



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Letter to the Editor

**Asymptomatic SARS coronavirus 2 infection:
Invisible yet invincible—Reply to
Malagón-Rojas et al**


The comments of Malagón-Rojas et al. on the need for a widely accepted definition of asymptomatic carriers and pre-symptomatic patients and to report asymptomatic individuals in official coronavirus disease 2019 (COVID-19) statistics are well acknowledged (Nikolai et al., 2020).

In a longitudinal follow-up of 202 airport employees, Malagón-Rojas et al. reported that no significant differences in cycle threshold (Ct) values were observed when comparing asymptomatic and symptomatic patients (median Ct 33.4 vs 34.1 in asymptomatic and symptomatic patients, respectively). Their findings are consistent with those of another study that examined asymptomatic individuals and symptomatic patients (Long et al., 2020).

The viral load is assessed semiquantitatively by the Ct value, which corresponds to the number of amplification cycles in the diagnostic RT-PCR assay. Ct values decrease with increasing viral load, and high Ct values correspond to low viral loads (Nikolai et al., 2020). In addition, the duration of virus detectability serves as an indicator of infectivity. Several PCR assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) use a Ct cut-off value of <40 for positivity, and in the early stages of infection patients usually have Ct values of 20–30 (Young et al., 2020). A recent narrative systematic review suggests that lower Ct values are associated with poorer outcomes and thus are beneficial in predicting the clinical prognosis of COVID-19 patients (Rao et al., 2020). Higher Ct values normally correlate with lower viral loads. However the Ct values are not directly proportional to the viral load, due to the dynamic range of the assay and/or the potential presence of any inhibitory factors in the samples used (Rao et al., 2020; Aquino-Jarquin, 2020).

The current literature indicates that the median duration of virus shedding is 11.5 days for pre-symptomatic patients, 28 days for those who are asymptomatic, and 31 days for mildly symptomatic patients (Li et al., 2020). Another study using a similar gene target ORF1ab as described by Malagón-Rojas et al. showed that median Ct values during hospitalization were significantly higher in asymptomatic patients (39.0, interquartile range 37.5–39.5) than in asymptomatic patients during the incubation period (34.5, interquartile range 32.2–37.0), indicating a significantly lower viral load (Zhou et al., 2020). Furthermore, Long et al. reported that the duration of virus shedding was longer in asymptomatic patients when compared to symptomatic patients and that virus shedding did not correspond to viral infectivity (Long et al., 2020).

We agree with the authors that the absence of respiratory symptoms such as sneezing or coughing limits the potential for viral spreading by asymptomatic individuals. However, the risk of virus transmission may be increased as a result of occasional and also more frequent sneezing during the allergy season (Busco et al., 2020). The risk still exists.

The asymptomatic and pre-symptomatic stages can currently be assigned only retrospectively, namely after the occurrence or non-occurrence of clinical symptoms, and it is virtually impossible to accurately determine the extent of asymptomatic infections. The true incidence of asymptomatic infection can only be determined if the closest level of surveillance and extensive testing are applied, and this is continued for a period of time exceeding the estimated average incubation period of at least 5 days, in order not to miss a possible onset of symptoms (Nikolai et al., 2020).

Asymptomatic infections are an important aspect of SARS-CoV-2 infection, in particular regarding viral transmission, and these infections remain a significant epidemiological challenge globally, as health systems could become severely overburdened and the pandemic could continue to elude control, hitting those with the least protection the hardest.

Funding source

Not applicable.

Ethical approval

Not applicable.

Conflict of interest

None declared.

Author contributions

Both authors have an academic interest and contributed equally.

References

- Aquino-Jarquin G. The raw Ct values from RT-PCR detection are not viral load quantitation units. *Clin Infect Dis* 2020; doi:<http://dx.doi.org/10.1093/cid/ciaa830>.
- Busco G, Yang SR, Seo J, Hassan YA. Sneezing and asymptomatic virus transmission. *Phys Fluids* 2020;32(1994):073309.
- Li W, Su YY, Zhi SS, Huang J, Zhuang CL, Bai WZ, et al. Virus shedding dynamics in asymptomatic and mildly symptomatic patients infected with SARS-CoV-2. *Clin Microbiol Infect* 2020; doi:<http://dx.doi.org/10.1016/j.cmi.2020.07.008>.
- Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 2020;26:1200–4.
- Nikolai LA, Meyer CG, Kremsner PG, Velavan TP. Asymptomatic SARS coronavirus 2 infection: invisible yet invincible. *Int J Infect Dis* 2020;100:112–6.

Rao SN, Manissero D, Steele VR, Pareja J. A systematic review of the clinical utility of cycle threshold values in the context of COVID-19. *Infect Dis Ther* 2020;9:573–86.

Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA* 2020;323:1488–94.

Zhou R, Li F, Chen F, Liu H, Zheng J, Lei C, et al. Viral dynamics in asymptomatic patients with COVID-19. *Int J Infect Dis* 2020;96:288–90.

Thirumalaisamy P. Velavan^{a,b,c,*}
Christian G. Meyer^{a,b,c}

^a*Institute of Tropical Medicine, Universitätsklinikum Tübingen,
Tübingen, Germany*

^b*Vietnamese German Center for Medical Research (VG-CARE), Hanoi,
Viet Nam*

^c*Faculty of Medicine, Duy Tan University, Da Nang, Viet Nam*

* Corresponding author at: Institute of Tropical Medicine,
University of Tübingen, Wilhelmstrasse 27, 72074 Tübingen,
Germany.

E-mail address: velavan@medizin.uni-tuebingen.de (T. Velavan).

Received 5 October 2020