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Short Communication

The incubation period of COVID-19: A meta-analysis

Check for updates

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ABSTRACT

Objectives: A valid measurement of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) incubation period is needed for case definitions and for adapting appropriate isolation measures but is challenging in an emergency context. Our objective was to systematically review recent literature reporting estimates of the distribution of the incubation period of SARS-CoV-2 and describe the distribution and its variability and dispersion through a meta-analysis.

Methods: A systematic review was carried out on studies published from 1 January 2020 to 10 January 2021 reporting the SARS-CoV-2 incubation period. Individual mean and standard deviation were used to produce the pooled estimate. Sources of heterogeneity were explored by age, gender and study design using a meta-regression.

Results: In total, 99 studies were eligible for analysis in our meta-analysis. The pooled estimate of the mean incubation period across the studies was 6.38 days, 95% CI (5.79; 6.97).

Conclusion: Calculation of the mean incubation period will help with the identification of time of exposure, however, determinants of its variations/range might be explored for potential links with the clinical outcome or pathogenic steps at the early stage of infection. A real-time meta-analysis, named the InCoVid Lyon, is proposed following this initial analysis.

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Introduction

COVID-19 is an infectious disease associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes lower respiratory tract infections; to date, it is responsible for more than 2 million deaths worldwide (Gisanddata map, 2020).

The incubation period is the interval between the moment a person is infected and the onset of the disease. Knowledge of the duration of the incubation period is essential for the case definition, management of emerging threats, estimation of the duration of follow-up for contact tracing and secondary case detection, and the establishment of public health programs aimed at reducing local transmission (Nishiura et al., 2012).

According to the World Health Organization (WHO), SARS-CoV-2 incubation periods ranging from 1 to 14 days have been reported (WHO, 2020). The distribution of the incubation period may vary between individuals as a result of certain determinants, including host factors.

There is a need to increase our knowledge on the incubation period distribution of SARS-CoV-2 to support effective outbreak investigations.

The objective of this study was to conduct a meta-analysis on summary estimates of the distribution of the incubation period of SARS-CoV-2 as reported in the literature.

Methods

A systematic literature search of peer-reviewed publications was conducted to identify studies reporting the incubation period

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of SARS-CoV-2. The following terms were used to select papers: 'Novel Coronavirus' OR 'COVID*' OR 'Coronavirus' OR '2019-nCoV' OR 'SARS-CoV-2' OR 'MERS-CoV' OR 'SARS' OR 'Severe Acute Respiratory Syndrome' AND 'incubation' OR 'incubation period'.

The search covered literature published from 1 January 2020 to 10 January 2021.

Articles or abstracts in languages other than English were excluded.

Data on the published article, the study characteristics, and summary measures of the incubation period were gathered. Measures of dispersion, as well as data on age and gender distribution, were collected where available. All studies reported at least 1 summary statistic of the incubation period distribution as a mean, median or range. The unit of measurement was days.

Individual mean and standard deviation were used to produce the pooled estimate. Inverse variance weighting was used for pooling individual estimation of mean, median, and 95th and 97.5th percentile of the incubation period. Heterogeneity between studies was assessed using the I2 statistic (Higgins and Thompson, 2002). Age, gender and study design were considered as candidate explicative covariables. All data analyses were done using R (version 3.6.3). Results of this meta-analysis are shared on the following site: InCoVid-Lyon (Incovid, 2020).

Results

In total, 99 articles were selected for analysis (.Supplementary appendix). The majority of the studies reported on cases in Asian countries. In total, 23 (23.2%) cohort, 61 (61.6%) case series, and 15 (15.2%) modeling studies were gathered, with a median age of 45 years, and a sex ratio >1. The median sample size was estimated at 52 individuals (IQR 20; 161).

Figure 1 shows that the mean incubation period was 6.38 days 95% CI (5.79; 6.97) ranging from 2.33 to 17.60 days. A range of 15.27 days was described among the studies analyzed. The median incubation period was estimated at 5.41 days 95% CI (4.74; 6.07). There was substantial heterogeneity between the studies ($I^2 = 95\%$).

In meta-regression or by subgroup analysis, this heterogeneity across the studies could be explained by the difference in study design. Shorter incubation periods were reported in cohort compared to case series or modeling studies (P < 0.01). No significant variation was identified by age or by gender. To our knowledge, no study reported infection with the English or South African variant of SARS-CoV-2.

Discussion

The results suggested that the mean incubation period of SARS-CoV-2 is 6.38 days, ranging from 2.33 to 17.60 days. Except for Zhang et al. who reported a longer incubation period, the range was within that quoted by the WHO, i.e. 1–14 days.

Longer incubation periods were observed with case-series compared to cohort studies. The incubation period should be carefully interpreted since the level of evidence differs between study designs. Estimating the range of the incubation time is challenging as it is difficult to pinpoint the exact source of infection and hence the exact timing.

The incubation period might be discussed as an epidemiological parameter and as a link with the early pathogenic process.

With no curative treatment available for SARS-CoV-2 understanding incubation time is paramount for isolating infected cases and quarantining case contacts (Wilder-Smith and Freedman, 2020; Kucharski et al., 2020). SARS-CoV-2 appears to be most contagious around the time of symptom onset; infectivity rapidly decreases thereafter to near-zero after approximately 10 days in

| Study | n | mean (days) | MRAW | 95%-CI |
|--|----------------|---------------------------------------|--------------|---|
| Huang et al | 6 - | | 2.33 | [0.75; 3.92] |
| Guan et al | 269 | • | 3.20 | [2.83; 3.57] |
| Xu et al | 29 399 | · | 3.33 3.50 | [3.10; 3.57] |
| Guan et al Böhmer et al | 16 | ÷ | 3.50 | [3.12; 3.88] [2.89; 4.17] |
| Guan et al | 1590 | • | 3.60 | [3.39; 3.81] |
| Qi et al | 73 | + | 3.67 | [3.07; 4.26] |
| Guan et al | 1191 | • | 3.70 | [3.46; 3.94] |
| Feng et al | 134 | • | 4.00 | [3.78; 4.22] |
| Guan et al | 130 | | 4.00 | [3.11; 4.89] |
| Haiyan et al Wei et al | 325 14 | - | 4.00 4.00 | [3.66; 4.34] [2.63; 5.37] |
| Xu et al | 56 | - | 4.00 | [3.66; 4.34] |
| Yang et al (5) | 12 | | 4.00 | [2.15; 5.85] |
| Gao et al (3) | 15 | + | 4.17 | [3.51; 4.83] |
| Guan et al (2) | 291 | • | 4.33 | [3.96; 4.70] |
| Nie et al | 473 | + | 4.33 | [3.93; 4.74] |
| Pung et al | 17 | | 4.33 | [3.40; 5.26] |
| Sun et al Jin et al | 33 21 | + | 4.33 4.67 | [3.78; 4.89] |
| Liu et al | 16 | | 4.80 | [3.55; 5.78] [3.53; 6.07] |
| Men et al | 25 | | 4.84 | [3.95; 5.73] |
| Yang et al (4) | 8866 | | 4.98 | [4.93; 5.04] |
| Fan et al | 148 | + | 5.00 | [4.58; 5.42] |
| Jeong et al | 25 | + | 5.00 | [4.49; 5.51] |
| Nie et al | 2907 | • | 5.00 | [4.86; 5.14] |
| Nie et al | 2412 | • | 5.00 | [4.85; 5.15] |
| Zhang et al (3) | 294 | • | 5.00 | [4.70; 5.30] |
| Li et al (3) | 425 | • | 5.20 | [4.88; 5.52] |
| Jin et al Li et al (2) | 195 | - | 5.33 | [4.88; 5.79] [4.89; 5.78] |
| Li et al (2) Xu et al | 74 27 | - | 5.33 5.33 | [4.89; 5.78] |
| Linton et al | 52 | | 5.33 | [4.60; 6.07] |
| Lauer et al | 181 | • | 5.50 | [5.28; 5.72] |
| Pongpirul et al | 83 | - | 5.50 | [4.80; 6.20] |
| Wong et al | 135 | • | 5.50 | [5.22; 5.78] |
| Men et al | 34 | | 5.54 | [4.68; 6.40] |
| Tan et al | 164 | · · · · · · · · · · · · · · · · · · · | 5.54 | [5.26; 5.82] |
| Han et al | 25 | + | 5.56 | [4.91; 6.21] |
| Lou et al | 80 | | 5.67 | [4.53; 6.80] |
| Qian et al | 88 | - | 5.67 5.70 | [4.99; 6.34] |
| Du et al Hong et al | 109 157 | 1 | 5.70 | [5.21; 6.19] [5.25; 6.15] |
| Linton et al | 158 | - | 5.80 | [5.36; 6.24] |
| Liang et al | 12 | . _ | 5.83 | [3.99; 7.68] |
| Men et al | 59 | | 5.84 | [5.09; 6.59] |
| Liu et al (2) | 58 | | 6.00 | [5.17; 6.83] |
| Liu et al (2) | 25 | | 6.00 | [4.73; 7.27] |
| Liu et al (5) | 55 | | 6.00 | [5.18; 6.82] |
| Wang et al (3) | 275 | • | 6.00 | [5.54; 6.46] |
| Liu et al (2) | 33 | | 6.10 | [4.99; 7.21] |
| Pan et al Jia et al | 52 44 | T | 6.11 6.28 | [5.19; 7.03] |
| Men et al | 24 | | 6.33 | [5.64; 6.92] [4.97; 7.69] |
| Kong et al (2) | 10 | | 6.33 | [3.90; 8.77] |
| Backer et al | 88 | ÷ | 6.40 | [5.92; 6.88] |
| Bui et al | 19 | | 6.40 | [5.03; 7.77] |
| Han et al | 7 | | 6.43 | [5.32; 7.54] |
| Yang et al | 178 | • | 6.71 | [6.36; 7.05] |
| Men et al | 32 | | 6.73 | [5.62; 7.84] |
| Jiang et al | 43 | - | 6.74 | [6.20; 7.29] |
| Patrikar et al | 268 10 | | 6.93 7.00 | [6.20; 7.29] [6.23; 7.63] [5.39; 8.61] |
| Xia et al Zhang et al (2) | 8 | | | [2.45; 11.55] |
| Zhao et al | 136 | | 7.00 | [6.24; 7.76] |
| Ma et al | 687 | • | 7.04 | [6.72; 7.36] |
| Cai et al | 16 | ÷ | 7.30 | [5.99; 8.61] |
| Gao et al (3) | 26 | | 7.33 | [5.34; 9.33] |
| Xu et al (2) | 15 | - | 7.33 7.33 | [5.35; 9.31] |
| Zhang et al (5) | 7 | | 7.33 | [4.90; 9.77] |
| Wang et al (2) | 483 | + | 7.42 | [7.02; 7.82] |
| Cai et al (2) | 149 | - | 7.48 | [6.86; 8.10] |
| Shen et al | 9 330 | + | 7.56 | [6.68; 8.43] |
| Lai et al (2) Xu et al (2) | 330 | | 7.67 7.67 | [7.11; 8.22] [5.50; 9.83] |
| Viego et al | 18 | | | [4.95; 10.85] |
| Chen et al | 18 | <u></u> | 8.00 | [5.59; 10.41] |
| Chen et al (2) | 12 | | 8.00 | [6.87; 9.13] |
| You et al | 169 | - | 8.00 | [7.28; 8.72] |
| Ai et al | 44 | | 8.08 | [6.58; 9.58] |
| Shen et al (2) | 6 | | | [6.08; 10.08] |
| Qin et al | 1084 | • | 8.29 | [8.06; 8.52] |
| Liu et al (7) | 49 136 | | 8.30 | [7.32; 9.28] |
| Kong et al Zhang et al (2) | 136 23 | | 8.30 8.33 | [7.65; 8.95 [5.94; 10.72 |
| Liu et al (3) | 85 | | 8.51 | [7.87; 9.14] |
| Gao et al (2) | 6 | | 8.54 | [7.34; 9.74 |
| Hua et al | 43 | | | [7.99; 10.21 |
| Guo et al | 341 | + | 9.33 | [8.85; 9.81 |
| Deng et al | 1211 | • | 9.40 | [9.38; 9.42 |
| Yu et al | 132 | + | 9.49 | [8.85; 10.13 |
| Song et al | 17 | | 10.00 | [9.13; 10.87 |
| Mao et al | 28 | | 10.30 | [8.88; 11.72 |
| Liu et al (6) | 93 | - | 10.40 | [9.62; 11.18 |
| Gao et al (3) | 21 | | | [9.00; 12.34 |
| | 46 | | | [9.17; 12.17] |
| | 104 | | | 10.31; 12.29] |
| Zhang et al (2) Qiu et al Xu et al (2) | | | 11 67 1 | |
| Qiu et al Xu et al (2) | 19 | <u> </u> | | 10.20; 13.13] |
| Qiu et al Xu et al (2) | | | | |
| Qiu et al Xu et al (2) Zhang et al | 19 21 | | → 17.60 | [9.53; 25.67] |
| | 19 21 el | | → 17.60 | |

Figure 1. Forest plot showing mean incubation period of COVID-19 from included studies.

mild-moderately ill patients and 15 days in severely-critically ill and immunocompromised patients (Rhee et al., 2020). A quarantine period of at least 10 days would be necessary to limit the transmission of the virus from the exposed cases. In the context of nosocomial cases or confined environments (i.e. classrooms in schools or cruise ships), knowing the incubation period will help to identify exposed individuals.

The incubation time is important for non-pharmaceutical public health interventions such as timely isolation and tracing and quarantining contacts.

The precise estimation of the incubation period is also relevant for exploring early pathogenetic mechanisms with potential links to clinical outcome (Vanhems et al., 2000).

Promptly after its emergence, SARS-CoV-2 was identified to be responsible for human transmission during the incubation period (Jin et al., 2020). Previous studies have suggested that a short incubation period could have an impact on the severity of infection caused by the coronavirus species (Virlogeux et al., 2016). More knowledge about the link between the incubation period and the viral load is essential to tailor clinical decision making and assess COVID-19 severity.

The need for an accurate definition of the incubation period has become urgent to better define cases and the duration of isolation measures. Applying different definitions may hamper case detection and the effectiveness of infection control measures.

Conflict of interest/disclosures

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Authors' contribution

CE and PV conceived and designed the study. PV coordinated the study. CE, AS and PL collected the data. MC and CE conducted data analyses. MC designed the Incovid-Lyon website. All authors contributed to data interpretation, the manuscript draft and approved the final version of the manuscript.

Ethical approval

Not applicable.

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References

- https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda759474 0fd40299423467b48e9ecf6 [accessed 24.01.21].
- Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
- https://incovidlyon.shinyapps.io/incubationPeriod/ [accessed 24.01.21].
- Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res 2020;7(1):4.
- Kucharski AJ, Klepac P, Conlan AJK, Kissler SM, Tang ML, Fry H, et al. Effectiveness of isolation, testing, contact tracing, and physical distancing on reducing transmission of SARS-CoV-2 in different settings: a mathematical modelling study CMMID COVID-19 working group. Lancet Infect Dis 2020;20(10):1151–60.
- Nishiura H, Mizumoto K, Ejima K, Zhong Y, Cowling B, Omori R. Incubation period as part of the case definition of severe respiratory illness caused by a novel coronavirus. Euro Surveill 2012;17(42)20296 [Published 18.10.12].
- Rhee C, Kanjilal S, Baker M, Klompas M. Duration of SARS-CoV-2 infectivity: when is it safe to discontinue isolation?. Clin Infect Dis 2020;ciaa344.
- Vanhems P, Hirschel B, Phillips AN, et al. Incubation time of acute human immunodeficiency virus (HIV) infection and duration of acute HIV infection are independent prognostic factors of progression to AIDS. J Infect Dis 2000;182:334–7.
- Virlogeux V, Park M, Wu JT, Cowling BJ. Association between Severity of MERS-CoV Infection and Incubation Period. Emerg Infect Dis 2016;22(3):526–8.
- https://www.who.int/news-room/q-a-detail/q-a-coronaviruses [accessed 24.01.21].
- Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. J Travel Med 2020;taaa020, doi: http://dx.doi.org/10.1093/jtm/taaa020.