The Journal of Infectious Diseases
CORRESPONDENCE

Response to Beran et al

To the Editor—We read the letter by Beran et al [1] and welcome the opportunity to address all the points raised. The authors consider our article [2] to be "promoting the need of vaccination and inflating the booster dose effectiveness," and they support this claim by several arguments questioning our methods. Our view, however, is that our methods are standard, previously used [3], and certainly not tailor made for vaccination and all their details are clearly described.

We start with the claim by Beran et al that it is incorrect to make "comparison of effectiveness over the periods of 2 vs 6 months." We believe that this objection stems from a misunderstanding: we evaluate the effectiveness *given that the individual finds itself in the period,* not *over the period,* as the authors appear to believe. Because our results can be interpreted as the average effectiveness of individuals, finding themselves in the corresponding interval, it does not matter that the intervals are different.

We cluster time into intervals for the sake of computability—in fact, we approximate waning patterns by piecewise constant functions. In the analyses encompassing hybrid immunity (interactions), 2 intervals per an immunity source were the maximum; if we wanted to include all possible interactions (with finer clustering) the model would have too many parameters to be estimated. The interval split points have been chosen to capture the waning pattern as clearly as possible: because waning of the postinfection immunity is slower than that of the postvaccination one (a fact we do not hide), the split point for the former should have been set longer (we chose 6 months) than that for the latter (we chose 2 months). Moreover, aware of model limitations, we ran several auxiliary analyses with a finer time granularity, also discerning between individual vaccines, but without interactions [2, supplementary material 2, sections 11–14].

Next, Beran et al request that the effectiveness of the boosters against severe outcomes be "compared with the protection provided by infection," yet this comparison easily stems from the published results. For instance, the protection against oxygen therapy for Omicron by the third (booster) dose comes out as 0.9 (95%-confidence interval [CI], .88–.92) during the first 2 months and 0.85 (95% CI, .8–.89) afterward (which is in fact 2–5 months after application, as the authors correctly point out). The protection by infection in months 2–6, on the other hand, is estimated as 0.81 (95% CI, .4–.94) [2, supplementary material 2, section 7]. Although the latter CI is rather wide, these values are comparable.

We agree with Beran et al that comparing the boost2+ category with the full2+ category (see [2]) may be seen as problematic owing to a different distribution of the individuals in each category; however, we refer the reader interested in a more compatible comparison (but without interactions) to analyses in our article's supplement [2, supplementary material 2, sections 11–14], where the interval 2–4 months, also comparable to the boost2+ category, is considered for full vaccination, giving full vaccination effectiveness comparable to that of the boosters. We stress that this does not in any way disprove the protective effect afforded by a booster dose, which is the only possibility for fully vaccinated individuals. Yet we agree that adding this note in the main text could have made things clearer.

The authors also state that mortality and case fatality rate should have been included. We did not consider case fatality rate, because it is a numerical indicator and thus out of the scope of our work. We agree that death is an important outcome; the reason why we did not include deaths is that they are, especially for the Omicron variant, too rare to give statistically correct results for interactions, which are our primary interest. (The analyses with death as the outcome can be made by running the script Vyvanuti/batch_omicron_additional from the repository at https://github.com/bisop-repo/omicronprotection.) Moreover, we disagree that "COVID deaths" are a good indicator of the "true state," as they have the same limitation as hospital admissions: a patient who tested positive could have died of a cause other than coronavirus disease 2019 (COVID-19); this is why we prefer oxygen therapy as the outcome indicating COVID-19, because it suffers less from this limitation. We also refer the readers to the study by Berec et al [4], where deaths are examined; this was possible because deaths were not so rare for the Delta variant, exclusively investigated in that study.

Next, Beran et al object that our results regarding hybrid immunity have not been reported for the intensive care unit admissions and oxygen therapy. In fact, analyses including interactions (ie, evaluating the hybrid immunity) have been done [2, supplementary material 2, sections 7–10], but with the interactions collected into just a single category owing to the rarity of the outcomes (many hybrid categories had no event). The results for the accumulated category, however, are superior to the postinfection immunity, probably insignificantly so. (To assess the statistical significance of this difference, an analysis similar to that by Berec et al [4], assessing vaccines, can be done).

Furthermore, our statement that "the best protective strategy before a coming wave is to vaccinate all individuals, whether previously vaccinated or with a previous COVID-19 infection" is

questioned. We insist on this because we have shown that (1) hybrid immunity gives nearly 100% protection against hospital admission, which clearly implies at least the same protection against severe outcomes; (2) recent booster (third dose) alone provides strong protection against hospital admission as well as severe outcomes; and (3) a past Delta infection alone gives solid, but not total, protection against severe outcomes, which can be elevated to nearly 100% by vaccination.

Beran et al also argue that our analyses should have been done separately for high-risk and low-risk groups, because "consistent vaccine effectiveness across all age groups (as assumed by the authors) is not valid." Following their advice, we ran the Omicron-oxygen analysis separately for the age groups >60 and <60 years. See the results in the Appendix of the present letter (Supplementary Materials) and compare them with the data in our article's supplement [2, supplementary material 2, section 7]. In particular, (1) results for the older group are nearly identical to those of the "joint" analysis (because most events came from there), (2) the results for the young group are imprecise (because the events there are rare), and (3) results for the younger group are far from significantly different from those for the older group, so the hypothesis of a uniform vaccine effectiveness (VE) cannot be rejected. To summarize: while we can hypothesize a heterogeneous VE, we cannot estimate it. Moreover, because the severe outcomes are rare in the young group, their VE is of less interest.

Finally, Beran et al suggest several alternative analyses that would "better interpret the data." However, as we explained above, the analysis involving deaths would not produce significant results, and splitting the population would not provide any additional information. The analysis with the required intervals (but without interactions) could be run by an easy modification of our code (available at https://github.com/bisop-repo/omicronprotection), but we do not expect it would bring any new insights.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

Potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Martin Šmíd,[1,©] Luděk Berec,[2] and Jan Trnka[3]

[1]Czech Academy of Sciences, Institute of Information Theory and Automation, Praha, Czech Republic; [2]Centre for Mathematical Biology, Institute of Mathematics, Faculty of Science, University of South Bohemia, Ceske Budejovice, Czech Republic; and [3]Department of Biochemistry, Cell and Molecular Biology, Third Faculty of Medicine, Charles University, Praha, Czech Republic

References

1. Vencálek O, Beran J, Fürst T, et al. More analyses are needed to evaluate the effectiveness of protection by vaccines and previous infection against the Omicron variant of SARS-CoV-2 [letter to editor]. J Infect Dis **2022**; 226:942–3.
2. Šmíd M, Berec L, Přibylová L, et al. Protection by vaccines and previous infection against the omicron variant of severe acute respiratory syndrome coronavirus 2. J Infect Dis **2022**. doi:10.1093/infdis/jiac161.
3. Tartof S, Slezak J, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet **2021**; 398:1407–16.
4. Berec L, Šmíd M, Přibylová L, et al. Real-life protection provided by vaccination, booster doses and previous infection against covid-19 infection, hospitalisation or death over time in the Czech republic: a whole country retrospective view. PLoS One **2021**. doi:10.1101/2021.12.10.21267590.

Received 22 June 2022; editorial decision 22 June 2022; accepted 22 June 2022; published online 28 June 2022

Correspondence: Martin Šmíd, Pod Vodárenskou věží 4, 182 00, Praha 8, Czech Republic (smid@utia.cas.cz).

The Journal of Infectious Diseases® 2022;226:944–5

https://doi.org/10.1093/infdis/jiac259