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Disputes in the management of COVID-19 infected subjects

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Coronavirus disease 2019 (COVID-19) is a newly emerging human infectious disease caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously called 2019-nCoV) [1,2]. Based on the rapid increase in the rate of human infections, the World Health Organization (WHO) has classified the COVID-19 outbreak as a pandemic [3-5]. Because no specific drugs are yet available [6], early diagnosis and management are crucial for containing the outbreak. Furthermore, the duration of immunization after clinical recovery is still unknown and this could be of particular concern regarding the future management and spread of infection.

Several case series have been published to date documented cases which turned polymerase chain reaction (PCR) negative in nasopharyngeal swab at discharge with resolution of symptoms and subsequently returned PCR positive in follow-up swab tests [7-12]. Usually, the patients had mild to moderate symptoms and the time of recurrence of positive tests ranging from few days to several weeks after discharge. Several hypothesis have been postulated to explain these findings: false negative PCR at the time of discharge due to improper sampling, transport or processing or laboratory errors or low viral load; all these conditions possibly related to false negative results. On the contrary, persistent positive tests could be attributed to false positive results due to contamination in sampling or in the laboratory, residual viral RNA or cross reaction with other viruses. As a consequence, as in all these case series viral culture and genetic analysis were not performed, these recurrences could be re-infections, viral relapses or laboratory errors. However, such uncertain results have significant implications regarding the variable presence of viral infection, the risk of re-infection and the need of quarantine for prolonged periods to prevent the spread of infection.

It has been recently documented from Hong Kong [13] a case of COVID-19 re-infection by a phylogenetically distinct strain; this finding leaded to several assumptions on long-term immunity, sampling technique standardization, viral mutation and efficacy of herd immunity. As a consequence, SARS-CoV-2 may continue to circulate among the global population despite herd immunity due to natural infection or vaccination. In particular, this case has a time gap of over 4 months, a laboratory proven different genotype resembling the European virus and the patient was also returning from Europe; all these considerations make it more likely that it is a re-infection rather than a recurrence.

CDC suggests that antibody response to COVID-19 lasts for 2-3 months; nevertheless, there is variability in duration among different individuals. Further, the antibody response to COVID-19 infection may be influenced by the immunological status of the single individual and by the use of immune-modulatory therapy. These observations make the risk of re-infection plausible, especially after exposure to a different strain of the virus. As a consequence, the concept of generating herd immunity seems practically difficult to achieve [14]. Thus, in the actual absence of global vaccination coverage, there is little we can do to prevent the spread of COVID-19, except for the use of personal protective equipment, physical distancing and lockdown strategies that have been shown to be useful in delaying and preventing precipitous rise of cases [15].

Prolonged shedding of SARS-CoV-2 is an intriguing issue on the long-term management of COVID-19 infected subjects. Several reports assessed that a significant amount of COVID-19 infected individuals remained positive for a very long time [16-19]. In particular, in the Italian population, older age has been associated with an augmented risk of prolonged viral shedding [17], whilst in Chinese studies male gender and advanced disease (patients underwent to mechanical ventilation) were also correlated [18,19]. The real infectivity and the risk of SARS-CoV-2 transmission of these individuals is still unclear, but their management during follow-up certainly needs special attention.

Recent reports of positive PCR tests after a variable period of negativity suggest that at least a proportion of recovered patients may still be virus carriers. These observations may have significant implications in daily life; in particular, criteria for hospital discharge, discontinuation of quarantine period and return to work are difficult to generalize to the entire population and, when possible, should be tailored on the single individual. In Italy, a circular of the Ministry of Health [20] established that an asymptomatic patient with COVID-19 infection may exit from the quarantine after 21 days from the diagnosis, even if nasopharyngeal swab persists positive, as it is believed that these subjects are non-infectious. Recently, we demonstrated that the median time for viral clearance in a cohort of Italian healthcare workers was over 30 days [21]. These findings should be considered when re-admitting at work these subjects and are in partial contradiction with the above mentioned circular. Given the lack of clear data on the non-infectious of subjects with prolonged viral shedding, is it ethically correct to return to the community 21 days after positivity if the healthcare worker, though asymptomatic, is still positive? Probably, in absence of clear evidences of non-infectious, the best and more cautious option would be to differentiate the criteria for quarantine exit and return to work according to the risk of possible contagiousness. In particular,

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those individuals who works closely with several people, as healthcare workers, should probably return to work only when there is absolute certainty that the nasopharyngeal swab for SARS-CoV-2 infection will be negative.

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