ongoing change in the epidemiological, clinical and diagnostic criteria of COVID-19. Ma et al. [57]

have been analyzed the seven versions of China's national guidelines. These included changes of case classification, in "suspected case," in "confirmed case," in clinical classifications, and in "severe case".

Case definition, among others, is an important factor that determines the number of COVID-19 cases. Variable case definition contributes to failure of progress in prevention and control of the disease. Failure to agree on a precise definition reduces the efforts of aligning findings from epidemiologists, clinicians, and researchers, and subsequently hinders progress towards improving outcomes. A standard case definition is essential for understanding the epidemiology and impact of any disease. In addition, it is important for education (of epidemiologists, scientists, and providers) as well as for benchmarking the quality of patient's care [58].

Reporting and research on COVID-19 focus on laboratory-confirmed cases and do not include suspected and probable cases [59]. In China on 13 February 2020 there was a single day steep increase of 13,332 COVID-19 cases due to broadening of case definition to include clinically confirmed cases (based on chest imaging without laboratory confirmation) together with the confirmed cases [60]. Tsang et al. [61] examined changes in the case definition for COVID-19 in China during the first epidemic wave. They reported that the case definition was initially narrow and was gradually broadened to allow detection of more cases (especially milder cases and those without epidemiological links). Thus the proportion of infections being detected as cases increased by 7.1 times. They recommended that these changes should be considered when making inferences on epidemic curves, doubling times and the reproductive number.

A significant proportion of cases are currently undiagnosed in many countries. This is attributed to many factors. The variability of case definitions, the populations that are screened and timeline of the outbreak, testing techniques and interpretation of laboratory results will affect the number of cases enumerated. In early phases of the epidemic there was a restrictive case definition of "suspect cases", with scarcity of laboratory test kits and testing was limited to "suspect cases". Thus fewer laboratory tests are done with few confirmed cases and many undiagnosed cases. With increased capability to do laboratory tests, more people were screened and the number of confirmed cases increased. The technical considerations of laboratory testing that affect the accuracy of disease counts include: specimen collection (variable collection methods); samples collected (from upper or lower respiratory tract), time of collection in relation to course of disease, different laboratory kits and test methods; trained manpower, approved laboratories and sensitivity of the test [62].

Despite the availability of excellent diagnostic techniques of symptomatic COVID-19 patients in well-equipped laboratories; gaps still exist in screening asymptomatic people who are incubating the virus, and in the determination of live viral shedding during convalescence to end isolation [63].

The current diagnosis of COVID-19 infection relies mainly on the centralized laboratory-based RT-PCR. It provides a relatively rapid result (within 3–4 h), it is limited by transportation to the laboratory and the requirement to batch samples in a large run. Public health sectors are in need for fast and reliable tests for COVID-19. Furthermore, a negative RT-PCR nasopharyngeal swab test is insufficient to rule out COVID-19. Thus, over-reliance on the results of the test may be dangerous, and the push for widespread testing may be overstated. The exact sensitivity and specificity of RT-PCR tests for COVID-19 are unknown and it appears that a positive test is highly suggestive of true COVID-19, but a negative test does not rule out the disease [64].

Conclusions

There is a marked variability in the concepts of case definitions of COVID-19. Awareness of health care providers about these terms and the correct application are essential steps for surveillance and proper management of the COVID-19 pandemic.

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