Healthy Vaccinee Bias

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[We should not be so easily fooled]

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What is healthy vaccine bias?

When **better underlying health** among the **vaccinated** population causes the vaccine to **appear more effective** than it is.

What is healthy vaccine bias?

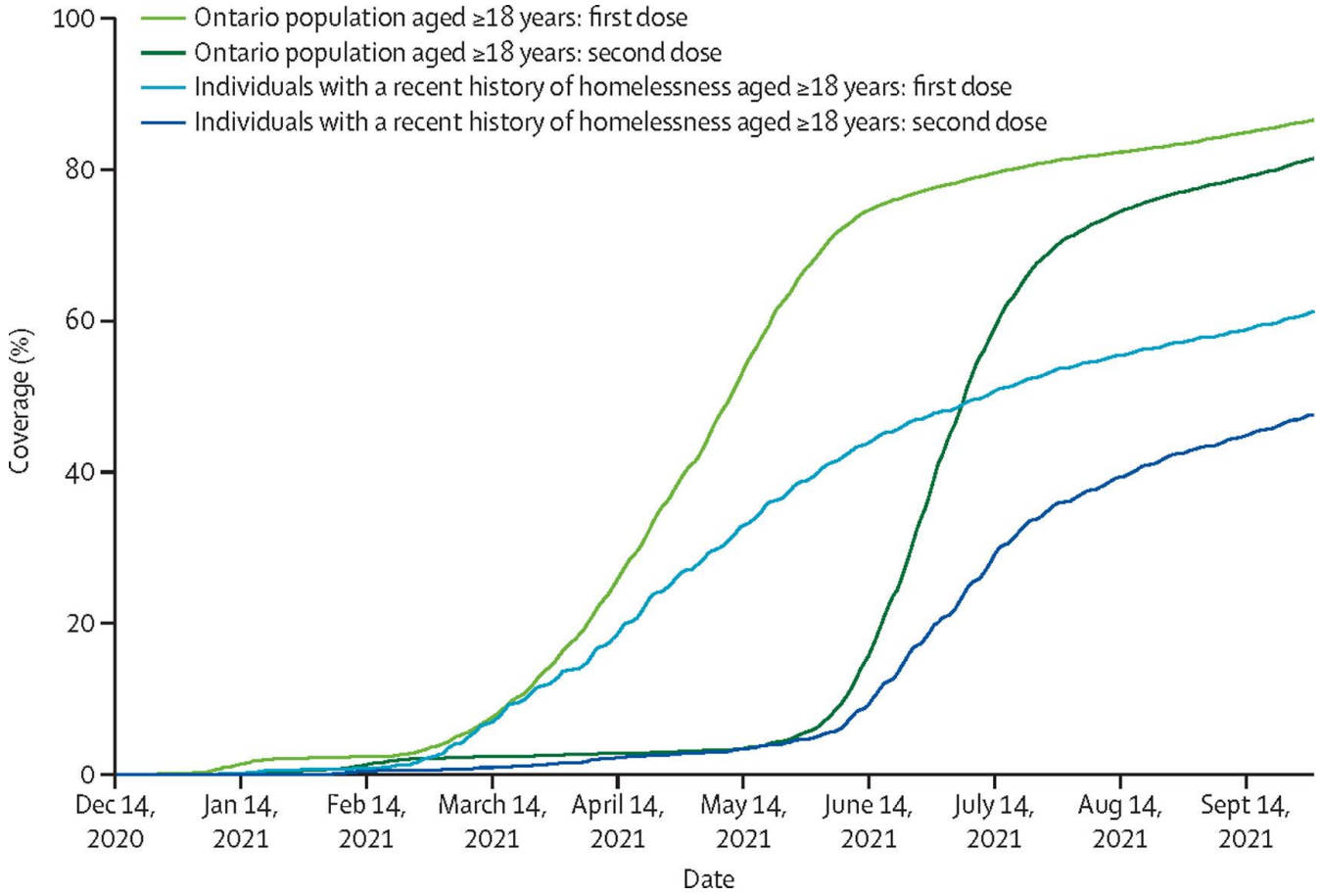
When **better underlying health** among the **vaccinated** population causes the vaccine to **appear more effective** than it is.

Ventilator giving oxygen by intubation tube to a patient in ICU. GETTY

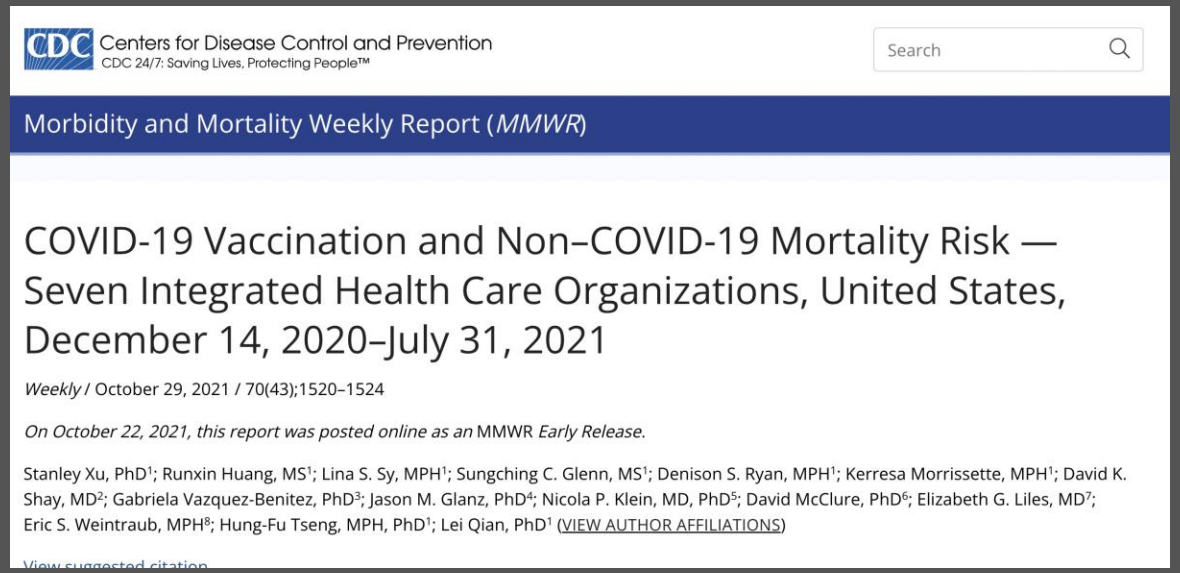
About 140 unhoused people live in tents and vehicles at the X Street safe ground site near Southside Park in Sacramento under the W/X freeway.

Chris Nichols / CapRadio

Figure 1:COVID-19 vaccine coverage from Dec 14, 2020, to Sept 30, 2021 among adults in Ontario with a recent history of homelessness compared to the general adult population of Ontario, by dose



Sharif S et al. The Lancet Public Health 2022 7e366-e377DOI: (10.1016/S2468-2667(22)00037-8)



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Morbidity and Mortality Weekly Report (*MMWR*)

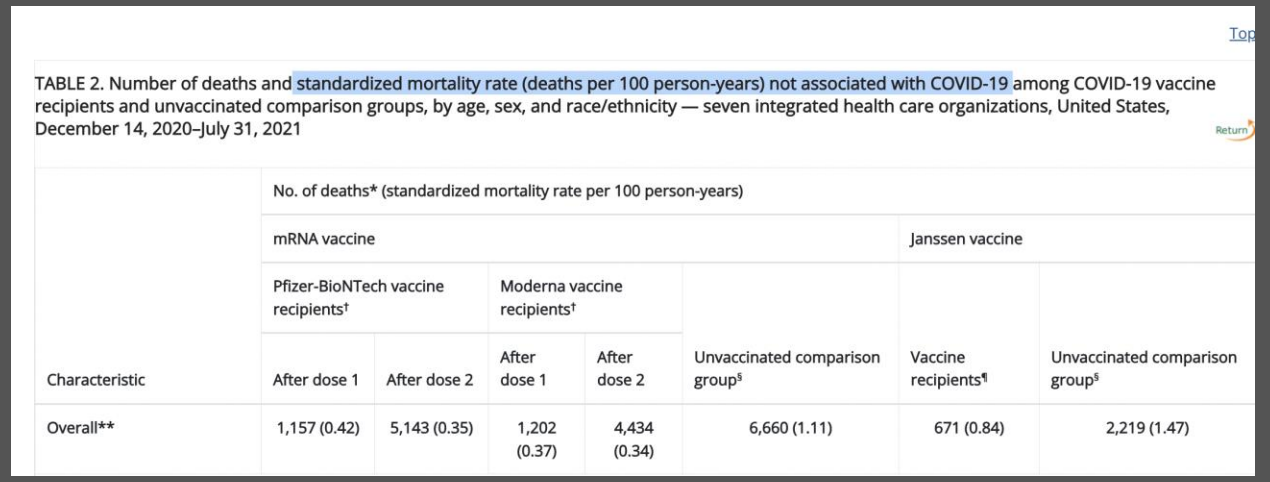
COVID-19 Vaccination and Non–COVID-19 Mortality Risk — Seven Integrated Health Care Organizations, United States, December 14, 2020–July 31, 2021

Weekly / October 29, 2021 / 70(43);1520–1524

On October 22, 2021, this report was posted online as an MMWR *Early Release.*

Stanley Xu, PhD[1]; Runxin Huang, MS[1]; Lina S. Sy, MPH[1]; Sungching C. Glenn, MS[1]; Denison S. Ryan, MPH[1]; Kerresa Morrissette, MPH[1]; David K. Shay, MD[2]; Gabriela Vazquez-Benitez, PhD[3]; Jason M. Glanz, PhD[4]; Nicola P. Klein, MD, PhD[5]; David McClure, PhD[6]; Elizabeth G. Liles, MD[7]; Eric S. Weintraub, MPH[8]; Hung-Fu Tseng, MPH, PhD[1]; Lei Qian, PhD[1] (VIEW AUTHOR AFFILIATIONS)

View suggested citation



Top

TABLE 2. Number of deaths and standardized mortality rate (deaths per 100 person-years) not associated with COVID-19 among COVID-19 vaccine recipients and unvaccinated comparison groups, by age, sex, and race/ethnicity — seven integrated health care organizations, United States, December 14, 2020–July 31, 2021

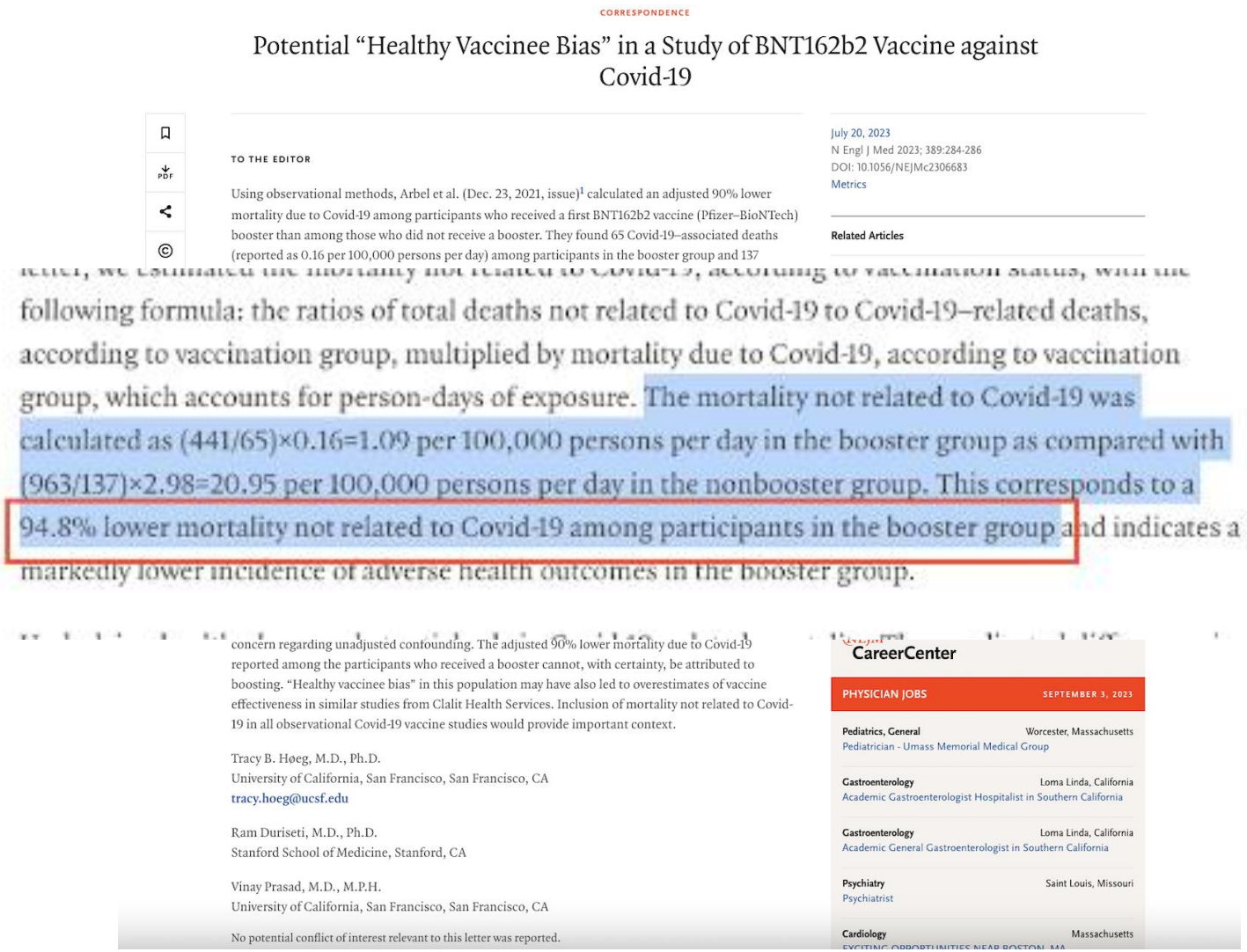
Return

	No. of deaths* (standardized mortality rate per 100 person-years)						
	mRNA vaccine					Janssen vaccine	
	Pfizer-BioNTech vaccine recipients†		Moderna vaccine recipients†				
Characteristic	After dose 1	After dose 2	After dose 1	After dose 2	Unvaccinated comparison group§	Vaccine recipients¶	Unvaccinated comparison group§
Overall**	1,157 (0.42)	5,143 (0.35)	1,202 (0.37)	4,434 (0.34)	6,660 (1.11)	671 (0.84)	2,219 (1.47)

Among 11 million people ≥12 in the US enrolled in Kaiser Permanente Healthcare

Unvaccinated almost 70% more likely to die of non-COVID-19 causes than those with two doses of mRNA vaccine

Høeg TB, Duriseti R, Prasad V Potential "Healthy Vaccinee Bias in a Study of BNT162b2 Vaccine Against COVID-19. N Engl J Med. 2023 Jul 20; 389:284-286 DOI: 10.1056/NEJMc2306683.



CORRESPONDENCE

Potential "Healthy Vaccinee Bias" in a Study of BNT162b2 Vaccine against Covid-19

TO THE EDITOR

Using observational methods, Arbel et al. (Dec. 23, 2021, issue)[1] calculated an adjusted 90% lower mortality due to Covid-19 among participants who received a first BNT162b2 vaccine (Pfizer–BioNTech) booster than among those who did not receive a booster. They found 65 Covid-19–associated deaths (reported as 0.16 per 100,000 persons per day) among participants in the booster group and 137

July 20, 2023
N Engl J Med 2023; 389:284-286
DOI: 10.1056/NEJMc2306683
Metrics

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following formula: the ratios of total deaths not related to Covid-19 to Covid-19–related deaths, according to vaccination group, multiplied by mortality due to Covid-19, according to vaccination group, which accounts for person-days of exposure. The mortality not related to Covid-19 was calculated as (441/65)×0.16=1.09 per 100,000 persons per day in the booster group as compared with (963/137)×2.98=20.95 per 100,000 persons per day in the nonbooster group. This corresponds to a 94.8% lower mortality not related to Covid-19 among participants in the booster group and indicates a markedly lower incidence of adverse health outcomes in the booster group.

concern regarding unadjusted confounding. The adjusted 90% lower mortality due to Covid-19 reported among the participants who received a booster cannot, with certainty, be attributed to boosting. "Healthy vaccinee bias" in this population may have also led to overestimates of vaccine effectiveness in similar studies from Clalit Health Services. Inclusion of mortality not related to Covid-19 in all observational Covid-19 vaccine studies would provide important context.

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No potential conflict of interest relevant to this letter was reported.

Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, Yaron S. BNT162b2 Vaccine Booster and Mortality Due to Covid-19. N Engl J Med. 2021 Dec 23;385(26):2413-2420. doi: 10.1056/NEJMoa2115624. Epub 2021 Dec 8.

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BNT162b2 Vaccine Booster and Mortality Due to Covid-19

Ronen Arbel, Ph.D., Ariel Hammerman, Ph.D., Ruslan Sergienko, M.A., Michael Friger, Ph.D., Alon Peretz, M.D., Doron Netzer, M.D., and Shlomit Yaron, M.D.

ABSTRACT

BACKGROUND

The emergence of the B.1.617.2 (delta) variant of severe acute respiratory syndrome coronavirus 2 and the reduced effectiveness over time of the BNT162b2 vaccine (Pfizer–BioNTech) led to a resurgence of coronavirus disease 2019 (Covid-19) cases in populations that had been vaccinated early. On July 30, 2021, the Israeli Ministry of Health approved the use of a third dose of BNT162b2 (booster) to cope with this resurgence. Evidence regarding the effectiveness of the booster in lowering mortality due to Covid-19 is still needed.

METHODS

We obtained data for all members of Clalit Health Services who were 50 years of age or older at the start of the study and had received two doses of BNT162b2 at least 5 months earlier. The mortality due to Covid-19 among participants who received the booster during the study period (booster group) was compared with that among participants who did not receive the booster (nonbooster group). A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association of booster status with death due to Covid-19, with adjustment for sociodemographic factors and coexisting conditions.

RESULTS

A total of 843,208 participants met the eligibility criteria, of whom 758,118 (90%) received the booster during the 54-day study period. Death due to Covid-19 occurred in 65 participants in the booster group (0.16 per 100,000 persons per day) and in 137 participants in the nonbooster group (2.98 per 100,000 persons per day). The adjusted hazard ratio for death due to Covid-19 in the booster group, as compared with the nonbooster group, was 0.10 (95% confidence interval, 0.07 to 0.14; P<0.001).

CONCLUSIONS

Participants who received a booster at least 5 months after a second dose of BNT162b2 had 90% lower mortality due to Covid-19 than participants who did not receive a booster.

From the Community Medical Services Division, Clalit Health Services, Tel Aviv (R.A., A.H., A.P., D.N., S.Y.), the Maximizing Health Outcomes Research Lab, Sapir College, Sderot (R.A.), and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheba (R.S., M.F.) — all in Israel. Dr. Arbel can be contacted at ronenarb@clalit.org.il or at Clalit Health Services Headquarters, Arlozorov 101, Tel Aviv, 6209804 Israel.

This article was published on December 8, 2021, at NEJM.org.

N Engl J Med 2021;385:2413-20.
DOI: 10.1056/NEJMoa2115624

Arbel R, Sergienko R, Hammerman A. BNT162b2 Vaccine Booster and Covid-19 Mortality. Reply. N Engl J Med. 2022 Mar 10;386(10):1000-1001. doi: 10.1056/NEJMc2120044. Epub 2022 Feb 9. PMID: 35139268.

over a 6-month period between participants who had received the BNT162b2 vaccine (15 deaths) and those who had received placebo (14 deaths); there were more cardiovascular- and sepsis-related deaths in the BNT162b2 group (12 deaths) than in the placebo group (6 deaths). Another informative variable would be the number needed to vaccinate with a booster dose to prevent one Covid-19–related death. Such comprehensive analysis of real-world data may inform the risk–benefit assessment of boosters and better guide public health decisions.

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No potential conflict of interest relevant to this letter was reported.

This letter was published on February 9, 2022, at NEJM.org.

1. Arbel R, Hammerman A, Sergienko R, et al. BNT162b2 vaccine booster and mortality due to Covid-19. N Engl J Med 2021;385:2413-20.
2. Thomas SJ, Moreira ED Jr, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med 2021;385:1761-73.

DOI: 10.1056/NEJMc2120044

TO THE EDITOR: Using real-world data from participants in Israel, Arbel et al. found that mortality due to Covid-19 was 90% lower among those who received a booster at least 5 months after the second dose of the BNT162b2 messenger RNA (mRNA) vaccine than among those who did not receive a booster. A previous observational study and public health measures regarding Covid-19.

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Graz, Austria
stefan.pilz@chello.at

No potential conflict of interest relevant to this letter was reported.

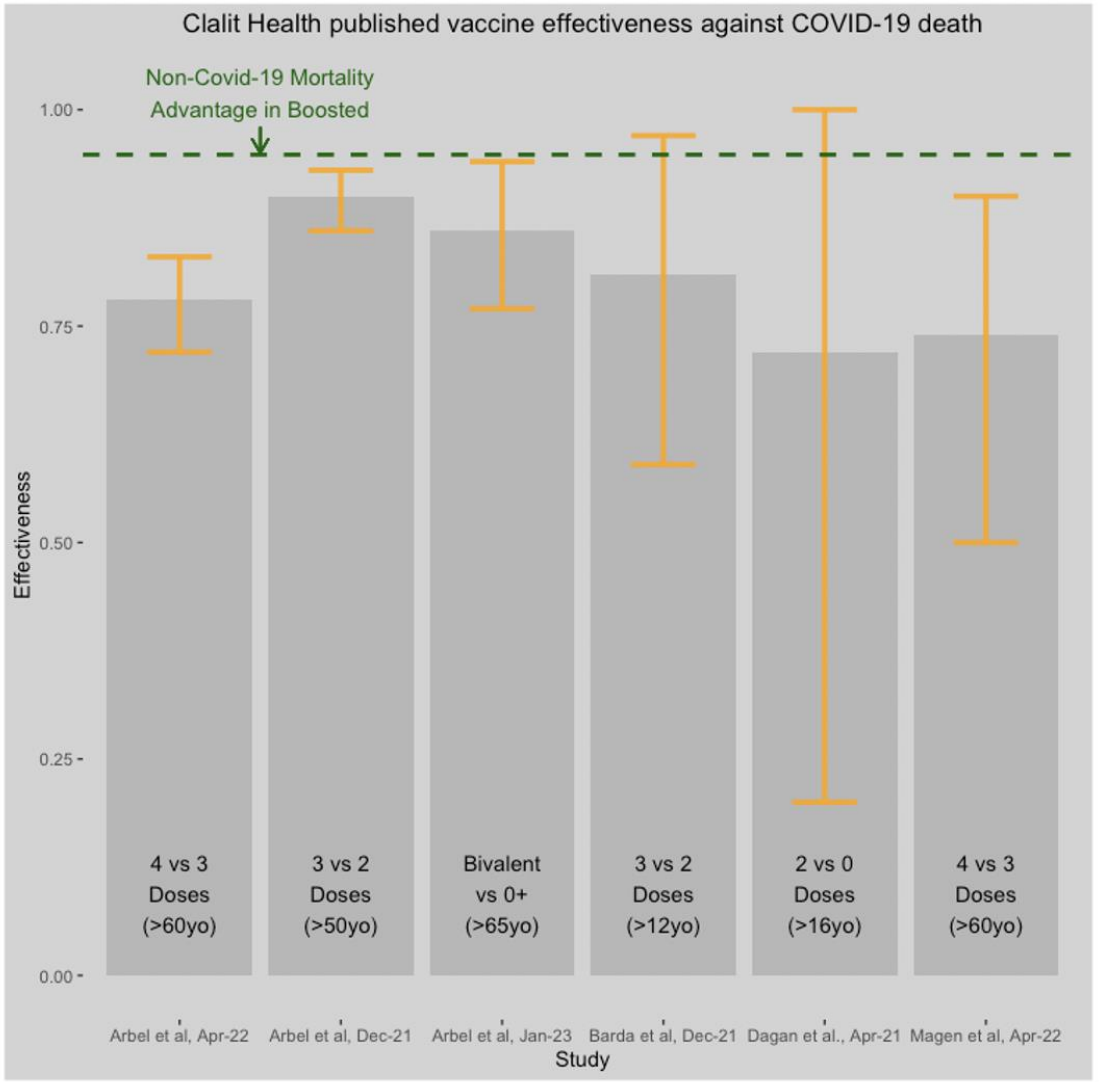
This letter was published on February 9, 2022, at NEJM.org.

1. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384:1412-23.
2. Levin EG, Lustig Y, Cohen C, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. N Engl J Med 2021;385(24):e84.

DOI: 10.1056/NEJMc2120044

THE AUTHORS REPLY: In response to Rohban: during our study period, 506 deaths occurred in the booster group (441 deaths were not related to Covid-19 and 65 were Covid-19–related), as compared with 1100 deaths in the nonbooster group (963 deaths were not related to Covid-19 and 137 were Covid-19–related). These results are in line with those of a large-scale population study in the United States,[1] which showed a 66% lower risk of non–Covid-19–related death among participants who received primary vaccination with two doses of the BNT162b2 vaccine than among unvaccinated participants. However, our reported figures regarding deaths not related to Covid-19 should be interpreted with caution, because they were not adjusted for the numerous factors that may affect all-cause mortality and are beyond the scope of our study.

All vaccine and booster studies of VE vs COVID mortality from Israel's Clality Health, by Høeg TB, Duriseti R, Prasad V [unpublished]



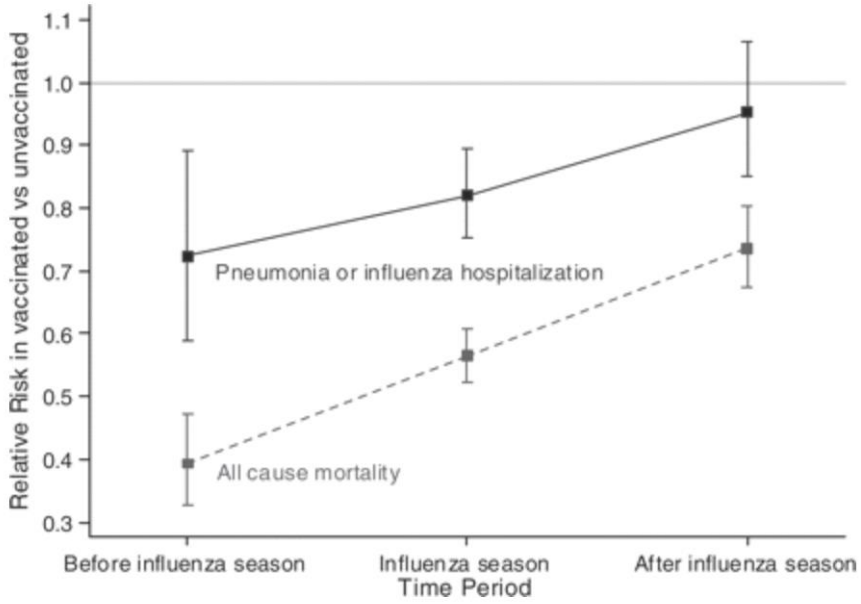
Healthy Vaccinee Bias in Influenza Vaccine Studies

Influenza Vaccine Effectiveness against mortality in ≥65 year olds

Healthy Vaccinee bias is a term originally applied to influenza vaccine research in 2009 by Jennifer Nelson

- =

Figure 1



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Relative risk (and 95% CI) of all cause mortality and pneumonia or influenza hospitalization in vaccinated seniors compared with unvaccinated seniors, during periods before, during, and after influenza seasons, September 1995 through August 2003.

Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. Int J Epidemiol. 2006 Apr;35(2):337-44.

Examples of Healthy Vaccinee Bias in many countries: influenza vaccine (all from the last 20 years)

Canada (Campitelli, et al; Hottes, et al)
Sweden (Örtqvist, et al)
USA (McGrath, et al; Jackson, et al)
Germany (Tessmer, et al)
Spain (Vila-Corcoles, et al)
40 country analysis (Johnstone et al)

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40 country analysis (Johnstone et al)

In 100% (4/4) that included a preseason all-cause mortality, HVB could explain the entire observed vaccine effectiveness.

Remschmidt et al, 2015

Recommendations

Prioritize Randomized trials which *should* eliminate healthy vaccinee bias

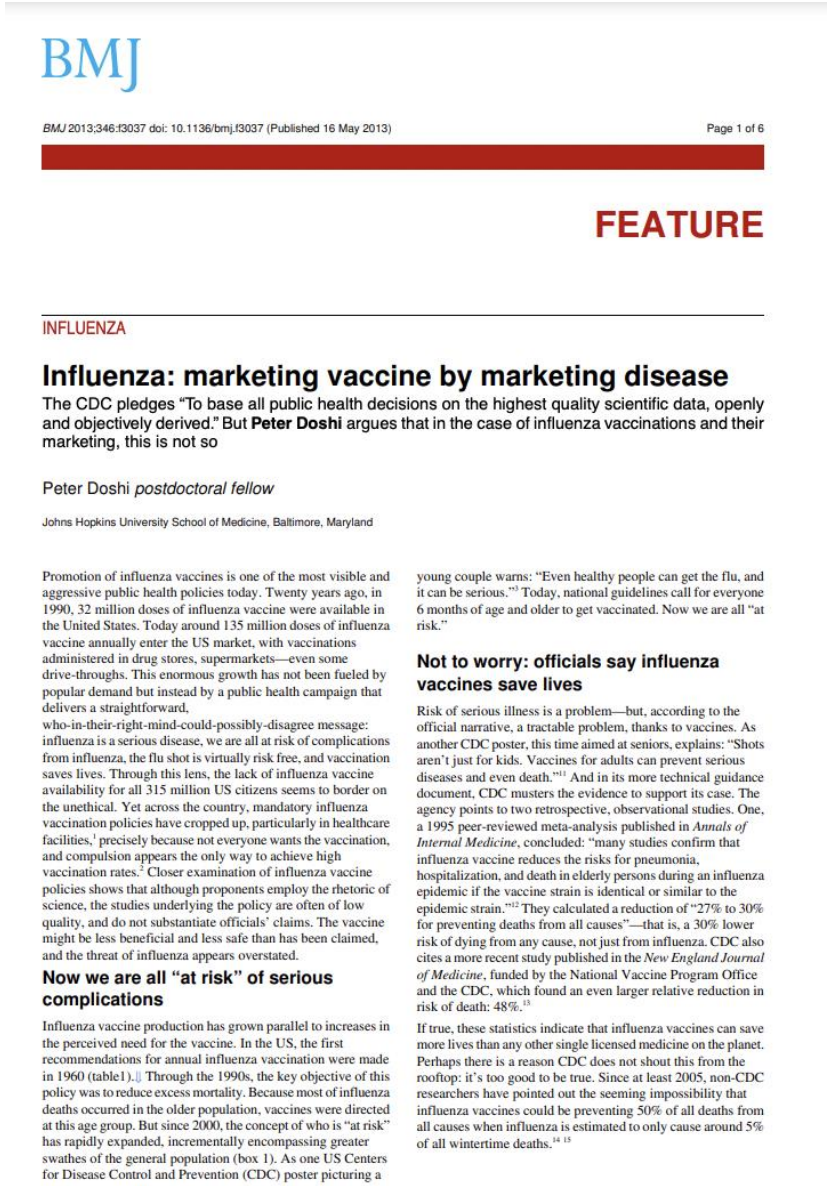
- why were randomized studies of the boosters looking at COVID-19 deaths not done?

Observational studies of vaccines should **require data on all-cause mortality** and hospitalization rate differences by **vaccine group**, preferably from the pre-study period

Do not assume test negative designs are unaffected by healthy vaccinee bias

"Healthy user bias" & the influenza vaccine

Doshi P. Influenza: marketing vaccine by marketing disease. BMJ. 2013 May 16;346:f3037. doi: 10.1136/bmj.f3037. Erratum in: BMJ. 2013;346:f3441. Erratum in: BMJ. 2013;347:f6770. PMID: 23682040.



BMJ

BMJ 2013;346:f3037 doi: 10.1136/bmj.f3037 (Published 16 May 2013)

FEATURE

INFLUENZA

Influenza: marketing vaccine by marketing disease

The CDC pledges "To base all public health decisions on the highest quality scientific data, openly and objectively derived." But **Peter Doshi** argues that in the case of influenza vaccinations and their marketing, this is not so

Peter Doshi *postdoctoral fellow*

Johns Hopkins University School of Medicine, Baltimore, Maryland

Promotion of influenza vaccines is one of the most visible and aggressive public health policies today. Twenty years ago, in 1990, 32 million doses of influenza vaccine were available in the United States. Today around 135 million doses of influenza vaccine annually enter the US market, with vaccinations administered in drug stores, supermarkets—even some drive-throughs. This enormous growth has not been fueled by popular demand but instead by a public health campaign that delivers a straightforward, who-in-their-right-mind-could-possibly-disagree message: influenza is a serious disease, we are all at risk of complications from influenza, the flu shot is virtually risk free, and vaccination saves lives. Through this lens, the lack of influenza vaccine availability for all 315 million US citizens seems to border on the unethical. Yet across the country, mandatory influenza vaccination policies have cropped up, particularly in healthcare facilities,[1] precisely because not everyone wants the vaccination, and compulsion appears the only way to achieve high vaccination rates.[2] Closer examination of influenza vaccine policies shows that although proponents employ the rhetoric of science, the studies underlying the policy are often of low quality, and do not substantiate officials' claims. The vaccine might be less beneficial and less safe than has been claimed, and the threat of influenza appears overstated.

Now we are all "at risk" of serious complications

Influenza vaccine production has grown parallel to increases in the perceived need for the vaccine. In the US, the first recommendations for annual influenza vaccination were made in 1960 (table1).[3] Through the 1990s, the key objective of this policy was to reduce excess mortality. Because most of influenza deaths occurred in the older population, vaccines were directed at this age group. But since 2000, the concept of who is "at risk" has rapidly expanded, incrementally encompassing greater swathes of the general population (box 1). As one US Centers for Disease Control and Prevention (CDC) poster picturing a young couple warns: "Even healthy people can get the flu, and it can be serious."[3] Today, national guidelines call for everyone 6 months of age and older to get vaccinated. Now we are all "at risk."

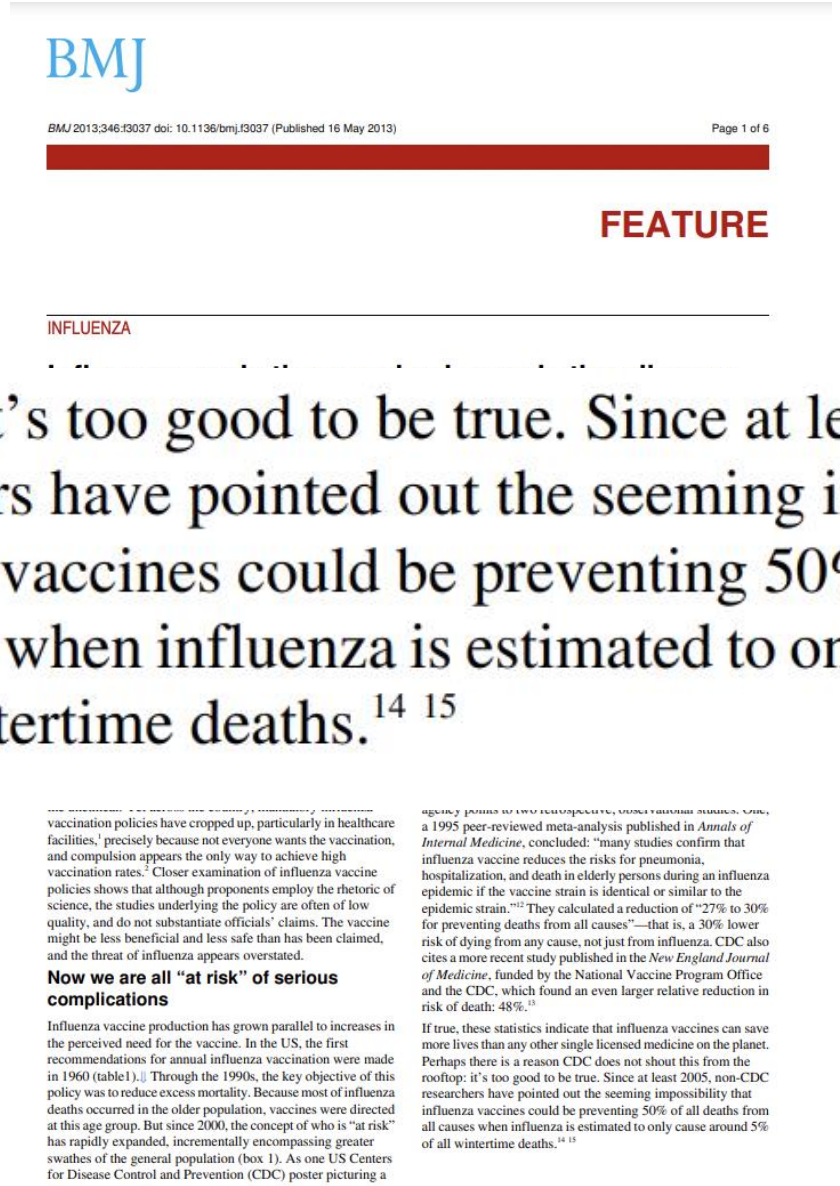
Not to worry: officials say influenza vaccines save lives

Risk of serious illness is a problem—but, according to the official narrative, a tractable problem, thanks to vaccines. As another CDC poster, this time aimed at seniors, explains: "Shots aren't just for kids. Vaccines for adults can prevent serious diseases and even death."[11] And in its more technical guidance document, CDC musters the evidence to support its case. The agency points to two retrospective, observational studies. One, a 1995 peer-reviewed meta-analysis published in *Annals of Internal Medicine*, concluded: "many studies confirm that influenza vaccine reduces the risks for pneumonia, hospitalization, and death in elderly persons during an influenza epidemic if the vaccine strain is identical or similar to the epidemic strain."[12] They calculated a reduction of "27% to 30% for preventing deaths from all causes"—that is, a 30% lower risk of dying from any cause, not just from influenza. CDC also cites a more recent study published in the *New England Journal of Medicine*, funded by the National Vaccine Program Office and the CDC, which found an even larger relative reduction in risk of death: 48%.[13]

If true, these statistics indicate that influenza vaccines can save more lives than any other single licensed medicine on the planet. Perhaps there is a reason CDC does not shout this from the rooftop: it's too good to be true. Since at least 2005, non-CDC researchers have pointed out the seeming impossibility that influenza vaccines could be preventing 50% of all deaths from all causes when influenza is estimated to only cause around 5% of all wintertime deaths.[14 15]

"Healthy user bias" & the influenza vaccine

Doshi P. Influenza: marketing vaccine by marketing disease. BMJ. 2013 May 16;346:f3037. doi: 10.1136/bmj.f3037.



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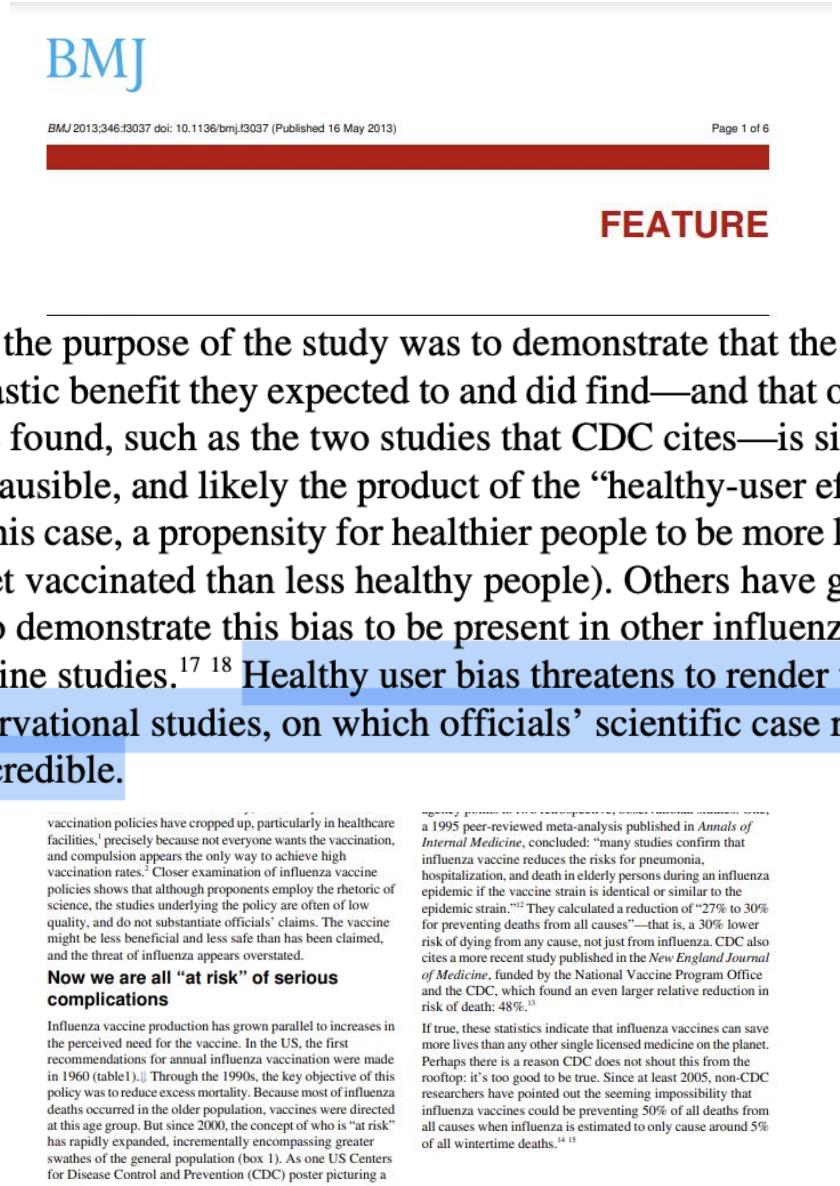

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FEATURE

this: the purpose of the study was to demonstrate that the fantastic benefit they expected to and did find—and that others have found, such as the two studies that CDC cites—is simply implausible, and likely the product of the "healthy-user effect" (in this case, a propensity for healthier people to be more likely to get vaccinated than less healthy people). Others have gone on to demonstrate this bias to be present in other influenza vaccine studies.[17 18] Healthy user bias threatens to render the observational studies, on which officials' scientific case rests, not credible.

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