20-Jan-2022
BMJ-2021-069761 entitled "COVID-19 from the SARS-CoV-2 Delta Variant in the United States: Clinical Severity and mRNA Vaccine Effectiveness"

Dear Dr. Self,
Thank you for sending us this paper and giving us the chance to consider your work. We sent it out for external peer review and discussed it at the manuscript committee meeting. We are, in principle, interested to proceed with the paper if you are able to amend it in the light of our and/or reviewers' comments.

The reviewers' comments are at the end of this letter.

The editors' comments are listed below:

We hope that you will be willing to revise your manuscript and submit it within the next 2 weeks since we are planning to proceed on a Fast Track basis.

The technical editor checklist is attached to this email to expedite the process. Please format your paper accordingly.

When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers.

Please note that resubmitting your manuscript does not guarantee eventual acceptance, and that your revision may be sent again for review.

Please click the the link to start the resubmission process: *** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

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I hope you will find the comments useful. Please don't hesitate to contact me if you wish to discuss this further.

Yours sincerely
Nazrul Islam, MBBS, MSc, MPH, PhD
Research Editor, The BMJ
nislam@bmj.com

Report from The BMJ’s manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Wim Weber (Chair), Julie Morris (Statistical editor), Timothy Feeney (first 40 minute), Nazrul Islam, Navjoyt Ladher, Elizabeth Loder, Joseph Ross, Jin-Ling Tang, Di Wang

Decision: put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

* Please include the data on VE in Omicron variant.

* Please elaborate on the selection of cases and control, and clarify the factors that were used for matching the cases and controls, if any.

* The the note above, please clarify if it was a conditional or unconditional logistic regression model that was used for the analysis.

* Please consider using UP TO 5 controls per cases to improve the statistical precision (as opposed to 1:1).

* "Participants were excluded from this analysis if they were partially vaccinated (defined as receipt of ≥1 dose of an mRNA vaccine but not fully vaccinated at the time of illness onset), received a COVID-19 vaccine other than a mRNA vaccine (e.g., the Ad26.COV2 vaccine from Janssen), or received a mixed primary series (e.g., Pfizer-BioNTech vaccine for one dose and Moderna vaccine for one dose)." Might you consider including them as well since these may offer some results for resource-poor settings, where they can only get 1 vaccine dose for now.

* Table 1 should present the characteristics by cases and control groups.

* Might you consider the following as confounder: comorbidities, smoking, care facility residence. If not, could you please justify in the Methods section.

* Could you please comment if the proportional odds assumption was met in the multivariable proportional odds regression model

* One Editor commented that "I am also not convinced that the study has completely dealt with different variants contaminating the study periods but this should make things more similar and hence their results are possibly conservative. This would just need adjusting in the text."

DISSEMINATION:
It is there, but add this as a separate section at the end of the manuscript. PPI section looks good, and is in the right place, however.

****

Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:
Review of Lauring et al BMJ 2021

The authors present results from an analysis about CV19 mRNA vaccine efficacy in the delta and pre-delta eras. It is based on data from a network of hospitals through a CDC sponsored surveillance project. In it, cases and controls were all hospitalized patients. Cases were those who had a syndrome consistent with COVID and a positive PCR. Controls were from two groups:1) syndromic

patients who were PCR negative (test negative controls); and 2) syndrome negative patients who were tested for CV19 for some other reason and were PCR negative.

While overall the paper was clear and the results somewhat reassuring in terms of the absence of much impact of Delta on a number of endpoints (even where the average symptom severity was higher, the adjusted OR was only 1.13 so did not point to a substantial increase in severity). My concerns came down to two primary issues:
1. How can you measure vaccine effectiveness for reducing hospitalizations when 100% of cases and controls were hospitalized?
2. Collider bias.

On issue 1, typically I think of measuring VE when comparing vaccinated and unvaccinated populations as one axis, and those hospitalized for CV19 on the other axis. Here, all were hospitalized, and the inferential analysis is looking at the odds of whether they were hospitalized and had COVID or were hospitalized for another reason vs. whether they were vaccinated or not. That feels perplexing to me and problematic because of issue 2.
This seems like a case where concerns about Collider bias are very germane. The collider is that all participants were hospitalized, and so we cannot draw inferences about the non-hospitalized fraction. Rather, I think the analysis is at risk for this kind of selection bias. This issue has been the focus of a number of papers in the CV19 era, one of which is a nice analysis of how to identify the problem and potentially address it through sensitivity analyses – see Griffith et al, Collider bias undermines our understanding of COVID-19 disease risk and severity
Nature Communications: doi: 10.1038/s41467-020-19478-2

In particular, please refer to figure 2C in that analysis, as this pertains to analysis when looking at a non-representative sample of hospitalized individuals and attempting to assess risk factors for PCR positivity. In the current analysis, the 'risk factor' would be vaccination status, and seems to me to be a very analogous example to that in the current submission.

In full disclosure, I harp on this point because I fell into the collider bias myself on a recent analysis, and since then have been thinking about it a lot. Our analysis concerned analyzing whether various co-morbid conditions (such as HTN or diabetes) were associated with PCR status in the post mortem setting (i.e., subjects were all deceased). In that analysis, we were a bit surprised to see so little association between risk factors that were highly prevalent in our cohort and that had been noted repeatedly to confer risk of severe covid outcomes. In some cases, the risk was reversed (e.g., cancer appeared to be protective against CV19 deaths). The collision in our cohort is because all subjects were deceased and therefore had to be quite sick. The collider there was because people have to die of something, and, unless they were hit by a truck, the death was either due to CV19 disease or to some other medical condition. What is missing from our analysis was the prevalence of the risk factor in those who did not die. In the current analysis, what is missing is data from those who were not hospitalized.

A minor point, but I found the terminology a bit confusing when looking at the increased severity due to vaccination analysis. Severity is a continuous scale, yet the results are presented as an odds ratio, which requires a dichotomous, not continuous, outcome. The paradox is solved in the methods where it is pointed out that the scale was dichotomized into high vs. low severity. Yet the way the results are described leads the reviewer to suspect we are looking at mean severity on that continuous scale.

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Please enter your name: Christopher Gill

Job Title: Associate Professor of Global Health

Institution: Boston U. School of Public Health

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Reviewer: 2

Recommendation:

Comments:
Thanks to the authors for their important and timely work.

Pages 7-8 of 58:
The Participants paragraph defines control cases simply as 3371 patients “hospitalized without COVID-19”. For readers unfamiliar with test-negative design studies this is confusing. The main outcomes and results appear to make no mention of control (non-COVID-19) cases, but rather emphasize vaccination versus non-vaccination and pre-Delta versus Delta.

Page 20 of 58, Study Limitations:
How do limits on hospitalization capacity affect the results? The syndrome-negative control group (accidents, elective surgeries, non-COVID diseases), which is included in vaccine effectiveness against hospitalizations calculations [Page 14 of 58, lines 325-327], may be constrained during low capacity time periods, perhaps skewing and limiting the composition of the control group(s).

Page 29 of 58, Table 1
Page 49 of 58, Table S4
Many of the result calculations exclude the syndrome-negative control groups. Should Table 1 and Table S4 split up the “All controls” column into “test negative” and “syndrome-negative” columns?

How do these results compare to the FDA approving clinical trial results for mRNA vaccines, mostly with the Alpha variant? Significant differences may point to other confounders of results. Corroboration may provide more confidence in the results.

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Job Title: retired

Institution: retired

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Reviewer: 3

Recommendation:

Comments:
This is an important article, but it should be revised so that it would be easier to understand for readers who are not experts in the field. A simple example is the failure to define VE in the abstract, but the larger issue is the frequent use of terminology that many physicians and researchers who care about the findings would be unlikely to understand. If the authors believe all the details are essential

to include, then they should be explained more clearly and the technical terms and abbreviations should be avoided when possible.

The supplemental materials are lengthy and a bit overwhelming, but I noticed that on page 35, pertaining to the Delta period the proportion of vaccinated patients who died is slightly higher than the proportion of unvaccinated patients who died. Even assuming that this is not statistically significant, this finding deserves to be discussed.

One other concern: Is it likely that everyone listed as an author has made the type of contribution that is considered appropriate for authorship?

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Please enter your name: Diana Zuckerman

Job Title: president

Institution: National Center for Health Research

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 4

Recommendation:

Comments:

Thank you for the opportunity to review this manuscript on vaccine effectiveness against hospitalization with Delta COVID-19 and clinical characteristics of hospitalized cases. The manuscript is well-written and nicely presented. This is an iterative case-control study, in that it builds on prior VE reports from the same data source (21 US Hospitals), this time adding ~2000 new participants for a total of 6456 (3085 cases and 3371 controls). The authors main findings are 1) the severity of Delta COVID-19 was higher than for previous types of COVID-19, 2) that the mRNA vaccines protects well against hospitalization with Delta COVID-19 and 3) that the mRNA also provides some protection against disease progression among hospitalized Delta COVID-19 cases.
1) Ct-values: Why not use a linear normal regression model that takes into account e.g. interval between symptom onset and testing? The authors find that the CT-values are lower among vaccinated cases than unvaccinated cases, and then argue that this is likely confounding. This could be directly assessed in a regression model.
2) Ct-values: Since the swabs are all tested at the same site, it should be possible to replace the Ct-values with viral load using the standard curve of the test. Would viral load not be more valuable to the reader?
3) Maybe, use aPOR instead of aOR – many will not be familiar with proportional odds regression and the interpretation (odds ratio increase per 1 step on the progression scale).
4) Please check that the prop odds model is reasonable. E.g. a(P)OR of 1.19 should correspond roughly to an aOR of 2.39 (1.19^5) going from "hospitalized without O2" to "death".
5) The time-since-vaccination results could be stratified to a greater degree, especially in the Delta period – this would be valuable in the debate on when to use booster doses. How was 120 days chosen?
6) I was not able to recover the result that BNT162b2 wanes more than mRNA-1273 against Delta from the Results section (or Table 2) – this is highlighted in the beginning of the Discussion.
7) Vaccine terminology: Both Pfizer-BioNTech and BNT162b2, and Moderna and mRNA-1273 is used.
8) A limitation to severity is that (also mentioned by the authors) clinical management could have improved over the study period – this would then underestimate Delta severity.

Anders Hviid

Head of Department (acting),
Professor of Pharmacoepidemiology,
M.Sc.,Dr.Med.Sci.
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Please enter your name: Anders Hviid

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Institution: Department of Epidemiology Research, Statens Serum Institut, Denmark.

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 5

Recommendation:

Comments:
COVID-19 from the SARS-CoV-2 Delta Variant in the United States: Clinical Severity and mRNA Vaccine Effectiveness
BMJ-2021-069761
This is a periodic update from the IVY Network focused on disease severity and outcomes from the Delta variant in the United States. It focuses on the hospitalization with progression to intensive ventilation and death as the primary outcome. The group is an experienced group of investigators in 21 hospitals across the US, who collect COVID cases and controls (both PCR or antigen test-negatives or syndrome-negatives [test negative without COVID symptoms]). The network has provided rapid prospective observational assessments of vaccine efficacy (primarily mRNA vaccination) using a test-negative design over the course of the pandemic, using routine surveillance and genomic surveillance. Their defined methodology has provided robust efficacy data which allows comparative analysis across time, which is a valuable feature with a shifting variant and vaccination landscape.
This analysis uses a time period from Mar to 15 Sep 2021 which included entry and dominance of the Delta variant into the US. Using two distinct time frames for pre-Delta (Mar through Jun 2021 inclusive; 36% of cases) and Delta periods (Jul through 15 Sep; 64%) the authors establish patterns in hospitalization accompanied by detailed breakdown for confounding factors eg immunocompromise, age, time from vaccination) accompanied by genomic sequencing in 43.5% of cases (with CT < 32). They establish importantly that VE against hospitalization during the Delta period and with Delta variants was not substantially different from that VE observed during the pre-Delta period and with Alpha variants. There was a drop in VE against disease progression in hospital during Delta period perhaps reflecting a higher risk population. The lack of vaccination efficacy was particularly notable in immunocompromised adults.
The manuscript provides a welcome comparative analysis and supports the literature on preservation of VE by mRNA vaccines against the severest outcomes of hospitalization and death from confirmed Delta infections. In addition it provides data that suggests that the virulence of COVID during the Delta period is not substantially different from that observed during the non-Delta period though there is trend towards increased mortality in hospital (8.8% vs 11.1%, p = 0.06). no difference with vaccination – small numbers? As a secondary benefit the authors provide a detailed listing of the 63 vaccine breakthrough deaths that occurred during the study, to allow better characterization of this population. Not clear that immune comormise or incr comorbiidites account for mostThe authors are careful not to extrapolate too much from their data given the multiple other shifts in treatment and vaccination patterns over the same time periods.

General comments:
This is a well-written expert paper that maximizes the observational test-negative design. Given their prior publications, particularly Tenforde MW et al 2021 the methodology has been well-established and accepted. There are limitations in this hospital-based survey – which captures the most severe outcomes and may not fully represent the full spectrum of COVID disease. As they note this may skew towards a higher risk population of immunocompromised or older adults with significant comorbidities. However this may be the most stringent test of vaccination so it is valuable to assess VE especially continuously over time.
Discussion, line 466: It is very clear that vaccination status changed dramatically over the course of the study period, reflecting the vaccination campaign, and the authors note that similar proportions of cases and controls were vaccinated. It would be useful to know more evidence for statement that vaccine coverage in controls tracked with the general population. Results, line 326: Similarly it would useful to provide more rationale for the pooling of controls in this study based on similar vaccine coverage () since the populations may overlap.
line 394: The observation that fully vaccinated cases had higher viral loads (based on lower RT-PCR cycle threshold values Table S5) is explained by delay to sampling in unvaccinated adults or earlier presentation in vaccinated adults. Neither of these is particularly satisfactory as explanation, given consistency across both time periods and with both N probes. Understanding the limitations of observational and virologic methods, however authors should comment on significance of different shapes of violin plots (Figure S2) and whether this relationship was seen in earlier analyses.
Line 402: Overall generally agree with efficacy conclusions which are reassuring. However 581/3085 cases were vaccinated (19%) and VE may have been reduced if patients not fully vaccinated (681; ~20% of total) would have been included. The drop off of these records – neither cases nor controls – could have impact on analysis as potential confounder. Was a sensitivity analysis done with different splits between cases and controls? line 407: Should also comment on immunocompromised as proportion of population and VE quantitatively since it is near zero during Delta period.
It might be useful to have paragraph on effect of time from dosing on VE against hospitalization and progression since it appears to be less substantial than potentially expected (Figure 3). There is a mention of differential effect by mRNA vaccine in Discussion which might obscure larger comparison.
Related comment: Table 2 defines time from vaccination from dose 1 (Day 0) while Figure 3 defines as 14 or more days from dose 2. The latter is consistent with line 282 which defines study population includes only those fully vaccinated or unvaccinated.
While progression to ventilation/death are key variables in severe COVID for policy makers, inclusion of a separate analysis of grades 4-6 of the WHO Clinical Progression scale (Table S2) for vaccinated vs unvaccinated in hospital might be useful for understanding impact on disease. These patients hospitalized with moderate outcomes might be valuable complement to less common severe outcomes, and add to aassessment of burden of COVID disease prevented by vaccination.
421 Delta deaths . Interestingly there was no difference in number of deaths with or without vaccination in Delta period – is this an artifact of small numbers of patients? 429 Hospitalization features of vaccinated vs unvaccinated: In Table S7 it seems either immune compromise or increasing comorbidities (not both) account for most deaths, would consider grouping them by Y/N immunocompromise.

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Please enter your name: Niranjan Kanesa-thasan

Job Title: Chief Medical Officer

Institution: Icosavax, Inc.

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Reviewer: 6

Recommendation:

Comments:
This is an interesting paper on findings from the IVY network on mRNA VE prior to and during the period of peak delta circulation in the US. These data are of public health importance and the research questions are timely. Nevertheless, the structure, language and scientific clarity of the written sections of the manuscript are suboptimal and there is more to be gleaned from the data. The figures and tables are good, and the primary finding is clearly stated in table S1 but not elsewhere. Independent statistical review of the methods is recommended if the manuscript is to be considered for publication.
Major comments
Statistical analysis
Lines 309 to 312. Given that the pre-Delta and Delta period definitions are key to the study findings and conclusions please refer to data shown later in the manuscript to support.
336 – 337 why was the 120-day threshold put in place? To take account of waning antibody titres?
342 "Non-overlapping 95% confidence intervals for VE against hospitalization estimates during the pre-Delta and Delta period were indicative of a significant difference in VE between periods." This statement is unclear– is this a finding in which case it needs to be in the results or an a priori assumption?
351 "An aOR >1.0 from this model indicated Delta period COVID-19 led to more severe in-hospital disease than pre-Delta period COVID-19 in the unvaccinated COVID-19 population." Same comment as above
Results
The results seem short compared with the other sections and some of the interesting data are only to be found in the tables, including the supplementary table. Are there other findings that have not been fully described that could be included in the text? Consider including a separate section on those with immunocompromising conditions, for example at present the lower aVE against hospitalisation is shown in table 2 but not sufficiently described.
379 the term "enrolled" is misleading as there was no informed consent process, please revise
384 How confident are the authors that those not sequenced did not have the Delta variant given that of those sequenced 11.1% were the Delta variant?
399 The cut-off used is 7-days. This has implications for public health measures such as quarantine, testing and prevention of onwards transmission. Please discuss.
417 What does the term "peak severity" mean? Please add this to the methods section (line 345)
425 – 431 Please refer to the tables where these data are shown
428 -431 This is an important public health message regarding the risk of death in younger, immunocompetent but unvaccinated individuals – please highlight in the conclusions
Discussion
The discussion needs some revision to reflect the primary object of the study, which was to review VE in the context of a changing dominant circulating strain of SARS-CoV-2 in the US. The language is at times vague. The major message seems to be that despite delta becoming the dominant variant, immunisation with mRNA vaccines that employ the Wuhan SARS-CoV-2 spike sequence remains effective. This is not stated until late in the discussion. Secondly, immunocompromise is a risk factor for low VE. This is important for public health strategies in the longer term.
445 – 447 "Although VE was largely maintained >120 days post vaccination, we observed greater waning of protection among those who received the BNT162b2 vaccine compared with the mRNA-1273 vaccine." This is an odd conclusion to lead with as it was not the primary object of the study. Suggest remove or deprioritise and support with data; n numbers >120 days are low in Table 2, so this is a difficult conclusion of which to be sure.
447 The results refer to VE (progression) but here the discussion is on hospitalisation. Please see the earlier comment on focussing on immunocompromising conditions. In particular, these were associated with no VE (progression); these conditions should be defined earlier in the text and more discussion on what this means for public health strategies.
449 "somewhat higher" vague, please rephrase
456 The section on strengths could be shortened in favour of discussion of the findings.
464 Consider reducing the section on limitations to those that impact the data.
Table 1
What is meant by "immunocompromising condition"? Please define
Figures

These are clearly presented. For Figure 2, it is helpful to have the data presented as a table to demonstrate the actual numbers.
Supplementary tables
S1. Clearly states the primary finding. Please include this finding in the manuscript.
S3. Shows the distribution of variants sequenced, please refer to this in the text.
S4. Shows the patient characteristics where the virus was sequenced. Please comment in the text how these differ from participants in the clinical efficacy/Phase III trials and in the discussion how this impacts the real-world effectiveness findings and what public health messages can be drawn.
S5. Demonstrates (inferred) lower viral load after 7 days. Is this important for onwards transmission?
S6 and S7. Demonstrates breakthrough infections leading to death in some of those fully vaccinated. Please comment in more detail on the reasons for this in the results and the discussion. See also my comment on line 428 – 431 and discuss how vaccination shifts the risk profile to older, more immunocompromised individuals with multi-morbidity; this is thus a key population for new treatment strategies.
Figure S2
Please refer to this figure in the text (line 391)
Minor comments
479-480 Check grammar, “the” is missing

Additional Questions:
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Please enter your name: Katrina Pollock

Job Title: Senior Clinical Research Fellow in Vaccinology and Honorary Consultant

Institution: Imperial College London

Reimbursement for attending a symposium?: Yes

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