Review of: "[Review] Early Real-World Evidence on the Relative SARS-CoV-2 Vaccine Effectiveness of Bivalent COVID-19 Booster Doses: a Narrative Review"

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Potential competing interests: No potential competing interests to declare.

[Review]

Early Real World Evidence on the Relative SARS-CoV-2 Vaccine Effectiveness of Bivalent COVID-19 Booster Doses: a Narrative Review

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I am reviewing the version sent to me on 23 May 2023 (v1).

This review covers 14 studies evaluating vaccine effectiveness of bivalent mRNA boosters againts SARS-CoV-2 infection outcomes: symptomatic infection (disease), hospitalization and death.

It is, as the author points out, a narrative about the findings of these studies, and not a metaanalysis due to highly differing designs of those studies, which, nonetheless revolve around the same question (bivalent vaccine effectiveness).

The article is well structured and, apart from some minor typing errors, well written.

Now, to the point.

This study finds „modest to moderate additional protection of vaccination with bivalent BA.4-5 or BA.1 mRNA-booster vaccines against COVID-19 associated illness and hospitalization, if compared with having received a monovalent dose as booster, during a period when BA.5 and other Omicron sublineage viruses predominated globally.“

The descriptive conclusion presented in the abstract, remains unchanged to the end of the article with no ambition to quantify more precisely some composite value of vaccine effectiveness integrating the intervals since previous vaccines, infection or both, and the duration of protectiveness following bivalent booster across the studies examined.

The author expresses some dissatisfaction with the immunogenicity studies taken to predict the degree and duration of protection, **but she is wrong on this point.** The fact that we do not have many studies of the correlation of neutralizing titers to protection, does not mean that the concept is useless.

Here I am attaching 2 references on neutralizing titer correlation against asymptomatic infection and clinical COVID-19:

1. Khoury DS et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2

infection. Nat Med 2021 Jul;27(7):1205-1211 https://doi.org/10.1038/s41591-021-01377-8

2. Regev-Yochay G et al. Correlates of protection against COVID-19 infection and intensity of symptomatic disease in vaccinated individuals exposed to SARS-CoV-2 in households in Israel (ICoFS): a prospective cohort study . www.thelancet.com/microbe Published online March 21, 2023 https://doi.org/10.1016/S2666-5247(23)00012-5

The author is in fact unclear about the terminology of protectiveness (this is how I understand her term „real world vaccine effectiveness“). She uses various terms which have different epidemiological and statistical definitions: vaccine effectiveness, efficacy, incremental protection, relative vaccine effectiveness (sometimes abbreviated as „VE“, and at other times as „rVE“), hazard ratio. Togehter with the purely descriptive assertion that the bivalent booster contributes a „modest to moderate additional protection“ this adds to the confusion and not the clarification of the „real world relative SARS-CoV-2 vaccine effectiveness“.

The author has drawn up a Table depicting the main results of the 14 studies to accompany the Results section where there is presentation of the studies' results by outcomes that were expected to be affected by bivalent boosters, and then, in the Discussion section, the same is repeated in more succint words. However, a true discussion of the findings is missing. By „true discussion“ I mean the synthesis of the presented findings, not merely mathematical, which would at any rate be unfeasible, but primarily interpretative and, where necessary, enriched by the knowledge of immunology that is valid in all cases of humoral response to (dead) vaccines, to infection, and to hybrid immunity, and which has also been validated with respect to the SARS-CoV-2 during the present pandemic.

Let me attach several references:

1. Widge AT et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. NEJM 2020 (Dec 3): https://10.1056/NEJMc2032195

2. : Di Chiara C et al. Long-term Immune Response to SARS-CoV-2 Infection Among Children and Adults After Mild Infection. JAMA Netw Open. 2022(Jul 13);5(7):e2221616. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2794167

3. Qu P et al. Durability of Booster mRNA Vaccine against SARS-CoV-2 BA.2.12.1, BA.4, and BA.5 Subvariants. NEJM, Sep 7, 2022: doi = 10.1056/NEJMc2210546. https://doi.org/10.1056/NEJMc2210546

4. Crotty S. Hybrid immunity. COVID-19 vaccine responses provide insights into how the immune system perceives threats. Science 25 Jun 2021;372(6549):1392-3. https://www.science.org/doi/10.1126/science.abj2258

5. Abu-Raddad LJ et al. Association of Prior SARS-CoV-2 Infection With Risk of Breakthrough Infection Following mRNA Vaccination in Qatar. JAMA. 2021;326(19):1930–1939. https://jamanetwork.com/journals/jama/fullarticle/2785918

6. Goldberg Y et al. Protection and Waning of Natural and Hybrid Immunity to SARS-CoV-2. NEJM 2022 (May 25). https://www.nejm.org/doi/full/10.1056/NEJMoa2118946

There is **no disconnection between the immune response and real world protection**against COVID-19. There are just very many variables that influence and modify the protective effect: the interval between the doses of the primary vaccination series, the interval to 1st and 2nd boosters, the interval between infection and vaccination or vice versa, the age of the individual, comorbidities, and last but not least, the emerging variants of SARS-CoV-2. It is very hard to arrive at a general formula for real world protectiveness, but I imagine that a set of guidelines can be formulated taking into account the main variables and how they impact the protectiveness over time.

The author has **missed the opportunity to put together the puzzle** using the 14 studies and previous knowledge of the immune response in general and against SARS-CoV-2 in particular, and give us a **workable and useful numerical appraisal of the real world bivalent vaccine protectiveness** against COVID-19 over time.

As for me, I am, time permitting, going to use this text to examine each selected study by myself, and try to find a more satisfactory answer to the question of immunogenicity and effectiveness, and the duration of either one, following the bivalent boosters. I am quite hopeful that a puzzle can be put together at least to the level of being able to say that, e.g., the bivalent booster given at … (5) months post primary series, provides a protective immunogenic response waning in … (4-6) months, and assures protection against symptomatic disease for … (6) months (in parentheses are hypothetical values that would have to be checked during the evaluation process against available litterature **AND** basic immunology).

All along this pandemic I have been preplexed at how those charged with managing the pandemic, invoked, as a pretext for their many uncertaintes, the lack of “scientific data” despite the fact that the **bulk of relevant knowledge had long been accumulated during the past 50 years or more**. I am citing the book by Benjamin Lee Gordon, “Essentials of Immunology”, 2nd ed., FA DAvis Co., Philadelphia, 1974 , where on pp 84-85 he draws, in freehand, the curve of primary and secondary immune response. Oddly enough, the curve of the scondary response returns to zero **at 90 days. How did he know then, what had to be discovered in 2020?** (see Widge AT et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. NEJM 2020 (Dec 3): https://10.1056/NEJMc2032195 . Widge shows that the immune response following the 2nd mRNA dose wanes **in 120 days**).

If this (Benjamin Lee Gordon's) knowledge had been used timely and properly, the**initial roll-out** of vaccines against COVID-19, when the Alpha-variant was dominant (index of reproduction 3.3, i.e. the necessary coverage to stop the spread approx. 70%), would have had to be completed within **3 months**, and the pandemic would have been stopped there (for the population covered). Even if the roll-out had been a little prolonged, the data of Widge would corroborate the realistic hope that a roll-out of 4 months would suffice. Instead, the sluggish roll-out allowed the pandemic to get inflamed with the Delta and Omicron variants, which required the coverage of 85% and > 90%, respectively. In fact, if you remember, Denmark achived 85% coverage in early September of 2021 and decided to lift most of the epidemiological measures. Mathematics works, even in medicine, but to trust it, takes solid knowledge that cannot be accumulated over night.

With these deliberations I recommend this article to be read in detail and taken as an incentive to move towards a more comprehensive measure of vaccine effectiveness garnered by correlation to immunogenicity data.