

PEER REVIEW HISTORY

BMJ Medicine publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of BNT162b2 mRNA, mRNA-1273, and ChAdOx1 nCoV-19 vaccines against severe COVID-19 outcomes in a nationwide mass vaccination setting: a cohort study of 11 million vaccinated adults aged 50 years or older and their controls
AUTHORS	Zureik, Mahmoud (contact); Bouillon, Kim; Baricault, Béangère; Botton, Jérémie; Jabagi, Marie-Joëlle; Bertrand, Marion; Semenzato, Laura; Le Vu, Stéphane; Drouin, Jérôme; DRAY-SPIRA, ROSEMARY; Weill, Alain

VERSION 1 - REVIEW

REVIEWER	Reis, Ben: Conflict of Interest - none
REVIEW RETURNED	28-Jan-2022

GENERAL COMMENTS	<p>This is a thorough nationwide study of the effectiveness of three covid-19 vaccines in France. The authors make use of detailed national data sources to study three covid vaccines administered in France. The study is very well organized and the presentation is clear.</p> <p>A few minor comments: (page numbers below refer to the page numbers of the complete pdf document, which may be different than the page numbers printed at the bottom of each page).</p> <p>A. Please include a population flow diagram showing how the final cohorts were arrived at through various stages of exclusion and inclusion criteria.</p> <p>B, p.8 lines 23-30: Some of the codes used in the case definition for COVID-19 seem to not be specific to SARS-CoV-2 infection/COVID-19. How were these codes chosen/were they validated?</p> <p>C. p. 10 line 20: Vaccinated people were "less likely to be infected by SARS-CoV-2" - is this before or after vaccination?</p> <p>D. Would be good to have an English language editor review the text for minor grammar and style items. A few small examples:</p> <p>p.6 of pdf line 16: "Few months after the start of mass vaccination campaigns" ==> "A few months after the start of mass vaccination campaigns"</p> <p>p.6 of pdf line 29: " among relatively small number" ==> "among a relatively small number"</p> <p>p. 11 line 7 "After completing full vaccination schedule" ==> "After completing the full vaccination schedule"</p>
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	<p>p. 12 15: "against Delta variant." ==> " against the Delta variant."</p> <p>p. 12 28: "among smaller number of" ==> "among a smaller number of"</p> <p>p. 12 46: "however" ==> "However"</p> <p>p. 14 8: "showed that three vaccine products, BNT162b2 mRNA, mRNA-1273, and ChAdOx1 nCoV-19 vaccines were" ==> "showed that three vaccine products, BNT162b2 mRNA, mRNA-1273, and ChAdOx1 nCoV-19 were"</p>
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REVIEWER	Bruxvoort, Katia. Conflict of Interest: I have received research funding from Dynavax, Gilead, GlaxoSmithKline, Moderna, Pfizer, and Seqirus.
REVIEW RETURNED	07-Feb-2022

GENERAL COMMENTS	<p>This large cohort study of COVID-19 vaccine effectiveness in France leverages nationwide data on vaccination and COVID-19-related hospitalization and in-hospital death and compares the effectiveness of three different vaccines, including ChAdOx1 nCoV-19. Consistent with other similar studies, the authors report high vaccine effectiveness against COVID-19-related hospitalization and in-hospital death, with limited decline over <6 months. Despite its strengths, the study was conducted prior to and during the delta era, which is less relevant since omicron became dominant. The findings are not particularly novel, but the setting, data sources, and comparison of multiple vaccines add import to this study. I have several comments for consideration.</p> <ol style="list-style-type: none"> 1. Page 4, introduction, and elsewhere: Although “full vaccination” was defined as 2 doses in the Introduction, it would be better to avoid this term as it may differ by country/time period. Please also avoid using “full effectiveness”. 2. Page 4, line 26: In the United States, the second dose of the BNT162b2 is administered 3 doses after the first dose, whereas the second dose of mRNA-1273 is administered 4 weeks after the first dose. Some countries use longer intervals between doses. Please consider revising. 3. Page 6, line 15: Was fast-track PMSI used consistently by all hospitals, or could there be bias in results if not all hospitals consistently used this system? 4. Page 6: Since other data sources were used for vaccine exposures and SARS-CoV-2 test results, can the authors comment on how comprehensive these sources are? Were there any challenges with linking data? 5. Page 6, outcomes: I was surprised that U04.9 was included, as this code is not specific to SARS-CoV-2; was this used for COVID-19 in France? Can the authors explain why codes were used instead of positive SARS-CoV-2 tests, and if this could have led to any misclassification? 6. Page 7, analyses: Were analyses pre-specified? Is there an available protocol, and was there any deviation from the protocol? 7. Page 7, analyses: I am not clear why an analysis was done adjusting only for matching variables. If there are other potential confounders (which there undoubtedly are), these should be included in the model, as in Model 2. 8. Page 8, results: In the main analyses, how is the exposure group
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	<p>handled for those who received different products for first and second dose? Should the analyses excluding these individuals be considered the main analysis, since those who received multiple products could potential have higher protection?</p> <p>9. The sensitivity analysis excluding matched pairs in which the unvaccinated individual became vaccinated is likely more biased because it is excluding individuals based on their future events. For example, those who did not get infected may have been more likely to get vaccinated and excluded, which could then overestimate incidence among the remaining unvaccinated individuals.</p> <p>10. Discussion, limitations: The authors explain that a risk reduction might have been observed in early days after vaccination due to healthy vaccinee bias, but this could also explain the similar reductions in later time points. Please discuss further.</p>
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REVIEWER	Perera, Rafael University of Oxford, Primary Care Health Sciences. Conflict of Interest: Members of my group are carrying out a similar analysis using UK data and have receive funding to do so by AstraZeneca.
REVIEW RETURNED	04-Mar-2022

GENERAL COMMENTS	<p>Large study based on electronic health records to evaluate vaccine efficacy (3 vaccines) for Covid-19 in France during May-Aug 2021 (mainly Beta, Gamma and Delta COVID-19 variants). Well carried out, the large scale and matching strategy allows adequate comparisons to be made.</p> <p>Main potential bias is that of 'healthy receiving vaccines' which is impossible to exclude using this design. This is partially addressed in the Discussion section but might be worth strengthening this discussion with further references of why this occurs and the potential implications. The high effectiveness observed for all vaccines is partially explained by this.</p> <p>The other adjustment required is that of updating manuscript in case further evidence of effectiveness of ChAdOx1 nCoV-19 vaccines has been published. This does not diminish the important findings in this study but might be useful to put the evidence in the right context. Favourable views for publication in BMJ Medicine assuming points above and other Reviewers' comments are addressed.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Ben Reis

Comments to the Author

This is a thorough nationwide study of the effectiveness of three covid-19 vaccines in France. The authors make use of detailed national data sources to study three covid vaccines administered in France. The study is very well organized and the presentation is clear.

Authors' response:

We thank the reviewer for taking the time to assess our manuscript and for this positive comment.

A few minor comments: (page numbers below refer to the page numbers of the complete pdf document, which may be different than the page numbers printed at the bottom of each page).

A. Please include a population flow diagram showing how the final cohorts were arrived at through various stages of exclusion and inclusion criteria.

Author's response to the comment A:

We thank the reviewer for suggesting this. We have now included the population flow diagram as Figure 1.

It was a great challenge to represent graphically the dynamic characteristic of the matching procedure which was undertaken on a daily basis. We tried to overcome this difficulty by giving detailed figure captions. We hope that these captions are sufficiently clear for readers.

B, p.8 lines 23-30: Some of the codes used in the case definition for COVID-19 seem to not be specific to SARS-CoV-2 infection/COVID-19. How were these codes chosen/were they validated?

Author's response to the comment B:

We thank the reviewer for pointing this out.

Among the ICD-10 codes for COVID-19-related hospitalisation we used, listed in the table below, the one which does not seem to be specific to SARS-CoV-2 infection/COVID-19 is U04.9 (severe acute respiratory syndrome, unspecified). We agree with the reviewer's point of view. We have included it in the study as this code was used at the beginning of COVID-19 epidemic. In fact, this code was seldom used at the time of the study: 4 hospitalisations out of 43158. Except for U04.9, all the other codes have been recommended by a national agency, ATIH (Technical Agency for Information on Hospital Care) (<https://www.atih.sante.fr/mise-jour-des-consignes-de-codage-des-sejours-covid-19>).

Code for COVID-19-related hospitalisation Label Frequency Percent

U07.10 COVID-19, respiratory form, virus identified 38970 90.30

U07.11 COVID-19, respiratory form, virus not identified 964 2.23

U07.14 COVID-19, other clinical forms, virus identified 3132 7.26

U07.15 COVID-19, other clinical forms, virus not identified 88 0.20

U04.9 Severe acute respiratory syndrome 4 0.01

Total 43158 100.00

C. p. 10 line 20: Vaccinated people were "less likely to be infected by SARS-CoV-2" - is this before or after vaccination?

Author's response to the comment C:

Indeed, this phrase needs to be more precise. The answer is: "less likely to be infected by SARS-CoV-2 before vaccination".

D. Would be good to have an English language editor review the text for minor grammar and style items. A few small examples:

Author's response to the comment D:

We have followed the reviewer's suggestion in revising our manuscript by an English language editor who works at The Home of Translation (<https://www.maison-de-la-traduction.fr/en/>)

p.6 of pdf line 16: "Few months after the start of mass vaccination campaigns" ==>

"A few months after the start of mass vaccination campaigns"

Author's response:

Thank you. This error has now been corrected.

p.6 of pdf line 29: " among relatively small number" ==> "among a relatively small number"

Author's response:

Thank you. This error has now been corrected.

p. 11 line 7 "After completing full vaccination schedule" ==> "After completing the full vaccination schedule"

Author's response:

Thank you. This error has now been corrected.

p. 12 | 15: "against Delta variant." ==> " against the Delta variant."

Author's response:

Thank you. This error has now been corrected.

p. 12 | 28: "among smaller number of" ==> "among a smaller number of"

Author's response:

Thank you. This error has now been corrected.

p. 12 | 46: "however" ==> "However"

Author's response:

Thank you. This typographical error has now been corrected.

p. 14 | 8: "showed that three vaccine products, BNT162b2 mRNA, mRNA-1273, and ChAdOx1 nCoV-19 vaccines were" ==> "showed that three vaccine products, BNT162b2 mRNA, mRNA-1273, and ChAdOx1 nCoV-19 were"

Author's response:

Thank you. This error has now been corrected.

Reviewer: 2

Dr. Katia Bruxvoort

Comments to the Author

This large cohort study of COVID-19 vaccine effectiveness in France leverages nationwide data on vaccination and COVID-19-related hospitalization and in-hospital death and compares the effectiveness of three different vaccines, including ChAdOx1 nCoV-19. Consistent with other similar studies, the authors report high vaccine effectiveness against COVID-19-related hospitalization and in-hospital death, with limited decline over <6 months. Despite its strengths, the study was conducted prior to and during the delta era, which is less relevant since omicron became dominant. The findings are not particularly novel, but the setting, data sources, and comparison of multiple vaccines add import to this study. I have several comments for consideration.

Authors' response:

We thank the Reviewer for taking the time to assess our manuscript and for this positive comment.

1. Page 4, introduction, and elsewhere: Although "full vaccination" was defined as 2 doses in the Introduction, it would be better to avoid this term as it may differ by country/time period. Please also avoid using "full effectiveness".

Author's response 1:

We have now deleted this term throughout the manuscript and replaced by "two-dose vaccine effectiveness".

2. Page 4, line 26: In the United States, the second dose of the BNT162b2 is administered 3 doses after the first dose, whereas the second dose of mRNA-1273 is administered 4 weeks after the first dose. Some countries use longer intervals between doses. Please consider revising.

Author's response 2:

We have now altered this phrase accordingly:

"12 weeks for ChAdOx1 nCoV-19 versus 4 weeks for mRNA vaccines" has been replaced by "i.e. approximately 12 weeks for ChAdOx1 nCoV-19 versus 4 weeks for mRNA vaccines in France"

3. Page 6, line 15: Was fast-track PMSI used consistently by all hospitals, or could there be bias in results if not all hospitals consistently used this system?

Author's response 3:

Fast track PMSI included data from all French hospitals and was used consistently by all of them. From April to July 2020, this system was asked to be used by all hospitals once a week or once a fortnight. From July 2020, the Technical Agency for Information on Hospital Care (Agence Technique de l'Information sur l'Hospitalisation (ATIH); <https://www.atih.sante.fr>), a public administrative institution overseen by the Minister for Health and Social Security, has made available, monthly, all information related to hospitalisation for COVID-19 through this system (Order of 21 July 2020 amending the order of 23 December 2016 on the collection and processing of medical activity data and the corresponding billing data produced by public or private public or private health establishments with an activity in medicine, surgery, obstetrics and odontology, and the transmission of data on medical activity to the surgery, obstetrics and odontology, and the transmission of information resulting from this processing under the conditions defined in Article L. 6113-8 of the public health code).

We have slightly modified this sentence.

"In April 2020, the French government encouraged hospitals to report all hospital stays due to COVID-19 once or twice a week through an exceptional fast -tracking procedure ("fast -track" PMSI)" has been replaced by "In April 2020, the French government encouraged hospitals to report all hospital stays due to COVID-19 once a week or once a fortnight until July 2020 and then monthly through an exceptional fast track procedure ('fast track' PMSI)"

4. Page 6: Since other data sources were used for vaccine exposures and SARS-CoV-2 test results, can the authors comment on how comprehensive these sources are? Were there any challenges with linking data?

Author's response 4:

Information on COVID-19 vaccine exposures is collected in the national database "VAC-SI" (Système d'Information Vaccin Covid). This database is implemented by the French National Health Insurance Fund which is also responsible for the SNDS. Therefore, we linked both databases without any challenge. Information on SARS-CoV-2 test results is collected in the national database "SI-DEP" (Système d'Informations de DEPistage). This database is managed by AP-HP (Public Hospitals of Paris). This database does not include all individuals positive for SARS-CoV-2 mostly for the following reasons: 1) SARS-CoV-2 tests were not made available in the first months of epidemic, 2) SI-DEP was implemented a few months after the start of epidemic, 3) all results from self-testing SARS-CoV-2 Antigen Rapid Tests were not collected. AP-HP anonymizes SI-DEP using the same algorithm than that used for SNDS. At the time of the study, in the SI-DEP database, it was difficult to distinguish data related to parents from that related to their children aged under 16 years old. Because our study included individuals aged 50 years or older (mean age >65 years old) and information on SARS-CoV-2 test results was used for adjustment purpose, we think potential bias in results related to this is small.

5. Page 6, outcomes: I was surprised that U04.9 was included, as this code is not specific to SARS-CoV-2; was this used for COVID-19 in France? Can the authors explain why codes were used instead of positive SARS-CoV-2 tests, and if this could have led to any misclassification?

Author's response 5:

We thank the Reviewer for pointing out this error.

Among the ICD-10 codes for COVID-19-related hospitalisation we used, listed in the table below, the one which does not seem to be specific to SARS-CoV-2 infection/COVID-19 is U04.9 (severe acute respiratory syndrome, unspecified). We have included it in the study as this code was used at the beginning of COVID-19 epidemic. In fact, this code was seldom used at the time of the study: 4 hospitalisations out of 43158. Except for U04.9, all the other codes have been recommended by a national agency, ATIH (Technical Agency for Information on Hospital Care) (<https://www.atih.sante.fr/mise-jour-des-consignes-de-codage-des-sejours-covid-19>).

We did not consider using positive SARS-CoV-2 tests as 1) our objective was to examine the effectiveness of vaccines against severe COVID-19 and 2) information on SARS-CoV-2 test results was not included in PMSI but in SI-DEP. Given the limitations we had with SI-DEP at the time of the study (please see Author's response 4), it would not have been possible to use it to define outcomes.

Code for COVID-19-related hospitalisation Label Frequency Percent

U07.10 COVID-19, respiratory form, virus identified 38970 90.30

U07.11 COVID-19, respiratory form, virus not identified 964 2.23

U07.14 COVID-19, other clinical forms, virus identified 3132 7.26

U07.15 COVID-19, other clinical forms, virus not identified 88 0.20

U04.9 Severe acute respiratory syndrome 4 0.01

Total 43158 100.00

6. Page 7, analyses: Were analyses pre-specified? Is there an available protocol, and was there any deviation from the protocol?

Author's response 6:

All analyses have been pre-specified based on previously published articles. We have provided below a short protocol for the Reviewer. We did not face any strong deviation from the initial version of protocol. However, our reflection on the present study has consolidated with time according to the course of COVID-19 vaccination campaign in France: 1) mRNA vaccines (BNT162b2 and mRNA-1273) were available first and 2) vaccination was prioritised to health care workers, persons living in nursing homes and those aged 75 years or older, as well as persons with severe or multiple chronic conditions. The first version of the protocol was initially based on mRNA vaccines and among adults aged 75 years or older. Please find below the protocol of our study.

7. Page 7, analyses: I am not clear why an analysis was done adjusting only for matching variables. If there

are other potential confounders (which there undoubtedly are), these should be included in the model, as in Model 2.

Author's response 7:

Model 1 adjusted only for matching variables (minimal set of covariables) corresponds to a "crude" analysis. Model 2 was fully adjusted. We observed that vaccine effectiveness estimates resulting from Models 1 and 2 were very similar. However, interpretation of results was based on results from Model 2.

8. Page 8, results: In the main analyses, how is the exposure group handled for those who received different products for first and second dose? Should the analyses excluding these individuals be considered the main analysis, since those who received multiple products could potentially have higher protection?

Author's response 8:

We thank the Reviewer for pointing out this. For individuals who received different products for first and second dose, we considered that their effectiveness was due to the product of their first dose.

In Table 5 in the Supplemental Material, already present in the previous version, we provide the description of vaccine products for the first and second doses. Those who received different products for first and second dose were highlighted in yellow. There were 2,269 (0.03%) in the BNT162b2 group, 2,800 (0.33%) in the mRNA-1273 group, and 320,295 (9.89%) in the ChAdOx1 nCoV-19 group.

We performed a sensitivity analysis excluding these individuals (Table 6 in Supplemental Material). When we compare these results with those included in Table 2 (main analysis), estimates of two-dose vaccine effectiveness did not change.

In main analysis:

Table 2. Vaccine effectiveness against COVID-19-related hospitalisation by follow-up time intervals

In supplemental material:

Table 6. Two-dose vaccine effectiveness against COVID-19-related hospitalisation after excluding individuals who received different vaccine products between the first and second doses and their matched controls

9. The sensitivity analysis excluding matched pairs in which the unvaccinated individual became vaccinated is likely more biased because it is excluding individuals based on their future events. For example, those who did not get infected may have been more likely to get vaccinated and excluded, which could then overestimate incidence among the remaining unvaccinated individuals.

Author's response 9:

When we compare results from the sensitivity analysis and those from the main analysis (please see below), the difference is small (1%). However, following the Reviewer's comment, we have preferred to delete Table 7 from the Supplemental Material.

In Supplemental Material:

Table 7. Two-dose vaccine effectiveness against COVID-19-related hospitalisation after excluding unvaccinated individuals who became vaccinated and their matched controls

In main analysis:

Table 2. Vaccine effectiveness against COVID-19-related hospitalisation by follow-up time intervals

10. Discussion, limitations: The authors explain that a risk reduction might have been observed in early days after vaccination due to healthy vaccinee bias, but this could also explain the similar reductions in later time points. Please discuss further.

Author's response 10:

We thank the Reviewer for suggesting this. We have now added the following paragraph:

"Indeed, thanks to the matching procedure, vaccinated and unvaccinated groups had a similar proportion of comorbidities except that vaccinated individuals were less likely to be socially disadvantaged, less likely to be infected by SARS-CoV-2 before vaccination, and more likely to be vaccinated against influenza compared to their unvaccinated controls (see Tables 2, 3 and 4 in the Data Supplement). We took into account observed differences by adjusting for these covariables and using specific outcomes related to COVID-19 vaccines.⁷⁹ However, it may be possible that a residual healthy vaccinee bias could have overestimated vaccine effectiveness against severe COVID-19."

Reviewer: 3

Prof. Rafael Perera, University of Oxford

Comments to the Author

Large study based on electronic health records to evaluate vaccine efficacy (3 vaccines) for Covid-19 in France during May-Aug 2021 (mainly Beta, Gamma and Delta COVID-19 variants). Well carried out, the large scale and matching strategy allows adequate comparisons to be made.

Authors' response:

We thank the Reviewer for taking the time to assess our manuscript and for this positive comment.

Main potential bias is that of 'healthy receiving vaccines' which is impossible to exclude using this design. This is partially addressed in the Discussion section but might be worth strengthening this discussion with further references of why this occurs and the potential implications. The high effectiveness observed for all vaccines is partially explained by this.

Authors' response:

We thank the Reviewer for suggesting this. We have now added the following paragraph:

"Indeed, thanks to the matching procedure, vaccinated and unvaccinated groups had a similar proportion of comorbidities except that vaccinated individuals were less likely to be socially disadvantaged, less likely to be infected by SARS-CoV-2 before vaccination, and more likely to be vaccinated against influenza compared to their unvaccinated controls (see Tables 2, 3 and 4 in the Data Supplement). We took into account observed differences by adjusting for these covariables and using specific outcomes related to COVID-19 vaccines.⁷⁹ However, it may be possible that a residual healthy vaccinee bias could have overestimated vaccine effectiveness against severe COVID-19."

The other adjustment required is that of updating manuscript in case further evidence of effectiveness of ChAdOx1 nCoV-19 vaccines has been published. This does not diminish the important findings in this study but might be useful to put the evidence in the right context. Favourable views for publication in *BMJ Medicine* assuming points above and other Reviewers' comments are addressed.

Authors' response:

Thank you for this suggestion. From the last literature review on COVID-19 vaccine effectiveness undertaken on the 10 December 2022, we have updated with that of the 8th April 2022. We found 12 new articles^[1–12] related to our study that we have referenced in the present version.

1 Saciuk Y, Kertes J, Mandel M, et al. Pfizer-BioNTech vaccine effectiveness against Sars-Cov-2 infection: Findings from a large observational study in Israel. *Prev Med* 2022;155:106947. doi:10.1016/j.ypmed.2021.106947

2 Fabiani M, Puopolo M, Morciano C, et al. Effectiveness of mRNA vaccines and waning of protection against SARS-CoV-2 infection and severe covid-19 during predominant circulation of the delta variant in Italy: retrospective cohort study. *BMJ* 2022;376:e069052. doi:10.1136/bmj-2021-069052

3 Andrews N, Tessier E, Stowe J, et al. Duration of Protection against Mild and Severe Disease by Covid-19 Vaccines. *N Engl J Med* 2022;386:340–50. doi:10.1056/NEJMoa2115481

4 Wright BJ, Tideman S, Diaz GA, et al. Comparative vaccine effectiveness against severe COVID-19 over time in US hospital administrative data: a case-control study. *Lancet Respir Med* 2022;;S2213-2600(22)00042-X. doi:10.1016/S2213-2600(22)00042-X

5 Nordström P, Ballin M, Nordström A. Risk of infection, hospitalisation, and death up to 9 months after a second dose of COVID-19 vaccine: a retrospective, total population cohort study in Sweden. *Lancet Lond Engl* 2022;399:814–23. doi:10.1016/S0140-6736(22)00089-7

6 Lin D-Y, Gu Y, Wheeler B, et al. Effectiveness of Covid-19 Vaccines over a 9-Month Period in North Carolina. *N Engl J Med* 2022;386:933–41. doi:10.1056/NEJMoa2117128

7 Nasreen S, Chung H, He S, et al. Effectiveness of COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe outcomes with variants of concern in Ontario. *Nat Microbiol* 2022;7:379–85. doi:10.1038/s41564-021-01053-0

8 Robles-Fontán MM, Nieves EG, Cardona-Gerena I, et al. Effectiveness estimates of three COVID-19 vaccines based on observational data from Puerto Rico. *Lancet Reg Health Am* 2022;9:100212. doi:10.1016/j.lana.2022.100212

9 Arregocés-Castillo L, Fernández-Niño J, Rojas-Botero M, et al. Effectiveness of COVID-19 vaccines in older adults in Colombia: a retrospective, population-based study of the ESPERANZA cohort. *Lancet Healthy Longev* Published Online First: 21 March 2022. doi:10.1016/S2666-7568(22)00035-6

10 Bruxvoort KJ, Sy LS, Qian L, et al. Effectiveness of mRNA-1273 against delta, mu, and other emerging variants of SARS-CoV-2: test negative case-control study. *BMJ* 2021;375:e068848. doi:10.1136/bmj-2021-068848

11 Katikireddi SV, Cerqueira-Silva T, Vasileiou E, et al. Two-dose ChAdOx1 nCoV-19 vaccine protection against COVID-19 hospital admissions and deaths over time: a retrospective, population-based cohort study in Scotland and Brazil. *Lancet Lond Engl* 2022;399:25–35. doi:10.1016/S0140-6736(21)02754-9

12 Rearte A, Castelli JM, Rearte R, et al. Effectiveness of rAd26-rAd5, ChAdOx1 nCoV-19, and BBIBP-CorV vaccines for risk of infection with SARS-CoV-2 and death due to COVID-19 in people older than 60

years in Argentina: a test-negative, case-control, and retrospective longitudinal study. *Lancet Lond Engl* 2022;399:1254–64. doi:10.1016/S0140-6736(22)00011-3