# I don't think this is a case of healthy vaccinee bias.

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*In a recent correspondence to the New England Journal of Medicine, Hoeg et al[1] suggested that a significant lowering of non-COVID-19 mortality in an observational study due to a booster shot was not possible and argued there must have been 'healthy vaccinee bias'. They estimated a difference of 95 %, but the actual observed was 77%[2].*

The notion that mRNA vaccines can generate significant heterologous protection against infectious agents and tumors by the induction of trained innate immunity is not disputed.[3] However, newer evidence[4] suggests mRNA COVID-19 vaccines protect against non-COVID-19 mortality more generally. For example, for **non-C18 mortality** in the vaccinated over the unvaccinated (1 or 2 doses) for a period covering up to the end of July 2021 (ie., notably before delta); a hazard ratio (HR) of about 0.3 was reached for ages 45-84. This reflected the induction of trained immunity by the mRNA vaccine which protects against infectious diseases, tumors and presumably non-infectious diseases. For the latter, it is most likely the reversion of immunosenescence of macrophages[5] by the mRNA vaccines that accounts for the reduced risks of

[1] Hoeg, TB, Duriseti R, Prasad V, Correspondence NEJM July 20, 2023.

[2] Reply Arbel R et al, Correspondence NEJM, July 20, 2023.

[3] Al B et al, J Allerg Clin Immunol June 14, 2023.

[4] Xu S et al, MMWR, 2021 [https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7043e2-H.pdf].

[5] Laderoute M, Discovery Medicine 2015; 2016.

cardiovascular, allergic, autoimmune, neurological and metabolic diseases in addition to infectious agents and tumors.[6]

The promotion of TI by mRNA vaccines however has its dangers because at 28 days after the second dose of BNT162b2, TI ***is completely aborted*** .[7] So if anything, this study was kept short (54 days) to minimize the loss of TI benefit caused by boosting on non-COVID-19 mortality.

A possible confounder was that it appears that for anyone who got infected at up to 3 days after being boosted, this data (1020 participants) was entirely excluded from the analysis. Plus, anyone infected from 4 days to 7 days post boosting was lumped in the control group ( how many?) so any associated deaths that occurred later would be associated with the control group.

Since 9/10 participants served as the control until boosted means there was no or little introduction of healthy vaccinee bias. HOWEVER, if we look at Table 1 (**Image 1**) for participant characteristics

[https://www.nejm.org/doi/full/10.1056/NEJMoa2115624],

we can see that following the booster dose an excess of 28,681 persons (8%) developed hypertension due to the 3rd dose, so if anything the risks of death became elevated once the participant was boosted. Hypertension (over 7 days) is a sign of immunosenescence[6] so it enables us to follow the loss of heterologous protection of TI.

[6] Laderoute M, Trained immunity involving HERV-K102 activated in foamy macrophages may promote recovery from COVID-19 providing a new innate immunity vaccination paradigm against pandemic RNA viruses. (resubmitted invited review, July 31, 2023).

[7] Yamaguchi Y et al, JCI Insight 2022; doi: 10.1172/jci.insight.163347.

Table 1. Characteristics of the Participants at Baseline.*

| Characteristic | All Participants (N=843,208) | Booster (N=758,118) | No Booster (N=85,090) | P Value |
|---|---|---|---|---|
| Age — yr | 68.5±10.6 | 68.9±10.5 | 64.8±10.9 | <0.001 |
| Age group — no. (%) | | | | |
| ≥65 yr | 506,016 (60) | 470,808 (62) | 35,208 (41) | <0.001 |
| 50–64 yr | 337,192 (40) | 287,310 (38) | 49,882 (59) | <0.001 |
| Female sex — no. (%) | 448,272 (53) | 400,300 (53) | 47,972 (56) | <0.001 |
| Population sector — no. (%) | | | | |
| General Jewish population | 732,493 (87) | 674,266 (89) | 58,227 (68) | <0.001 |
| Arab population | 86,162 (10) | 62,042 (8) | 24,120 (28) | <0.001 |
| Ultra-Orthodox Jewish population | 24,297 (3) | 21,633 (3) | 2,664 (3) | <0.001 |
| Unknown | 256 (<1) | — | — | — |
| Score for socioeconomic status — median (SD)† | 5.9 (2.2) | 6 (2.2) | 4.8 (2.2) | <0.001 |
| Clinical risk factors — no. (%) | | | | |
| Diabetes | 244,746 (29) | 220,959 (29) | 23,787 (28) | <0.001 |
| Chronic obstructive pulmonary disease | 41,449 (5) | 37,291 (5) | 4,158 (5) | 0.68 |
| Asthma | 51,360 (6) | 46,198 (6) | 5,162 (6) | 0.75 |
| Chronic kidney failure | 51,636 (6) | 47,187 (6) | 4,449 (5) | <0.001 |
| Hypertension | 391,654 (46) | 358,517 (47) | 33,137 (39) | <0.001 |
| Ischemic heart disease | 142,742 (17) | 131,058 (17) | 11,684 (14) | <0.001 |
| Chronic heart failure | 37,297 (4) | 33,524 (4) | 3,773 (4) | 0.87 |
| Obesity | 278,097 (33) | 249,152 (33) | 28,945 (34) | <0.001 |
| Lung cancer | 5,661 (1) | 5,132 (1) | 529 (1) | 0.06 |
| History of cerebrovascular accident | 60,343 (7) | 54,328 (7) | 6,015 (7) | 0.30 |
| History of transient ischemic attack | 29,145 (3) | 26,586 (4) | 2,559 (3) | <0.001 |
| History of smoking | 348,654 (41) | 314,226 (41) | 34,428 (40) | <0.001 |

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Scores for socioeconomic status range from 1 (lowest) to 10 (highest).

**Image 1. Characteristics of Study Participants from the Arbel R et al 2021 NEJM paper [https://www.nejm.org/doi/full/10.1056/NEJMoa2115624].**

If we look at the HR for non-COVID-19 versus COVID-19 mortality (**Image 2**) we see that generally the risk factors greatly impacting for COVID-19 severity and death are generally not shared by those risk factors for non-COVID-19 mortality where for the latter they are often less (see male sex and chronic renal failure). However, we note that the boosted have much higher risks of non-COVID-19 related lung cancer death. I would take a guess that the risk for hypertension related non-COVID-19 deaths would have also skyrocketed, perhaps even more because upon boosting more people had hypertension while the number of participants who had lung cancer remained the same (within 1%) for both the boosted and non-boosted groups in **Image 1**.

**Table 1. Association of Confounding Variables with Death Not Due to Covid-19.***

| Variable | Hazard Ratio for Death Not Due to Covid-19 (95% CI) |
|---|---|
| Booster vaccine received | 0.23 (0.20–0.26) |
| Male sex | 1.27 (1.13–1.42) |
| Age | 1.11 (1.10–1.11) |
| Socioeconomic status | 1.00 (0.98–1.03) |
| Diabetes | 1.12 (1.00–1.25) |
| Chronic obstructive pulmonary disease | 1.41 (1.20–1.65) |
| Stroke | 1.53 (1.34–1.74) |
| Chronic renal failure | 1.95 (1.71–2.21) |
| Ischemic heart disease | 1.11 (0.99–1.26) |
| Heart failure | 2.01 (1.75–2.31) |
| Obesity | 0.95 (0.85–1.07) |
| History of smoking | 1.07 (0.95–1.12) |
| Lung cancer | 4.46 (3.47–5.72) |
| Transient ischemic attack | 0.90 (0.73–1.10) |

* Age was a continuous variable, and socioeconomic status was an ordinal variable; all other variables were dichotomous (present vs. absent). Covid-19 denotes coronavirus disease 2019.

https://www.nejm.org/doi/pdf/10.1056/NEJMc2306683?articleTools=true

**Table 2. Association of Confounding Variables with Death Due to Covid-19.***

| Variable | Hazard Ratio for Death Due to Covid-19 (95% CI) | P Value |
|---|---|---|
| Booster received | 0.10 (0.07–0.14) | <0.001 |
| Age | 1.10 (1.09–1.12) | <0.001 |
| Male sex | 2.49 (1.82–3.41) | <0.001 |
| Socioeconomic status | 0.98 (0.92–1.04) | 0.45 |
| Diabetes | 1.29 (0.96–1.72) | 0.09 |
| Chronic obstructive pulmonary disease | 1.31 (0.86–1.99) | 0.22 |
| Chronic kidney failure | 2.27 (1.63–3.15) | <0.001 |
| Ischemic heart disease | 0.96 (0.69–1.32) | 0.79 |
| Chronic heart failure | 1.41 (0.95–2.09) | 0.09 |
| Obesity | 1.17 (0.87–1.58) | 0.30 |
| Lung cancer | 3.20 (1.49–6.87) | 0.003 |
| History of cerebrovascular accident | 1.54 (1.08–2.17) | 0.02 |
| History of transient ischemic attack | 0.87 (0.50–1.51) | 0.63 |
| History of smoking | 1.10 (0.82–1.49) | 0.52 |

* Age was a continuous variable, and socioeconomic status was an ordinal variable; all other variables were dichotomous (present vs. absent). Covid-19 denotes coronavirus disease 2019.

https://www.nejm.org/doi/full/10.1056/NEJMoa2115624

## Image 2. Lung cancer NON-COVID-19 death rates skyrocketed upon the booster dose. What about hypertension?

So today, I requested this missing information on hypertension from the lead author, Dr. Ronen Arbel as well as information on what the data would look like if the 1020 excluded SARS-COV-2 infections in the boosted were included in that group along with any other infections that occurred up to 7 days. I have also requested the extension of the data over time such as at 4 months.

We know that for the MMWR data[4] the authors purposefully chose a period of time (December 14, 2020 to July 31, 2021) prior to the dominance of the delta variant (before August 2021). As shown in **Image 3** heterologous protection by the vaccine (green area) was dominant in the 50 plus age group and reflected in the negative excess non-COVID-19 mortality. The vast majority of UK citizens over 50 received at least one dose of vaccine during this period (data not shown).

**% Excess Deaths (Non-COVID-19) by Age Group, Sex & Month (that week ended in)**
**England**
**Weeks Ending 27Mar20 - 26May23**
Source Data:- Office for Health Improvement and Disparities
Graphic:- **@OutsideAllan**

| | | 0-24 | | 25-49 | | 50-64 | | 65-74 | | 75-84 | | 85+ | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | Mont | Females | Males | Females | Males | Females | Males | Females | Males | Females | Males | Females | Males | |
| 2020 | 3 | -10.0% | -23.0% | -2.8% | 2.1% | 0.2% | -3.7% | -8.4% | -2.0% | -5.5% | -0.6% | -6.3% | -1.8% | -3.8% |
| 2020 | 4 | -5.8% | -20.5% | 7.5% | 0.2% | 12.4% | 16.1% | 13.4% | 18.2% | 25.4% | 25.9% | 40.6% | 36.1% | 26.9% |
| 2020 | 5 | -15.8% | -12.0% | -1.6% | -2.3% | 3.7% | 4.9% | -1.8% | -4.2% | -0.5% | -1.8% | 10.9% | 0.2% | 1.9% |
| 2020 | 6 | -23.9% | -21.7% | -8.0% | -7.3% | -6.0% | -2.4% | -3.3% | -8.0% | -8.6% | -10.6% | -11.3% | -13.2% | -9.4% |
| 2020 | 7 | -16.6% | -9.0% | 0.7% | 0.3% | -6.5% | 2.6% | -3.1% | -4.8% | -7.1% | -7.4% | -9.2% | -13.9% | -7.2% |
| 2020 | 8 | 1.4% | -1.3% | 1.8% | 5.9% | 2.4% | 4.1% | -5.2% | -2.5% | -0.7% | -1.2% | -2.7% | -5.4% | -1.8% |
| 2020 | 9 | -1.4% | -15.4% | 5.6% | 6.0% | 1.6% | 5.8% | 0.2% | 2.4% | 0.4% | -0.1% | -2.2% | -1.9% | 0.1% |
| 2020 | 10 | -24.0% | -11.4% | 2.3% | 7.4% | 4.1% | 4.0% | 0.9% | -3.0% | -2.4% | -4.2% | -3.8% | -4.6% | -2.3% |
| 2020 | 11 | -11.3% | -6.1% | 3.6% | 5.1% | 1.9% | 5.9% | -7.5% | -2.9% | -8.1% | -7.0% | -7.3% | -10.7% | -5.8% |
| 2020 | 12 | -5.2% | -8.2% | 5.5% | 6.0% | -5.8% | 3.1% | -10.2% | -10.9% | -14.9% | -16.1% | -14.9% | -17.7% | -12.6% |
| 2021 | 1 | -3.1% | -8.1% | 0.3% | -11.0% | -10.4% | -6.3% | -17.0% | -16.4% | -19.9% | -23.1% | -22.8% | -26.7% | -20.1% |
| 2021 | 2 | 2.0% | 4.6% | 2.9% | -1.2% | -8.2% | -3.7% | -12.6% | -15.1% | -18.2% | -17.4% | -19.3% | -24.9% | -16.7% |
| 2021 | 3 | 16.4% | -1.2% | -4.0% | 5.4% | -7.7% | -3.4% | -13.3% | -14.2% | -18.2% | -20.6% | -22.3% | -25.2% | -17.8% |
| 2021 | 4 | -12.5% | -13.8% | 2.4% | -5.3% | -5.9% | 0.6% | -9.0% | -11.4% | -13.5% | -14.3% | -16.3% | -19.3% | -13.1% |
| 2021 | 5 | -9.0% | 7.9% | 2.1% | 1.2% | -5.6% | 3.2% | -10.1% | -7.5% | -8.8% | -7.5% | -10.0% | -10.4% | -7.7% |
| 2021 | 6 | 9.3% | 3.5% | -2.4% | 5.2% | -0.9% | 6.6% | -4.6% | -5.0% | -5.1% | -3.3% | -5.6% | -7.2% | -3.9% |
| 2021 | 7 | -7.5% | 0.7% | 2.4% | 3.8% | 7.0% | 7.2% | 0.2% | 2.2% | 0.7% | 1.7% | -0.3% | -2.0% | 1.1% |
| 2021 | 8 | -8.3% | -5.6% | -0.5% | 2.9% | 5.8% | 6.8% | 5.3% | 1.2% | 2.7% | 0.0% | 3.9% | 1.2% | 2.6% |
| 2021 | 9 | -4.2% | -6.7% | 6.2% | 5.9% | 8.3% | 4.8% | 7.7% | 6.5% | 6.0% | 4.5% | 4.1% | 1.2% | 4.6% |
| 2021 | 10 | 1.0% | 5.9% | 1.0% | 11.8% | 9.9% | 10.3% | 3.5% | 3.3% | 0.1% | 0.9% | 1.2% | -0.1% | 2.4% |
| 2021 | 11 | 10.1% | 9.9% | 1.0% | 3.4% | 2.5% | 9.0% | 6.4% | 6.5% | 4.5% | 0.6% | 5.7% | 0.1% | 3.9% |
| 2021 | 12 | 2.2% | 5.3% | -4.2% | 3.1% | 6.8% | 6.9% | 1.9% | 2.0% | 0.8% | -3.8% | 0.4% | -3.7% | 0.0% |
| 2022 | 1 | -10.4% | -9.8% | -2.6% | -9.7% | -8.3% | -4.2% | -14.2% | -12.3% | -14.7% | -17.4% | -20.7% | -23.4% | -16.8% |
| 2022 | 2 | 7.5% | 16.2% | -2.7% | -4.6% | -3.8% | 3.6% | -8.1% | -5.0% | -11.5% | -13.8% | -16.0% | -18.6% | -11.7% |
| 2022 | 3 | 10.3% | 8.7% | -6.1% | 4.4% | -8.3% | 3.4% | -7.5% | -6.3% | -9.2% | -12.0% | -14.7% | -15.2% | -10.3% |
| 2022 | 4 | -28.2% | -1.4% | -5.6% | -5.0% | -2.0% | -3.8% | -8.9% | -7.3% | -8.9% | -10.9% | -9.5% | -12.1% | -9.0% |
| 2022 | 5 | -12.3% | 6.4% | 4.9% | -5.0% | 2.5% | 8.9% | -0.1% | 1.6% | 1.7% | 2.4% | 3.2% | 1.4% | 2.3% |
| 2022 | 6 | 17.9% | 16.5% | 14.8% | 8.1% | 18.4% | 17.0% | 8.9% | 9.2% | 10.4% | 7.5% | 8.8% | 9.3% | 10.0% |
| 2022 | 7 | 12.2% | 5.5% | 6.2% | 8.8% | 4.6% | 11.0% | 4.7% | 5.5% | 7.1% | 2.8% | 8.3% | 6.9% | 6.5% |
| 2022 | 8 | 10.5% | 7.8% | -4.9% | 10.2% | 17.1% | 12.5% | 0.2% | 7.2% | 4.5% | 5.6% | 10.8% | 4.1% | 7.1% |
| 2022 | 9 | -0.6% | 10.4% | 9.5% | 8.1% | 13.7% | 16.9% | 7.9% | 5.2% | 5.8% | 6.7% | 7.6% | 7.5% | 7.8% |
| 2022 | 10 | 3.9% | 5.0% | 16.7% | 9.2% | 11.8% | 10.1% | 7.5% | 6.3% | 6.3% | 6.4% | 9.0% | 7.4% | 7.9% |
| 2022 | 11 | 11.7% | 6.7% | 7.9% | 11.9% | 10.5% | 13.2% | 9.9% | 6.8% | 2.5% | 1.8% | 6.6% | 1.9% | 5.5% |
| 2022 | 12 | 26.3% | 6.1% | 6.3% | 4.1% | 13.4% | 12.4% | 6.4% | 3.7% | 9.6% | -0.5% | 7.6% | 3.6% | 5.9% |
| 2023 | 1 | -4.9% | 1.6% | 18.4% | 4.0% | 13.1% | 16.2% | 7.6% | 7.8% | 10.4% | 2.2% | 10.2% | -0.2% | 7.1% |
| 2023 | 2 | 17.9% | 16.7% | 7.4% | 11.1% | 2.7% | 11.4% | 5.1% | 2.7% | 0.9% | -3.2% | -2.1% | -7.4% | -0.4% |
| 2023 | 3 | 9.1% | 13.2% | 8.0% | 9.1% | 3.8% | 9.6% | 0.6% | -1.6% | -5.8% | -4.6% | -4.5% | -6.8% | -2.7% |
| 2023 | 4 | 3.4% | 14.9% | 4.6% | 3.4% | 5.3% | 11.7% | 1.3% | 1.5% | -0.1% | -2.0% | -1.8% | -2.0% | 0.3% |
| 2023 | 5 | -2.8% | 29.5% | 16.4% | 15.7% | 8.2% | 16.9% | 2.1% | 8.6% | 5.8% | 7.1% | 8.3% | 3.4% | 7.5% |

| Scale | | | | | | |
|---|---|---|---|---|---|---|
| < -10% | < -5% | < 0% | > 0% | > 5% | >10% | >15% |

## Image 3. UK Excess Non-COVID-19 Mortality By Age And Sex For March 2020 Through May 2023 Shows In The 50 + There Was A Significant Period Of Negative EXCESS Non-COVID-19 Mortality For The Period Covering December 14, 2020 To July 31, 2021. [8]

[8] https://twitter.com/OutsideAllan/status/1646813568107511809 based on UK data. The UK Office for Health Improvements and Disparities (UKHID) released a downloadable database on June 8, 2023 [https://www.gov.uk/government/statistics/excess-mortality-in-england-and-english-regions and click on https://app.powerbi.com/view] and charts of the excess mortality data by month, sex and age were made available by Stuart A @OutsideAllan on twitter on June 8 2023.