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A response to "Global estimates of lives and life-years saved by COVID-19 vaccination during 2020-2024", by John Ioannidis et al.

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A response to "*Global estimates of lives and life-years saved by COVID-19 vaccination during 2020-2024*", by John Ioannidis et al.

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Introduction

In this paper [1], John Ioannidis and colleagues estimate the number of lives (and life years) saved worldwide by the Covid vaccinations, by using very simple and straightforward mathematical modelling, based among other things on rough estimates of the Infection Fatality Rate (IFR) and Vaccine Effectiveness (VE). Based on their analysis, they estimate that approximately 2.5 million deaths were averted worldwide, and approximately 15 million life years were saved in 2020-2024. This is actually at least an order of magnitude lower than the most-cited earlier estimates (which is in itself remarkable and shows how variable these estimates can be), but nevertheless suggests large numbers of lives saved by the vaccines.

While we generally appreciate Ioannidis' work, this is not at all a convincing paper. The main thing to realize is that this is a *modeling* study, based on many very debatable assumptions, captured in parameters such as assumed VE and assumed IFR per age stratum and so on. Everything depends on those assumptions and the model. In that sense, the model will just tell you what you, as a researcher, put in. Assume a positive VE and assume some IFR even just a little bit higher than 0, and you will 'find' (the model will say that) the vaccines saved many lives (and life years).

Perhaps the best thing about this paper is that Ioannidis et al. are at least open about all this, and in multiple places emphasize that the assumptions may be incorrect and that many things are unclear

and uncertain. But an experienced researcher like Ioannidis should know that those nuances will get lost in the general coverage of the paper, and people (especially those who are defending the vaccines and whose impartiality may be questioned, like policy makers and their advisers) will just say: "You see, even Ioannidis, always so critical of Covid-policies, has shown that the vaccines saved millions of lives!". We do not think this is a justified conclusion at all, which we will explain now.

As we already mentioned, this is a modeling paper. Assumptions and model choices are unavoidable when modeling, but for the model outcomes to be relevant and realistic, the assumptions and the modeling approach must both be reasonable. Are they? We claim that this is not the case. Again, to be fair, Ioannidis et al. do discuss this in some detail, and admit the large uncertainties and their worries about many of them. It is worth looking into some of them detail – to see how reasonable they actually are. We discuss four (interrelated) assumptions and choices, namely:

1. IFR estimates;
2. VE estimates;
3. Ignorance of adverse events;
4. The (implicit) decision to model 'Covid deaths' as something independent of other (or all) causes of death.

IFR

By their own admission, despite claiming in some places that their IFR estimates are "conservative", their IFR estimates may in fact be overestimations for 2021 and beyond (when vaccines were available), because they are based on 2020 data. In their words:

"Moreover, our IFR estimates are derived from national seroprevalence studies before vaccination. For unvaccinated individuals, IFR in the second year (the pre-Omicron period that matters for calculation of lives saved) may have been lower with some effective treatments (e.g. dexamethasone) becoming available, better organization of healthcare services, and more experience in managing severe COVID-19."

Going much further than these carefully phrased remarks, there is now strong evidence that certainly in the first few Covid waves (in 2020), treatment of Covid was far from ideal; remember the discussion around (overuse of) ventilation, the lack of proper antibiotic treatment of secondary pneumonia often accompanying the Covid viral infection, et cetera. Regardless of any potential criticism of treatment in that early period (that is beside the point here), we cannot generalize IFR from 2020 to 2021 and beyond, for many reasons:

1. Besides vaccines, more knowledge and more effective treatments were available;
2. A significant portion of the most Covid-vulnerable part of the population had died (e.g. in nursing homes);
3. The first waves in an epidemic are typically the worst;
4. There was already substantial natural immunity from previous (often undetected) infections among many people.

It is, therefore, quite likely that the IFR in 2021, and even more in 2022 and later (Omicron-period), was significantly lower than what was estimated in, and for, 2020 – and therefore should be lower in these model calculations.

Having said that, a positive thing about this paper is that at least it makes an effort to take into account much lower and more realistic IFR for young people in general, much lower IFR in the Omicron period (2022-2024), and the impact of natural immunity from previous infection on IFR.

VE

As for the VE estimates, the authors write:

"Vaccine effectiveness for death: we assumed VE = 75% during the pre-Omicron period and 50% during the Omicron period. This is an aggregate estimate considering the large heterogeneity of vaccination experiences (different vaccines, some of which had probably lesser effectiveness than others), waning effectiveness especially with long term follow-up, and also different vaccination experiences including many people who received only one or two doses in the pre-Omicron period."

Are these reasonable estimates? Given the original Covid vaccines trial results, as well as many peer-reviewed observational studies, they may appear to be, and appear to even be "conservative", as claimed. The original Covid vaccines trials claimed very high VE, much higher than this 50 to 75%: the trials reported 80-95% against symptomatic infection, and 95-100% against Covid hospitalization and Covid death (highest for the novel mRNA vaccines which were eventually used the most). However, later re-analyses of those trials (e.g. by Christine Stabell-Benn [2]) suggest that their external validity is limited and doubtful, especially when it comes to mortality. This is due to several factors (among others):

1. A very limited follow-up time of only several months after vaccination (after which protection against infection wanes quickly);

2. Counting the first few weeks after vaccination as being 'unvaccinated' (or 'vaccination incomplete'), when in fact infection probability appears to be actually increased during that time window;

3. A lack of focus on all-cause mortality (ACM; as opposed to symptomatic Covid infection or Covid death), whereas ACM metrics show little to no benefit for the vaccines in the trials;

4. Under-representation of vulnerable groups in the trials (those most vulnerable to Covid and with the weakest immune system), making external validity doubtful.

This means that those clinical trials almost certainly vastly overestimated real-world VE.

Not surprisingly, retrospective observational studies, performed later after large-scale roll-out in the real world, show very mixed results and cast doubt on actual real-world ACM protection. There is no consensus at all about what a realistic real-world VE is, but there is consensus that it is much lower than those 90-100% numbers, and that whatever protection there is wanes quickly (hence the rather sudden introduction of repeated boosters). Reports vary widely, from the more optimistic ones of around 90% (lasting for a few months) to effectively 0%.

Equally important, there is evidence for serious statistical artefacts affecting the observational studies: systematic biases distorting the results and leading to artificial overestimation of VE. These include strong healthy vaccinee effects (HVE, a well-known effect in vaccine studies) as well as vaccination status artefacts and misclassification issues. In our own work ([3], in Dutch), we similarly find evidence of very strong HVE affecting the previously reported very high VE numbers ([4], analyses by government health agencies). In particular, this appears to be mainly HVE of the short-duration kind, resulting from very vulnerable people close to death not having been vaccinated. This is apparent, among other things, by very large apparent 'protection' from the vaccine against Non-Covid deaths (cancer, cardiovascular disease, dementia, etc.), much larger even than protection again Covid death, especially in the 4 weeks directly following large-scale vaccination in the spring of 2021. Second, our results suggest significant misclassification bias, that is, many people who were vaccinated were not registered as such, and therefore count as 'unvaccinated' - with a bias toward people who were very vulnerable and/or who died shortly after vaccination. Together, these biases explain (that is, explain away) almost completely the previously reported very high VE. Without those artefacts, in our analysis no evidence remains of a VE greater than 0 when it comes to protection against death.

It is worth taking a detailed look at the three main studies that Ioannidis et al. refer to, which they use to justify their estimates of a VE of 75% pre-Omicron and 50% during Omicron: [5], [6] and [7]. Do those studies provide support for these VE numbers using in the modeling? In our opinion, they do not.

The first one [5] is a retrospective observational study, and it does report high (approximately 90%) and fairly long-lasting (measured up to 8 months after the first dose) protection against *Covid* deaths. No All-Cause mortality metrics are presented, making it possible that a large number of these deaths are 'cause of death replacement' deaths (as described above), or that secondary negative mortality effects are ignored or masked.

The second study [6] is a meta-study assessing only randomized clinical trials, not observational studies. They did assess all-cause mortality, but with very short follow up times: "The median follow-up range of assessment varied from 35 to 92 days after randomization for all outcomes". Interestingly, and similar to Stabell-Benn's work [2], they found evidence that the viral vector vaccines (AstraZeneca, J&J, Sputnik) did give substantial (but limited time, see above) protection against all-cause mortality, with a VE of approx. 75% -- but the mRNA vaccines (Pfizer, Moderna) did not, even though they did prevent Covid infection very well. Note that the mRNA vaccines were predominantly used world-wide, so this clearly has relevance to estimates of overall lives and life years saved.

The third study [7] looked at Covid deaths and non-Covid deaths, and actually includes Ioannidis as one of the authors. It concludes:

"VE estimates for COVID-19 deaths and reinfections exceeded 75% until the end of 2021 but decreased substantially with extended follow-up. The risk of non-COVID-19 death was lower in those vaccinated versus unvaccinated. […] The extremely low COVID-19 mortality, regardless of vaccination, indicates strong protection of previous infection against COVID- 19 death. Lower non-COVID-19 mortality in the vaccinated population might suggest a healthy vaccinee bias."

Thus, this study at the same suggests that Covid mortality as a proportion of total mortality was very low, that strong protection from previous infection probably played a very big role, that all-cause

mortality was (therefore) not reduced very much by the vaccines, and that whatever apparent protection there was may have been influenced by unresolved (healthy vaccinee) bias.

We do not see at all that these three studies support the assumption of an overall, aggregate VE of 75% pre-Omicron and 50% during Omicron.

Adverse events

We quote from the paper [1] (with our emphasis):

"Assessment of absolute net benefits in these populations, if any, require careful consideration of potential additional benefits for non-lethal outcomes (e.g. hospitalizations and other symptomatic disease), as well as any deaths and other consequences from adverse effects (not included in our calculations)."

It seems rather absurd not to take adverse effects into account when computing net benefits and potential lives and life years saved by the vaccines. Vaccines may have 'non-specific' effects [2] on the body and on health, and may cause adverse events affecting overall health and even death. By now it is well-established that (among other things):

1. Very vulnerable, elderly people died relatively often after and from Covid vaccines (e.g. results from Norway), after which vaccination for those subgroups was largely discontinued;

2. The AstraZeneca vaccine is associated with a relatively high probability of thrombosis-related serious adverse events, esp. for relatively young women (after which AZ vaccine administration was stopped in many countries);

3. The Pfizer and Moderna mRNA vaccines are associated with a relatively high probability of myocarditis-related serious adverse events, esp. for young men, and with various other adverse events.

Overall morbidity and mortality impact from this and other secondary effects, including overall non-specific immune system effects, are as of yet not completely known and continue being studied; but in any case they reaffirm the importance of looking at all-cause mortality and morbidity as opposed to just Covid mortality and Covid disease, when attempting to estimates "lives and life years saved by the covid vaccines". In our opinion, therefore, this is a crucial oversight, or error, in the approach of Ioannidis et al.

Is Covid mortality independent of all-cause mortality?

This brings us to the important issue of considering 'Covid deaths' as something completely independent of other, or all, causes of death (all-cause mortality - ACM), and the corresponding decision of Ioannidis et al. to model it as such. This is, essentially, an assumption that any Covid death just adds up to the overall tally of deaths, and that if Covid hadn't happened, these people would have continued living. Is that reasonable? As argued by e.g. Stabell-Benn [2], ourselves [3], and many others, this is unwarranted.

To a large extent, and even more so after the first few Covid waves of 2020, many of the so-called 'Covid deaths' are actually people dying *with* Covid rather than *from* Covid. During Covid waves, deaths from other respiratory disease (especially influenza) are greatly reduced, and so are (to a lesser extent) deaths from other 'old-person' causes of death such as dementia (and associated disease), cardiovascular disease, and cancer – suggesting that an official 'Covid death' often simply *replaces* another cause of death. This phenomenon was exacerbated by the official WHO guidelines which instructed government agencies to label any death a Covid death if a positive Covid infection was detected or even (in some cases) only suspected. Furthermore, there is anecdotal evidence suggesting that after vaccination roll-out, vaccinated people who died with/from Covid were much less likely to be labeled a 'Covid death', compared to unvaccinated people. The analyses of Stabell-Benn et al., ourselves, and others suggests that when looking at ACM rather than Covid mortality alone, most evidence of protection by the vaccines either disappears or appears to be largely based on statistical artefacts.

Ioannidis et al. seem to hint at these difficulties when they write, in somewhat fuzzy terms:

"In principle, if a disease/condition/event kills anyone regardless of health status, e.g. a nuclear bomb, then f=1; conversely, for a condition that appears exactly when a patient is dying from other co-existing ailments, f approaches infinity. The exact positioning of COVID-19 in that spectrum and the relative share of over- and under-counting of COVID-19 deaths are still debated with substantial consequences for estimated disease burden and vaccination benefits."

Nevertheless, they continue with their assumptions on Covid deaths as separate and independent of ACM.

Conclusion

We conclude that this paper is severely flawed in several respects. It models (does not *measure*!) overall lives and life years saved by the vaccines not only in an overly simplistic way, but more importantly, its assumptions are downright unrealistic and overly optimistic with respect to the vaccines.

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