23-Dec-2021
BMJ-2021-069317
Public Health Impact of Coronavirus Disease Vaccines in the United States

Dear Dr. Suthar,

Thank you for sending us your paper, manuscript #BMJ-2021-069317 entitled "Public Health Impact of Coronavirus Disease Vaccines in the United States". We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Yours sincerely,

Joseph S Ross MD MHS
Associate Editor BMJ
joseph.ross@yale.edu

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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 present for the entire meeting: Elizabeth Loder (chair), Angie Wade (statistician), Tim Feeney, Naz Islam, Navjoyt Ladher, Joseph Ross, Jin-Ling Tang, Tiago Villanueva, Di Wang, Wim Weber, Sophie Cook and Emma Rourke (BMJ Medicine editors), Amy Price (patient editor)

Decision: Put points (revise and reconsider)

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

editorial committee. In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Editor's summary:
Ecological study from investigators at the U.S. CDC, who use county-level case surveillance and vaccine administration data reported from December 14, 2020 – August 13, 2021 in order to evaluate the effects of vaccine scale-up on population-level mortality and transmission in the U.S. County level vaccine coverage (for adults, ages 18 and up) was categorized as very low coverage (0-9%), low coverage (10-39%), medium coverage (40-69%), and high coverage (≥70%). Main findings, not surprisingly: Higher vaccination coverage is associated with lower rates of population-level COVID-19 mortality and transmission in the U.S. This is crude and straightforward, but valuable. Important limitations include lack of age-standardization (perhaps this smooths over at the county level?) and no accounting for other public health measures (and that the study is measuring incidence, not transmission).

Statistical editor's comments (in addition, please see official statistical review below - reviewer #3):
- There are concerns of the extent to which transmission can be ascertained. In the list of documentation of new cases, it seems that the date a person is tested is given equal weighting to a laboratory confirmed test or confirmation of COVID-19 by a clinician. This clearly requires some further delineation and sensitivity analyses.
- Regarding the specified sensitivity analyses, these dichotomise coverage at 50% rather than maintaining the 4-category coverage used elsewhere. It would be preferable to use a more refined scale for both. Can coverage be treated as a continuum?
- The weekly data has been aggregated, with a county being deemed to be in the lower vaccination category for two weeks before moving to the next category for analysis purposes. Some investigation of the lag-time used should be given as a sensitivity analysis. This applies whether the coverage is treated as continuous (preferable) or remains in the categorisation mooted (4 categories).
- There does not appear to be any account taken of within county correlation, models should incorporate a random effect for this. There are time trends in coverage which may vary by county and these should be accounted for (or at least investigated) in any analysis. Presumably within each county there was movement in coverage even across the categories as given?
- Is it possible to adjust for any within county variables (for example the age or socio-demographic status of each county)?
- I would like to see more data at the county, or at least jurisdiction, level. What is the range of coverage within counties? Does it vary greatly at the end of follow up (August 2021)? A plot of incidence rates versus coverage percentage over time within jurisdiction (47 lines) would be helpful. And/or a plot summarising change across the 4 coverage categories chosen for the aggregates within county (there are probably repetitive patterns between counties and we should know how often these occur)– to illustrate the data, even if not using in the analyses.
- As this is observational data, 'effect' should be removed where it occurs in the text and replaced by a suitable non-causal inference.

Other editors' comments:
- As a non-American editor, authors need to better explain counties, what they represent as municipalities, for non-U.S. readers.
- Would it be possible to provide some sense of differences by type of vaccine?
- Perhaps the findings will help address vaccine hesitancy, but the authors are too conclusive in their language given the lack of accounting for non-rx, public health intervention variation across U.S. counties.
- Needs to better account for confounding. At a minimum, results should be age-standardized.
- Authors assume that vaccination is the only intervention to account for, while we know that there were so many differences across these counties in the public health measures embraced (large gatherings, eating meals indoors, etc.)
- Could authors quantify whether there is a threshold effect?
- Should pursue more advanced analyses, as had been done in 2 very relevant preprint publications (https://www.medrxiv.org/content/10.1101/2021.11.16.21266360v1.full-text and https://dx.doi.org/10.2139/ssrn.3908476). These studies used rather stronger methodology, and adjusted for a range of county-level variables including NPIs, SES, and so many other variables. The

medRxiv paper used data from more counties than this one. At the least, differences should be explained.
- Authors should comment on waning of vaccine effectiveness, impact of omicron variant.
- Minor:
1) The number of reported cases as a proxy of transmission is not well justified, why not use it directly as secondary outcome?
2) Might be nice to have a table 1 that presented number of counties, number of cases and deaths, number of population, vaccine coverage, county weeks observed…by vaccination coverage categories.
3) Generalizable?
4) Was the county level incidence by 100,000 population also standardised by factors like age and sex?

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
The manuscript describes an important attempt to quantify the public health impact of COVID-19 vaccination as measured by mortality and infection rates as a function of vaccine coverage. This type of ecologic analysis complements ongoing work in assessing the effect of vaccination on the pandemic using individual level data.

line 35ff the authors mention the importance of assessing the effect of population immunity on transmission. However, as they mention, there are multiple unmeasured factors. The outcome should be described throughout the manuscript as COVID-19 infections rates or documented COVID-19 etc. This type of analysis cannot quantify vaccine effects on transmission.

The study did not discuss the effect of age composition on mortality. Would we not expect that counties with a higher proportion of elderly persons would have more COVID mortality? This might not be reflected in overally coverage rates

Results section - would be helpful to show percentages - how did low vacc. counties account for deaths compared to high vacc. It seems that very low accounted for ~50% of cases and deaths while only about 25% of the follow-up cohort
In figure three, each outcome had the primary analysis and 3 sensitivity analyses. The effect measures (squares) were hard to interpret because there was an additional square under the delta-predominance row. Did the rows just move down accidentally?

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Please enter your name: Eric Haas

Job Title: Director of Department of Routine Immunizations

Institution: Israel Ministry of Health

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Reviewer: 2

Recommendation:

Comments:
There have already been, of course, several investigations of the real-world effectiveness of Covid vaccines (i.e. in rollout, beyond clinical trials), but another is very much welcome, especially hen carried out on the vast database available to the US CDC.

The summary results look entirely plausible, and potentially valuable, but I do have some questions about the analysis, as follows.

1. Abstract says "Conclusions: Higher vaccination coverage is associated with lower rates of population-level COVID-19 mortality and transmission in the U.S." In fact, the study apparently does not demonstrate a reduction in transmission (between individuals), only in incidence (within individuals). Transmission might have been reduced, but I think that's not proven in this work.

2. Vaccine "coverage" is defined, quite coarsely, as "at least one dose of a COVID-19 vaccine in adults >= 18yr". But 2 doses are almost certainly more effective, and efficacy also depends on the type of vaccine used (as they say in the intro). So can the data, and the analysis, be disaggregated by these characteristics?

3. "Coverage" is classified into 4 groups, but why not use coverage as a continuous independent x-variable in the analysis, with the unit of analysis being each of the 2512 counties, and the y-variable being incidence or mortality rate?

4. The number of doses is referred to (and apparently dismissed) in sensitivity analysis, but is not considered a possible primary determinant of vaccine effectiveness. They say (line 239) "Our sensitivity analysis defining vaccinated as being fully vaccinated found similar reductions in mortality and transmission." So a second dose, compared to the first only, had no discernible effect? Or was the analysis not done so as to investigate this point (e.g. they only compared IRRs across vaccine coverage groups, which might be the same as in the overall analysis) .

5. Vaccine effectiveness (at population level) should depend, not on coverage at any one moment (week 51 of 2020), but cumulative coverage. They allude to "county-weeks" in the Methods, but I'm not exactly sure what this means, and appears not to be reflected in the definition of coverage (as in 2 above).

6. The incidence rate of cases or deaths in any county will depend on (a) the status of the epidemic in that county and (b) vaccine coverage and effectiveness. So far as I can tell, this analysis does not allow for differences between counties in (a), but surely it ought to, even if a secondary effect. As it stands, variation in (a) would, I guess, introduce extra noise into the analysis. Bias/confounding also needs to be excluded e.g. counties with high vaccine coverage have less COVID-19 for other reasons, such as their populations are wealthier.

7. "8.00 deaths per 100,000 population weekly" (line 174) is presumably the average per week over the period of analysis?

8. "Transmission.181 As vaccination coverage increases, the incidence rate of COVID-19" (line 181). Ass suggested above, I don't think this is necessarily about transmission, but rather individual infection that leads to COVID-19. They don't know how much of the protection is due to herd immunity?

9. Figs 1 and 2 should also plot the CI on points.

Chris Dye 25 November 2021

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Please enter your name: Christopher Dye

Job Title: Professor of Epidemiology

Institution: Oxford University

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Reviewer: 3

Recommendation:

Comments:
There are concerns of the extent to which transmission can be ascertained. In the list of documentation of new cases, it seems that the date a person is tested is given equal weighting to a laboratory confirmed test or confirmation of COVID-19 by a clinician. This clearly requires some further delineation and sensitivity analyses.

Regarding the specified sensitivity analyses, these dichotomise coverage at 50% rather than maintaining the 4-category coverage used elsewhere. It would be preferable to use a more refined scale for both. Coverage should ideally be treated as a continuum (a point raised by reviewer 2).

The weekly data has been aggregated, with a county being deemed to be in the lower vaccination category for two weeks before moving to the next category for analysis purposes. Some investigation of the lag-time used should be given as a sensitivity analysis. This applies whether the coverage is treated as continuous (preferable) or remains in the categorisation mooted (4 categories).

There does not appear to be any account taken of within county correlation, models should incorporate a random effect for this. There are time trends in coverage which may vary by county and these should be accounted for (or at least investigated) in any analysis. Presumably within each county there was movement in coverage even across the categories as given?

Is it possible to adjust for any within county variables (for example the age, population density and/or socio-demographic status of each county)? Is there information on mask wearing and other preventative measures within this dataset that could also be incorporated?

I would like to see more data at the county, or at least jurisdiction, level. What is the range of coverage within counties? Does it vary greatly at the end of follow up (August 2021)? A plot of incidence rates versus coverage percentage over time within jurisdiction (47 lines) would be helpful. And/or a plot summarising change across the 4 coverage categories chosen for the aggregates within county (there are probably repetitive patterns between counties and we should know how often these occur)– to illustrate the data, even if not using in the analyses.

It does seem that there is a lot of data available from this source – weekly counts of coverage and incidence that is not being utilised. Overall the analyses are too simplistic and rely too much on aggregation to fully investigate the information available and address the question posed: is there any association between vaccination coverage at county level and incidence rates (taking into account changes in both over time and any available potential confounders)?

Would it be possible to estimate a level of coverage that is associated with favorable incidence reduction?

As this is observational data, ‘effect’ should be removed where it occurs in the text and title, and replaced by a suitable non-causal inference.

How can the study conclude that vaccination is the best tool to combat COVID-19 on the basis of this study when no other tools were considered or compared?

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Please enter your name: Angie Wade

Job Title: Professor of Medical Statistics

Institution: UCL Great Ormond Street Institute of Child Health

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