A debate on the paper

“Global Estimates of Lives and Life-Years Saved by COVID-19 Vaccination During 2020-2024

by J.P.A. Ioannidis et al., JAMA Health Forum July 2025;6;(7):e252223.

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This comparative effectiveness study found that COVID-19 vaccinations averted 2.5 million deaths during 2020-2024 (sensitivity range estimates, 1.4-4.0 million) and saved 15 million life-years (sensitivity range estimates, 7-24 million life-years). The estimated benefits was mostly limited to a minority of the population of older individuals.

Alberto Donzelli and Paolo Bellavite have written a commentary to this paper with the title “COVID-19 vaccines and mortality. The debate on lives saved is far from over”. The commentary was published on August 25, 2025 in the same Journal under the original paper.

The effectiveness of COVID-19 vaccination campaigns is still the subject of considerable debate, and estimates vary widely, depending on the data sources and epidemiological models used. Furthermore, there may be obvious differences depending on the age of the affected patients, the circulating variant-of-concern period, and different regions of the world.

In a recent paper (1) Ioannidis et al. provide estimates of overall benefit from COVID-19 vaccination, by calculating the number of lives saved worldwide over the period 2020-2024. The article received a lot of media coverage and was used to support the validity of past vaccination campaigns. This analysis estimates the benefit of vaccination in terms of lives saved globally at approximately 2.5 million, a much more conservative conclusion than previous calculations that gave estimates of between 14 and 20 million for the first year of vaccination alone (2). Another merit of the cited publication is that it confirmed and consolidated the evidence that the benefits in terms of lives saved concerned almost exclusively the most advanced ages, a very important piece of data for evaluating the vaccination strategies implemented.

The article is interesting and documented, but in our view there are some methodological aspects that still need to be considered. The Authors state that prior studies… depend on strong modeling assumptions with unaccounted uncertainty. However, also they depend on strong modeling assumptions, and the fact of admit the uncertainty intervals does not guarantee valid estimates. There is no attempt to cross-check these modeled ‘lives saved’ against observed mortality trends in highly vaccinated vs. less vaccinated populations. They don’t cross-check against real data even the hypothesis that vaccinating the youngest may protect the elderly, although they admit that VE against infection rapidly wanes.

Indeed, the problem well beyond VE waning is its negativization, as clearly showed by multiple researches. Eg, even the young Qatar population showed a progressive, dramatic VE negativization since seven months after the booster/third dose (3). Regarding the fourth dose (vs. no vaccine), Ioannidis himself co-authored an Austrian nationwide retrospective study (4), showing that hazard ratio against SARS-CoV-2 infection was nearly 8, in about four millions of previously infected individuals, age and gender adjusted, after seven months since the last dose. A significant VE negativization has begun since the second month. Even the VE against mortality decreases over time, making unreliable the authors (1) fixed assumptions of VE 75% before Omicron and 50% during Omicron.

We agree that a comprehensive assessment of the effectiveness of vaccination campaigns must include not only estimates of COVID-19 mortality, but also all-cause mortality. While it is generally believed that in elderly population the fatal adverse effects of vaccines are rarer than those of COVID-19, it must also be recognized that in general the assessments were made in the short term, and it is difficult to rule out that chronic diseases such as autoimmune, cardiovascular, or neurological conditions (e.g. cognitive decline)

could influence the medium-to long-term effects of vaccines. In any case, it is important to consider the results of cohort studies with long follow-up and a careful correction of major confounding factors afflicting the observational studies, or at least keeping them in mind, when a proper adjustment is impossible (such as for the healthy-vaccinee bias, or for the case-counting window bias).

Indeed, real mortality data were calculated in the population of an Italian Province (5) that released the mortality data by vaccination status, allowing a long follow-up: 2021 and 2022. In this Province, the careful correction for the immortal-time bias, common in observational studies, nullified any mortality benefit of the 3rd COVID-19 vaccine doses compared to the unvaccinated. Moreover, a significant higher mortality was confirmed in people vaccinated with 1 or 2 doses (5).

Consistently, a retrospective analysis by age groups and vaccination status of the data published by the UK Office for National Statistics (ONS) from April 2021 to May 2023 (6), led to similar conclusions. Indeed, across all age groups, all-cause standardized mortality ratios (SMRs) of ever vaccinated were initially much lower than 1 (using the value of the unvaccinated as a reference). However, as the months pass, the vaccinated SMRs increased in a linear way, and for the 18-39, 80-89 and 90+ age groups they exceeded the reference value by May 2023, when the ONS stopped publishing the mortality data by vaccination status. Provided the (similar) trend is maintained for the other age groups, the date at which each SMR would surpass 1 was predicted, at the latest within one year after the ONS data were no longer published. Interestingly, non-COVID-19 SMRs' trends were very similar to all-cause mortality trends, suggesting biases in the ONS dataset, as it is implausible that COVID-19 vaccines protect against non-COVID-19 deaths, very strongly soon after the vaccinations, and then with declining protection (until it reverses, at least in the age groups indicated above).

Not only all-cause deaths, but even COVID-19 deaths may reserve counterintuitive surprises, when analyses are based on real data and not on unverified assumptions. For instance, a study (7) compared the COVID-19 deaths between the pre-vaccines and the vaccination eras, to observe how vaccination impacted COVID-19 vaccination trajectory worldwide. The death numbers originate from a complete enumeration and census of every COVID-19 deaths reported to World Health Organization (WHO) from all countries, territories and regions of the world. This involves no sampling procedure nor forecasted deaths from mathematical modeling, with its limitations and biases that could undermine the projections accuracy. The COVID-19 deaths and vaccination rates in WHO database till June 2023 showed that COVID-19 mortality increased in the vaccination era, especially in regions (Europe, Americas) with higher vaccination coverage. Waiting to explain how much of these differences is attributable to different elderly percentages, these results caution against relying on models not validated by comparison with real data.

In conclusion, we believe that speculations about the risk/benefit ratio of COVID-19 vaccination campaigns are still premature. Indeed, too many variables are still not well defined, and this currently does not allow for sufficiently valid estimates.

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