Effect of changing case definitions for COVID-19 on the epidemic curve and transmission parameters in mainland China: a modelling study

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Summary
Background When a new infectious disease emerges, appropriate case definitions are important for clinical diagnosis and for public health surveillance. Tracking case numbers over time is important to establish the speed of spread and the effectiveness of interventions. We aimed to assess whether changes in case definitions affected inferences on the transmission dynamics of coronavirus disease 2019 (COVID-19) in China.

Methods We examined changes in the case definition for COVID-19 in mainland China during the first epidemic wave. We used exponential growth models to estimate how changes in the case definitions affected the number of cases reported each day. We then inferred how the epidemic curve would have appeared if the same case definition had been used throughout the epidemic.

Findings From Jan 15 to March 3, 2020, seven versions of the case definition for COVID-19 were issued by the National Health Commission in China. We estimated that when the case definitions were changed, the proportion of infections being detected as cases increased by 7.1 times (95% credible interval [CrI] 4.8–10.9) from version 1 to 2, 2.8 times (1.9–4.2) from version 2 to 4, and 4.2 times (2.6–7.3) from version 4 to 5. If the fifth version of the case definition had been applied throughout the outbreak with sufficient testing capacity, we estimated that by Feb 20, 2020, there would have been 232,000 (95% CrI 161,000–359,000) confirmed cases in China as opposed to the 55,508 confirmed cases reported.

Interpretation The case definition was initially narrow and was gradually broadened to allow detection of more cases as knowledge increased, particularly milder cases and those without epidemiological links to Wuhan, China, or other known cases. These changes should be taken into account when making inferences on epidemic growth rates and doubling times, and therefore on the reproductive number, to avoid bias.

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Introduction When a newly emerging infectious disease is first identified, specifying appropriate case definitions can help to identify individuals who are infected in an efficient manner. Often a hierarchy of case definitions will be used, so that a suspected case can be defined based on broad epidemiological and clinical criteria—eg, patients with particular exposures or in particular geographical locations, with particular signs or symptoms, at a particular time. A confirmed case can be defined as a suspected case in which the pathogen of interest is identified or isolated with a specific laboratory test. Epidemiological and clinical information for patients who meet a case definition can inform the source or sources of infections, potential modes of transmission, transmission dynamics, and severity of the infection. All this information is important for establishing optimal control measures.

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The novel virus was first identified in a cluster of patients with atypical pneumonia in Wuhan, China, in December, 2019. At the end of January, 2020, it became clear that infection was spreading efficiently from person to person, and also that there was a broader clinical spectrum of infections. As a consequence of the evolving information on the epidemiological and clinical spectrum of infections, there have been several revisions to the case definition for COVID-19 in mainland China.

Here, we review the various COVID-19 case definitions that have been used in mainland China as of March 13, 2020, and examine the implications of changes in case definitions on the epidemiology of COVID-19, aiming to quantify the effect of changes in the case definition on inferences about transmission parameters based on the epidemic curve.

Methods

Sources of data
We obtained the officially published guidelines on diagnosis and treatment of COVID-19 from the National Health Commission and other public sources. The first two editions were not originally released publicly, while
the third edition onwards have been released by the National Health Commission.7 Epidemic curves by onset date and report date from Dec 2, 2019, to Feb 20, 2020, in China were extracted from the data presented in the report of the WHO-China Joint Mission on Coronavirus Disease 2019 in February, 2020.8

Statistical analysis
We reviewed the case definitions and highlighted the key changes in sequential updates. We fitted an exponential growth model to the incidence of cases to quantify the effect of changing case definitions on the epidemic curve for laboratory-confirmed cases (appendix p 2). In the model, we assumed that each change in case definition increased the proportion of cases that would be detected among all infections. Also, we assumed the effect of changing case definition was the same for all regions in China. To account for the control measures, such as the lockdown in Wuhan and other cities in China on Jan 23, 2020, and the subsequent days,7 we allowed the growth rate to change on this date. Because the interventions acted to prevent infections but the epidemic curve was based on date of symptom onset in our analysis, the effect of the interventions would be expected to have a slightly delayed effect on the epidemic curve, which we accounted for by incorporating the incubation period distribution (appendix p 2). The incubation period was assumed to follow a log-normal distribution with a mean of 5·2 days (SD 3·9).4

When changing the case definition, there could be a backfill of cases that fulfilled the new case definition around the change time. We allowed for backfill up to 10 days before each change in case definition by assuming that a change in case definition could have a partial effect on incidence before the change date, accounting for the reporting delay, which was estimated from the onset time series and report time series (appendix p 2). We estimated the growth rate as one of the model parameters, and we estimated the doubling time using log(2) divided by the estimated growth rate. We fitted separate models for Wuhan, Hubei province excluding Wuhan, and the rest of mainland China excluding Hubei province, to account for the regional differences in growth rates, epidemic timing, and potential transmissibility. We estimated the basic reproductive number \( R_0 \), corresponding to the mean number of secondary infections from one case at the start of the outbreak, using the formula: 1 divided by \( M/(-r) \),9 where \( r \) was the growth rate and \( M \) was the moment generating function of the generation time distribution. We assumed the generation time distribution followed the same gamma distribution as a...
previously estimated serial interval distribution with a mean of 7.5 days (SD 3.4). As a sensitivity analysis, we used another estimated serial interval distribution with the mean of 4.7 days (SD 2.9). In addition, we did a sensitivity analysis allowing backfill for up to 15 days before each change in case definitions.

To account for the uncertainty in estimates of the onset-to-reporting interval, and to allow us to quantify the uncertainty in model parameters including the growth rates, we did our analysis in a Bayesian framework and constructed a Markov chain Monte Carlo algorithm, which allowed joint parameter estimation (appendix p 3). Substantial differences in parameters (eg, growth rate and doubling time) were defined as the non-overlap of their credible intervals (CrI), meaning that the probability that the two parameters were the same was less than 0.05. On the basis of the modelling results, we estimated the number of cases if version 5 of the case definition had been applied throughout the outbreak (appendix p 4). All statistical analyses were done using R version 3.5.2. All data and code required to reproduce the analysis are available online (appendix p 4).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
We analysed the changes of the case definition for COVID-19 applied in China from Jan 15 to March 3, 2020. Before Jan 15, 2020, we were unable to identify the case definition that was used in Wuhan.
to identify the earliest 41 confirmed cases. The first national guideline for diagnosis and treatment was issued on Jan 15, 2020, and required six specific criteria to be met for a patient to be a confirmed case of COVID-19 (figure 1, appendix p 6). Notably, patients needed to have an epidemiological link to Wuhan or a wet market in Wuhan and had to fulfil four clinical conditions indicative of viral pneumonia to be identified as suspected cases. They then had to have a respiratory specimen tested by full genome sequencing showing a close homology with SARS-CoV-2 for the final confirmation of COVID-19. In the following days and weeks, several revisions were made to the case definitions, allowing gradually greater sensitivity in the criteria required for case confirmation (figure 1). We present the seven versions of cases definitions in the appendix (pp 6–18).

The second edition of the case definitions removed the requirement for failure of antibiotic treatment to identify suspected cases and allowed PCR confirmation in addition to whole genome sequencing. There was no change in case definitions in the third edition, but classifications of severe and critical cases were modified and clarified. The fourth edition allowed patients to have an epidemiological link to other areas with reported cases, instead of being restricted to Wuhan, and suspected cases required only two, instead of all three, types of clinical manifestations in addition to an epidemiological link. The greatest change was in the fifth edition, which introduced a new category of cases (ie, clinically confirmed cases), specifically for Hubei province, which was the epicentre of the outbreak and had the largest number of cases identified in the country. Here, clinically confirmed cases were patients that met clinical criteria and had radiological evidence of
pneumonia with or without a certain epidemiological link but did not need to have a virological confirmation of infection. In the sixth edition, this criterion for diagnosis of clinically confirmed cases was removed and no distinction was made between cases inside or outside Hubei province. In the seventh edition, serology was added as an additional option for laboratory confirmation.

We modelled the effects of changes in case definition from version 1 to version 2, from version 2 to 4, and from version 4 to 5. We did not explore the effects of changing from version 2 to 3 because version 3 applied the same definitions for suspected and confirmed COVID-19 cases as version 2 but only included updates to the severity classifications and therefore had no effect on the incidence or the epidemic curve. We were not able to explore the change after version 5 as we only analysed data up to Feb 20, 2020, which included just the first 2 days after the release of version 6. We were not able to find publicly available information on incidence of cases by illness onset date after Feb 20, and had to censor our analysis at that point.

The changes in case definitions had a clear effect on the proportion of infections that were identified and counted as confirmed cases. As of Feb 20, 2020, there were 55,508 confirmed cases in China, among which 27,000 were from Wuhan, 16,000 were from the rest of Hubei province, and 13,000 were from the rest of China. We estimated that the mean onset-to-reporting delay was 8·6 days (95% CrI 7·4–10·1) and the 95th percentile of this distribution was 15·7 days (13·0–20·1). Allowing for a 10 day backfill of cases, we estimated that when the case definitions were changed from version 1 to 2, version 2 to 4, and version 4 to 5, the proportion of infections being identified as COVID-19 cases was increased by 7·1 times (95% CrI 4·8–10·9) from version 1 to 2, 2·8 times (1·9–4·2) from version 2 to 4, and 4·2 times (2·6–7·3) from version 4 to 5 (figure 2).

Based on the model, we estimated that if the case definitions from version 5 had been applied throughout the outbreak, and there had been sufficient availability of laboratory testing with RT-PCR from the early phase of the epidemic, 232,000 cases (95% CrI 161,000–359,000)
could have met the case definition and could have been detected by Feb 20, 2020, of which 127,000 cases (86,000–198,000) were from Wuhan, 55,000 (38,000–86,000) were from the rest of Hubei province excluding Wuhan, and 50,000 (34,000–78,000) were from the rest of China excluding Hubei (figure 3). Among the 127,000 cases that we estimated in Wuhan by Feb 20, we estimated that there could have been approximately 11,000 infections (95% CrI 7000–21,000) that met version 5 of the case definition with illness onset by Jan 1, 2020. In the observed data, there were 114 confirmed COVID-19 cases with illness onset by Jan 1, 2020, corresponding to around 1% of our estimated total. Before Jan 23, we estimated that 92% (95% CrI 88–95) of cases were undetected.

We estimated that after implementation of control measures on Jan 23, the growth rate declined substantially to less than 0, from 0·08 to 0·15 in Wuhan, which was a change of –0·23 (95% CrI –0·27 to –0·20). The corresponding changes in growth rate were –0·26 (–0·30 to –0·22) for the rest of Hubei province excluding Wuhan, and –0·28 (–0·32 to –0·25) for the rest of China excluding Hubei. These findings suggested that the control measures were very effective, reducing the effective reproductive number to well less than 1. Specifically, using a mean serial interval of 7·5 days, the effective reproductive numbers were reduced to 0·21–0·28 for the three regions, while the estimates were reduced to 0·36–0·44 with a mean serial interval of 4·7 days.

After adjusting for the changes in case definitions, we estimated that the epidemic growth rate before Jan 23, 2020, was around 0·08 to 0·10 and the doubling time was around 7·0 to 8·7 days for these three geographical areas, and the differences among them were not substantial (table). If instead the change in case definitions was unaccounted for, the growth rate would have been substantially overestimated and the doubling time would have been substantially underestimated (table). Using a growth rate of 0·08–0·10 with a mean serial interval of 7·5 days would lead to $R_t$ estimates in the range of 1·8–2·0. If we instead used the growth rate estimates of 0·15–0·19 (table), we would obtain $R_t$ estimates in the range of 2·8–3·5. In a sensitivity analysis, using a mean serial interval of 4·7 days, $R_t$ estimates using a growth rate of 0·08–0·10 were in the range of 1·4–1·5, while using the growth rate estimates of 0·15–0·19 (table) we would obtain $R_t$ estimates in the range of 1·9–2·2.

In a sensitivity analysis allowing for 15 days of backfill each time the case definition changed, the proportion of infections being identified as COVID-19 cases was increased by 3·0–8·8 times. We estimated that 253,000 cases (95% CrI 158,000–436,000) would have met the case definition and could have been detected by Feb 20, 2020. These estimates were slightly higher, but as expected, given the backfill period was longer.

### Discussion

We estimated that changes in case definitions of COVID-19 in China led to stepwise increases in the proportion of all infections identified as cases, by 7·1 times from version 1 to 2, 2·8 times from version 2 to 4, and 4·2 times from version 4 to 5. Overall, we estimated that around 232,000 cases could have been confirmed in the first wave of COVID-19 in China by late February, 2020, if, hypothetically, version 5 of the case definitions had been used throughout as opposed to the 55,508 confirmed cases reported. The number of individuals who were infected is likely to be greater than 232,000 because many mild cases were not tested or confirmed, and some infections were asymptomatic. We estimated that many cases were undetected when using an earlier case definition, which is consistent with the study by Li and colleagues, which estimated that around 85% of cases were undetected before Jan 23, when case definition 2 was used. Our results were also consistent with another modelling study indicating clear differences between earlier and later cases identified in Wuhan. The estimated case numbers were considerably higher than the observed case numbers, suggesting a so-called clinical iceberg phenomenon, which is common for a disease that can cause both mild and severe illnesses like COVID-19. As a result, when case definitions were broadened, more mild cases could be detected.

The introduction of clinically confirmed cases in the fifth version of the case definitions allowed many individuals who were highly suspected to be cases but who did not receive a virological test due to insufficient testing capacity to be isolated and treated in time, allowing reallocation of laboratory testing resources for identifying and then isolating cases in the community as part of the containment efforts. This category was removed within a week in the sixth edition of case definitions because laboratory testing was deemed sufficient to confirm all cases and the clinically confirmed category was unnecessary. However, confirmation of viral pneumonia with radiological evidence could be an important alternative for diagnosis and surveillance of...
COVID-19 in locations with limited laboratory testing capacity, and could also be a good option if or when a surge in COVID-19 consultations exceeds local laboratory capacity. This method could be combined with testing a portion of the clinically confirmed cases to correct the actual case numbers afterwards.19

Case definitions are often developed for outbreak investigations in which the objective is to identify the source of infections,18 while case definitions are used for surveillance only later if an epidemic occurs. In the case of the COVID-19 epidemic in China, the initial case definitions for COVID-19 allowed investigation of potential animal exposures and infections epidemiologically linked with the epicentre, Wuhan, but might not capture cases linked with wider areas potentially affected by COVID-19.19 Similarly, the earlier case definitions had more specific requirements for clinical manifestations given the limited knowledge of the novel virus, leading to a low sensitivity for case identification including an under-detection of milder infections.20,21 As evidence for the clinical spectrum for case identification including an under-detection of milder infections,18,20 as well as evidence for the clinical spectrum for case identification including an under-detection of milder infections,18,20 as well as evidence for the clinical spectrum for case identification including an under-detection of milder infections,18,20 as well as evidence for the clinical spectrum for case identification 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In conclusion, we have shown that changes in case definitions had a substantial effect on the proportion of all infections identified as cases as time progressed, and therefore also had a substantial effect on the epidemic curve. We estimated that there could have been 232,000 cases by Feb 20, 2020, if, hypothetically, version 5 of the case definitions had been used throughout the epidemic. Still, this would be an underestimate of the number of infections up to that point because it would not have captured some mild or asymptomatic cases. Serological studies will be useful to estimate the cumulative incidence of infections.

Contributors

TKT, PW, GML, and BJC were responsible for study design. PW, YL, and EHLYL were responsible for data collection. TKT, PW, and YL were responsible for data analysis. TKT, PW, EHLYL, GML, and BJC were responsible for data interpretation. TKT wrote the first draft of the manuscript. All authors contributed to the final draft.

Declaration of interests

BJC reports honoraria from Sanofi Pasteur and Roche. All other authors declare no competing interests.
Data sharing
The data and computer code (in R languages) for the data analysis can
be downloaded online.

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