Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Paper

In pursuit of the right tail for the COVID-19 incubation period

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ABSTRACT

Definition of the incubation period for COVID-19 is critical for implementing quarantine and thus infection control. Whereas the classical definition relies on the time from exposure to time of first symptoms, a more practical working definition is the time from exposure to time of first live virus excretion. For COVID-19, average incubation period times commonly span 5–7 days which are generally longer than for most typical other respiratory viruses. There is considerable variability reported however for the late right-hand statistical distribution. A small but yet epidemiologically important subset of patients may have the late end of the incubation period extend beyond the 14 days that is frequently assumed. Conservative assumptions of the right tail end distribution favor safety, but pragmatic working modifications may be required to accommodate high rates of infection and/or healthcare worker exposures. Despite the advent of effective vaccines, further attention and study in these regards are warranted. It is predictable that vaccine application will be associated with continued confusion over protection and its longevity. Measures for the application of infectivity will continue to be extremely relevant.

Introduction

With the continuing COVID-19 pandemic, it would be assumed that tangible epidemiological variables would be well understood and applicable to disease prevention. Despite epidemiological data from other human coronavirus infections including Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome, and despite ongoing observations from COVID-19, it is noteworthy that some concerning uncertainty prevails in regards to key parameters for public health.[1–7] Amidst the haste to understand and cope with the alarming consequences of the pandemic, it is crucial to reanalyze some of these variables for their application and potential impact. One such critical epidemiological parameter that attracts such attention is the 'incubation period'.[8] There are many potential practical applications of the incubation period to working medicine if not the basic sciences of infection, but one of the most tangible is that of determining quarantine for exposed individuals.[9]

Research and methodological approach

This narrative review examines features of the incubation period that warrant further consideration and that provide the stimulus for further hypothesis testing in the context of COVID-19 and other respiratory infections. The substance for this narrative was accumulated after thorough review of related publications as abstracted from PubMed, EMBASE, CINAHL Plus, and the Cochrane Library. These databases were assessed for information that was contemporary to February 15, 2021.

A synthesis of review results and related discussion

Anticipating problems with cumulative analyses

Even when incubation periods are defined for an infectious disease, the actual use of such concepts may be stretched to inconvenience thereafter.[8,10] When elements as basic as incubation period are of concern, there is a multiplier effect on potentially jeopardizing effective infection control as the timing of infectivity similarly becomes a matter for some debate.[11] Gussow et al. place a novel angle of relevance to this topic by suggesting through their model that the incubation period of a virus may correlate with disease severity.[12]

The COVID-19 era was already well-served by experience from SARS, and templates from the World Health Organization (WHO) were available to cut-and-paste into COVID-19 planning.[13] As proposed, estimates of incubation period could be rapidly obtained in a large epidemic or pandemic, and an approximation of 200 exposure incidents could suffice to acquire a reasonable statistical

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conclusion. The latter presupposes however that the baseline data are accurate and that a model would fit all populations and age groups. Concerns with the issue of outliers were clearly delineated in the WHO document. As well, specific focus on the late (right) tail end of the incubation period was emphasized given the potential impact on quarantine and given the stated historic understanding that mammalian coronaviruses generally have longer terminal distributions than other common respiratory viruses.

In practice, there is rarely a perfect study, but there may be many that are better than others. The epidemiology of COVID-19 has already been blessed with several meta-analyses for particular parameters.[14–21] Why then would this discussion linger given the latter well-intended and labor-intensive studies? The potential hazards of conducting meta-analyses are broadly discussed in the medical sciences. The use of data that is non-randomized and largely observational attracts heterogeneity to individual studies. There tends to be considerable risk of confounding variables whether measured, unmeasured, or unrecognized. The combined aggregate data may not be adjusted for potential confounding variables. What jeopardy would there be for any individual studies of COVID-19?

The first concern arises with the definition of 'incubation period'. Fig. 1 highlights various aspects of intervals that are important to consider in this context. Time 'A' represents the exposure event(s). Whether one, several in close sequence, or continuous, the exposure in itself can occur over a wide interval of time. For example, in the circumstances of family, work, or school contacts, the interval may range from seconds to many days and anywhere in between.[22] Prolonged exposures provide ambiguity. Evidently, it is important to secure data where a definitive and reasonably timed single contact occurs. Widening the latter creates bias especially when recall is of concern.[23] The exposure impact might also biologically vary due to other biases in the reporting structure, variance in routes of acquisition, and inoculum. For example, in animal models, the route of inoculum and dose of inoculum can have influence on the rapidity and extent of disease.[24,25] The assumption that infectiousness is equally distributed through a contact time is unlikely to be true given variability in viral loads of respiratory samples or their excretion pattern.[26] Conventionally, the incubation period is the time from exposure and acquisition to the first point of clinical symptoms (Fig. 1, time A to B), and most SARS-CoV-2 studies use such a definition. A few studies, however, have used a hybrid of both exposure to time of disease onset and exposure to time of first laboratory confirmation.[27,28] The time from first exposure to first laboratory confirmation of infectiousness, however, is more commonly termed the 'latent period' (Fig. 1, time A to D).[9,29,30] Although some patients may very well have both first positive detection and/or excretion at the same time as symptom onset, it is conceivable that most patients indeed do not. Therefore the use of hybrid data as exemplified above and the integration of any such studies into meta-analyses has the potential to magnify bias. A few studies may fail to define incubation period altogether. Such concern was duly hinted by Evans.[31]

The time between the latent period and incubation period can be considerably variable and appears to be so for COVID-19. Laboratory confirmation to determine a veritable latent period requires frequent testing from the time of exposure which is rarely had; most such analyses prove to be chance observations due to testing for symptomatic patients or testing for asymptomatic contacts. As laboratory testing with predominantly molecular techniques does not typically differentiate live from inactive virus, and given the potential for viral RNA to be detected well after resolution of the illness or infectivity, routine diagnostics may also lead to considerable variability in defining the latent period. The diagnostic tests may be susceptible to sampling variability or technological nuances for threshold determination. Using solely clinical criteria for case definition was a major stumbling block in the SARS era.[32] Infectivity during times between the true latent period and the incubation period is commonly referred to as the period for presymptomatic transmission (Fig. 1, time D to B). Such transmission has now become well accepted for COVID-19.[33–40] Estimates of presymptomatic transmission have generally been in the range of 1–5 days. Fraser et al. conceptualize this issue mathematically, and a key proposition yet holds truism.[41] Defining R_0 as the basic reproduction number (i.e, number of secondary infections as a measure of infectivity) and Θ as the proportion of infections transmitted either presymptomatically or asymptomatically, the measures of $\Theta < 1/R_0$ and $\Theta > 1/R_0$ have applicable relevance to COVID-19. From variable publications thus far, COVID-19 straddles these confines enough to cause ambiguity in different populations so far assessed.

Given the above, the use of the traditional incubation period is also complicated by the finding of COVID-19 infections which are generally or purely asymptomatic. The frequency of asymptomatic disease in given populations is also variable.[3,42,43] In this context, the latent period is the practical surrogate for incubation period, but again the accurate determination of any such timing would necessarily depend on repeat serial testing of the individuals so exposed. Prolonged excretion of presumably infectious virus was known for other coronaviruses.[2,3,44] Such prolonged excretion has also been cited for SARS-CoV-2 among unique patients.[11,45–48] Past an asymptomatic pre-excretion period, excretion of live virus after the onset of the symptomatic state may variably exceed ten days.[11,49,50]

Imprecisions in the determination of the incubation period must therefore be commonplace as many biases can be introduced.[9,29] Concern with the uses of 'coarse data' are very appropriate but at times practically motivated.[30] Other approaches could conceivably include estimation of the incubation period with serial intervals (time of symptom onset in index case to time of symptom onset of subsequently linked infections) data.[26] For respiratory infections with very short incubation periods or latent periods, the latter may have some accuracy, but the aforementioned variables of concern must certainly make such an application difficult for COVID-19. Early parameter estimates have the propensity to change with cumulative changes in assessment.[14] As Cowling et al. suggested for SARS, many incubation period events cannot be directly observed.[32] Environmental contamination and its effect as an

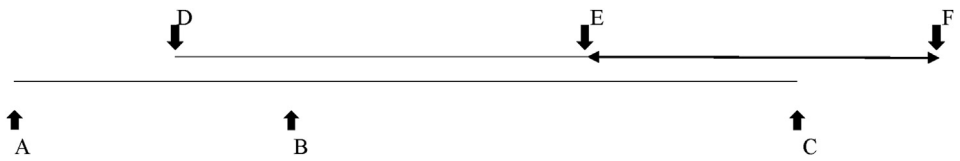

Fig. 1. Elementary constructs for incubation period (conventional time A to time B), latent period (time D to time B), and infectivity (typically time D to time E, but potentially to time F for prolonged asymptomatic excretion). [A = point or interval of exposure; B = symptomatic period begins for those who develop symptomatic disease; C = symptomatic period largely resolved; D = start of infectious excretion; E = end of infectious excretion; F = end of asymptomatic excretion].

infectious source have the potential to considerably confound the exposure event(s).[4,51] It is conceivable that various data, especially for timings, may change during the course of an outbreak.[41] There may be assumptions that individuals mix homogeneously; other mobility is also of general concern.[41,52] Overall, debates about the incubation period and its application are justified.[53]

Given the availability of animal models, especially simian, it could be anticipated that experimental exposure studies could better target exact timings for determining either the incubation or latent periods. Such experimental data, however, may not adequately capture the inherent variability in the biological world. Likewise, overdependence on human experimental infection may not capture such biological variability especially when a fixed dose of challenge inoculum, a fixed route of infection, and a fixed time of exposure are used.[10] Hence, most common discussions of incubation period do not duly depend on experimental information.

An integration of clinical and statistical modeling

How much variation can we expect on the basis of either direct observation or biological variability? Distribution assumptions and observations provide the basis for modeling of the incubation period (Fig. 2). Both parametric and nonparametric models may be applicable. Early in the course of an outbreak, the application of a nonparametric technique may provide a standard.[32] Practically speaking, however, parametric distribution models have taken most interest for SARS or COVID-19. The latter have variably included lognormal, Weibull, and gamma distributions or others which bear crude similarity as shown in Fig. 2. Sartwell and many others have raised concern about the skew of the right-hand distribution curve well in advance.[8] As a general principle, uncertainty of any model increases in the tail ends of distribution.

There were several key observations in the SARS era from mathematical modeling. As suggested in the sentinel WHO paper, coronaviruses generally were regarded as having long right-hand tails for the incubation period.[13] Others re-emphasized the latter when studying either other respiratory virus infections or SARS.[9,29] Crucial to complicating these models was the limitation of diagnostic testing which was largely based on genetic, rather than live virus, technologies. Nevertheless, given the problem with virus excretion outliers, the finding of the best model to account for the right-handed distribution skew proved a matter for debate. Cowling et al.[32] proposed that the lognormal distribution provided the longest right-sided tail. Nishiura projected utility of the lognormal distribution.[9] With their unique approach, Kuk and Ma[26] supported a Weibull distribution. Reich et al.[30] applied the concepts of doubly interval-censored data and interval-reduced data. What emerged was the practical view that good data collection should be followed by studies of distribution using the best fitting models after direct comparisons. The latter approach could be strengthened by application of proposed models to different data sets. In regards to being conservative to ensure safe public health application, a parametric test could be chosen with the longest right-hand tail.

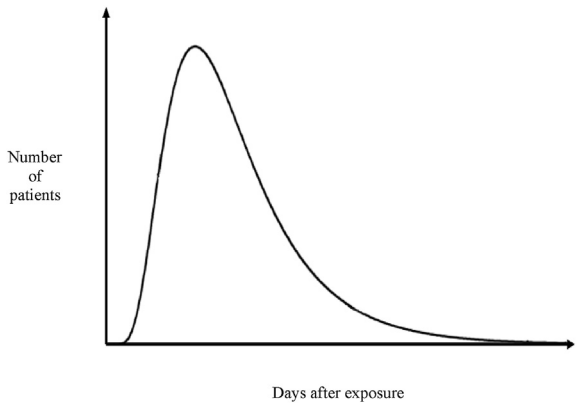

Fig. 2. Lognormal distribution pattern anticipated for an incubation period.

For COVID-19, the uncertainty about the right-hand distribution has been duly raised.[17] Application of various models has attracted some variation in choice. Lognormal distribution was distinctly discussed by some investigators.[33,54–56] The Weibull model has been selected by others.[57–61] Tindale et al.[40] chose the gamma distribution. Comparisons of different models have also been detailed.[33,40,54,55,57,59,62–64] Qin et al.[65] discuss application of a renewal theory to calculations. Men et al.[64] did not find a good fit for parametric models and chose a nonparametric design. Do these detailed analyses provide any consolidation for how to view the right-hand skew of observations?

Summary of incubation period publications

Previous analysis of incubation period data for human coronaviruses concluded that a typical timing varied from 2 to 5 days with a mean approaching 4 days, and the right tail of distribution for the 95th percentile was between 10 and 11 days.[29] In comparison to other more commonly studied respiratory viruses, these estimates must be tempered by the relatively small number of studies from which such data could be extracted. However fallible nevertheless, the estimates implied a longer incubation period than several other respiratory viruses.

For COVID-19, several themes emerge (Tables 1 and 2). Smaller sample sizes are more commonly associated with wider confidence intervals. Ranges for mean and median incubation periods have varied from 4.2 to 10.4 and 2.9–8.5 days, respectively. In relevance to scrutinizing the right-hand tail of distributions, the 95th and 97.5th percentiles have ranged 3.2–17.8 and 11.1–19.3 days. For studies reporting the data estimates, 12/15 (80%) and 6/15 (40%) would be found to extend the incubation period past 10 and 14 days at the 95th percentile. For the 97.5th percentile, the frequencies would be 9/9 (100%) and 5/9 (55.6%) at 10 and 14 days. Two studies found 99th percentile ends of incubation period to be over 20 days.[62,81] Household contacts may become symptomatic or test positive at the 14 day threshold.[84] Gender did not appear to have a role in influencing the incubation period times.[56,60,64] In some research, children had longer incubation periods than adults, but adults have had an age-progressive increment in incubation periods.[58,60,63,64,69,73] Yang et al.[61] did not find age-related differences in contrast. The incubation period may appear to change over the course of the epidemic period.[40,60] For example, it may increase with each generation of spread.[83] Some have found no difference in incubation periods for those with mild or severe illnesses.[72] Yet others have proposed shorter incubation periods for those with more severe or prolonged eventual illnesses.[27,54]

China compared with other countries

The majority of studies relating to incubation period have emanated from China or have used data publicly available from Chinese sources. In the SARS era, a difference in incubation periods for different countries was suggested by Cowling et al.[32] Another concern is that some or most data acquired in countries outside of China actually rely on patients having likely acquired the infection from travel to early Chinese endemic regions.

One study suggested that the incubation periods cited from China were cumulatively longer than those from other countries.[19]

Table 1
Individualized estimates of the incubation period from countries excluding or not exclusively China.

Country	Samples	Mean	Median	95% CI	Interquartile	Percentiles					Reference
						2.5	5	95	97.5	99	
Argentina	18	7.9		4.6–11.1							66
Asia (several countries)	687	7.0	6	6.7–7.3		1.0			17.0		38
Brunei	135		5		1–11						67
India	268	6.9		6.1–7.8			1	17.8	19.3		28
Hong Kong	100	4.2		4–4.5			1.3	14.0	17.6		54
Saudi Arabia	309		6								68
Singapore	164	5.5	5	5.2–5.9							69
Singapore	93	4.9		4.4–5.7							40
South Korea	35		2.9	2.3–3.5							33
South Korea	47		3.0	0.6–8.2							56
Taiwan	55		6	1–13							36

CI = confidence interval; mean, median, confidence intervals, and percentiles are expressed in days.

In examining Tables 1 and 2, however, and now with more data, the estimated average incubation period is remarkably similar between China and other pooled countries.

Inside and outside Wuhan district

Although there are many studies emanating from China, it has been unclear at times as to how much of the data from different studies has been partially duplicated. Likewise, for studies outside of China, some have extrapolated on the basis of public data which again may not make amendments for duplicate data sets even if only partial.

Yang et al.[61] make a distinction of incubation periods for those patients infected locally or imported to Wuhan. Gao et al.[71] also found considerable variation for patients with or without Wuhan connections. Leung describes the incubation period to be longer and statistically more volatile among those with no travel to Hubei province.[59]

Other features of the incubation period

Cowling et al. proposed that incubation times for SARS could be different among various occupations but especially in reference to healthcare workers versus the general population.[32] Any such difference has not been confirmed for COVID-19. Conceptually, such differences, if they occurred, could be potentially ascribed to variable factors of transmission such as infecting dose, route of transmission, or number of infectious contacts. On the other hand, such an observation by chance alone cannot be excluded.

Practical considerations and future needs

The incubation period for COVID-19 is longer than many other common virus respiratory illnesses. There are several inconsistencies in data collection that have potential for estimates to be varied. Among the most important such variables are the contact period, asymptomatic excretion and transmission, the interval

Table 2
Individualized estimates of the incubation period from China.

Locale	Samples	Mean	Median	95% CI	Interquartile	Percentiles					Reference
						2.5	5	95	97.5	99	
Outside Wuhan	88	6.4		5.6–7.7		2.1	2.7	10.3	11.1	11.9	57
Shenzhen, Guangdong	183	4.8		4.2–5.4			1.6	14.0			70
Changsha, Hunan	149	7.48	7		4–10						27
Shiyan, Hubei	180	6.5	5.1	5.4–6.7		1.2		14.3		18.7	58
Wuhan centric	1211		8.5	7.2–9.2				14.6		21.2	62
Beijing	62		4.5								71
Mainland China	1099		4		2–7						72
Mainland China	85 (pediatric)		9		6–13						73
Shanghai	10		6		3.5–9.5						35
Outside Hubei	136		8.3	7.4–9.2			2.3	(90%ile 14.2)			63
Outside Wuhan	111	5.1		4.5–5.8		2.2			11.5		55
Hubei and non-Hubei	175		1.8	1.0–2.7				3.2			59
			7.2	6.1–8.4				14.6			
Wuhan	425	5.2		4.1–7.0				12.5			74
Outside Wuhan	158	5.6	5.0	5.0–6.3				10.8		14.2	75
Jilin	87	10.4			(range 2–25)						76
Mainland China	1158		7.2	6.9–7.5					15.1	18.7	60
Outside Hubei	59	5.8	5.0	5.1–6.6		2.7			12.9		64
Outside Wuhan	1084		7.8	7.2–8.5				(90%ile 14.3)			65
Outside Wuhan	104		6								77
Outside Hubei	98	5.3		4.6–6.0				11.1		16.1	39
Mainland China	24		4.2	3.5–5.1							78
Wuxi, Jiangsu	46	4.8		3.6–5.9				12			79
Tianjin	135	7.5		6.8–8.6							40
Outside Hubei	106	4.9		4.4–5.4		0.8	1.1	9.9	11.1	12.5	80
Shiyan, Hubei	178	5.4		4.8–6.0		1.1		13.7	15	17.8	61
Shanghai	132		7.2	6.4–7.9				16.0		20.4	81
Dequan	18		8		4–12						82
Sichuan	77	7–10			2–15						83

CI = confidence interval; mean, median, confidence intervals, and percentiles are expressed in days.

between the latent and classic incubation periods, and potential prolonged excretion of live virus. As such, calculations based on time to symptoms versus time to first live virus excretion can lead to ambiguity.

In essence, there are two versions of 'incubation period' to consider. The first is the classic definition of contact to first clinical symptomatology. The second is that of contact to first live virus excretion. For the purposes of quarantine and infection control, the most important version is the latter which then provides substance to veritably define infectivity (i.e., from first live virus excretion to end of live virus excretion).

The right-hand tail of distribution is of concern due to its inherent variability and especially for COVID-19. Studies cumulatively suggest that a small but important percentage of individuals may have an incubation period that exceeds 14 days. Whereas the 14 day incubation period has been most widely adopted, some would propose a practical curtailment of the same with risk mitigation strategies.[85,86] The latter would certainly increase the potential for secondary spread although variably so and perhaps minimally so.[87] Mathematical models to predict such mitigating interventions rely on existing data.[88,89] Where implementation is possible, however, the prolongation of the late incubation time to up to 21 days has some appeal. As such, the 'right tail' takes on a double meaning. Research is further required to examine the right-handed skew of the incubation period distribution. Research is further required to examine the right or appropriate statistical fit(s) for that prolonged distribution.

From a strictly fundamentalist viewpoint, the longer the incubation period definition for interval, the more disease prevention that may be had especially for outliers within that distribution. From a pragmatic perspective, prolongation of the right-hand confine will place burden on patients and medical staff for segregation.[86] The risk-benefit for defining incubation periods and their application is complex and very much dependent on societal needs, public health needs, and healthcare worker availability. The latter juxtapositions are only more so evident when given the considerable patient numbers and massive healthcare exposures in some jurisdictions.[7] The maintenance of strict standards for many individuals thereafter engenders difficulty at times with compliance and real-life application. Failed compliance thereafter has the potential to jeopardize control more than the change in working application of the incubation period.[86]

Better data are still yet welcome since it is reasonably conceivable that SARS-CoV-2 will become the fifth of the common endemic respiratory coronaviruses.[2] In the interim, for patient populations where the numbers of infections is very low and where resources are available, the adherence to a wider incubation time has considerable merit given that an abundance of caution has the ability to contribute towards maintaining the numbers of new infections low. There is merit to driving the virus to extinction provisionally in regions of low endemic status. For those populations where infection rates are quite high, longer incubation periods would be useful to maintain, but potentially very impractical to enforce especially for limited healthcare worker availability. In the latter context, innovative and adaptive strategies for society and healthcare worker integration may be requisite. The definition of incubation period however should be no different on a scientific basis but would be practically amended with added precautions to achieve a working solution. In effect, one would scientifically determine a more accurate and protective incubation period, but practical application in complicated circumstances would allow one to work backwards as the context demands and as the populace can understand. Even when effective vaccines may be widely used, the importance of the incubation period in further control will remain highly relevant and continues to deserve our attention. Given human nature, it is inevitable that vaccination applications of highly but partially protective products will create consternation for infection control procedures that should accompany the same.[90] Society will likely be faced with convoluted paradigms for protecting the remaining susceptible populations. All of the latter is likely to change over time as immunity varies with or without vaccine or natural infection.[91] The prospect of repeat infections adds further concern as SARS-CoV-2 has the potential to become permanently endemic.[2,91,92] In the interim, clear definitions of central epidemiological principles are warranted.

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