National Centre for Infectious Diseases

ACADEMY OF MEDICINE SINGAPORE

College of Physicians

Position Statement from the National Centre for Infectious Diseases and the Chapter of Infectious Disease Physicians, Academy of Medicine, Singapore – 23 May 2020

Period of Infectivity to Inform Strategies for De-isolation for COVID-19 Patients

1. This joint paper by the National Centre for Infectious Diseases (NCID) and the Chapter of Infectious Disease Physicians, Academy of Medicine, Singapore, seeks to set out the current understanding of the infectiousness of persons with COVID-19 infection, from epidemiologic, clinical and microbiologic data, and thence to inform de-isolation strategies.

Overview of Causative Agent, Incubation Period, Symptomatology and Infectiousness

2. COVID-19 is caused by the SARS-CoV-2 virus, a beta-coronavirus which emerged in Wuhan, China in December 2019. The median period of incubation (infection till the onset of symptoms) is estimated to be ~5 days (range 2-14 days) [1]. The most common symptoms of COVID-19 include fever, dry cough, fatigue, shortness of breath, chills, sore throat, muscle aches, loss of smell, and headaches[2,3]. Initial estimates from China including a study of over 72,000 patients indicated an asymptomatic infection rate of about 1%[3], however growing evidence and increased testing indicates that a larger proportion of infected persons might remain asymptomatic and estimates of asymptomatic infection have been wide, ranging from 17.9% - 78%, depending on the context of the study[4,5]. For symptomatic cases of COVID-19, about 80% will remain mild and relatively well, whereas about 15% will develop more severe disease (mainly pneumonia) and about 5% may require critical care [3].

Epidemiologic Data for Period of Infectivity

3. In a study of 77 well characterised infector-infectee pairs in Hong Kong, it was estimated that the serial interval (duration between symptom onset of a primary case to symptom onset of its secondary case) of COVID-19 was 5.8 days (mean), with 7.6% of serial intervals distributed negatively (i.e. the infectee developed symptoms prior to infector), strongly implying pre-symptomatic transmission [6]. Assuming a median

incubation period of 5.2 days (based on other studies), the study estimated that the infectious period of SARS-CoV-2 started 2.3 days before onset of symptoms, peaking at 0.7 days, and declining within 7 days.

4. Another study of 100 COVID-19 infected patients and 2761 close contacts in Taiwan identified 22 paired index-secondary cases, and all 22 cases arose from contact with the index case within 5 days of symptom onset (22 of 1818 contacts, attack rate 1%) and none (0 cases from 852 contacts) arose from contact 5 days or after[7].

Microbiologic Data for Period of Infectivity and Viral RNA Shedding

5. Local data, based on an analysis of 766 patients, indicate that by day 15 from onset of illness, 30% of all COVID-19 patients are PCR-negative by nasopharyngeal swab, this rises to 68% by day 21 and 88% by day 28 and by day 33, 95% of all patients are negative by PCR (NCID data). While the duration of viral shedding[1] by PCR may extend to a month and sometimes longer for a small group of patients, and several jurisdictions including Singapore have been using it to guide de-isolation and discharge policies, it is important to note that **viral RNA detection by PCR does not equate to infectiousness or viable virus**.

6. A surrogate marker of 'viral load' with PCR is the cycle threshold value (Ct). A low Ct value indicates a high viral RNA amount, and vice versa. As noted above, detection of viral RNA does not necessarily mean the presence of infectious or viable virus. In a local study from a multicenter cohort of 73 COVID-19 patients, **when the Ct value was 30 or higher (i.e. when viral load is low), no viable virus (based on being able to culture the virus) has been found**. In addition, **virus could not be isolated or cultured after day 11 of illness**. These data corroborate the epidemiologic data and indicate that while viral RNA detection may persist in some patients, such persistent RNA detection represent non-viable virus and such patients are non-infectious.

7. Supporting this, a small but important study from Germany found that the degree of viral shedding was very high in the first week of symptoms with active replication confirmed by viral replicative RNA intermediates (viral subgenomic messenger RNAs, sgRNA), which are only present in actively-infected cells [8]. In sputum, sgRNA declined over days 10 - 11, and in throat swabs, sgRNA was not detected after day 5. Infectious virus was cultured from throat and lung specimens in the first week of symptoms, but none after day 8 in spite of high viral loads detected by regular PCR.

8. These molecular data interpreted together with the epidemiologic data indicate that infectiousness begins just before and with the onset of symptoms and rapidly declines by

[1] In severely immunocompromised persons (e.g. those receiving chemotherapy, steroids other immunosuppressant medications, or with underlying diseases leading to immunocompromise) and severe disease, shedding of viable virus might be more prolonged because inactivation of virus may be less effective due to immunocompromised, and it may be appropriate to extend the period of infection control precautions to protect vulnerable persons.

the end of the first week of disease. These findings are in keeping with available evidence summaries which indicate that SARS-CoV-2 seems to have a consistent trajectory, and while viral RNA may be detectable for about 2-4 weeks from onset of disease, the infectiousness diminishes after 7-10 days[9].

Clinical Data for Period of Infectivity and Phenomenon of Positive PCRs after Initial Negatives

9. Countries which have adopted a policy of repeating respiratory sample PCRs to determine negativity (e.g. two negative PCRs 24 hours apart) to guide discharge and de-isolation policies (e.g. China, Korea) have reported that some patients have recurrent positive PCRs after initial negatives[10,11]. This has led to some speculation of a 'persistent carrier state' or 'recurrent infections' but these have not been substantiated, to date. In the widely cited Chinese report [10], the four patients described all remained asymptomatic, with stable radiographic findings, and no-onward transmission was described. In Korean reports[11], 180 of such cases were noted but again, no onward transmission nor isolation of live virus by viral cultures was reported. A subsequent review by the Korean CDC concluded that these were due to detection of non-viable RNA from dead virus[12].

Areas of Uncertainty, Asymptomatic and Pre-Symptomatic Infection

10. Robust data are lacking regarding infectiousness of asymptomatic and pre-symptomatic individuals and how much asymptomatic infection drives transmission. However, asymptomatic persons may have similar viral shedding patterns[13]. A Singapore study found pre-symptomatic transmission of SARS-CoV-2 in ~6.4% of 157 locally acquired cases, but no asymptomatic transmission [14].

Summary and Conclusion

11. Based on the accumulated data since the start of the COVID-19 pandemic, the infectious period of SARS-CoV-2 in symptomatic individuals may begin around 2 days before the onset of symptoms, and persists for about 7 - 10 days after the onset of symptoms. Active viral replication drops quickly after the first week, **and viable virus was not found after the second week of illness despite the persistence of PCR detection of RNA.** These findings are supported by epidemiologic, microbiologic and clinical data. These new findings allow for revised discharge criteria based on the data on the time course of infectiousness rather than the absence of RNA detection by PCR testing, taking into consideration both the clinical and public health perspectives, including the individual patient's physical and mental well-being. In addition, given these findings, resources can focus on testing persons with acute respiratory symptoms and suspected COVID-19 in early presentation, allowing timelier public health intervention and containment.

References:

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