Letter to the Editor

To solve the discharge equation for COVID-19: biting the dragon by the "tails"

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The sustained community transmission of SARS-CoV-2, and the increasing pressure on healthcare facilities and laboratories, led the European Centre for Disease Prevention and Control (ECDC) to update criteria for hospital discharge and self-isolation for COVID-19 patients (1), to optimize and preserve healthcare capacity.

According to the new criteria, patients may be discharged based on the symptoms clinical resolution and laboratory results. However, ECDC warns that in the context of widespread community transmission and limited testing capacity, clinical criteria should gain priority and may be adapted for specific patient groups. According to the clinical picture, isolation might terminate 8–14 days after symptoms onset, and three days after fever resolution. ECDC only recommends clinical follow-up for certain subgroups of patients previously hospitalized, and not for subjects infected but not hospitalized.

The major criticalities in the construction of a conceptual framework to define the parameters to discontinue isolation are: the residual infectivity and the quantitative trends depicting the number of infected over recovered subjects over time. Unfortunately, a paucity of data is currently available on the consequences of COVID-19 infection, especially in case of mild cases. Furthermore, many other parameters composing such a "discharge algorithm" are still not clarified.

Firstly, the viral load necessary to infect humans by SARS-CoV-2 has not been determined yet and there is no definitive evidence on the duration of viral shedding after symptoms resolution (1). As acknowledged in the background of the ECDC document, prolonged viral RNA shedding has been reported from nasopharyngeal swabs extending up to 37 days after onset of symptoms among adult patients {[1] and references therein}. In paediatric patients, viral RNA was found in faces more than one month after infection {[1] and references therein}. In moderate cases, viral RNA has been detected in different body fluids for up to 5 weeks {[1] and references therein}. The growing evidence of persistent viral positivity, even after cessation of symptoms and independently on their severity, is concerning (2,3).

Secondly, there is a relative lack of knowledge about the number of infected, deceased, and recovered patients, because according to International Health Regulations (4) each country has to notify WHO only the number of confirmed cases and the number of deaths. Due to the differences in each government testing policies and the different criteria to report COVID-19 related mortality across countries, these data are not fully reliable. Furthermore, each country is autonomously assessing the

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timing of self-isolation termination, making it even more difficult to have a clear global situation picture.

An important point regards the definition of recovered patients: it is sobering to note that two countries, Italy and Spain, with a similar epidemiological situation and health care systems, adopted two different criteria. While in Italy two negative tests at 24 hours intervals are necessary to declare recovery (5), in Spain only one negative test suffices for hospitalized patients, while for mild cases no swab is needed (5,6). When comparing epidemiological data from both countries, in Italy the recovered percentage is 23.77% of the total reported cases, while in Spain it is 40.44% [data retrieved on April 17th, 2020 from (5-7)]. Despite the onset of the outbreak in Spain occurred later than in Italy, the recovered rate is almost double among Spanish patients. Assuming the standard of care equivalence in both the countries, it is clear that these statistics can be heavily biased by definition criteria and testing modalities. Furthermore, the sensitivity of RT-PCR-based tests to detect SARS-CoV-2 has been shown to decrease with time after infection (2). It would be therefore possible to speculate that assessing viral clearance by a single swab might result in a return to daily activities of a significant number of falsely negative subjects, still potentially infectious.

Finally, SARS-CoV-2 transmission can occur by direct contact with infected and indirect contact with surfaces in the immediate environment or with objects used on the infected person (8). ECDC advises the use of a surgical mask only for healthcare workers on duty, for up to 14 days after symptoms onset. However, the use of face masks and correct observance of hygiene measures by every symptomatic person have been advocated to reduce viral transmission (9). On the other hand, low availability or misuse of personal protective equipment, as well as inconsistent adherence to hygiene measures by subjects still potentially infectious, could be responsible for sustaining viral transmission (8).

US CDC guidelines for discontinuation of isolation in non-healthcare settings have also been changing (10). They propose either a test-based strategy or a non-test-based strategy. Originally, the first implied two negative swabs in a 24 hours interval; later, only one negative swab would suffice to interrupt isolation. As far as the non-test-based strategy, 7 days since the first appearance of symptoms or diagnostic test positivity are required to interrupt isolation. Similarly, the latter strategy would easily lead to misconsider as recovered potentially still infective subjects.

Moreover, the WHO accepted this clinical framework in its "Criteria for releasing COVID-19 patients from isolation" published on June 17th, 2020 (11).

In conclusion, there are still many uncertainties on SARS-CoV-2 biological and clinical behaviour. A reliable knowledge of the number of subjects molecularly and clinically recovered would be fundamental to draw a reliable epidemiological trend, and an "equation" to predict and control transmission and diffusion. These data would allow to estimate the pressure on the health care facilities and consider the best strategies to attenuate lockdown measures. From the currently available evidence, it seems that the adoption of too liberal criteria to terminate isolation or avoiding confirmatory tests to define recovery might lead to inadvertently neglect cases, which could still constitute an infection source.

If scientific data do not permit a complete evaluation of the risk, should we appeal to the precautionary principle and adopt an over-prudent approach guaranteeing a longer period before discontinuing isolation?

The median values normally dominate statistics and decision-making in Medicine, but with such a poorly understood pathogen, should we trust more the tails of the curves?

What is the risk-benefit balance in adopting a stricter strategy, when considering that a premature restart of the economical and social activities might potentially lead to a new course of infection?

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