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 107 (2021) 251

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Letter to the Editor

Comment to the manuscript by William P. Hausdorff and Jorge Flores: Low-dose and oral exposure to SARS-CoV-2 may help us understand and prevent severe COVID-19, IJID 103 (2021) 37–41

New data and concepts related to protective immunity towards SARS-CoV-2 infection oblige me to comment on the manuscript by Hausdorff and Flores.

An essential point in their manuscript is the assumption that low-dose or oral SARS-CoV-2 may lead to immunization.

Several lines of evidence (most of them established after submission of the manuscript by Hausdorff and Flores) indicate, however, that natural infection with SARS-CoV-2 does not necessarily lead to protective immunity.

1) Khatri et al. (2020) reported on the high affinity between SARS-CoV-2 surface protein and its cellular receptor ACE2. They therefore concluded that only IgG with high affinity for the S protein can efficiently interfere with infection.
2) Recent findings show frequent incomplete avidity maturation of IgG towards SARS-CoV-2 nucleoprotein (NP), surface protein-1 (S1) and receptor-binding domain (RBD) (Strömer et al., 2020; Liu et al., 2020; Bauer et al., 2020, 2021). Avidity (i. e. the strength of binding between IgG and epitope) matures in parallel to affinity. More than 70 percent of Covid-19 outpatients do not generate high avidity IgG at five months after the onset of disease (Bauer et al., 2020, 2021). Kinetic analysis revealed that avidity maturation stopped in parallel to the break in IgG production (Bauer et al., 2020, 2021) which seems to be leading to waning antibody levels (Seow et al., 2020). Therefore, in the majority of cases, IgG directed towards SARS-CoV-2 RBD can be predicted not to be efficient with respect to interference with the high affinity interaction between ACE2 and RBD.
3) In many viral systems, the failure to achieve complete avidity maturation leads to a failure in protection towards infection and disease (reviewed in Bauer, 2021).
4) The immature avidity of the IgG response towards seasonal coronaviruses (Bauer et al., 2020, 2021) might be the biological basis for the observed repeated cycles of reinfections by these viruses (Edridge et al., 2020; Galanti and Shaman, 2020).

These findings indicate that vaccination, leading to a neutralizing IgG response towards RBD/S1, characterized by high avidity, seems to be the only chance to stop the present pandemic (Bauer, 2021). This goal seems to be achievable, as vaccination is not hampered by the negative effect of SARS-CoV-2 infection on germinal centers of secondary lymphoid organs, the site of B cell maturation (Kaneko et al., 2020).

In the line of these novel findings, I feel that it is appropriate to reevaluate the potential risk for participants in the study proposed by Hausdorff and Flores.

Conflicting interests

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding Source

Publication costs will be sponsored by the Medical Faculty of the University of Freiburg, Germany. No other funding was obtained.

Ethical approval

No ethical approval was required for this work.

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Received 24 February 2021

http://dx.doi.org/10.1016/j.ijid.2021.03.084