Clinical Infectious Diseases

BRIEF REPORT

Estimating the Latent Period of Coronavirus Disease 2019 (COVID-19)

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Using detailed exposure information on COVID-19 cases, we estimated the mean latent period to be 5.5 (95% CI: 5.1–5.9) days, shorter than the mean incubation period (6.9 days). Laboratory testing may allow shorter quarantines since 95% of COVID-19 cases shed virus within 10.6 (95% CI: 9.6–11.6) days of infection.

Keywords. SARS-CoV-2; COVID-19; latent period; incubation period.

The latent period of an infectious disease is the time interval between infection and becoming infectious [1]. This can be contrasted with the incubation period, which is the time interval between infection and the appearance of clinical symptoms [1]. One of the notable features of coronavirus disease 2019 (COVID-19) transmission is the observation of presymptomatic transmission events, indicating that, at least in some cases, the latent period is shorter than the incubation period [2].

The latent period is typically proxied by the time interval between infection and having detectable virus in a respiratory specimen. While there are quite a number of published estimates of the incubation period [3], there are relatively few empirical estimates of the latent period distribution [2, 4, 5]. Comprehensive large-scale nucleic acid–testing strategies using polymerase chain reaction (PCR) assays have been widely used in mainland China since April 2020 to control local outbreaks of COVID-19 [6]. Close contacts of confirmed cases were quarantined for 14 days, during which samples were repeatedly collected regardless of whether any symptoms were reported [6], providing a unique resource for estimation of the latent period. In this study, we aimed to estimate the latent period distribution of COVID-19 and compare it with the incubation period distribution.

METHODS

Data Collection

We retrospectively collected information on laboratory-confirmed symptomatic and asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases from local outbreaks that occurred in 8 provinces in China from 10 July 2020 to 2 April 2021. For each case, we extracted demographic and clinical information from epidemiological investigation reports and the National Reporting System of Notifiable Infectious Diseases. To allow estimation of the latent period distribution, we extracted data on the earliest and latest dates of exposure to infection, informing the lower and upper bound on the infection time, respectively. We obtained data on repeated laboratory testing results, including sampling dates of the last negative PCR test before the first positive PCR and the first positive PCR test, which provided a time window during which detectable virus shedding began. We obtained information on onset dates for symptomatic cases to allow estimation of the incubation period distribution. Additional details of the case definitions and eligibility criteria are provided in the Supplementary Materials.

Statistical Analysis

The latent periods were typically doubly censored—that is, the time of infection and the time of viral shedding were only known to fall within a particular interval, but neither times were known exactly. We fitted parametric models using maximum likelihood accounting for the doubly interval censoring and accounting for the fact that most cases were recruited in the decreasing phase of outbreak (see Supplementary Materials for details). We used gamma, log-normal, and Weibull distributions and selected the best-fitting distribution as the one with the lowest Akaike information criterion (AIC) score. The latent period was estimated overall, and also for symptomatic cases and asymptomatic cases separately. We also estimated the incubation period distribution by using information on exposure window and onset date with the same parametric models.

A parametric bootstrap approach with 1000 resamples was used to obtain 95% confidence intervals (CIs) for each parameter [7]. In sensitivity analyses, we estimated the latent period and the incubation period only based on the information of the cases with definite earliest dates of exposure. We also conducted sensitivity estimation using different exponential decay rate (from −0.10 to −0.18) to address possible sampling bias during the exponential decay phase of epidemic. All analyses were

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performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We analyzed data from 177 cases (Supplementary Materials), of which 143 (80.8%) were symptomatic cases and 34 (19.2%) were asymptomatic cases. Eighty-five were male (48.0%). The median age was 45 years (interquartile range [IQR]: 30–58 years), with most cases (82.5%) younger than 65 years. Asymptomatic cases presented with younger age than symptomatic cases (Supplementary Table 1). Asymptomatic cases also tended to have wider exposure windows than symptomatic cases (Supplementary Figure 1).

Gamma, log-normal, and Weibull parametric models were fitted for the latent period distribution and the AICs slightly smaller for the gamma distribution (Supplementary Table 2, Supplementary Figure 2). The mean estimate of latent period for overall cases was 5.5 days (95% CI: 5.1–5.9 days), with 95% of cases started shedding virus before 10.6 days (95% CI: 9.6–11.6 days) after infection (Figure 1A, Supplementary Table 3).

The mean latent period among symptomatic cases was estimated to be 5.5 days (95% CI: 5.1–6.0 days), similar to the estimated mean of the latent period overall (Figure 1). The mean latent period in symptomatic cases was 1.4 days shorter than the mean incubation period (6.9 days; 95% CI: 6.3–7.5 days) (Supplementary Table 3). The estimate of the 95th percentile of the latent period in symptomatic cases was 10.6 days (95% CI: 8.6–11.7 days) after infection (Supplementary Table 3). Among asymptomatic cases, the mean latent period was 5.2 days (95% CI: 4.3–6.1 days) (Figure 1C, Supplementary Table 3).

Estimates of the mean latent period were similar under log-normal and Weibull distributions and the gamma distribution (Supplementary Table 2, Supplementary Figure 2). After only including cases with definite lower bound on the exposure window, the mean estimate of the latent period (4.9 days) and incubation period (6.5 days) was slight shorter among symptomatic cases, but the latent period was approximately 1.6 days shorter than the incubation period, which was similar to the overall results. With the exponential decay rate from −0.18 to −0.10 (Supplementary Figures 3 and 4), the mean estimates of the latent period among symptomatic cases decreased from 5.8 days to 5.3 days, the mean estimates of the incubation period decreased from 7.3 days to 6.4 days, and the latent period was 1.2–1.4 days shorter than the incubation period (Supplementary Table 4).

DISCUSSION

We estimated the latent period of COVID-19 to be 5.5 days, with a 95th percentile of 10.6 days. The mean latent period was 1.4 days shorter than the mean incubation period, consistent with the observation of presymptomatic transmission for COVID-19 [2]. Some countries, including China, have been using quarantine as an effective component of control measures against COVID-19. Quarantine periods were initially specified at 14 days based on the upper bound of the incubation period distribution [8], and some locations have extended that to 21 or even 28 days. If laboratory testing is performed during quarantine and at the end of quarantine, the latent period may be a more appropriate distribution to use when specifying the quarantine period, and our results here indicate that a laboratory test on day 12 could detect more than 95% of persons who were infected prior to entry to quarantine.

Noting that a fraction of infected persons could remain asymptomatic and be missed by symptomatic monitoring during quarantine, Johansson et al [8] estimated that a 7-day quarantine with symptom monitoring and PCR test at day 5–6 had a similar impact to a 14-day quarantine with symptom monitoring, In the United States, exposed individuals who remain asymptomatic are permitted to end quarantine at day 10 without testing or end at day 7 with a negative test result, but daily symptom monitoring and nonpharmaceutical interventions should continue through quarantine day 14 [9]. However, reducing the duration of quarantine could increase the risk of post-quarantine transmission, compared with the current 14-day quarantine. Therefore, reducing the duration of quarantine could be an option that balances the pandemic scale, burden to public health, compliance to contact tracing and quarantine, and the small but nonzero risk of post-quarantine transmission. In places aiming for zero cases it should be recognized that there is a greater cost if infections are introduced into the community [8, 9].

An important feature in our analysis is that we allowed for interval censoring of infection times and the time of detectable viral shedding. Uncertainty in these times was captured in our analysis, and it would have been valuable to have data from more frequent testing to reduce uncertainty about the time of detectable virus shedding. In addition, we accounted for the fact that most of the cases were collected in the decreasing phase of outbreak in the estimation (Supplementary Materials), which may include relatively more persons with a longer latent period or longer incubation period.

One of the limitations in our study is that we could not directly observe the onset of contagiousness, although we used the onset of detectable virus shedding by reverse transcription (RT)-PCR as a proxy for this. It is possible that contagiousness precedes detectable viral RNA, and modeling studies that estimate the latent period based on transmission dynamics have reported a slightly shorter latent period distribution [10, 11]. Moreover, 1 epidemiological study did note that no infection was found among close contacts with the latest exposure date being 2 days before the onset of their index cases [12]. Another limitation is the potential for recall bias due to the self-reported time of exposure and illness onset.

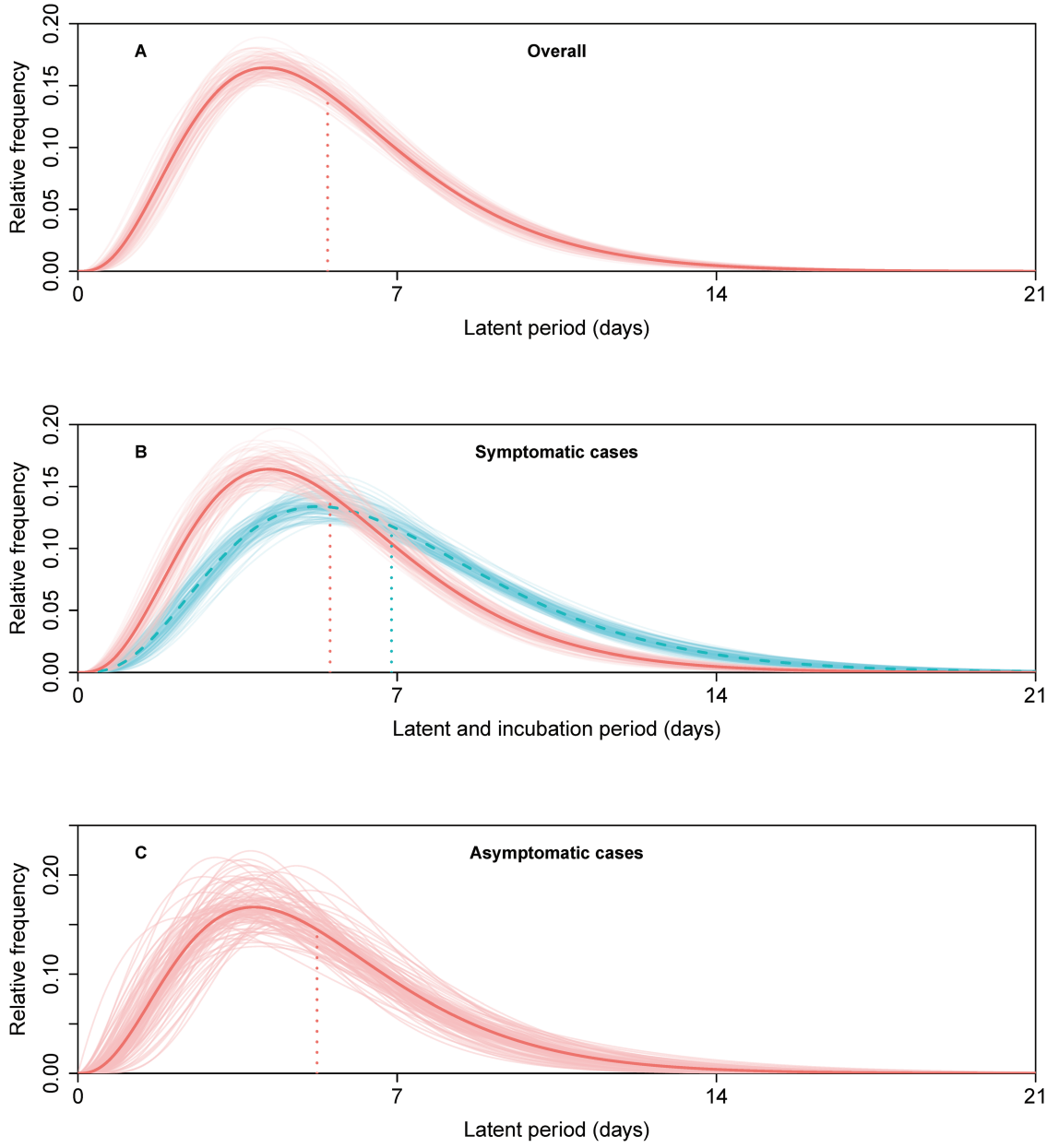

Figure 1. Estimated latent period and incubation period assuming a gamma distribution. *A*, Overall latent period distribution (solid red line) for both symptomatic and asymptomatic cases with uncertainty illustrated by 100 parametric bootstrap resamples (light red lines), with mean estimation (dotted red line). *B*, Latent period (solid red line) and incubation period (dashed blue line) for symptomatic cases only and associated uncertainty illustrated by 100 parametric bootstrap resamples (light red lines for latent period and light blue lines for incubation period), with mean estimation of latent period (dotted red line) and mean estimation of incubation period (dotted blue line). *C*, Latent period for asymptomatic cases (solid red line) with uncertainty illustrated by 100 parametric bootstrap resamples (light red lines), with mean estimation (dotted red line).

In conclusion, we estimated the latent period distribution of COVID-19 to be 5.5 days, on average, with a 95th percentile of 10.6 days. This could justify shorter quarantine periods when repeated laboratory testing is used in combination with symptom monitoring during quarantine and would be an important input into studies of the transmission dynamics of COVID-19.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. The study was conceived by P. W. and Z. L.. Data collection and cleaning were conducted by Y. L., Z. L., Y. Q., and L. W.. Data analyses were conducted by H. X., Y. L., and T. K. T.. H. X. wrote the first draft of the manuscript. All authors provided critical review and revision of the text and approved the final version. All authors meet the ICMJE criteria for authorship.

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Potential conflicts of interest. B. J. C. consults for Roche, GSK, Moderna, AstraZeneca, and Sanofi Pasteur. All other authors report no other potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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