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REVIEW ARTICLE

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COVID-19: Filling the Gaps in the Natural History of the Disease for Controlling the Pandemic

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Abstract

The Global pandemic of novel coronavirus disease 2019 (COVID- 19) caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome- Corona Virus -2) is progressing on an unprecedented scale. The WHO declared the novel coronavirus outbreak (2019-nCoV) as Public Health Emergency of International Concern (PHEIC) on January 30,2020 and it was further declared as a Pandemic on March 11, 2020. Gaps in the natural history of the disease to delineate accurately the longest incubation period, period of quarantine, the period of communicability, isolation period, chances of re-infection , immunity after infection, the time kinetics for viral clearance and its association with clearance of symptoms, the role of asymptomatic infection, modes of transmission needs to be addressed to control the pandemic. In order to halt a pandemic, setting up of a suitable quarantine period is essential by investigating incubation periods, so that at least 95% of the cases developing symptoms could be captured and henceforth control of pandemic becomes viable. This 14-day quarantine period does not seem to cover the incubation period of 95% of known cases. The number of subjects missed by using the mean or median incubation period should be explored and considered while making policy decisions. When the serial interval is less than the mean or median incubation period, it implies that the transmission could have occurred during the incubation period. The knowledge about the transmission dynamics, proportion of asymptomatic cases and the period of communicability in asymptomatic cases is very limited. The pandemic shows no signs of slowing down and the development of an effective vaccine seems far way. Hence filling the gaps in the natural history of this virus is essential for battling the pandemic.

Key word: Novel coronavirus disease 2019, COVID- 19, SARS-CoV-2, Quarantine, Period of communicability, 95th percentile of incubation period, Serial interval.

INTRODUCTION:

The Global pandemic of novel coronavirus disease 2019 (COVID- 19) caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome- Corona Virus -2) is progressing on an unprecedented scale. As on May 30, 2020, 10 am CEST (Central European Summer Time) ,1.30 pm IST (Indian Standard Time) , there have been 5,817,385 confirmed cases of COVID-19, including 362,705 deaths globally, reported to WHO and 1,73,763 confirmed cases of COVID-19 with 4,971 deaths in India reported to WHO.[1] Several countries in the world have been locked down for months and are being unlocked in a phased manner. In 2019 December, several cases of pneumonia of unknown origin were reported from Wuhan province in china.[2, 3] Later the cause of this viral pneumonia was identified as a type of coronavirus and was named as 2019-novel coronavirus (2019-nCoV) by the WHO and the disease as coronavirus disease 2019 (COVID-19) On 11 February 2020.[4, 5] Then the virus was named as SARS-CoV-2 by the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of viruses.[6] Although most of the cases were initially linked to a wholesale sea food market in Wuhan province in china in December 2019, later human to human transmission became more evident.[2, 7-9] The WHO declared the novel coronavirus outbreak (2019-nCoV) as Public Health Emergency of International Concern (PHEIC) on January 30,2020 and it was further declared as a Pandemic on March 11, 2020.[10] With several gaps in the natural history of the disease, the pandemic shows no signs of slowing down. The development of an effective vaccine also seems far way. Gaps in the natural history of the disease to delineate accurately the longest incubation period, period of quarantine, the period of communicability, isolation period, chances of re-infection , immunity after infection, the time kinetics for viral clearance and its association with clearance of symptoms, the role of asymptomatic infection, modes of transmission needs to be addressed to control the pandemic.[11, 12] In this editorial review, these gaps which need to be addressed are being stressed in order to get the attention of the medical community and policy makers for prioritization of research in these fields.

GAPS IN INCUBATION PERIOD AND QUARANTINE:

The Incubation period is defined as the time taken from infection or identifiable exposure to onset of the illness.[13] Understanding this concept of incubation period is essential in determining the Quarantine period.[14, 15] Thus, this time period is used effectively to control outbreaks of covid-19 by restricting the movement of those apparently healthy contacts who were exposed to cases . [14, 15] In order to halt a pandemic, setting up of a suitable quarantine period is essential by investigating incubation periods, so that at least 95% of the cases developing symptoms could be captured and henceforth control of pandemic becomes viable. A clear knowledge of the incubation period of an infectious disease and its characteristics is essential in designing public health measures such as monitoring of active cases, their contacts and modelling for measures such as lockdown. The Incubation period also goes a long way in estimating the basic reproduction number (R0) and in understanding the relative infectiousness of the disease.[13, 16, 17]

Quarantine is "the restriction of the activities of asymptomatic persons who have been exposed to a communicable disease, during or immediately prior to the period of communicability, to prevent disease transmission".[18, 19] Quarantine is different from isolation, which "is the separation, for the period of communicability, of known infected persons in such places and under such conditions as to prevent or limit the transmission of the infectious agent".[19-21] According to WHO, the contacts of laboratory-confirmed COVID-19 patients should be quarantined for at least 14 days from the date of exposure to the patient.[20]

According to WHO[20], for the purpose of quarantine,

"a contact is a person who is involved in any of the following from 2 days before and up to 14 days after the onset of symptoms in the patient:

1. Having face-to-face contact with a COVID-19 patient within 1 meter and for >15 minutes;
2. Providing direct care for patients with COVID-19 disease without using proper personal protective equipment;
3. Staying in the same close environment as a COVID-19 patient (including sharing a workplace, classroom or household or being at the same gathering) for any amount of time;
4. Travelling in proximity with (that is, within 1 m separation from) a COVID-19 patient in any kind of conveyance;
5. And other situations, as indicated by local risk assessments".

But this 14-day quarantine period does not seem to cover the incubation period of 95% of known cases. In a hospitalized cohort study, Jiang X et al[22] found that the incubation period ranged from 0 to 33 days among 2015 cases with a median incubation periods of 7-days in adults and 9 days in children. 11.6% (n=233) of the cases had incubation period longer than 14 days implicating that WHO quarantine period could capture only 88.5% of the subjects developing Covid-19. But 98.3% of the cases could have been captured if a quarantine period of 21 days had been introduced. They also observed that based on data modelling, 94.8% of cases could have been captured with a 17 day quarantine period.[22] Lauer SA et al[23] in their study observed that the median incubation period was 5.1 days with 95% C.I. of 4.5 to 5.8 days. They also observed that of symptomatic subjects, 97.5% developed symptoms within 11.5 days with 95% C.I. of 8.2 to 15.6 days. Based on their estimates, out of every ten thousand cases, 101 will develop symptoms after 14th day of quarantine.

Although mean incubation period is less than 14 days in all the known studies, many studies have failed to consider the number of subjects missed by using the median or mean incubation period. Guan WJ et al[24] found that among 1099 patients in their study, the median incubation period was 4 days with interquartile range of 2 to 7 days. Backer JA et al[25] found that among 88 travellers from Wuhan, China the mean incubation period was 6.4 days with 95% confidence interval (C.I.) of 5.6 to 7.7 days. They also observed that in subjects with closed exposure window, the mean incubation period was further shortened to 4.5 days (95% C.I. of 3.7 to 5.6 days). Liu T et al[26] observed a mean incubation duration of 4.8 ± 2.6 days with range from 2 to 11 days among 830 cases in Wuhan, China. But Linton NM et al[13] in their study observed that the incubation period falls within the range of 2–14 days with 95% confidence with a mean of 5 days. Similarly, Li Q et al[7] also observed that among 425 subjects, mean incubation period was 5.2 days with 95% C.I. of 4.1 to 7 days but in their study also, the 95th percentile of the distribution was 12.5 days with 95% C.I. of 9.2 to 18 days. Based on these published studies, the average incubation period was around 5 to 7 days and 14 day Quarantine period captured around 90% of population developing COVID-19.[13, 22-26] If the quarantine period had been increased to 21 days, more than 95% of the population developing COVID-19 could be captured.[22] These studies were comparable to SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East respiratory syndrome) epidemic studies.[27-31]

GAPS IN ORIGIN AND PATHOGENECITY:

2019 novel coronavirus is sufficiently different from the SARS coronavirus to the extent that it can be considered as a new human infecting beta coronavirus belonging to subgenus Sarbecovirus.[32] Even though bats are the original hosts as recorded in the literature[33], phylogenetic analysis has revealed that there could have been-

Table 1: Mean Incubation period and 95th percentile of incubation period reported from various epidemic studies:

Author	Agent	Sample size	Mean Incubation period in days*		95th percentile of incubation period in days*	
			Mean	95% C.I.	95th percentile	95% C.I.
Backer JA et al[25] (2020)	2019-novel coronavirus	88 (travellers from wuhan, china)	6.8	5.7 to 8.8	13.3	9.9 to 20.5
Virlogeux V et al[31] (2016)	MERS-coronavirus	115 (south korea)	7	6.3 to 7.7	13.7	11.9 to 16.1
Virlogeux V et al[31] (2016)	MERS-coronavirus	34 (Saudi arabia)	5	4.0 to 6.6	11.4	8.5 to 17.5
Assiri A et al[29] (2013)	MERS-coronavirus	23 (eastern province of Saudi Arabia)	5.2 (median)	1.9 to 14.7	12.4	7.3 to 17.5
Cowling BJ et al[28] (2007)	SARS-coronavirus	317 (149 from Toronto and 168 from Hongkong)	5.1	4.6 to 5.5	12.9	11.7 to 14.5

(Table idea adopted from Backer JA et al[25]) ***Based on lognormal distribution**

intermediate hosts like the animals which were sold in the seafood market at Wuhan enabling the virus emergence in human beings.[32] There is a clear missing link which is not evident with regards to the intermediate host as coronaviruses and bats have been evolving together for millions of years. The greater the severity of symptoms in COVID-19, the number of deaths is also high.[34, 35] The time to death and progression to death is also not consistent.[36] This gap is hindering us from providing lifesaving treatments.

GAPS IN TRANSMISSION DYNAMICS - PERIOD OF COMMUNICABILITY, MODES OF TRANSMISSION AND SERIAL INTERVAL:

The definitive period of communicability for COVID-19 is not known at this time. Isolation is done for the period of communicability. Rothe C et al[37] had observed very early before the declaration of pandemic that there is potential transmission during the incubation period and the infection can be transmitted from pre-symptomatic subjects or subjects in their incubation period. The time taken from onset of symptoms in the primary case to the time of onset of symptoms in their contacts is called the serial interval. When the serial interval is less than the mean or median incubation period, it implies that the transmission could have occurred during the incubation period. Several studies have observed a serial interval of less than 5 days.[16] The median serial interval was around 4.6 days with 95% C.I. of 3.5 to 5.9 days in the study by Nishiura H et al.[16] Du Z et al[38] in their study on 468 confirmed cases observed that the mean serial interval was 3.96 days with 95% CI 3.53 of 4.39 days. They also observed that in 12.6% of their cases, there was pre-symptomatic transmission. The knowledge about the transmission dynamics and the period of communicability in asymptomatic cases is very limited. It was estimated that about 17.9% (95% C.I. of 15.5% to 20.2%) of the infections were asymptomatic based on the model of Diamond Princess cruise ship.[39] Asymptomatic subjects also pose a threat similar in potential to symptomatic subjects as the viral load in asymptomatic subjects has been in comparable proportion to symptomatic patients or minimally symptomatic patients as observed by Zou L et al.[40] Although reports from various media claim the incidence of asymptomatic infections to be more than 80%, there are no well documented studies to support this fact. Hence there is a need for large scale multi-centric studies to determine the prevalence of asymptomatic COVID-19 infections so that resources for pandemic control efforts can be properly utilised. There are no well-defined studies to our knowledge to support the possibility of re-infection after recovery. It has been reported that shedding of viral RNA drops with resolution of symptoms but may remain for days to weeks.[40, 41] But it does not mean the patient is infectious as clinical recovery has been correlated with the development of immunity. This could have been misinterpreted as re-infection.

Although being largely depicted as a respiratory disease with respiratory droplets as the primary mode of transmission, chances of feco-oral transmission have been also reported in studies across the world. But the precise mechanisms by which SARS-CoV-2 interacts with the gastrointestinal tract remains unknown. [42-44]

There is also uncertainty regarding the role of 'super-spreaders' in the transmission and this term is not very well defined. These people have greater than the usual inclination in infecting a huge number of susceptible people like Typhoid mary.[45, 46] But these terms can lead to undeserved moral blame or they can hide the heterogeneity in transmission or a missing link.[46]

The reproduction rate, or Ro (pronounced R-naught), of a virus measures the average number of new infections generated by each case. Ro of 1, means on average each infected person will infect one other person they come in contact. Ro >1 means transmission is exponentially increasing overwhelming healthcare systems. Ro <1 means transmission is decreasing or subsiding.[47] During the fast-spreading initial outbreak of the coronavirus in Wuhan, China, the reproduction rate was estimated at around 2 to 2.5, according to WHO.[48] There are no well-established studies in India to estimate the Ro. There is a clear correlation between the trajectory of the number of cases and the projected Ro. Ro can helps us in determining the effectiveness of pandemic control activities and give a clue about achieving herd immunity, in case if it is viable. Breaking the chain at the 'mode of transmission' is one of the most important ways to interrupt the spread of infection. The findings of a systematic review of 172 studies (44 comparative studies; n=25697 patients) on COVID-19, SARS, and MERS provide the best available evidence that current policies of at least 1 m physical distancing are associated with a large reduction in infection, and distances of 2 m might be more effective.[49] These data also suggest that wearing face masks protects both health-care workers and the general public against infection and that eye protection could confer additional benefit.[49] But their compliance remains to be questioned in the long run and may be only a temporary solution till the vaccine is made available. Dynamic disease transmission models incorporating periods of lockdown and factors such as social distancing need to be evaluated beyond the commonly used SEIR models (Susceptible, Exposed , Infectious, Recovered).[50] Hence filling the gaps in the natural history of this virus is essential not only for battling the pandemic but also for deciding the time of administration of vaccine in relation to exposure.

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