Bad science is a feed for disinformation and scientific negationism.

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1. Introduction

The recent publication from the Frontiers of Medicine, *"Evaluation of post-COVID mortality risk in cases classified as severe acute respiratory syndrome in Brazil: a longitudinal study for medium and long term"* by Rodrigues NAC et Andrade MKN[1] sparked controversy on social media as its biased results gave rise (once again) to negationist, anti-vaccine voices within society. The study was received with surprise by the scientific community due to its unexpected conclusion: the protective effect of COVID-19 immunization lasted for one year after symptoms onset, after which "the effect was reversed, showing an increased risk of death for those vaccinated."

It is crucial to highlight the study's many methodological flaws. Additionally, we emphasize the importance of abiding to established scientific protocols for reporting results (which might have avoided the selection and information bias in the study), as well as to the need of relying on reviewers acquainted to the subject of the study. Unfortunately, as detailed below, none of these conditions were met when publishing the study.

2. Pitfalls to address

The reviewing process

The authors aimed to evaluate the impact of an intervention (the COVID-19 vaccine). Impact evaluation in health is a specialized field of knowledge that is frequently discussed but not always thoroughly understood, as seems to be the case here. One reviewer is a computer scientist with training in bioinformatics, and the other is a specialist in nanotechnology – neither of whom has qualifications in public health, epidemiology, evaluation, or quantitative analysis methods that would enable them to serve as qualified reviewers for the article.

The mischaracterization of the study design

To "*investigate the factors associated with post-COVID mortality of severe acute respiratory syndrome (SARS) cases from 2020 to 2023*", the authors used the SIVEP-Gripe database. This is a national epidemiological surveillance database in Brazil,

managed and made publicly available by the Ministry of Health (MoH), implemented in 2009 in response to the H1N1 pandemic. It gathers data on hospitalized and/or deceased cases of SARS. The SIVEP is a passive surveillance system relying upon the active notification of cases by health professionals. The authors used data on COVID-19 cases from 2020 to 2023, including date of first symptoms, vaccination status, outcome, as well as comorbidities and socio-economic data.

The authors described the study as a "retrospective cohort", which is technically inaccurate since a cohort implies the use of longitudinal data. This is not the case with SIVEP, where data is reported irrespectively of the sequence of symptoms onset and vaccination dates. Vaccination data is linked from the National Vaccination Information System (SIPNI), but the authors did not mention whether (or how) the time interval between vaccination and symptoms onset was considered. Therefore, it cannot be assumed that the exposure (vaccination) preceded the outcome, a fundamental requirement of cohort studies. This bias of information is too important to be ignored. Moreover, it is important to note that SIPNI is a reliable and internationally recognized information system that was largely used for Covid-19 vaccine efficacy and safety studies.[2-4]

Furthermore, the analytical techniques are inadequately described, lacking a clear definition of essential aspects such as the timescale employed in the Cox models, and there is no well-defined rationale for the choice. For instance, the authors include hospitalization as a predictor, which, in fact, acts as a mediator in the causal pathway between COVID-19 and death. It must be added to the issue that the database includes only hospitalized cases or deaths occurring inside the hospital.

Selection bias

Using the SIVEP as the sole information source for sampling for the proposed analysis was a completely misguided option, generating a cascade of errors that inevitably invalidate any statistical inference.

All analyses were based on a biased selected sample, which might go unnoticed by readers unfamiliar with SIVEP (as it likely did for the reviewers). However, this error could be easily identified if the protocols for reporting scientific findings such as the STROBE or RECORD checklist) were followed. On the contrary, the methodology description in the manuscript fails to clarify inclusion and exclusion criteria. Additionally, the study population description is misleading as it doesn't emphasize that the study population is limited to patients who "remained hospitalized and alive" three months after symptoms onset (indeed, sample selection was described in two instances, but the term 'hospitalized' was never mentioned). The SIVEP focuses on acute cases, and records showing deaths months or years post symptoms onset likely reflect data entry mistakes. We evaluated the SIVEP database, and approximately 99% of cases fall within 84 days of the first symptoms, and only 0.07% happen more than 1 year after.[5]

From this "major mistake" (let's call it that), the results presented are most likely the outcome of systematic errors classically described in epidemiology: selection bias and survival bias, which are outlined below:

a) The study automatically excludes all cases of vaccinated individuals who were not hospitalized (and the lower hospitalization and death rates among vaccinated individuals

compared to unvaccinated individuals have already been widely reported in previous robust studies);[2-4,6]

b) By using data restricted to SARS hospitalization, only deaths directly or indirectly related to SARS were counted, making the criteria "not directly attributable to COVID-19" designed in the paper a flaw. To assess deaths "not directly attributable to COVID-19," the authors should evaluate all-cause mortality in the period, not restricting to those hospitalized or deceived due to SARS.

c) Since all cases with discharge or death within three months of symptoms onset are excluded, only cases who survived the most critical period (i.e., when the highest proportion of deaths occurs among COVID-19 patients) were included. It is thus plausible to assume there would be a higher proportion of vaccinated individuals among the less severe patients, i.e., those who survived the critical period of the disease. The fact that the study does not show a flowchart with quantities of individuals in each of these phases by outcome and exposure categories demonstrates a lack of expertise in reporting the results of epidemiological studies and a carelessness in presenting results with such a significant impact on public health decisions.

3. Discussion

It is concerning that neither the authors nor the reviewers or editors took the time to carefully examine the results of a study that contradicts what other studies have consistently shown in recent years. Failing to address limitations of data sources and potential bias deriving from choices made during epidemiological analysis potentially affects the scientific community as a whole. Scientists and publishers alike should abide by the responsibility of reporting scientific results. Using well-established and openly available checklists for reporting results and choosing field-specific competent reviewers are easy approaches for avoiding this awkward and harmful situation.

In this comment, we have briefly highlighted some flaws committed by the authors when producing the manuscript. Additionally, it is pertinent to address the publishing entity behind the journal *Frontiers in Medicine*, Frontiers Media. This editorial group has experienced rapid expansion in recent years and comprises numerous journals across diverse fields. Notably, the group has previously been categorized as a predatory publisher. This and other facts raise concerns about its commitment to promoting reliable scientific communication[7], as exemplified by the publication of the manuscript under discussion. Nevertheless, it is important to emphasize that Brazilian researchers widely utilize Frontiers journals to disseminate their scientific work.

Finally, we recommend that the authors provide the original dataset along with a detailed explanation of the data-extracting process, including inclusion and exclusion criteria, to enable an independent reanalysis to assess the impact of COVID-19 vaccination on late mortality.

References

1   *Rodrigues NCP, Andrade MKN. Evaluation of post-COVID mortality risk in cases classified as severe acute respiratory syndrome in Brazil: a longitudinal study for medium and long term. Front Med (Lausanne). 2024 Dec 18;11:1495428. doi: 10.3389/fmed.2024.1495428.*

2   Cerqueira-Silva T, Katikireddi SV, de Araujo Oliveira V, Flores-Ortiz R, Junior JBS, Paixão ES, Robertson C, Penna GO, Werneck GL, Barreto ML, Pearce N, Sheikh A, Barral-Netto M, Boaventura VS. Vaccine effectiveness of heterologous CoronaVac plus BNT162b2 in Brazil. Nat Med. 2022; 28:838–843. doi.org/10.1038/s41591-022-01701-w

3   Katikireddi SV, Cerqueira-Silva T, Vasileiou E, Robertson C, Amele S, Pan J, Taylor B, Boaventura VS, Wreck GL, Flores-Ortiz R, Agrawal U, Docherty AB, McCowan C, McMenamin J, Moore E, Ritchie LD, Rudan I, Shah SA, She T, Simpson CR, Barreto ML, de Araujo Oliveira V, Barral-Netto M, Sheikh A. 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. 2022; 399:25–35. doi.org/10.1016/ S0140-6736(21)02754-9

4   Florentino PVT, Millington T, Cerqueira-Silva T, Robertson C, de Araújo Oliveira V, Júnior JBS, Alves FJO, Penna GO, Katikireddi SV, Boaventura VS, Werneck GL, Pearce N, McCowan C, Sullivan C, Agrawal U, Grange Z, Ritchie LD, Simpson CR, Sheikh A, Barreto ML, Rudan I, Barral-Netto M, Paixão ES. Vaccine effectiveness of two-dose BNT162b2 against symptomatic and severe COVID-19 among adolescents in Brazil and Scotland over time: a test-negative case-control study. Lancet Infect Dis. 2022; 22:577–86. doi.org/10.1016/S1473-3099(22)00451-0

5   Cerqueira-Silva T, Barral-Netto M, Boaventura VS. A má ciência ameaça a saúde pública: como análises incorretas fazem vacinas parecerem perigosas. The Convesation Brasil. https://theconversation.com/a-ma-ciencia-ameaca-a-saude-publica-como-analises-incorretas-fazem-vacinas-parecerem-perigosas-247172

6   HDR UK COALESCE Consortium. Undervaccination and severe COVID-19 outcomes: meta-analysis of national cohort studies in England, Northern Ireland, Scotland, and Wales. Lancet. 2024; 403:554–66. doi.org/10.1016/ S0140-6736(23)02467-

7   *Wikipedia, The Free Encyclopedia*. Frontiers Media. *Available at* https://en.wikipedia.org/w/index.php?title=Frontiers_Media&oldid=1268128650. *Accessed* 15 Jan 2025.