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Short Communication

# Diagnostic precision of local and World Health Organization definitions of symptomatic COVID-19 cases: an analysis of Mexico's capital

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## ARTICLE INFO

## ABSTRACT

*Objectives:* Case definitions are vital in a pandemic to effectively identify, isolate, and contact trace, particularly where testing is slow, scant, or not available. While case definitions have been developed in the COVID-19 pandemic, their diagnostic properties have not been adequately assessed. This study's objective is to determine the diagnostic properties of local and World Health Organization (WHO) COVID-19 case definitions in the large metropolitan area of Mexico City.
*Methods:* We calculated the diagnostic properties of five COVID-19 definitions (three of the Mexican government and two of the WHO) using open data of suspected COVID-19 cases in Mexico City from March 24th, 2020, until May 15th, 2021.
*Results:* All 2,564,782 people included in the analysis met the WHO suspected case definition (sensitivity: 100%, specificity: 0%). The WHO probable case definition was met by 1.2%, while the first and second Mexican suspected case had sensitivities of 61% and specificities of 61% and 67%, respectively. Confirmed case by epidemiological contact had a low sensitivity (32%) but slightly higher specificity (81%).
*Conclusions:* Case definitions should maximize sensitivity, especially in a high-transmission area such as Mexico City. The WHO suspected case definition has the potential for detecting most symptomatic cases. We underline the need for routine evaluation of case definitions as new evidence arises to maximize their usefulness.

## Introduction

Epidemiologic case definitions for a disease are vital in surveillance during epidemics. In this context, the aim of a case definition is to be highly sensitive as to miss the fewest true cases of the disease. In low-income countries, case definitions are valuable to make decisions on isolation, contact tracing, and monitoring disease trends since definitive tests might be scarce, unavailable, and highly expensive.[1] During the COVID-19 pandemic, the World Health Organization (WHO) released case definitions for suspected, probable, and definitive COVID-19 cases, which have been periodically updated.[2] Countries also released definitions with irregular updating, even though they should be revised according to new scientific evidence as to increase their diagnostic value.[1–4]

Mexico released the first version of its COVID-19 suspected case definition in March 2020, with the aim of determining who should be tested. Only one in ten ambulatory suspected COVID-19 patients would be tested, as well as all hospitalized ones. An update in the case definition was published in August 2020 with minor changes, but the testing strategy remained the same.[3,4] Considering this deliberate undertesting, suspected case definitions become especially important to account for disease undercounting, initiate contact tracing (which has not been a feature of Mexico's pandemic response, but is elsewhere), and starting individual treatment. An important caveat is that the people who design these definitions are in many cases not the same people that have to apply them on the field. Thus, dissociation could occur between intended and actual use.

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Mexico City is a large metropolitan area with 9,209,944 habitants.[5] In this analysis, we calculated the diagnostic properties of the definitions of COVID-19 cases of Mexico's Ministry of Health (from now on, simply Mexico) and those of the WHO to determine their adequacy for epidemiological monitoring purposes.

## Methods

We used open data from the Mexico City government for reported cases of suspected COVID-19 between March 24th, 2020, and May 15th, 2021.[6] We calculated the diagnostic properties (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], positive likelihood ratio, and negative likelihood ratio), as well as post-test probabilities of five different epidemiological COVID-19 case definitions: three issued by Mexico for COVID-19 surveillance purposes (suspected case, updated suspected case definition, and suspected case 'confirmed' by epidemiological linkage to a laboratory-confirmed case) and two WHO-recommended definitions (suspected and probable).[2−4]

A comparison between these definitions is provided in Table 1. Mexico's COVID-19 suspected case definition was issued in March 2020 and included anybody seeking care for at least one of the following symptoms starting within the 7 previous days: cough, dyspnea, fever or headache; with at least one of the following: myalgia, arthralgia, sore throat, thoracic pain, rhinorrhea, polypnea, or conjunctivitis.[3] COVID-19 suspected case definition was updated by Mexico in August 2020 (adding chills, anosmia, and dysgeusia and expanding the period of symptoms onset from 7 to 10 days).[4] The case definition for COVID-19 confirmed by epidemiological linkage to a laboratory-confirmed case (anyone meeting the COVID-19 suspected case criteria that have had contact with a laboratory-confirmed case within the previous 14 days).[4] We substituted contact with 'confirmed case' with contact with an 'individual with respiratory symptoms,' as only information on this variable was available.[6] Mexico's COVID-19 case definition is the same case definition used for surveillance activities of seasonal Influenza. Only one in ten symptomatic ambulatory patients is tested, while all hospitalized patients are tested, and no asymptomatic testing occurs.[3] There are no pre-established criteria on which ambulatory patients are tested for SARS-CoV-2, and decisions about testing depends heavily on clinical judgment and tests availability on sentinel sites. The revised WHO COVID-19 case definitions for suspected (which includes a set of different options of clinical and epidemiological criteria, as shown in Table 1) and probable cases (which requires the presence of the clinical criteria in suspected cases: acute onset of fever and cough OR acute onset of any three or more of the following symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status in combination) in combination with chest imaging showing findings suggestive of COVID-19 disease, which we replaced with the variable 'clinical diagnosis of pneumonia' since no data on chest imaging were available.[2−4]

Since all tested patients in Mexico are symptomatic, the diagnostic gold standard for our calculation of the diagnostic properties of case definitions was having either a positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) or a positive antigen test. Post-test probabilities of COVID-19 were calculated using the daily proportion of positive molecular or antigen tests and graphed using 7-day rolling means.

All analyses were performed with R, version 4.0.0.

## Results

A total of 2,564,782 people were registered in the Mexico City open database during the study period. There were 631,342 (24.6%) cases confirmed by RT-PCR or antigen test and 1,932,440 (75.3%) negative tests.

Both Mexican definitions of suspected COVID-19 cases had similar diagnostic properties, with slightly better characteristics in the updated definition (Table 2). All patients met the WHO definition of suspected COVID-19 case, with a perfect sensitivity, specificity of 0%, PPV of 25%, and NPV of 0%. Meanwhile, the WHO case definition for probable COVID-19 was met by very few patients (30,839, 1.2%), showing a sensitivity of 3%, specificity of 99%, PPV of 66%, and NPV of 76%. It is noteworthy that all patients that did not meet the probable case definition met the suspected case definition.

Post-test probability varied greatly according to the pretest probability and the definition utilized, with a mean probability of 39% (standard deviation [SD]: 15) for the first Mexican case definition, 43% (SD: 15) for the second definition, 41% (SD: 15) for the Mexican definition of confirmed case by epidemiological contact, 30% (SD: 13) for the WHO definition of suspected case, and 54% (SD: 16) for the WHO definition of probable case. Post-test probabilities along the study period for each definition are shown in Fig. 1.

## Discussion

Epidemiological case definitions are indispensable for surveillance but are riddled with challenges. When tallying COVID-19 cases according to case definition, changing it can increase the number of cases several-fold.[7] We observed that the three COVID-19 case definitions used by Mexico have poor sensitivity (32−61%) in contrast to the WHO suspected case definition. This has the obvious implication that Mexico's suspected case definition is not being used as intended (as a screening test to decide who should be considered for testing). Considering that theoretically it should have a sensitivity of 100%, it is fortunate that it is not being used as planned, as almost 40% of currently observed cases would be missed.

A suspected case definition that is not met by many confirmed cases is not useful, for epidemiologic purposes or otherwise. Our analysis underlines the importance of this, as Mexico is a country that tests a small percentage of symptomatic people. In our context, suspected cases based on symptoms should include all but asymptomatic individuals as the WHO suspected case definition does and be formally counted and included in epidemiologic surveillance, as most do not have access to confirmatory tests.

Thus, the high sensitivity of the WHO suspected case definition could potentially reduce case subestimation and should be preferred when guiding testing decisions in Mexico City and elsewhere. We consider results would be similar if we replicated the analysis country wide; unfortunately we do not have the data to do so.

As only symptomatic people are being tested, clinical judgment remains key and patients should be retested in case of a negative result if prevalence remains high.[8] Point-of-care tests might be very useful in these contexts, as their low cost allows for repeated testing.[8]

### Strengths and limitations

Our study has several limitations. We did not have information on several variables, such as anosmia, dysgeusia, and radiological imaging. The incidence of anosmia and/or dysgeusia in Mexican COVID-19 patients is unknown, but elsewhere it has been reported in 35%.[9] This could improve the sensitivity of Mexico's second definition. Only one in ten ambulatory patients is tested, and these patients could differ in ways that we are unable to account for, such as subjective disease severity. Furthermore, false-negative tests are well known and limit

**Table 1**
Comparison of Mexican Ministry of Health and World Health Organization (WHO) COVID-19 case definitions.

| Mexican Ministry of Health COVID-19 definitions | | | WHO COVID-19 definitions | |
|---|---|---|---|---|
| Suspected case (March 24, 2020 definition) | Suspected case (August 25, 2020 definition) | Confirmed case by epidemiological link (August 25, 2020 definition) | Suspected case of SARS-CoV-2 infection | Probable case of SARS-CoV-2 infection |
| Any person that presented in the last seven days any one of these symptoms: cough, dyspnea, fever or headache AND at least one of the following:<br>- Myalgias<br>- Arthralgias<br>- Sore throat<br>- Chest pain<br>- Rhinorrhea<br>- Polypnea<br>- Conjunctivitis | Any person that presented in the last ten days any one of these symptoms: cough, dyspnea, fever or headache AND at least one of the following:<br>- Myalgias<br>- Arthralgias<br>- Sore throat<br>- Chills<br>- Chest pain<br>- Rhinorrhea<br>- Polypnea<br>- Conjunctivitis<br>- Anosmia<br>- Dysgeusia | Any person that presented in the last ten days any one of these symptoms: cough, dyspnea, fever or headache AND at least one of the following:<br>- Myalgias<br>- Arthralgias<br>- Sore throat<br>- Chills<br>- Chest pain<br>- Rhinorrhea<br>- Polypnea<br>- Conjunctivitis<br>- Anosmia<br>- Dysgeusia<br>**AND**<br>Contact with a laboratory-confirmed COVID-19 case during the last 14 days. | One of three options must be met, A through C:<br>A. A person who meets the clinical **AND** epidemiological criteria:<br>Clinical criteria:<br>1. Acute onset of fever **AND** cough;<br>**OR**<br>2. Acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness, fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status.<br>**AND**<br>Epidemiological criteria:<br>1. Residing or working in a setting with high risk of transmission of the virus: for example, closed residential settings and humanitarian settings, such as camp and camp-like settings for displaced persons, any time within the 14 days before symptom onset;<br>**OR**<br>2. Residing in or travel to an area with community transmission anytime within the 14 days before symptom onset;<br>**OR**<br>3. Working in health setting, including within health facilities and within households, anytime within the 14 days before symptom onset.<br>**B**. A patient with severe acute respiratory illness (SARI: acute respiratory infection with a history of fever or measured fever of $\geq$38 C°; **AND** cough; with onset within the last 10 days; **AND** who requires hospitalization).<br>**C.** An asymptomatic person not meeting epidemiologic criteria with a positive SARS-CoV-2 antigen −detecting rapid diagnostic test (Ag-RDT) | One of the four options must be met, A through D:<br>**A.** A patient who meets clinical criteria of suspected case AND is a contact of a probable or confirmed case or is linked to a COVID-19 cluster.<br>**B.** A suspected case (described earlier) with chest imaging showing findings suggestive of COVID-19 disease.<br>C. A person with recent onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause.<br>D. Death, not otherwise explained, in an adult with respiratory distress preceding death AND who was a contact of a probable or confirmed case or linked to a COVID-19 cluster. |

**Table 2**
Diagnostic properties of COVID-19 epidemiological case definitions in Mexico City.

| Definition | | Positive RT-PCR or antigen test | Negative RT-PCR and antigen test | Properties | |
|---|---|---|---|---|---|
| Mexico's first suspected case definition | Yes | 383,951 | 746,930 | Sens | 61% |
| | | | | Spec | 61% |
| | | | | PPV | 34% |
| | No | 247,391 | 1,186,510 | NPV | 83% |
| | | | | LR+ | 1.56 |
| | | | | LR- | 0.64 |
| Mexico's second suspected case definition | Yes | 382,560 | 643,748 | Sens | 61% |
| | | | | Spec | 67% |
| | | | | PPV | 37% |
| | No | 248,782 | 1,289,692 | NPV | 84% |
| | | | | LR+ | 1.85 |
| | | | | LR- | 0.58 |
| Mexico's confirmed case by epidemiological contact | Yes | 199,587 | 359,748 | Sens | 32% |
| | | | | Spec | 81% |
| | | | | PPV | 36% |
| | No | 431,755 | 1,573,692 | NPV | 78% |
| | | | | LR+ | 1.68 |
| | | | | LR- | 0.84 |
| WHO's suspected case definition | Yes | 631,342 | 1,933,440 | Sens | 100% |
| | | | | Spec | 0% |
| | | | | PPV | 25% |
| | No | 0 | 0 | NPV | 0% |
| | | | | LR+ | 1 |
| | | | | LR- | * |
| WHO's probable case definition | Yes | 20,285 | 10,554 | Sens | 3% |
| | | | | Spec | 99% |
| | | | | PPV | 66% |
| | No | 611,057 | 1,922,886 | NPV | 76% |
| | | | | LR+ | 3 |
| | | | | LR- | 0.98 |

LR+: positive likelihood ratio; LR-: negative likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; RT-PCR: real-time reverse-transcriptase polymerase chain reaction; Sens: sensibility; Spec: specificity; WHO: World Health Organization.
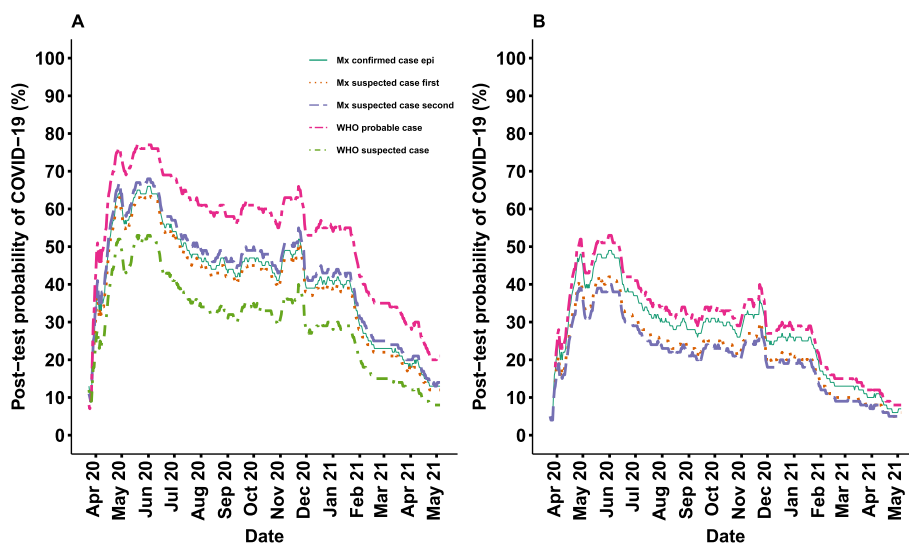


**Fig. 1. Post-test probability of COVID-19 according to several case definitions**. A) shows post-test probabilities in case of meeting a given case definition. B) shows post-test probabilities in case of not meeting the case definition. Mx confirmed case epi: Mexico's definition of confirmed case by epidemiological contact; Mx suspected case first: Mexico's first suspected case definition; Mx suspected case second: Mexico's second suspected case definition; WHO probable case: WHO's probable case definition; WHO suspected case: WHO's suspected case definition. Gold standard was considered to be either a positive molecular or antigen SARS-CoV-2 test. As WHO's suspected case definition had a negative predictive value of 0%, it does not appear in B). WHO: World Health Organization. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

our definition of gold standard.[10–12] This is especially important given the high post-test probability observed throughout the study period (>10%). Accounting for false-negative tests would increase the post-test probability, and thus, a negative test would not rule out the disease in high-prevalence areas such as this.

*Conclusion*

Our analysis supports that case definitions should be formally evaluated as to ensure their usefulness. Those with low sensitivity, especially in places with high disease burden and/or limited testing,

should not be used. Given its high sensitivity, places in need of a local definition should adopt the WHO suspected case definition.

## Author statements

*Ethical approval*

This study did not require ethics board approval because it used publicly available anonymized data, with no interaction between the researchers and individuals.

*Competing interests*

None.

*Data availability*

Data are freely available at the official Mexico City government COVID-19 website.[6] Code used for the analyses is available at https://github.com/isaac-nunez/covid19_case_definition.

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