Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Infectious Diseases 103 (2021) 278–279

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Editorial

COVID-19: A PCR-defined pandemic

The numbers of coronavirus disease 2019 (COVID-19) cases are increasing steadily in many parts of the world, and the global and devastating impact of the current pandemic on all aspects of our life is evident. The number of positive molecular diagnostic tests, which are largely based on real-time (RT) PCR assays that detect genetic material of the causative agent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), still forms the basis for reporting both symptomatic and asymptomatic cases worldwide. These figures are also used to calculate the basic reproduction number, defined as R-zero (R_0), a value relating to the average number of people an infected individual will infect. Asymptomatic carriers of the virus, including those super-spreading the virus, are not routinely captured in common testing strategies, which rather concentrate on symptomatic individuals, returnees from high-risk areas, and other high-risk groups (Nikolai et al., 2020). Clearly, any ascription of positive results to a COVID-19 diagnosis requires the occurrence of clinical symptoms and further evaluation and confirmation by physicians, including the appraisal of distinct laboratory parameters.

In diagnostic SARS-CoV-2 assays, RT-PCR is based on the detection of the amount of distinct genetic fragments of the virus in an individual. The amount of gene fragments is routinely determined semi-quantitatively through the cycle threshold (Ct) value, which corresponds to the number of PCR amplification cycles in the diagnostic assays required to yield positive results. The Ct value increases with a decreasing viral load, and a low Ct value indicates a high viral load (Velavan and Meyer, 2020). In ambiguous cases, true quantitative assays can be applied.

When assessing impending public health risks, as in the current pandemic, and when imposing local or countrywide lockdown measures, it is important to establish whether infection and infectivity can be determined based only on positive results of individual and mass diagnostic PCR tests.

While the presence of RNA fragments identified by qualitative SARS-CoV-2 PCR tests certainly indicates prior contact with the viral genome or parts of it, no reliable statement can be made with regard to the actual infectivity of an individual. During the clinical course of COVID-19, the release of virus particles from somatic cells and shedding of the virus does not necessarily imply that the virus is contagious. Questions to gauge the reliability and dependability of PCR tests and their significance and impact on the clinical presentation have arisen, due to the finding of positive tests results during the phase of physical recovery from COVID-19 in patients who have already been discharged from hospital on the basis of several negative test results (Lu et al., 2020).

Observations so far suggest a mean incubation period of 5 days and median incubation period of 4–5 days (Lauer et al., 2020; McAloon et al., 2020) from exposure to the onset of symptoms. Viral RNA is detectable in the airways 2–3 days before the onset of symptoms, peaks at the onset of symptoms, and decreases over the following 7–8 days in most patients (Rhee et al., 2020; Team, 2020; To et al., 2020; Wolfel et al., 2020; Zou et al., 2020). Viral load kinetics and the duration of viral shedding are vital elements in determining the SARS-CoV-2 infectivity. A systematic review and meta-analysis has confirmed that SARS-CoV-2 viral shedding may be longer and is proportional to the severity of illness. However, the viability of the virus is short and not beyond 9 days of illness (Cevik et al., 2020).

Studies evaluating the duration of SARS-CoV-2 infectivity based on cell culture and/or secondary infection rates clearly imply that the virus cannot be cultured from respiratory samples after day 8 of clinical disease (Bullard et al., 2020; Cevik et al., 2020; La Scola et al., 2020). A detailed virological analysis of COVID-19 cases confirmed that the virus can only be cultured from respiratory samples during the first week of symptoms, but not after day 8, in spite of persisting high virus loads as determined by quantitative RT-PCR (Wolfel et al., 2020). In addition, the US Centers for Disease Control and Prevention collected data from adults in various age groups and with varying disease severity, and indicated that the virus could not be cultured more than 10 days after the onset of symptoms (CDC, 2020a). Furthermore, virus culture has been found to be unfeasible in cases with a Ct value exceeding 33 (La Scola et al., 2020; Rhee et al., 2020). Of note, the US CDC reasonably recommends a symptom-based decision for returning from isolation, specifically rejecting the exclusively test-based strategy, unless it would result in an earlier decision.

A prospective cohort study involving the first 100 COVID-19 patients in Singapore also showed that attempts to culture the virus failed in all PCR-positive samples with a Ct value >30 (Young et al., 2020). A study by the Korean Centers for Disease Control and Prevention, including 285 patients who had recovered from COVID-19 clinically and had been discharged from hospital, showed that these individuals tested positive again by PCR an average of 45 days after the onset of the first symptoms (CDC, 2020a; CDC Korea, 2020b). Ct values are lowest shortly after symptom onset and correlate significantly with time elapsed since the onset of symptoms (Salvatore et al., 2020).

https://doi.org/10.1016/j.ijid.2020.11.189

Defining the duration of infectivity of SARS-CoV-2 has major implications in determining incidences. Several studies now suggest that persistent positive RT-PCRs do not necessarily indicate the presence of replication-competent viruses (Alexandersen et al., 2020; Rhee et al., 2020). In fact, sustained RNA detection does not indicate sustained infectivity, and SARS-CoV-2 genomic and subgenomic RNAs in diagnostic samples are not an indicator of active virus replication (Alexandersen et al., 2020). It has also been shown that the contagiousness in patients with mild or moderate COVID-19 decreases rapidly to near zero approximately 10 days after symptom onset (Rhee et al., 2020).

Early testing for SARS-CoV-2 in individuals with symptoms is important to determine infectivity based on low Ct values, and early isolation practices to effectively interrupt SARS-CoV-2 transmission should be commenced when first symptoms appear. However, testing individuals 7 days after the onset of symptoms, which is more likely to be done in low- and middle-income countries, but also occurs in developed countries, only contributes to the assessment of the case numbers. Thus, the veracity of the testing strategy with regard to an estimation of infectivity is questionable. It has to be considered whether only laboratory diagnoses of SARS-CoV-2 by RT-PCR are sufficient to allow the assessment of infectivity.

The availability of SARS-CoV-2 antigen testing offers advantages over the diagnosis of SARS-CoV-2 by RT-PCR in terms of reliability. Rapid antigen testing works best in cases of high viral load, in pre-symptomatic and early symptomatic cases up to 5 days after the onset of symptoms. Rapid antigen testing is sensitive enough for cases with a high viral load or low RT-PCR cycle threshold (Ct <25). The European Centre for Disease Prevention and Control (ECDC, 2020) agrees on antigen testing with a World Health Organization performance requirement of >80% sensitivity and >97% specificity. Compared to diagnoses of SARS-CoV-2 by RT-PCR, rapid antigen testing can help to reduce further transmission through early detection, allowing a rapid start of contact-tracing (ECDC, 2020).

As there is a strong correlation between PCR results and the feasibility of virus culture with respect to Ct values, guidelines could be implemented in order to provide sound recommendations, e.g., inclusion of antigen tests or determination of the RNA copy number, on the self-isolation of health-care workers, quarantined individuals from high-risk areas, and others. Clinical parameters, as well as prolonged infectivity in immunocompromised individuals, need to be taken into account. Such evidence-based guidelines might exert an enormous societal impact.

Author contributions

Both authors have an academic interest and contributed equally. TPV is a member of the Pan African Network for Rapid Research, Response, and Preparedness for Infectious Diseases Epidemics consortium (PANDORA-ID-NET RIA2016E-1609).

Funding source

The authors acknowledge the Federal Ministry of Education and Research (BMBF-01KI2052).

Ethical approval

Not applicable.

Conflict of interest

All authors disclose no conflict of interest.

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Received 25 November 2020