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Silent transmission of "COVID-19": A major concern

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ABSTRACT

"Coronavirus disease 2019 "(COVID-19)" has been proclaimed as a public health exigency of global scope by "World Health Organization" and is the latest threat to universal health. Despite of manifesting imperceptible clinical symptoms, asymptomatic carriers of the disease are known to be infectious. The prevalence of "COVID-19" is rising persistently, despite meticulous global confinement and quarantine endeavors. An important element in the devastating transmissibility potential of "COVID-19" is the high titre of virus in oropharynx in the initial progression of disease. On the contrary influenza virus has low titres in upper respiratory tract than lower respiratory tract. Therefore, making the symptom-based assessment strategies less effectual in case of "SARS-CoV-2" According to recent reports, symptomless population along with the individuals with mild disease, are radical transmitters in the proliferation of "COVID-19". The phenomenon of Viral shedding emphasizes the reasons of asymptomatic patients being rapid transmitters in "SARS-CoV-2" than "SARS-CoV-1". The significant role of incubation span, cycle threshold values, serial interval cannot be overlooked in asymptomatic transmission. This pandemic is an absolute reminder of the existing challenge posed by the virulent pathogen on modern medicine. Thus, we intend to comprehensively elaborate various outlooks on the asymptomatic spread of "SARS-CoV-2", including the pathophysiology, viral shedding, cycle threshold, serial interval, incubation span, herd immunity, inefficient testing, prevention and prospective treatment of "COVID-19".

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INTRODUCTION

"COVID-19", a proclaimed public health exigency by "World Health Organization" (WHO) is the latest scare for universal public health. Its inception was in the month of December 2019. These cases were related to "Wuhan Huanan Seafood Wholesale Market" that trades in freshly butchered game animals, which were the primary contagion originator (Fauci *et al.*, 2020). According to the present data, the game animals were presumably intermediary hosts of the "SARS-CoV-2" that emanated from "Chinese horseshoe bat" (Ye *et al.*, 2020). This virus is constitutionally analogous to the virus that provokes "Severe acute respiratory syndrome (SARS)." In comparison to "SARS" and "Middle East respiratory syndrome (MERS)", that are two anteceding occurrence of emergencies caused by coronavirus, the "COVID-19" pandemic has given rise to perilous challenges for global health, medical and research fraternities (de Wit *et al.*, 2016). Most of the "COVID-19" sufferers manifest vague symptoms like fever,

dry cough, and sore throat and have recovered successfully. However, some of the patients have been in critical condition and eventually demised. Some of the fatal complications that these patients suffered from are "pulmonary edema, severe pneumonia, organ failure, septic shock and Acute Respiratory Distress Syndrome (ARDS)" (Kumar *et al.*, 2019; Tayde and Kumar, 2013). The prevalence of "COVID-19" is rising persistently, despite of meticulous global confinement and quarantine endeavors (Sohrabi *et al.*, 2020). According to reports, it has been advocated that a considerable amount of "COVID-19" positive cases had very mild or no symptoms at all. In spite of the fact that these patients are asymptomatic, they are as contagious as the ones with symptoms. Thus, this sub-population is a paramount contributor in the spread of "COVID-19", since it often eludes exposure by public health surveillance systems (Aguilar *et al.*, 2020).

Pathophysiology

"SARS-Cov-2" belongs to Beta-coronavirus family, which mainly infects the lower respiratory tract and evinces in the form of pneumonitis in human beings. "SARS-CoV-2" binds with the Angiotensin Converting Enzyme 2 (ACE2) receptors via surface glycoprotein S, which has an affinity towards the respiratory epithelium. These ACE2 receptors have similar characteristics to that of receptors present in "SARS". The lab corroboration of "COVID-19" is done by "real-time reverse transcription-polymerase chain reaction (rRT-PCR)," which indicates existence of "SARS-CoV-2 nucleic acid" (Chen *et al.*, 2020b). As per current figures, mortality rate identified with "COVID-19" patients is approximately 6.17% worldwide. At present, there is a lack of precise antiviral therapy or vaccines to fight against "COVID-19", even though certain drugs such as hydroxychloroquine are under exploration.

Course of Spread

Not many studies explain the pathophysiology of "COVID-19", thus there is quandary concerning its escalation mechanism. Other viruses similar to "SARS-CoV-2" transmit within individuals via respiratory fomites. Classically, patients with symptoms are the ones who have the most contagious respiratory virus. But, as suggested earlier, reports have proven that the viral transmission also occurs throughout the symptomless incubation phase of "COVID-19". This stretch has been approximated to be betwixt 2-10 days (Rothe *et al.*, 2020; Li *et al.*, 2020b). Interhuman transference of "SARS-CoV-2" transpires mostly between close friends and family having an intimate exposure with patients and asymptomatic carriers. A significant transmission has also taken place among healthcare workers. In contrast to the "SARS-CoV-2" transmission, the transferal of "SARS-Cov" and "MERS-CoV" chanced predominantly via nosocomial route. However, the deduced prime course of "SARS-CoV-2" spread is direct exposure to intermediary host animals (Guo *et al.*, 2020).

The foremost occurrence was recognized in Wuhan city, China and the disease did not require much time to spread to other parts of China. Further propagation of the disease occurred globally involving "European Region, Region of the Americas, Western Pacific region, Eastern Mediterranean Region, South-East Asia Region and African Region." Top ten countries most affected by the pandemic are "United States, India, Brazil, Russia, Peru, Columbia, Mexico, South Africa, Spain and Argentina.

Rapid Asymptomatic Transmission

The confinement and alleviation strategies have a huge impact on the efficiency of transmission of any respiratory virus. Strategies similar to the ones that were successful in controlling SARS in 2003 were implemented during the initial "COVID-19" outbreak, which includes detection based on symptoms and ensuing investigation leading to patient isolation or quarantine. This stratagem was implemented looking at the resembling features of "SARS-CoV-1" and "SARS-CoV-2" such as prominent gene association, similar incubation period, course of transmission via droplets and lower respiratory tract infections exhibiting symptoms of pyrexia, cough and breathlessness. In spite of similar control strategies, the ambits of these outbreaks have swerved in substantially different directions (Gandhi *et al.*, 2020). An important element in the devastating transmissibility potential of "COVID-19" is the high titre of virus in oropharynx in the initial progression of disease, thus making the symptom-based assessment strategies less effectual in case of "SARS-CoV-2" in comparison to "SARS-CoV-1" (Fauci *et al.*, 2020; Gandhi *et al.*, 2020). In case of influenza, asymptomatic patients have lower perceptible viral titres in upper respiratory tract secretions in contrast to those from lower tract and a brief span of viral shedding than symptomatic individuals, thus reducing the risk of spread from patients presenting few symptoms (Gandhi *et al.*, 2020).

Viral shedding and cycle threshold

The RT-PCR assays are conducted to check for the presence of "SARS-CoV-2 RNA" in "nasopharyngeal swab specimens", assembled following the WHO specifications. The collected samples are computed and the outcomes are manifested in the form of

"cycle threshold value (Ct value)", which can be described as "the number of cycles required for the fluorescence signal to cross the threshold (i.e. exceed the background level)." Outcomes are reckoned positive if Ct-value of the N gene is $\leq$40, where, lesser "Ct values" evince a higher viral load. According to a study by Rui Zhou et al, the "median Ct-value" of patients that remained asymptomatic throughout the hospitalization (APs) was significantly higher than that of the asymptomatic patients in incubation (presented symptoms after admission) (APIs), suggesting a lower viral load in the first group. In spite of the decreased viral load of the APs, the period of viral shedding endured alike in the two groups, proposing the probability of transference during the asymptomatic span of the APs (Zhou *et al.*, 2020). Xi et al, suggested that "SARS-CoV-2" shedding may commence 2-3 days preceding the manifestation of the first symptoms, that is, soon after the outset of symptoms, viral titres dropped uniformly (He *et al.*, 2020; Zou *et al.*, 2020; To *et al.*, 2020). Another study that accounted for prompt disease transferal in a cluster of young adults outside Wuhan, Lei et al concluded that "SARS-CoV-2" infection demonstrated dynamic pathogenicity throughout the incubation phase thus providing a rational evidence substantiating effective asymptomatic spread of the disease (Huang *et al.*, 2020). Hence, Asymptomatic individuals render a critical part in the transference of "SARS-CoV-2", as symptom based diagnosis solely has lacked detection of a high percentage of contagious cases which was not sufficient to contain the spread (Gandhi *et al.*, 2020; Arons *et al.*, 2020).

Serial Interval and Incubation span

The potency of regulation strategies is based on various epidemiological variables such as, the "serial interval (time between symptom onsets of successive cases in a transmission chain) and the incubation span (duration between infection and onset of symptoms)" (He *et al.*, 2020). The approximated median serial interval for "SARS-CoV-2" is four days, which demonstrates meteoric phases of transference from one cohort to another. This interval is brief in comparison to the serial interval for "SARS", inferring that contact tracing methods must be efficient enough to suffice against the expeditious expansion of the disease. More significantly, the shorter median serial interval is seen as compared to the mean incubation period of approximately five days (Li *et al.*, 2020b; Linton *et al.*, 2020). As illustrated in Figure 1, if the deduced median serial interval is shorter as compared to the mean incubation period, it signifies that a considerable fraction of transference could have transpired prior to the development of symptoms (Nishiura *et al.*, 2020b). A considerable segment of secondary transmission taking place prior to illness outset denotes that several transmissions can seldom be averted merely via seclusion of symptomatic cases. This is because the patients might have already become contagious themselves and engendered secondary cases before contact tracing (Fraser *et al.*, 2004; Nishiura *et al.*, 2020a). If the spread occurs within the symptomatic term of the primary case, the serial interval is prolonged than the incubation period. This association can be inversed when pre-symptomatic spread occurs. Additionally, it is likely that the secondary case may sustain symptom activation ahead of the outset in their infector (Nishiura *et al.*, 2020a).

Herd Immunity

There are two ways of evincing "acquired immunity" at the individual level: naturally through pathogen infection or immunization via a vaccine. Herd immunity is fortified when an individual's immunity gets appraised to an extent that it protects non-immune individuals. It is the oblique protection from illness accorded to amenable individuals when an adequately greater segment of individuals with immunity prevails in population. The concept is usually supposed to be in relation to vaccination programs, that intend to evince herd immunity such that the ones who cannot be vaccinated, are yet protected from the infection (Randolph and Barreiro, 2020). The juncture of descend of distribution of susceptible individuals beneath the edge required for spread is identified as "herd immunity threshold." Beyond this herd immunity begins, and the amenable people are benefited through oblique safeguarding from illness as depicted

The edge of the "herd immunity" pivots on basic reproduction number (R_o). This cites to the tally of cases engendered by affected person in a populace where all people are prone to infection (Anderson and May, 1985). According to the study records, Ro of "SARS-CoV-2" is valued to be about 2.2, varying from 1.4 to 6.5. This infers that on an average, every unique diseased person spreads the virus further to two individuals, taking into assumption, no immunity persists in the populace (Holshue *et al.*, 2020; Zou *et al.*, 2020). Statistically, the "herd immunity" threshold is denoted by "1-1/R_0", which infers that the more contagious an infectant, the larger its corresponding R_0 and the larger are the number of people that must be resistant in order to obstruct prolonged transmission. R_0 is explained by both the infectant and the particular populace in which it propagates. Therefore, according to the attributes and transference dynamics of the cohort encoun-

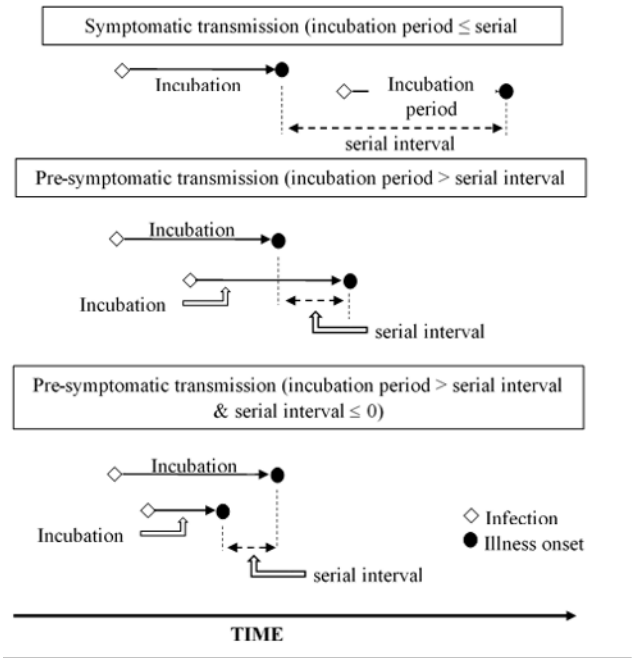

Figure 1: The correlation between incubation period and serial interval

tering the outbreak, a single contagion may have numerous R_0 values. This intrinsically suggests that the "herd immunity" edge will differ within the populace. Another akin variable significant for acknowledging herd immunity is the "effective reproduction number (R_e or R_t), defined as the average number of secondary cases generated by a single index case over an infectious period in a partially immune population." (Delamater *et al.*, 2019). This R_e does not presume an entirely vulnerable populace and, hence, will differ as per the present immune state of the populace, which will undergo a dynamic reform with the occurrence of an epidemic or vaccination campaign. Eventually, the aim of immunization campaigns is decimation of R_e less than one. It takes place when cohort percentage of immunity transcends up to "herd immunity" threshold, thus making it difficult to maintain the disease spread, resulting in a downfall in the numbers of diseased individuals within the populace. Though the clinical trials oriented to assess the effects of vaccine and various drug therapies for "SARS-CoV-2" are ongoing, but until the trial is completed whether it will foster effective results or not is questionable. Without a vaccine, acquiring "SARS-CoV-2 herd immunity" naturally remains conceptual as there is no elementary, ethical approach to accomplish this objective.

Inefficient Testing

Another barrier in the elimination of "COVID-19" is inefficient testing. Most of the qPCR assays involve a Ct cutoff of 40 to contemplate the test positive, enabling evaluation of very few starting RNA molecules. This high sensitivity for viral RNA can be helpful for initial diagnosis. However, reporting as a binary positive or negative result removes useful information that could inform clinical decision making. As per Xiao et al., even after the complete cessation of the symptoms, the test results might come positive for extended duration, maybe for weeks. Hence, prolonged positive "SARS-CoV-2" RT-qPCR results raise questions about the sufficiency and sustainability of current isolation guidelines (Tom and Mina, 2020).

Prevention and Treatment

A high mortality insists that the traditional approach needs to be changed, especially for the protection of communities at risk until alternative prophylactic measures such as a vaccine are obtainable. Guidelines on prevention of further propagation of "COVID-19" have been issued by various associations including "World Health Organization and US Centers for Disease Control and Prevention (CDC)." These include, refraining from travel to susceptible areas, avoiding proximity with persons who show symptoms and abstaining from consumption of meat from localities with notable COVID-19 flare-up. Ensuring fundamental hand sanitation standards, such as regular and thorough cleansing of hands using alcohol-based hand rub or washing them with soap and water for no less than 20 seconds. Asymptomatic spread of "SARS-CoV-2" can be contained by mass screening of the residents in vulnerable areas, which would enable pertinent isolation of the infected individuals and quarantine of the

exposed individuals (Gandhi *et al.*, 2020). Containment and mitigation strategies render a pivotal role in the reduction of transference of "SARS-CoV-2". Such strategies include social distancing and quarantine, isolation of ill persons, school closures, closure of congested places, and telecommuting where possible. WHO has recommended maintenance of at least 1-meter distance from any person that manifests symptoms of coughing and sneezing and utilization of PPE such as face masks to the persons with as well as without symptoms.

Currently, no successful antiviral vaccination is obtainable against "SARS-CoV-2". Though, vigorous endeavors are currently in progress to commence a vaccine against "SARS-CoV-2". The ongoing therapy is mainly concentrated on symptomatic and respiratory support while copious investigational approaches are being explored. To patients with refractory hypoxemia, "extracorporeal membrane oxygenation (ECMO)" has been recommended by WHO. Few critical patients were also administered plasma therapy and immunoglobulins G. Research is in progress regarding intravenous administration of hyperimmune globulin and monoclonal antibodies from recovered patients, which could give enticing prospects in prior treatment (Røsjø *et al.*, 2011; Liu *et al.*, 2020). Based on the experience of combating against the previous coronavirus epidemics "SARS-CoV" and "MERS-CoV", certain antiviral treatment strategies have been adapted. These include, "antiviral medications lopinavir-ritonavir, interferon-1β, RNA polymerase inhibitor remedesivir, chloroquine, as well as other medicines for symptomatic treatment." Verifying that the investigative products are assessed in well-organized and ethically sound bodies, is crucial, even in times of an emergency outbreak (Chen *et al.*, 2020a; Zumla *et al.*, 2016; Li *et al.*, 2020a).

CONCLUSION

According to the literature, "COVID-19" is a novel and occasionally lethal pulmonary illness, emanated in a live animal market in China that escalated expeditiously all through that country and further to the world, with cases now being reported throughout the world. It is an arduous task to contain the transference of "COVID-19" with such a widespread transmission spectrum. To avert the transmission of "COVID-19", quarantine alone may not be sufficient, and the worldwide ramification of viral infection is one of the aggravating concerns. More advanced research is definitely essential to determine the accurate mechanism of disease spread from "human-to-human and animal-to-human" in order to aid in establishment of the viral vaccine. "COVID-19" outbreak and its pandemic potential mandate the need of constant surveillance and an ongoing monitoring to trace and possibly anticipate its future culmination. This pandemic is an absolute reminder of the existing challenge of emergence of modern virulent pathogens, and the necessity for rigorous scrutiny to appreciate the fundamental mutation of the virus thereby rendering individuals more vulnerable. This does not culminate the need of investigating the asymptomatic transmission, which also has a larger impact on the community under the garb "COVID-19". However, as a healthcare fraternity, the responsibility increases and one should be well acquainted with the above mentioned signs and symptoms.

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Conflict of Interest

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