Incubation period of COVID-19: a meta-analysis

Christelle Elias[1], Abel Sekri[2], Pierre Leblanc[2], Michel Cucherat[2], and Philippe Vanhems[1]

[1]CIRI
[2]HCL

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Abstract

A valid measurement of the SARS-CoV-2 incubation period is needed for case definitions and for adapting appropriate isolation measures but is challenging in an emergency context. The objective was to systematically review recent literature of reported estimates of the distribution of incubation period of SARS-CoV-2 for describing the distribution and its variability and dispersion through meta-analysis. A systematic review search was carried out up to July 1st 2020 of all identified references available reporting the SARS-CoV-2 incubation. Individual mean and standard deviation were used to produce the pooled estimate. Heterogeneity was also assessed using I2 statistics and sources of heterogeneity were explored using a meta-regression. The main outcome was the SARS-CoV-2 incubation period defined as the time from exposure to onset of clinical illness. In total, 43 studies were eligible, including 12 (27.9%) cohorts and 31 (72.1%) case reports and series. The pooled estimate of the mean incubation period across the studies was 6.24 days, 95% CI [5.80;6.69] ranging from 2.33 to 17.60 days. Shorter incubation periods were reported in cohorts compared to case series ($p<0.01$) and among studies with high proportions of males ($p<0.05$). The mean incubation period will help for identification times of exposure but determinants of its variations/range might be explored for potential links with clinical outcome or early pathogenic steps. The impact of individuals with extreme values of incubation on the outbreak dynamic should be evaluated taking account for the basic reproductive number. A real time of meta-analysis, called the InCoVid Lyon, is proposed.

Introduction

A novel coronavirus emerged in China in late 2019. This new strain was quickly identified, and genome sequencing established that this severe acute respiratory syndrome coronavirus (SARS-CoV-2) was derived from bats [1]. On March 11, 2020, the World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) to be pandemic. As of July 18, 2020, SARS-CoV-2 has been responsible for more than 14000000 cases and more than 600000 deaths worldwide [2].

Incubation period is the interval time elapsed between the moment a person is infected until the onset of the disease. Knowledge of the incubation period is essential for the case definition, management of emerging threats, estimation of the duration follow-up for contact tracing and secondary case detection and the establishment of public health programs aimed at reducing local transmission [3]. Valid measurement of the incubation period might be challenging in an emergency context.

According to the WHO, SARS-CoV-2 incubation period ranging from 1 to 14 days has been reported [4]. Distribution of the incubation period may vary between individuals as a result of certain determinants such as host factors.

A paradox might be occurring; as the number of reported cases increases, the quality of the parameter increases, with a reduction of the range or the 95% confidence interval. However, the waiting time for obtaining results from large sample size delays optimal decisions for the outbreak investigation. Moreover, in case of a R_0 of 2.5 to 3.0, even outliers with a long incubation period may generate secondary cases. Thus,

measures of dispersion are as important as measures of central tendency. Despite the lack of knowledge regarding transmission during the incubation period, that interval conditions the amount of contacts to investigate.

The situation is evolving daily and there is an urgent need to correctly estimate the incubation period distribution of SARS-CoV-2 in order to support effective outbreak investigations in various contexts such as large or restricted geographic areas.

Therefore, the objective was to systematically review recent literature of reported summary estimates of the distribution of incubation period of SARS-CoV-2 with the aim of describing the distribution of incubation period and identifying variations through a meta-analysis.

Methods

Research questions and Population/Infectious agents/Comparator/Outcome (PICO) elements

- What is the incubation period distribution of SARS-CoV-2 in humans?
- Is there heterogeneity between the reported incubation times amongst studies?

Population: Confirmed cases of SARS-CoV-2 during the 2019-2020 pandemic

Infectious agent: SARS-CoV-2

Comparator: Host factors such as gender and age

Outcome: Time from exposure to onset of clinical illness as described by the authors

Search strategy and selection process

A systematic literature research of peer-reviewed publications on PubMed and pre-print articles to identify case-series, observational or experimental studies reporting incubation period of SARS-CoV-2 was conducted with the following terms: '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'.

A reference list of review papers, pre-print reviews and epidemiological reports from international and public health institutions were also screened to identify other relevant studies reporting incubation period of SARS-CoV-2 that may have been missed in the original search. The search was carried out from inception to July 01, 2020.

Each article went through a screening process as follows: #1) Screening of title and abstracts for articles reporting on SARS-CoV-2 or COVID-19, #2) Screening of full texts reporting incubation period.

Articles or abstracts in languages other than English were excluded.

Data extraction

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

Statistical analysis

Individual mean and standard deviation were used to produce the pooled estimate. In absence of reporting of standard deviation, we recalculate it from confidence interval limits if available, or from the 1^{st} and 3^{rd} quartiles or from the range using approximation formula [5]. Inverse variance weighting was used for pooling individual estimation of mean, 95^{th} end 97.5^{th} percentile of the incubation period. A random-effects model was used. Heterogeneity between studies was assessed using I^2 statistics, with an I^2 of more than

50% indicating substantial heterogeneity [6]. We explored sources of heterogeneity with a meta-regression for continuous explicative covariables and by subgroup analysis for qualitative explicative covariables. Age, gender and study design were considered as candidate explicative covariables. All data analyses were done using R (version 3.6.3) with R package meta and the metamean function. Results of this real-time meta-analysis are shared on the following site: InCoVid-Lyon [7].

Results

Among all the articles screened for selection in the meta-analysis, 43 were analyzed (Supplementary appendix 1). No study reported the incubation period outside Asia. In total, 12 (27.9%) cohorts and 31 (72.1%) case reports and series were gathered, with a median age of 40.1 years, and a sex ratio greater than 1. The median sample size was estimated at 56 [IQR 16 ; 163] individuals.

Figure 1 shows that the mean incubation period is equal to 6.24 days 95% CI [5.80;6.69] ranging from 2.33 to 17.60 days. A magnitude of 15.27 days was described among the studies analyzed. In addition, studies are substantially heterogeneous ($I^2 = 95\%$) between each other.

In meta-regression or by subgroup analysis, this large amount of heterogeneity across studies could be explained by difference between studies in gender distribution or study design. Shorter incubation periods were reported in cohorts compared to case series ($p<0.01$) and among studies with high proportions of males ($p<0.05$). However, no significant variation was identified by age.

Discussion

A systematic review was undertaken to describe the distribution of incubation period of SARS-CoV-2. The results suggested that the mean incubation period of SARS-CoV-2 is 6.24 days, ranging from 2.33 to 17.60 days. These values are within the range quoted by international organizations reporting 1 to 14 days [4], except for Zhang and al reporting a longer incubation period.

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

Without any vaccination or treatment available against SARS-CoV-2, incubation time is paramount for isolating infected cases and the quarantine of case contacts [8]. In the light of the results, a quarantine period of at least 14 days would be necessary to limit the transmission of the virus from the exposed cases. The retrospective investigation of cases is also associated with a relevant incubation definition. In the context of nosocomial cases or confined environments (i.e. classrooms in schools or cruise ships), knowing incubation will help for identification of exposed individuals.

The duration of incubation could also be relevant for establishing the prognosis of COVID-19 as illustrated in other studies (i.e. acute human immunodeficiency viruses for which a shorter incubation was associated with a faster disease progression [9]).

Integration of the virus to the host cell corresponds to the moment when a subject becomes is infected and the onset of the incubation period. Promptly after its emergence, the SARS-CoV-2 strain was identified to be responsible for human transmission during the incubation period [10]. In addition, previous studies have suggested that a short incubation period could have an impact on the severity of infection caused by coronavirus species [11]. Therefore, more knowledge about the link between the duration of incubation period and the viral load is essential to tailor clinical decision making and assess COVID-19 severity.

Some limits should be discussed. All studies were made from Asian case series and cohorts which might have induced a selection bias. Although these data can be extrapolated to other populations, that can be done carefully if incubation period is associated with underlying diseases or prevalence of some individual characteristics (i.e. obesity). Additionally, it has already been shown that one virus can have various incubation periods in different populations [12], which could be explained by host factors, the potential of mutation of the viral strain and the unknown animal reservoir. This meta-analysis was based on available data online. Some studies are still at the pre-print stage and had not yet been peer-reviewed. Definition

of cases might differ across studies. Furthermore, study populations are made up of cases that have been investigated as part of point source outbreaks where incubation period was not the main goal of investigation.

Conclusion

The mean incubation period was estimated at 6.24 days 95% CI [5.80;6.69], that fits well in the range of the recommended periods by international health institutions. The COVID-19 situation is evolving daily and there is a global need to ascertain an accurate definition of the incubation period in order to better define cases and duration of isolation measures including quarantine. Discrepancies among sources may hamper case detection and the effectiveness of infection control measures. Following this report, an online real-time analysis is now provided on a website (InCovid-Lyon) [7].

Conflict of interest/Disclosures

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Author contributions

CE and PV conceived and designed the study. PV coordinated the study. AS 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.

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`Figure_1_Vanhems.docx` available at https://authorea.com/users/347757/articles/473313-incubation-period-of-covid-19-a-meta-analysis