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Analysis of COVID-19 transmission: Low risk of presymptomatic spread?

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More than 6 million confirmed cases of COVID-19 (coronavirus disease 2019) have been identified worldwide and a number of case reports[1-5] have indicated that COVID-19 has the potential to be transmitted prior to disease onset. Studies have also shown that infectious virus can be isolated from presymptomatic COVID-19 cases[6] and although it is unknown what level of infectious virus is needed to confer efficient transmission potential, detection of infectious virus in the upper respiratory tract indicates that presymptomatic transmission of COVID-19 is plausible. Fear of asymptomatic and presymptomatic transmission of COVID-19 has led to considerable concern among public health policy makers, frontline healthcare workers and the public in general. In response, many city, state, and federal leaders have asked for increased testing via reverse transcriptase-polymerase chain reaction (RT-PCR) and serological assays in order to identify asymptomatic cases and potential spreaders. Individual case studies are important for bringing attention to this topic but they do not provide information regarding the overall proportion of transmission events that occur before or after symptom onset. A better understanding of COVID-19 transmission is needed to control this pandemic and although some recent studies have provided new insight, others have fueled increased concerns.

Recent modeling of 77 transmission pairs indicated that 34 instances (44%) of COVID-19 transmission occurred before symptom onset with peak transmission at 0.7 days before symptom onset[7]. This is an unusual outcome because most respiratory viruses, including influenza or Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), spread most efficiently at or after symptom onset and not before. There are also several limitations to this study. The model was not based on direct contact tracing but instead relied upon publicly available data sources and news media reports for determining presymptomatic vs. post-symptomatic exposures and transmission intervals. The authors noted that they used a previously published estimate of the COVID-19 incubation period that, if overestimated, had the potential to inflate the proportion of presymptomatic transmission. Sensitivity analysis of different incubation periods is currently underway (M.K. Slifka, L. Gao, unpublished data, 6/01/2020). Regardless of the study, clinical data based on personal recollection may be subject to recall bias. This may be

particularly important for COVID-19 transmission models if subjects are reluctant to admit they were travelling or not following proper precautions while symptomatic due to pandemic-associated societal pressure and fear of condemnation for their actions. Although it is unclear how these various factors may have impacted this particular study, review of other COVID-19 and SARS transmission studies provide an interesting counterpoint.

In contrast to He *et al.*[7], a study examining 468 confirmed COVID-19 cases in China indicated that only 59 (12.6%) of case reports resulted from presymptomatic transmission[8]. Although this study was also based on secondary data sources, they obtained reliable information from confirmed cases in online reports from 18 provincial centers for disease control and prevention. Perhaps the most convincing study on presymptomatic transmission of COVID-19 was performed in Singapore[9]. Direct contact tracing of 157 locally acquired cases indicated that just 10 (6.4%) of the cases occurred through presymptomatic transmission. Together these studies indicate COVID-19 transmission is 10- to 20-fold more efficient after symptom onset.

Asymptomatic transmission raises similar concerns for contact tracing/isolation procedures, but a study of 24 asymptomatic cases of COVID-19 found that only one asymptomatic carrier transmitted the virus to another person[10]. Bearing in mind that COVID-19 has a reproductive number (R_0) = 2-3 (meaning on average, one infected person transmits to 2-3 other people), the spread of virus by asymptomatic carriers appears very inefficient and may have an R_0<0.1 if this preliminary study is representative of asymptomatic cases among other groups. Similar results were observed with SARS. Of 669 close contacts to symptomatic SARS patients, 101 (15.1%) developed symptoms whereas when 363 others had close contact to SARS patients during the incubation period (i.e. presymptomatic), none (0%) developed symptoms[11]. Interestingly, most people are not effective at spreading COVID-19. A recent study found that the distribution of individual R_0 values was highly over-dispersed, with 80% of infections being caused by ~9% of cases[12]. There are many factors that may impact transmission efficiency

including duration of exposure, type of exposure/environment (indoor vs. outdoor, home vs. hospital, public transportation, etc.), role and timing of social distancing interventions, and age/health status of the infector as well as the infectee. Nevertheless, the various coronavirus studies described here indicate that if we focus on one parameter of transmission (pre-symptom vs. post-symptom onset exposure), we find that although presymptomatic transmission of COVID-19 is possible, it appears inefficient compared to transmission after symptom onset.

A common issue with analysis of COVID-19 transmission rates is the lack of consistent data collection and differences in symptom definitions. At a minimum, data collection should include symptoms such as fever, cough, sore throat, shortness of breath/difficulty breathing, headache, muscle pain, recent loss of taste or smell, and importantly, recollection of chills or night sweats since some individuals may not have directly measured fever during acute symptom onset. Location of exposure (if known) should also be documented when possible. One formidable challenge has been the lack of consensus on the definition of fever in COVID-19. For instance, the Centers for Disease Control and Prevention (CDC) defines COVID-19 fever as 38°C/100.4°F whereas fever was defined as 37.5°C/99.5°F in Wuhan, China[13]. Thus, an infected individual with a temperature of 37.8°C/100.0°F would be considered asymptomatic in one country and clearly symptomatic in the other. Even within the U.S., there is no consensus on the definition for COVID-19 fever. States such as Georgia, Ohio, and Pennsylvania use a cutoff value of 38°C/100.4°F, Texas uses 37.8°C/100°F, and other states including Minnesota and Delaware use 37.5°C/99.5°F for routine temperature screening[14]. Although no single definition for fever will be perfect in every circumstance, we propose using 37.5°C/99.5°F to increase the sensitivity for detecting mildly symptomatic COVID-19 cases at the earliest stages of disease onset. Since transient spikes in body temperature can occur for a variety of reasons (environment, physical exertion, etc.), specificity for detecting fever may be increased by re-testing positive subjects after 20-30 minutes of acclimation to confirm an elevated temperature if needed. In summary, coordinated development and standardization

of clinical criteria among countries, and even between different states and clinical research groups, will be necessary to reduce confusion in the field and improve the ability to compare and interpret COVID-19 study outcomes in the future.

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