PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of Influenza Vaccination on GP-Diagnosed COVID-19 and All-Cause Mortality – A Dutch Cohort Study
AUTHORS	van Laak, Arjan; Verhees, Ruud; Knottnerus, André; Hooiveld, Mariëtte; Winkens, Bjorn; Dinant, Geert-Jan

VERSION 1 – REVIEW

REVIEWER	Hosseini-Moghaddam, Seyed M University Health Network, University of Toronto
REVIEW RETURNED	12-Apr-2022

GENERAL COMMENTS	Data in this study were collected from an extensive database of General practitioners in the Netherland. The main issue in this cohort is the outcome definition. Otherwise, I do not see any specific methodological point. The observation period to detect the outcome was limited to March 2020 (when the 1st case of COVID-19 was diagnosed in the Netherland) to November 2020 (when diagnostic codes of COVID-19 were introduced). PCR testing was introduced in the middle of the observation period (I.e., June 2020). The outcomes were not confirmed and were not virologically proven. Patients with COVID-19 have a clinical diagnosis. According to the study method, COVID-19 diagnosis codes were introduced in Nov 2020 when observation period for COVID-19 diagnosis in this cohort was closed. Thus, all acute infections of upper airways, other respiratory infections, influenza, pneumonia, and broad medical terms such as "other viral disease", "other infectious disease", "shortness of breath", or "coughing" were considered a positive outcome. I would suggest to modify the outcome of interest in this cohort to " respiratory tract infection during COVID-19 pandemic".

REVIEWER	Rodrigues, Agatha Statistics Department of Mathematics and Statistics Institute (EMI) – USP
REVIEW RETURNED	22-Apr-2022

GENERAL COMMENTS	The manuscript is well written and it has interesting objectives. You can find below some issues: 1) The p-values should be presented in Table 1 2) What do you mean by "If patients died before being clinically diagnosed COVID-19, then they were considered censored in the clinically diagnosed COVID-19 analysis"?Are they censored at what time? Time zero? This part should be better explained.

	3) In the sentence "For the all-cause mortality models, clinically diagnosed COVID-19 was also incorporated in the models as a covariable" what information from clinically diagnosed COVID-19 was included? 4) Please share the dataset and statistical code for reproducibility.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Seyed M Hosseini-Moghaddam, University Health Network
Comments to the Author:
Data in this study were collected from an extensive database of General practitioners in the Netherland. The main issue in this cohort is the outcome definition. Otherwise, I do not see any specific methodological point. The observation period to detect the outcome was limited to March 2020 (when the 1st case of COVID-19 was diagnosed in the Netherland) to November 2020 (when diagnostic codes of COVID-19 were introduced). PCR testing was introduced in the middle of the observation period (I.e., June 2020). The outcomes were not confirmed and were not virologically proven. Patients with COVID-19 have a clinical diagnosis.
According to the study method, COVID-19 diagnosis codes were introduced in Nov 2020 when observation period for COVID-19 diagnosis in this cohort was closed. Thus, all acute infections of upper airways, other respiratory infections, influenza, pneumonia, and broad medical terms such as "other viral disease", "other infectious disease", "shortness of breath", or "coughing" were considered a positive outcome. I would suggest to modify the outcome of interest in this cohort to " respiratory tract infection during COVID-19 pandemic".

We thank Dr. Hosseini-Moghaddam for the elaboration and suggestion to change the outcome definition. We understand that the term ‘clinically diagnosed COVID-19’ was not clear and we have now modified the outcome in all parts of the manuscript (abstract, main document and the supplementary data section). We would propose to change the term to ‘GP-diagnosed COVID-19’, because the outcome is a subset of acute respiratory infections and this way, it provides better coverage of the actual outcome. The diagnosis has been made by a general practitioner who recorded the symptoms as indicating a COVID-19 infection. This diagnosis could have been given because there was a suspicion (by symptoms and/or by given circumstances such as test-confirmed COVID-19 positive housemates) or it could have been supported by a laboratory (COVID-19) confirmation (mostly after June 2020). In our study design/data collection, we have differentiated between ‘no COVID-19’ and (GP-diagnosed) COVID-19 cases.

Reviewer: 2
Mrs. Agatha Rodrigues, Statistics Department of Mathematics and Statistics Institute (EMI) – USP
Comments to the Author:
The manuscript is well written and it has interesting objectives. You can find below some issues:
1) The p-values should be presented in Table 1
We also thank Mrs. Rodrigues for the review and the suggestions. We understand the rationale of presenting the p-values in Table 1. We have now incorporated the p-values in Table 1 and we would case suggest modifying the table by including an extra column (at the right side) with all p-values and by removing the asterisks. Please note that we have changed the term ‘clinically diagnosed COVID-19’ to ‘GP-diagnosed COVID-19’, as a change was proposed by Dr. Hosseini-Moghaddam.

2) What do you mean by "If patients died before being clinically diagnosed COVID-19, then they were considered censored in the clinically diagnosed COVID-19 analysis"? Are they censored at what time? Time zero? This part should be better explained.
We agree that this is unclear. We meant that if –in our database– the date of death was earlier than the recording date of clinically diagnosed COVID-19, we equalized the date of clinical COVID-19 diagnosis and date of death. This could be caused by a registration delay such as a waiting time for a COVID-19 test result. As this happened a maximum of 3 times, we propose to omit this sentence from the manuscript. It would be an irrelevant and confusing part of the methods section, especially since it is a large sample size.

3) In the sentence "For the all-cause mortality models, clinically diagnosed COVID-19 was also incorporated in the models as a covariable" what information from clinically diagnosed COVID-19 was included?
We agree that this is unclear, as this is also an outcome of our study. We have now adjusted the sentence and clarified the sentence by adding 'status' (yes vs no) to it.
We have included the COVID-19 status as a covariable. As we hypothesized it would be valuable to incorporate the COVID-19 status as a predictor in the mortality models, we have included it as a covariable in all-cause mortality models. So, if patients were diagnosed with COVID-19 (by a GP and/or laboratory confirmation), patients were labelled as 'yes' for this (yes vs. no) covariable.

4) Please share the dataset and statistical code for reproducibility.
We have shared the dataset and statistical code in the BMJ Open portal. In terms of reproducibility, we structured the SPSS-Syntax (so it is easy to follow) and we also ran all analyses again and double-checked the outcomes. Please note that in some cases, Hazard Ratios were corrected (mostly by just ±0.01 and never for our main variable 'influenza vaccination'). We suspect that this could have been caused by using a newer SPSS version this time, but it did not impact any of the conclusions or discussion points. The syntax 'guide' is as follows: for the analyses corresponding with Table 1 and Figures 1–4 in the manuscript, (syntax) steps 9–13 can be followed, respectively.

Please find attached a revised version of our manuscript. We hope that the revisions in the manuscript and our response will be sufficient to make our manuscript suitable for publication in the BMJ Open.