

BRIEF REVIEW

A Review of Quarantine Period in Relation to Incubation Period of SARS-CoV-2

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Abstract

Introduction: The period from exposure to a potential pathogen to the manifestation of symptoms, *i.e.* the incubation period, is time the virus spends replicating in the host. An estimation of this period and subsequent quarantine of the host can limit potential spread, particularly in asymptomatic carriers. Effective contact tracing, length of self-quarantine, repeat testing, and understanding of disease transmission are all contingent on a true estimation of this incubation period.

Methods: Articles in English published since December 1st, 2019, on Google scholar, PubMed, and Research Gate, along with bulletins from the World Health Organization and the Centers for Disease Control and Prevention, were identified using the keywords, “SARS-CoV-2,” “COVID-19,” “median incubation period,” “mean incubation period,” “symptom onset,” “quarantine,” and “exposure interval” and reviewed independently by two authors to establish consensus. Travel to Wuhan, or in absence of travel, the earliest possible exposure, were used to calculate mean or median incubation period. Correspondingly, we reviewed the advised lengths of quarantine period.

Results: Five studies with a combined sample size of 505

patients were reviewed for mean/median incubation period. Four studies recommended periods for self-quarantine, ranging from 2 to 14 days. Linton *et al.* reported the shortest estimate of median incubation period at 4.3 days (95% confidence interval [CI] 4.5–5.6), whereas the longest was by Backer *et al.* at 6.4 days (95% CI 4.5–5.8). Similarly, the shortest estimation of mean incubation period was by Liu *et al.* ($n=16$) at 4.8 days (95% CI 2.2–7.4) days while the longest at 5.5 days (95% CI 4.5–5.8) was by Lauer *et al.* ($n=181$). Although the range for quarantine in these four studies was 12.5–14 days, all four recommended 14 days as the optimum for self-quarantine.

Conclusion: An estimate of incubation period is instrumental in outlining an effective quarantine measure. Calculation of the incubation period using mathematical models has established an accurate measure, albeit with uncertainty increasing towards the tail of each distribution. Based on a thorough review of these studies, a quarantine period of 14 days can be recommended, allowing 97.5% of the infected people to show symptoms. These symptomatic patients would be further evaluated based on their respective state health guidelines so that they may be effectively isolated and treated.

Introduction

The geographic spread of COVID-19 pandemic highlights the need to study the natural history and incubation period of SARS-CoV-2. Incubation period is defined as the period between exposure to an infectious agent and the development of the first symptom.[1]

A precise calculation of the incubation period is critical in estimating the time required for disease monitoring, restriction of movement of people (quarantine), estimating the extent of the pandemic and predicting the temporal spread of the disease.[2, 3] An accurate incu-

bation period can be used effectively for carrying out contact tracing and restricting the point of entry in several countries, while enabling a better understanding of the disease transmission as well.[4, 5] The migration of patients to an affected area presents the rare advantage of limiting the probability of time of exposure and contraction of the virus to the duration of stay, thereby enabling the precise calculation of the incubation period. This in turn allows us to understand and predict the course of the pandemic.

The purpose of the review article is to evaluate the role that the incubation period and to arrive at a consensus

Table 1. Summary of incubation periods and recommended quarantine length.

Name	Sample size (<i>n</i>)	Incubation period		Recommended quarantine (days)
		Range	Mean/median [95% CI]	
Linton <i>et al.</i> [2]	210	2–14	Median: 4.6 [3.7–5.7] Mean: 5.6 [4.4–7.4]	14
Backer <i>et al.</i> [6]	88	2.1–11.1	Median: 6.4 [5.6–7.7]	14.1
Lauer <i>et al.</i> [8]	181	2.2–11.5	Median: 5.1 [4.5–5.8] Mean: 5.5	14
Li <i>et al.</i> [7]	10	N/A	Mean: 5.2 [4.1–7.0]	12.5
Liu <i>et al.</i> [20]	16	2–11	Mean: 4.8 [2.2–7.4]	N/A

Abbreviations: CI, confidence interval.

for an effective public health measures to prevent disease transmission.

Methods

The databases Google scholar, PubMed, Research gate, the World Health Organization (WHO), and the Centers for Disease Control and Prevention (CDC) with the key words, “SARS-CoV-2”, “COVID-19”, “median incubation period”, “mean incubation period”, “symptom onset”, “quarantine” and “exposure interval” were queried. The resulting original research study articles, case series and case reports were considered along with public health news bulletins from the WHO and the CDC. Two authors independently reviewed the full text of each article and any discrepancies were resolved by discussion to reach a consensus. For each article, we recorded the travel history to Wuhan, mean or median incubation period, the time to symptom onset, time to hospitalization and the possible range of the incubation periods obtained. Only articles where the incubation period fit into a lognormal, Weibull or gamma distribution were used. We also recorded the advised quarantine periods in each article when available. In cases where there was no travel history to Wuhan, but exposure to an infectious source was present, the possible interval of SARS-CoV-2 exposure was taken as the maximum possible interval of exposure to the infectious person, including the time before the person was asymptomatic. All articles considered had cases reported at the earliest on December 1, 2020 and in continuum to present day. Our exclusion criteria included all articles in any language other than English, research articles that used data for incubation period calculation after the commencement of community transmission in the respective country of study.

Results

Five original research studies were analyzed for the mean or median incubation period. Four of them gave quarantine period recommendations (Table 1). The combined sample size of these studies were 505 patients over the course of January, February and March of 2020.

The shortest observed incubation period was 2 days and the longest, 14 days. The shortest estimate of the median of incubation period was by Linton *et al.* at 4.3 days (95% CI 4.5–5.6), whereas the longest was by Backer *et al.* at 6.4 days (95% CI 4.5–5.8). Similarly, the shortest estimation of mean of the incubation period was by Liu *et al.* (*n*=16) at 4.8 days (95% CI 2.2–7.4) days while the longest stands at 5.5 days (95% CI 4.5–5.8) from a study by Lauer *et al.* (*n*=181). The range of quarantine periods estimated in four independent studies was between 12.5–14 days (Figure 1).

Discussion

Very few studies have been done to establish the mean, median and range of incubation periods. This has primarily been secondary to the difficulty of contact tracing to determine the time of exposure and because of community based spread of the virus to regions outside Wuhan. Most studies conducted had their patient pool from the Hubei province of China with only two studies assessing the incubation period length in patients outside Wuhan where the pandemic broke out.

Li *et al.* evaluated the incubation period by assessing 10 patients. They established an incubation period of 5.2 days (95% CI 4.1–7.0) with 95% of the patients presenting with symptoms before 14 days.[6] This observation formed the original basis for the proposed 14-day quar-

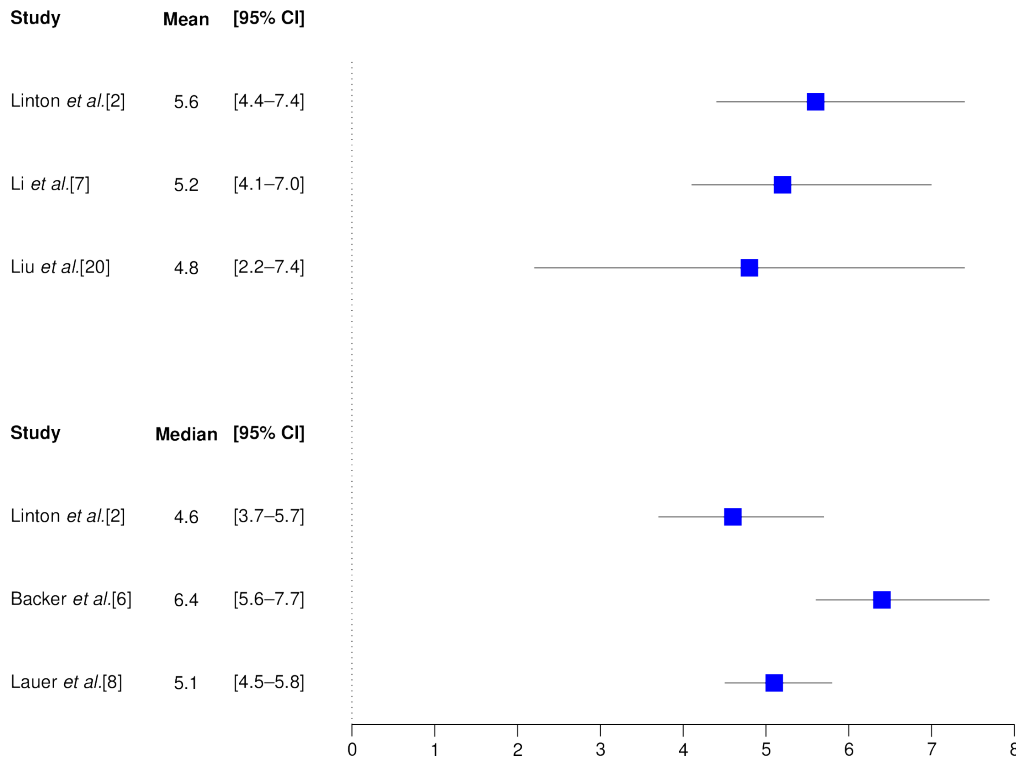


Figure 1. Forest plot of average incubation period.

antine period.[7] This study however included only the patients who were residents of Wuhan and had an exposure to the seafood market linked to the virus outbreak and did not include visitors.

In contrast, Linton *et al.* ($n=210$) included residents of Wuhan as well as travelers to the city in their study. The Bayesian estimates for incubation period were obtained by fitting the probability density function along lognormal, Weibull and gamma distributions, of which the lognormal distribution was found to best fit the data. Through this, the mean incubation period was found to be 5.6 days (95% CI 5.0–6.3) when Wuhan residents were included and 5.0 days (95% CI 4.2–6.0) when they were excluded. With right truncation, this figure increased to 5.6 (95% CI 4.4–7.4).[2] Similarly, the median incubation period was found to be 5.0 (95% CI 4.4–5.6) when Wuhan residents were included and 4.3 (95% CI 3.5–5.1), when they were excluded with right truncation again increasing the incubation period to 4.6 days (95% CI 3.7–5.7).[2]

The exclusion of Wuhan residents therefore provided a more accurate result when one considers the difficulty in tracing contacts among people who have resided over a long time-period in the city and the larger points of contact they may have had with infectious sources. Moreover, the occurrence of local transmission makes the period of exposure less firm in these patients. Con-

sequently, this study had the overall advantage of additional case data and fitted left exposure dates, when compared to an earlier study by Backer *et al.* based on the same model, where unknown left exposure dates were fixed during analysis. Despite this drawback, the study by Backer *et al.* yielded similar results with the mean incubation period estimated to be 6.4 days (95% CI 5.6–7.7) in a Weibull distribution which, in contrast to the study by Linton *et al.* used a Lognormal distribution and allowed a better fit for the data.[6]

Lauer *et al.* analyzed cases from Wuhan and from outside the city ($n=181$). The study showed a median incubation period 5.0 days (95% CI 4.4–5.6) within a range of 2–14 days for patients outside China (mostly travelers to Wuhan) compared to 4.8 days (95% CI 4.2–5.6) within a span of 2.5–9.2 days for mainland Chinese patients.[8] This stands in stark contrast with the earlier study by Linton *et al.* where the incubation period for the pool with patients from Hubei was longer compared to the pool constituting travelers from outside.

Establishing a quarantine period

It appears that the estimates of the incubation period are accurate and allow establishing a quarantine period to slow the spread of the pandemic. Li *et al.* were the first to note that 95% of their patients presented with symptoms before day 14.[6, 7] This formed the original

basis for the most frequently used quarantine period of 14 days. Backer *et al.* whose results showed that 99% of their study patients presented with symptoms within 12 days of infectious source exposure.[6] Only one study, by Linton *et al.* presented data wherein 5% of the study patients presented after day 14 and 1%, after day 19 of incubation with symptoms. However, with 95% of their patients having presented within 12.3 days (95% CI 9.1–19.8), the authors agreed that a 14 days quarantine period would be adequate to contain the spread of the disease.[2]

Lauer *et al.* advocated that a 14-day quarantine period was adequate to isolate infected patients with only 101 out of every 10,000 cases (99th percentile, 482) developing symptoms after 14 days of active monitoring or quarantine. It was found to be highly unlikely that further symptomatic infections would be undetected among high-risk persons with a mean of 1.0 undetected infections per 10,000 persons with the current 14-day quarantine guideline. Extended quarantine was advised only in extreme cases or heavily impacted geographic regions with a judgement based on the cost of missing out cases.[8] Indeed, a 14-day quarantine for people who are suspected of being exposed to SARS-CoV-2 has been established as one of the most effective public health measures to contain the ongoing COVID-19 pandemic.

Challenges in estimating the incubation period

Despite efforts to make a precise and accurate calculation of the incubation period for SARS-CoV-2 a detailed review of current literature has determined certain drawbacks in the methods used. An infection event in most cases cannot be directly observed and the presence of multiple contacts has limited straightforward estimation, with this being especially true among

residents of an affected region. Additionally, the crude incubation period has been difficult to estimate even among travelers with known sources of exposure when the length of travel with the infectious source is long.[9] Finally, in all mentioned studies, the possibility of an asymptomatic infection and carrier state have not been taken into account due to only recent evidence suggesting the plausibility of such a state.[10-12]

Asymptomatic transmission compounded by the high viral shedding exhibited during the incubation period of SARS-CoV-2 has raised concerns on the validity of determining the quarantine period based on incubation period alone.[13] Many countries are increasingly adopting additional public health measures such as a region-wide lockdown to factor in and compensate for the uncertainties in reaching an effective quarantine period and the challenges in diagnosing contagious asymptomatic patients in latent periods.[14-16] This has prompted some experts to advise mandatory testing of close contacts whether immunologic or radiographic to eliminate the possibility of transmission through viral shedding during incubation period and mitigate public risk.[15, 17-19]

In conclusion, it is imperative to have estimates that are reliable for taking necessary measures in prevention of the pandemic spread. Calculation of the incubation period using mathematical models has established an accurate measure, with uncertainty increasing towards the tail of each distribution. The estimates from four different studies have allowed us to reach a consensus on the quarantine period. Fourteen days in quarantine have been recommended, allowing 97.5% of the infected people to develop symptoms. It is assumed that symptomatic persons will further be evaluated and further quarantined based on respective state health guidelines thereby limiting the spread of the virus.

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