Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Authors' reply

We thank Udit Singhal and colleagues for their Correspondence regarding our Article.[1] They raise crucial questions regarding our statistical considerations during study planning.

We agree that the non-inferiority limit should not exceed the effect size of the active treatment; however, during study planning, the effect of antibiotic prophylaxis was unknown because almost all previous studies had been done with antibiotic prophylaxis. Only two retrospective studies from 1984 and 1986 were available when planning our study in 2018.[2,3] The confidence intervals in those studies were wide and indicated that rates of sepsis might be 8–13% higher or 3–16% lower without antibiotic prophylaxis than with antibiotic prophylaxis. Consequently, they were underpowered to give any conclusion on the effect of antibiotic prophylaxis.

In the absence of reliable data, we believe that transrectal biopsies, the most commonly used biopsy method in this field, were relevant to consider in the planning of our study. By choosing a 4% limit, we could compare sepsis rates between the study populations and compare results to the most commonly used biopsy method applied worldwide. However, the lower non-inferiority limits proposed by Singhal and colleagues would require the inclusion of several thousand patients, which is practically impossible for most centres.

Singhal and colleagues also claim that use of χ^2 statistics for sample size estimation was inappropriate and that the recommended test is the Farrington-Manning test. We were unfamiliar with the Farrington-Manning test, but acknowledge it is an alternative. However, our position remains that χ^2 statistics are used widely and are appropriate for assessing dichotomous outcomes in two independent populations.

The idea of post-hoc sample size estimation and power analyses is fundamentally flawed and it is highly inappropriate to do such analyses when interpreting observed results.[4] The power of observed effects is evident from the width of the confidence intervals or the size of the p values.

We found a difference in sepsis rates of 0·0% (95% CI –1·37 to 1·37), and we find it peculiar that Singhal and colleagues did not make any comments on these results. The width of our 95% CIs indicate that the study was adequately powered and that it is unlikely that the true sepsis rate is higher then 1·37%, making the 4% limit and any post-hoc power analyses irrelevant. Whether clinicians are willing to accept a possible 1·37% higher sepsis rate when performing transperineal biopsies without antibiotic prophylaxis versus with an antibiotic prophylaxis is another question and is open for debate.

Finally, Singhal and colleagues asked whether it is always necessary to conduct an adequately powered trial to change clinical practice. Because current guidelines and most clinicians continue to recommend and use antibiotic prophylaxis despite knowledge obtained from single-arm studies, the obvious answer is yes. The narrow width of the confidence intervals in our randomised controlled trial show that the study is adequately powered, and we believe the study provides new information that adds valuable evidence to current knowledge and, hopefully, tips the balance in favour of omitting routine antibiotic prophylaxis. Omitting routine antibiotic prophylaxis was also encouraged in a recent editorial citing our study,[5] showing that at least some believe the question is no longer unanswered.

We declare no competing interests.

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BNT162b2 vaccine effectiveness against SARS-CoV-2 omicron BA.4 and BA.5

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SARS-CoV-2 omicron (B.1.1.529) subvariants BA.4 and BA.5 were first detected in South Africa in December, 2021. Their spike (S) proteins are identical (hereafter referred to collectively as BA.4/5) and include L452R and F486V mutations in the receptor binding domain, which might lead to increased immune evasion or the ability to infect host cells, or both.[1] Evidence also suggests that COVID-19 vaccine responses are less effective at neutralising BA.4/5 than BA.1 or BA.2 subvariants of omicron.[2] Subsequently, BA.4/5 have become the predominant subvariants in the USA and globally.[3] To our knowledge, no studies evaluating the effectiveness of COVID-19 vaccines against BA.4/5 have been published to date.

Using the same test-negative design approach as in our previous analyses,[4] we determined the effectiveness of BNT162b2 (Pfizer–BioNTech) against BA.4/5 among members of the health insurance provider Kaiser Permanente, based in Southern California, CA, USA aged 18 years or older, who were diagnosed with an acute respiratory infection and tested for SARS-CoV-2

	Hospital	Emergency department	Urgent care	Outpatient
Two doses of BNT162b2				
<6 months since second dose	NC	30 (–86 to 74)	50 (10 to 72)	30 (4 to 49)
≥6 months since second dose	–4 (–118 to 50)	44 (20 to 61)	7 (–11 to 22)	19 (9 to 29)
Overall	–4 (–116 to 50)	44 (19 to 61)	11 (–7 to 25)	21 (11 to 30)
Three doses of BNT162b2				
<3 months since third dose	NC	71 (18 to 90)	59 (35 to 74)	55 (41 to 65)
3–5 months since third dose	72 (13 to 91)	36 (–3 to 60)	28 (10 to 42)	23 (11 to 33)
<6 months since third dose	73 (25 to 91)	43 (10 to 63)	34 (18 to 46)	29 (19 to 37)
≥6 months since third dose	38 (–31 to 71)	37 (8 to 57)	11 (–7 to 26)	6 (–7 to 17)
Overall	50 (–1 to 76)	39 (14 to 57)	20 (5 to 33)	17 (7 to 26)
Four doses of BNT162b2†				
<3 months since fourth dose	66 (20 to 85)	65 (35 to 82)	35 (10 to 54)	28 (10 to 43)
≥3 months since fourth dose	33 (–112 to 79)	78 (50 to 91)	20 (–23 to 48)	11 (–18 to 34)
Overall	60 (11 to 82)	69 (44 to 83)	32 (7 to 50)	25 (7 to 39)

Data are vaccine effectiveness, with 95% CIs in parentheses. NC=not calculated (ie, fewer than five total cases). *Adjusted for week of COVID-19 health-care encounter, age, sex, race or ethnicity, previous SARS-CoV-2 infection, BMI, Charlson score, and history of previous influenza and pneumococcal vaccination, and nirmatrelvir plus ritonavir receipt. †Analysis done among individuals aged ≥50 years (for whom a fourth dose was recommended at the time of the study).

Table: **Adjusted effectiveness* of BNT162b2 vaccine against omicron (B.1.1.529) subvariants BA.4 and BA.5, by highest level of care and number and timing of receipt of BNT162b2 doses**

by PCR at one of four health-care settings (in ascending order of acuity of care: outpatient visits [including virtual appointments], urgent care centres, emergency departments, and the hospital) between May 9 and Aug 26, 2022 (appendix p 2). Variant sublineage was defined using a combination of whole genome sequencing, S-gene target failure as measured by TaqPath COVID-19 Combo Kit (ThermoFisher, Waltham, MA, USA), and calendar time (additional methods are in the appendix [p 2]). We assessed effectiveness of BNT162b2 against omicron subvariants BA.4 and BA.5, by highest level of care and number and timing of receipt of BNT162b2 doses. Kaiser Permanente's institutional review board granted a waiver for informed consent.

See Online for appendix

24 356 health-care encounters comprised the primary analyses of two-dose and three-dose effectiveness. Of which, 5182 (38%) of 13 718 outpatient, 1556 (20%) of 7977 urgent care, 575 (31%) of 1867 emergency department, and 123 (16%) of 794 hospital encounters had a positive SARS-CoV-2 test. Overall, 5793 (24%) of 24 356 patients who had a health-care encounter during this time were unvaccinated and 5997 (25%) had received two doses and 12 566 (52%) had received three doses of BNT162b2 vaccine (appendix p 3). Median age was 44 years (IQR 32–58), 15 755 (65%) patients were women, 8599 (35%) were men, fewer than six (<1%) had missing sex data, 12 536 (51%) were Hispanic, 5726 (24%) were White, 2519 (10%) were Asian, 2068 (8%) were Black, and 1507 (6%) were other races or ethnicities. Participant characteristics by vaccination status and outcome are shown in the appendix (pp 4–6). In adjusted analyses, point estimates for vaccine effectiveness against BA.4/5 after two doses were 50% or lower (albeit with wide 95% CIs for most estimates), regardless of outcome and time since last dose (table). At less than 6 months after a third dose of vaccine, vaccine effectiveness was 73% (95% CI 25–91) against BA.4/5-related hospitalisation; however, point estimates were less than 50% against milder outcomes (table). Vaccine effectiveness point estimates were greater than 50% against BA.4/5-related outpatient, urgent care, and emergency department encounters only in the first 3 months after a third dose of vaccine (table). At 6 months or longer after a third dose of vaccine, less protection was seen against BA.4/5 than at earlier timepoints, even for hospitalisation, although 95% CIs were wide (table; appendix p 7).

Among eligible participants aged 50 years and older, 3029 (24%) of 12 630 had received a fourth dose of vaccine. A fourth dose improved protection beyond that seen 6 months or longer after a third dose, back to levels that were comparable to those at less than 6 months after a third dose among all adults (table). Excluding immunocompromised individuals yielded similar results (appendix p 8).

Our study has several limitations, including the potential for unmeasured confounding between vaccinated and unvaccinated individuals. Additionally, although we controlled for week of SARS-CoV-2 infection, it is possible that natural immunity, which we could not sufficiently measure, affected our estimates. Specifically, if many unvaccinated individuals gained undocumented natural immunity during omicron BA.1 or BA.2 waves, this could bias our vaccine effectiveness estimates downward.

Our results suggest that two doses of BNT162b2 offered little protection against all BA.4/5 outcomes measured, including hospital admission. A booster (third or fourth dose) did provide protection against BA.4/5, but this protection probably wanes after 3 months against milder outcomes like outpatient, urgent care, or emergency department encounters and after roughly 6 months against BA.4/5-related hospitalisation.

Approximately half of individuals who are eligible for a booster vaccination in the USA have not yet received a booster dose,[5] and of those who have, many did so at least 6 months ago. Moreover, only a third of US individuals aged 50 years and older who previously received a booster have received a

second booster.[5] Thus, much of the US population—and other populations globally—probably have low levels of vaccine-derived immunity, underscoring the importance of booster programmes. The degree to which protection will be extended by BA.4/5-adapted vaccines in the real-world setting, however, is still unknown and requires future assessments in the months ahead.

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The effect of cilgavimab and neutralisation by vaccine-induced antibodies in emerging SARS-CoV-2 BA.4 and BA.5 sublineages

Since the first detection of the SARS-CoV-2 omicron variant (B.1.1.529 and sublineages) in November 2021 in South Africa, Botswana, and Hong Kong, several omicron sublineages have evolved. Some of these sublineages, including BA.2.75, BA.4, and BA.5, have shown augmented resistance against antibody-mediated neutralisation.[1–3]

Thus, these sublineages outcompete earlier Omicron sublineages in populations with pre-existing immune responses due to either infection, or vaccination, or both.[4] In the past months viruses that belong to different BA.4 and BA.5 sublineages and which have mutations at residue R346 (R346T, R346S, or R346S) within the receptor-binding domain of the viral spike S-protein have been detected with increased frequency[5] (appendix p 1) This increased frequency has been detected for sublineages BA.4.6 (R346T or N658S), BA.5.9 (R346I), and BF.7 (R346T). Since the protein S mediates viral entry into cells and constitutes the key target for neutralising antibodies, we investigated whether mutation at R346T, R346S, or R346S might increase infectivity, or neutralisation resistance, or both. For this, we used pseudovirus particles ($_{pp}$), which have been shown to faithfully model SARS-CoV-2 host-cell entry and its neutralisation.[6]

Cell entry by BA.4/5 (R346T, R346S, or R346S)$_{pp}$ was reduced compared with entry by BA.4/5$_{pp}$ (reduced by around 1·6 times [Vero, Caco-2] to 2·0 times [293T, Calu-3]) (appendix p 1). By contrast, particles bearing BA.4.6 S protein (BA.4.6$_{pp}$), which contains mutation R346T jointly with mutation N658S, entered cells with the same efficiency as BA.4–5$_{pp}$. This result suggests that mutation N658S compensates the negative effect of mutation R346T on host-cell entry. We further investigated S protein-driven cell–cell fusion, which is believed to contribute to pathogenesis.[7] No differences between BA.4/5, BA.4/5 (R346T, R346S, or R346S), and BA.4.6 S-proteins were observed (appendix p 1).

Next, we analysed neutralisation by monoclonal antibodies for COVID-19 treatment. In line with previous studies,[1,8] five of ten antibodies (casirivimab, bamlanivimab, etesevimab, tixagevimab, and regdanvimab) failed to neutralise BA.4/5$_{pp}$. Furthermore, two antibodies (imdevimab and sotrovimab) showed more than ten times reduced efficacy against BA.4/5$_{pp}$ compared with B.1$_{pp}$, which harbours the S-protein of a virus that was circulating early during the pandemic. Three antibodies (cilgavimab, bebtelovimab, and S2H97), two of which are in clinical use (cilgavimab and bebtelovimab), retained appreciable neutralisation efficiency against BA.4/5$_{pp}$. However, BA.4/5 (R346T, R346S, or R346S)$_{pp}$, and BA.4.6$_{pp}$ largely lost sensitivity against cilgavimab, being only efficiently neutralised by bebtelovimab (appendix p 3).

Finally, we assessed neutralisation of S protein-driven cell entry by antibodies elicited upon triple vaccination with different combinations of the BNT162b2 mRNA and AZD1222 adenovirus-based vaccines, and early omicron wave (ie, February–May, 2022, in Germany) breakthrough infection in triple vaccinated individuals (appendix,

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See **Online** for appendix