Re: Describing the population experiencing COVID-19 vaccine breakthrough following second vaccination in England: A cohort study from OpenSAFELY

4th March 2022

Dear Dr. Lucy Dunbar,

We would like to thank BMC Medicine for considering our proposal, and thank the reviewers for their informed and helpful comments. We are pleased to re-submit the manuscript (number BMED-D-21-02626) entitled "***Describing the population experiencing COVID-19 vaccine breakthrough following second vaccination in England: A cohort study from OpenSAFELY***" for consideration as a Research Article in BMC Medicine. We would also like to extend our sincere gratitude to the Reviewers for their positive and constructive feedback.

We have carefully reviewed the reviewers' comments and provide point-by-point responses to their comments below, describing exactly what amendments have been made to the manuscript text and where these can be viewed. As a result of increasing the follow-up time (as per the reviewers suggestions) we have updated all corresponding tables, figures and numbers in the text accordingly and also added in a few additions to the discussions to reflect on this increased follow-up, these changes are detailed below, after our replies to the reviewers comments. With the increase in the numbers of outcomes, we have been able to include an additional outcome which was previously not included due to small numbers; COVID-19 related critical care admission. In addition, to help inform decisions around rollout of vaccine/booster programmes for patients at high risk of adverse outcomes we have separated out chronic kidney disease from dialysis and transplant. All changes to the manuscript are indicated in the text by yellow highlights.

Due to the longer follow-up time, as expected, there has been a rise in all rates (calculated per 1000 person-years); Positive SARS-CoV-2 test from 12.33 (12.14-12.51) to 98.06 (95% CI 97.93-98.19); COVID related hospitalisation from 0.70 (0.65-0.74) to 2.31 4.77 (4.74-4.8); COVID related death from 0.12 (0.1-0.14) to 0.64 1.07 (1.06-1.09). But reassuringly, breakthrough cases seem to be remaining mild; 579,780 Positive SARS-CoV-2 tests vs 6,435 COVID-19 related deaths, with the majority (~80%) of deaths occurring in those over 70 years of age.

We believe that the revised manuscript is now improved and has addressed all reviewer comments – with textual changes, and more detailed explanations of our methods and assumptions. Our manuscript continues to have important findings which we believe will be of great interest to the general medical community

Thank you again for your consideration.

Yours Sincerely,

Amelia Green and Ben Goldacre, on behalf of the OpenSAFELY collaborative.

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author

I believe this manuscript provides a good analysis of the risk profile for breakthrough infections, and highlights the decreased risk of severe illness with a robust data approach. I will defer to a statistical reviewer for any questions as to whether the time-risk is adequately analyzed (e.g. number of events versus days at risk), and the 43 day follow up is a short interval, but given that this manuscript was looking at breakthrough of fully vaccinated rather than analysis of effects of waning, I think this is appropriate. Ideally, I'd see the short follow up acknowledged as one of the limitations, as well as the fact that the time period predates current strains (e.g. this is pre- Delta). But these are minor points.

Overall, the question of breakthroughs is of interest to clinicians, but is not as novel as it was, particularly given the pre-delta population. Extending to include a longer follow up, and include the Delta era and stratify accordingly, would be useful. The work is well written, referenced, and has appropriate logic. The biggest weakness of this methodology is the lack of a comparator- e.g. there was no control of breakthroughs among fully vaccinated/non boosted, though this is a descriptive work, and thus controls are not strictly necessary. The conclusions are reasonable based on the data shown.

6. Are the methods appropriate and well described?
7. Does the work include the necessary controls?
8. Are the conclusions drawn adequately supported by the data shown?

Response: We thank the reviewer for these positive comments and agree the initial short follow-up was a limitation. We have since extended the follow-up period, and the study now includes data from December 2020 until November 2021 (we chose not to go further than this due to the roll out of booster vaccinations), during which two different variants of SARS-COV-2 were dominating in England at different times; the Alpha variant (B.1.1.7) between January 2021 and May 2021, and the Delta variant (B.1.617.2) after June 2021[1]. Given the longer follow-up, stratifying results by the two variants and comparing the rates would be useful, however accurately determining the presence of certain variants of concern is only possible if an individual's SARS-CoV-2 test is sequenced, which only occurs in a small minority of cases. The completeness and accuracy of data that we have access to which would allow us to compare breakthrough rates between the two variants is therefore limited. In addition, to the issue of vaccine waning, which would need to be accounted for in order to sensibly compare rates, due to the different time periods that the variants dominated, the characteristics of people vaccinated will be different and thus susceptibility to breakthrough infection.

We have acknowledged this as one of the limitations, and have added the following to the bottom of the limitations section of the discussion section on page 8:

This study includes data from December 2020 until November 2021, during which time two different variants of SARS-COV-2 were dominating in England at different times; the Alpha

variant (B.1.1.7) between January 2021 and May 2021, and the Delta variant (B.1.617.2) after June 2021[1]. These have since been supplanted by other variants, in particular the Omicron variant. This is a descriptive study and does not aim to quantify the contribution of vaccine breakthrough due to the change in dominant variant from Alpha to Delta or the extent of waning in the months immediately following vaccination. Further studies are needed to assess vaccine waning and rates of breakthrough COVID-19 between different variants and in newer, more prevalent variants, such as Omicron (B.1.1.529).

We also agree that having a comparator group (i.e. unvaccinated) would be useful for public health messaging but the focus of this study was on describing the population experiencing COVID-19 vaccine breakthrough following second vaccination, for example to inform service use and identify those who remain at high-risk of severe COVID outcomes. The primary aim is to identify those at highest risk among people who have completed the vaccination programme. The study was not intended to compare rates of outcomes between different vaccinated and unvaccinated individuals as such analyses are difficult to conduct robustly given the many complex biases at play, and are being considered by our group in other work.

Reviewer: 2

Comments to the Author

This study includes a large number of individuals who are fully vaccinated and provides descriptive information about those with vaccine breakthroughs. It does not utilize any complex statistics, however there are a number issues that need to be clarified throughout the paper. This includes providing more background information, improving definitions used, and consideration of further discussion related to waning immunity.

Major issues to be addressed:
- The finding that rates of positive SARS-CoV-2 tests were highest 0-4 weeks after full vaccination and decreased with time since being fully vaccinated is confusing. Is it possible that the study included patients that had a positive SARS-CoV-2 test in recent proximity to vaccine dose 2 and the finding of a positive test was co-incidental? Would it be better to exclude anyone with a positive SARS-CoV-2 tests obtained since first vaccination through 2 weeks after dose 2?

Response: we agree that the trend in time since being fully vaccinated rates are confusing and that the rates for 0-4 weeks are higher than expected. As it is possible to continue testing positive for weeks or even months after having the virus, the study does potentially include some patients whose positive SARS-CoV-2 test was related to a previous infection pre second vaccination. However, given that (1) individuals with COVID-19 who have symptoms should wait to be vaccinated until they have recovered from their illness before getting vaccinated and (2) individuals were excluded if they tested positive for SARS-CoV-2 or had been hospitalised or died due to COVID-19 within the two weeks after their second dose (as stated in the second sentence of the study population sub-section of the methods section on page 4), we felt that the 14 day period was long enough to exclude the majority of people whose positive SARS-CoV-2 test was unrelated to the vaccination event.

We agree that excluding anyone with a positive SARS-CoV-2 test obtained since first vaccination through to two weeks after their second dose could help to exclude individuals whose positive SARS-CoV-2 test was coincidental, but given COVID re-infection is increasingly common and that time between first and second vacation could be up to 12+ weeks, excluding anyone with a positive SARS-CoV-2 test obtained since first vaccination could end up excluding a large number of individuals (especially as there a high amount of repeated screening in some of the highest risk groups, i.e., dialysis patients and those in care homes), some of whom may just be more prone to re-infection, which would bias findings.

We have added the following to the limitations section of the discussion on page 8:

While individuals were excluded if they tested positive for SARS-CoV-2 or had been hospitalised or died due to COVID-19 within the two weeks after their second dose, we acknowledge that there is still the potential that some patients will have been included whose outcome was related to a previous infection pre second vaccination, in particular in some of the highest risk groups such as dialysis patients and those in care homes where there a high amount of repeated screening in, resulting in a potential increase in rates.

- It would be helpful to know the predominant circulating SARS-CoV-2 variant(s) during the study period and if breakthrough infections varied based on the predominant variant of the time.

Response: our study now includes data from December 2020 until November 2021 (we choose not to go further than this due to the roll out of booster vaccinations), during which two different variants of SARS-COV-2 were dominating in England at different times; the Alpha variant (B.1.1.7) between January 2021 and May 2021, and the Delta variant (B.1.617.2) after June 2021[1]. Given the longer follow-up, stratifying results by the two variants and comparing the rates would be useful, however accurately determining the presence of certain variants of concern is only possible if an individual's SARS-CoV-2 test is sequenced, which only occurs in a small minority of cases. The completeness and accuracy of data that we have access to which would allow us to compare breakthrough rates between the two variants is therefore limited. In addition, to the issue of vaccine waning, which would need to be accounted for in order to sensibly compare rates, due to the different time periods that the variants dominated, the characteristics of people vaccinated will be different and thus susceptibility to breakthrough infection.

We have acknowledged this as one of the limitations, and have added the following to the bottom of the limitations section of the discussion section on page 7:

This study includes data from December 2020 until November 2021, during which time two different variants of SARS-COV-2 were dominating in England at different times; the Alpha variant (B.1.1.7) between January 2021 and May 2021, and the Delta variant (B.1.617.2) after June 2021[1]. These have since been supplanted by other variants, in particular the Omicron variant. This is a descriptive study and does not aim to quantify the contribution of vaccine breakthrough due to the change in dominant variant from Alpha to Delta or the

extent of waning in the months immediately following vaccination. Further studies are needed to assess vaccine waning and rates of breakthrough COVID-19 between different variants and in newer, more prevalent variants, such as Omicron (B.1.1.529).

-It is curious that there is no discussion related to waning immunity and how that may impact results as one of the groups at higher risk of COVID-19 vaccine breakthrough infection resulting in hospitalization or death was individuals in care-homes who were the first priority group to receive vaccines. Some discussion about this should be added.

Response: we agree that some discussion about waning immunity should be added. We have added the following

"there are concerns that the effectiveness of the vaccines may fade over time, due to the vaccines being less effective against the delta variant, and/or the waning of the immune response"

to the Background section on page 2 and

"There is strong evidence that the UK's COVID-19 vaccination programme has reduced infection and severe outcomes in vaccinated individuals[2,3]. However, breakthrough infections after vaccination against SARS-CoV-2 are increasingly reported[4] and there are concerns that the effectiveness of the vaccines may reduce over time, due to the vaccines being less effective against the delta variant, and/or the waning of the immune response[5]. While we did find that breakthrough infections were more frequent in the earlier-vaccinated individuals, potentially due to waning vaccine efficacy or impaired immune response, further studies are needed to gain a clearer picture of the long-term effectiveness of COVID-19 vaccines."

to the Findings in Context section of the discussion on page 8:

- Please describe what COVID-19 vaccines are being administered and dosing schedule.

We have amended the first paragraph in the background section (page 2) to:

The vaccination programme for COVID-19 in the United Kingdom (UK) was started on 8 December 2020. Vaccination was in order of priority groups determined by the Joint Committee on Vaccination and Immunisation (JCVI) expert advisory group[6]: initially to people aged 80+ years, health and care workers and care home residents, people aged 70-79 and those extremely clinically vulnerable, followed by remaining adults in order of decreasing age or at increased risk. The Medicines and Healthcare products Regulatory Agency (MHRA) has so far approved four COVID-19 vaccines for use in the United Kingdom (UK), with each of the three vaccines currently in use requiring two doses to produce maximum protection[7]. To allow a higher percentage of the population to receive one vaccine dose quicker, second doses initially followed a 12-week interval from the first. This interval has since been shortened. These vaccines and their date of first administration and current second dose schedule are as follows: the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine (BNT162b2; first administered 8 Dec 2020, second dose at least 21 days later); the

Oxford-AstraZeneca ChAdOx1 nCoV-19 vaccine (ChAdOx1; first administered 4 Jan 2021, second dose between 4 and 12 weeks later); the Moderna mRNA-1273 vaccine (mRNA-1273; first administered 7 April 2021, second dose 28 days later); and the Janssen Ad26.COV2.S vaccine (Ad26.COV2.S; not yet administered).

- Median follow-up was only 43 days, why is median follow-up so short if vaccinations began December 8, 2020 and follow-up was through June 30, 2021? Providing more information about the COVID-19 vaccine dosing schedule used in England may inform the shorter duration of follow-up time than one would expect if vaccines were administered 21 days apart (i.e., the median follow-up time for the study is 43 days, however the study period goes from 12/8/2020 - 6/30/21, if only 21 days between vaccine administrations, I would anticipate the median follow-up to be closer to 90 days)

We agree that given the median follow-up time of 43 days when the study period was December 2020 - June 2021 seems short, and is potentially still the case even though the study period is now until November 2021; median follow up is now 149 days. However, the median follow-up time reflects the inclusion of individuals who were not part of the initial priority groups, and who received their second dose much later and thus follow-up time is systematically different amongst individuals included in this study and no adjustment for this has been made. This is reflected in the breakdown of follow-up time by priority group in table 1 and is already highlighted as the second limitation in the limitations section on page 7. In addition, when the vaccines were first rolled out, in order to allow a higher percentage of the population to receive one vaccine dose quicker, second doses followed a 12-week interval from the first. We hope that the additional information now included (as per response above) above about the COVID-19 vaccine dosing schedule used in England will help to make this clearer.

Minor issues:

- Page 4
o Line 9 - "aged over 16" please add "years" to better define age group
Added “years”

o Line 46 - "age 16 or over" - please add "years" - "age 16 years or over". Also, please insert by what date a person must be 16 years or over.
Added “years”.
We have already started by what date a person must be 16 years or over in the last line on page 3: In line with the national reporting specification, most criteria were ascertained using the latest available data at the time of analysis, with the exception of age which was calculated as at 31 March 2021 as recommended by Public Health England.

o Line 56, remove the colon after "of"
Removed

- Page 5
o Line 4, please define HES
Now defined (Hospital Episode Statistics (HES))

o Line 11, please list actual ICD-10 codes used rather than having readers sent to a website
Added (U071, U072). Note we have left the reference as this backs up the use of these codes.

- Page 5/6 - key demographic and clinical characteristics should be combined with codelists and implementation section
The information covered in the "Codelists and implementation" subsection generically describes the derivation of all variables in the study, including inclusion/exclusion criteria and outcomes. It therefore relates to the entire methods section, not just the "covariates" subsection.

We have changed "covariates" to "variables" in this section to reflect this.

- Page 6
o Line 1 - missing ending parenthesis
Removed unnecessary parenthesis rather than adding one.

Additional updates due to extended follow-up time:

Abstract, page 1

Background section

- To reduce word count:
    - Changed “While the vaccines against COVID-19 are considered to be highly effective, COVID-19 vaccine breakthrough is likely and a small number of people will still fall ill, be hospitalised, or die from COVID-19, despite being fully vaccinated. With the continued increase in numbers of positive SARS-CoV-2 tests, describing the characters of individuals who have experienced a COVID-19 vaccine breakthrough could be hugely important in helping to determine who may be at greatest risk.” to “While the vaccines against COVID-19 are highly effective, COVID-19 vaccine breakthrough is possible despite being fully vaccinated. With SARS-CoV-2 variants still circulating, describing the characteristics of individuals who have experienced COVID-19 vaccine breakthroughs could be hugely important in helping to determine who may be at greatest risk.”

Results section

- Added in COVID-19-related critical care admission outcome
- To reduce word count:
    - The last two sentences have been changed from “*when broken down by the initial priority group, higher rates of hospitalisation and death were seen in those in care homes. Comorbidities with the highest rates of breakthrough COVID-19 included renal replacement therapy, organ transplant, haematological malignancy, and immunocompromised*” to “*The highest rates of breakthrough COVID-19 were seen in those in care homes, and in patients with chronic kidney disease, dialysis, transplant, haematological malignancy, or who were immunocompromised*”

Conclusion:

- Added in
    - the emergence of the Omicron variant of COVID-19 coupled with the number of positive SARS-CoV-2 tests still occurring is concerning
    - and boosted
    - to assess vaccine waning and rates of breakthrough COVID-19 between different variants

Results, page 5

Added in

- Testing behaviours varied between priority groups with individuals in care homes testing more regularly than other groups; 91% of care home residents had 3+ SARS-CoV-2 tests since being fully vaccinated vs 41%-73% in other groups.
- COVID-19-related critical care admission outcome
- Updated all numbers in text

Discussion, page 7

Added in

- While it is possible to adjust rates (as demonstrated for patients with chronic kidney disease in Supplementary Table S1) to help inform decisions around rollout of vaccine/booster programme for patients at high risk of adverse outcomes
- the emergence of the Omicron variant of COVID-19 coupled with the number of positive SARS-CoV-2 tests still occurring is concerning
- and boosted
- to assess vaccine waning and rates of breakthrough COVID-19 between different variants

REFERENCES

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