In response to Sentilhes et al.: our findings are primarily applicable to low- and middle-income countries similar to the study locations. A-PLUS raises questions for future studies in high-income countries.

As Dall'Asta et al. suggested, we performed a post hoc analysis in which the 107 women with cases of sepsis in which tachycardia was the sole evidence of organ dysfunction were excluded. The incidence of maternal sepsis or death in each group was similar to that in the primary analysis, albeit slightly lower (1.3% in the azithromycin group and 1.9% in the placebo group; relative risk, 0.65; 95% confidence interval, 0.54 to 0.79). We used a relatively high threshold for tachycardia (≥120 beats per minute), and the conditions in many of these 107 women met criteria for endometritis or other localized infections (the risk of which is reduced by azithromycin) or might be further adjudicated as sepsis. In light of the results of our previous trial of azithromycin,[3] the drug has been included in regimens used to prevent surgical-site infections in patients undergoing unscheduled cesarean delivery. It is also routinely used in pregnancy to prevent maternal and newborn infection after preterm premature rupture of membranes. Our findings are also consistent with those of another study conducted in low-income settings[4] and provide important information for clinicians and policymakers.

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Since publication of their article, the authors report no further potential conflict of interest.

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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 (reported as 2.98 per 100,000 persons per day) among those in the nonbooster group — a 94.6% difference. In a subsequent letter (March 10, 2022, issue),[2] Arbel et al. reported 441 deaths not related to Covid-19 in the booster group and 963 deaths not related to Covid-19 in the nonbooster group.

We did not have access to the data and could not account for the timing of the receipt of boosters or adjust for the covariates included in the analyses. However, using the person-days of exposure included in the 2021 article by Arbel et al. and the deaths not related to Covid-19 reported in the subsequent letter, we estimated the mortality not related to Covid-19, according to vaccination status, with the 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.

Underlying health plays a substantial role in Covid-19–related mortality. The unadjusted dif-

ferences in mortality related to Covid-19 and mortality not related to Covid-19, according to vaccination status, were essentially the same in the 2021 study by Arbel and colleagues. These findings arouse strong 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.

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THE AUTHORS AND COLLEAGUES REPLY: With regard to a potential healthy vaccinee bias, all participants in our study started at an "unboosted" status, which was changed to a "boosted" status 7 days after vaccination, and 9 of 10 participants contributed follow-up data in both statuses (i.e., to both the booster group and the nonbooster group). Therefore, we used a Cox proportional-hazards regression model with time-dependent covariates to estimate vaccine efficacy.

With adjustment for the same covariates that were included in the analyses of Covid-19–related death in our article, the adjusted hazard ratio for death not due to Covid-19 was 0.23 (95% confidence interval [CI], 0.20 to 0.26) among participants who received the booster (Table 1), a finding that is 2.3 times as high as the adjusted hazard ratio for death due to Covid-19 (hazard ratio, 0.10; 95% CI, 0.07 to 0.14). However, a strong, unexplained association between the use of the booster and lower mortality not related to Covid-19 remains. During the B.1.617.2 (delta) wave in the United States, similar associations were observed between the use of mRNA vaccines and lower mortality not related to Covid-19[1] and mortality from any cause.[2] However, the associations between vaccination and deaths not due to Covid-19 should be interpreted cautiously because numerous potential confounders exist.

The policy in Israel prioritized the administration of boosters to persons in the community setting who were at the highest risk. However, boosters were generally not administered to hospitalized patients who were at high risk for death from any cause. Therefore, we explored hospitalization for any cause as an additional risk factor. The results, which are shown in Table S1 in the Supplementary Appendix (available with the full text of this letter at NEJM.org), indicate that hospitalization was significantly associated with mortality not related to Covid-19 (hazard ratio, 9.1; 95% CI, 8.1 to 10.2; P<0.001), and adjustment for hospitalization slightly modified the estimated association between receipt of the booster and mortality not related to Covid-19 (hazard ratio

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.

for death among participants who received the booster, 0.27; 95% CI, 0.24 to 0.31).

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Ms. Razi and Dr. Duskin-Bitan report no potential conflicts of interest relevant to this letter. Since publication of his article, Dr. Hammerman reports being employed by Medison Pharma, which distributes the mRNA-1273 (Moderna) vaccine against Covid-19 in Israel and in Central and Eastern Europe. No further potential conflict of interest relevant to this letter was reported.

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Postexposure Doxycycline for Sexually Transmitted Infections

TO THE EDITOR: Luetkemeyer et al. (April 6 issue)[1] report evidence that doxycycline treatment within 72 hours after condomless sex was an effective means of preventing sexually transmitted infections (STIs) among men who have sex with men who had had gonorrhea, chlamydia, or syphilis in the past 12 months. However, sexual behavior is the most crucial risk factor for STIs.[2] In the cohort of persons living with HIV infection, the percentage of participants with two or more STIs in the past 12 months was lower in the doxycycline group than in the standard-care group (33% vs. 47%), as was the number of sexual partners in the past 12 months (median, 7 vs. 10.5). In the study, no placebo was given to the participants in the standard-care group, which may have led to differences in measures of subsequent sexual behavior, such as the frequency of condomless sex and act frequency, between the intervention groups and the control groups, as most previous studies of preexposure prophylaxis have shown.[3,4] The study carefully documented the baseline sexual behavior of the participants, including the number of sexual partners and sexual acts in the past 3 months. However, follow-up data on these measures are important for an understanding of the findings.

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

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THE AUTHORS AND A STUDY TEAM MEMBER REPLY: We agree that investigating changes in sexual behavior during the use of doxycycline postexposure prophylaxis (doxy-PEP) is important. Sexual behavior was assessed with the use of quarterly questionnaires and a mobile app throughout the