CORRESPONDENCE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

TO THE EDITOR: Polack et al. (Dec. 31)[1] report a vaccine efficacy of 94.8% against Covid-19 after two doses of the messenger RNA (mRNA) vaccine BNT162b2 (Pfizer–BioNTech). The authors also report a vaccine efficacy of 52.4% from after the first dose to before the second dose, but in their calculation, they included data that were collected during the first 2 weeks after the first dose, when immunity would have still been mounting.[1] We used documents submitted to the Food and Drug Administration[2] to derive the vaccine efficacy beginning from 2 weeks after the first dose to before the second dose (Table 1). Even before the second dose, BNT162b2 was highly efficacious, with a vaccine efficacy of 92.6%, a finding similar to the first-dose efficacy of 92.1% reported for the mRNA-1273 vaccine (Moderna).[3]

With such a highly protective first dose, the benefits derived from a scarce supply of vaccine could be maximized by deferring second doses until all priority group members are offered at least one dose. There may be uncertainty about the duration of protection with a single dose, but the administration of a second dose within 1 month after the first, as recommended, provides little added benefit in the short term, while high-risk persons who could have received a first dose with that vaccine supply are left completely unprotected. Given the current vaccine shortage, postponement of the second dose is a matter of national security that, if ignored, will certainly result in thousands of Covid-19–related hospitalizations and deaths this winter in the United States — hospitalizations and deaths that would have been prevented with a first dose of vaccine.

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Dr. De Serres reports having received grant support from Pfizer for an unrelated study of meningococcal antibody sero-

Table 1. Efficacy of BNT162b2 against Covid-19 According to Analysis Period.

Analysis Period	Vaccine (N=21,669)	Placebo (N=21,686)	Vaccine Efficacy, % (95% CI)*
	no. of cases		
After dose 1 to before dose 2 (per Polack et al.[1])	39	82	52.4 (29.5–68.4)
Beginning 7 days after dose 1 to before dose 2 (derived†)‡	18	57	68.5 (46.5–81.5)
Beginning 14 days after dose 1 to before dose 2 (derived†)§	2	27	92.6 (69.0–98.3)
≥7 Days after dose 2 (per Polack et al.[1])	9	172	94.8 (89.8–97.6)

* The derived vaccine efficacies were calculated as 100×(1−[risk among vaccinated patients/risk among unvaccinated patients]), on the basis of those remaining at risk according to the specified analysis period. The vaccine efficacies reported by Polack et al. were calculated as 100×(1−IRR), where IRR is the calculated ratio of confirmed cases of Covid-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group.
† The values were derived with the data reported by the manufacturer in Figure 13 of the Vaccines and Related Biological Products Advisory Committee briefing document.[2]
‡ Before day 7, a total of 21 cases had accrued in the vaccine group and 25 cases in the placebo group.
§ Before day 14, a total of 37 cases had accrued in the vaccine group and 55 cases in the placebo group.

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

This letter was published on February 17, 2021, at NEJM.org.

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-15.
2. Pfizer–BioNTech COVID-19 vaccine (BNT162, PF-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. December 10, 2020 (https://www.fda.gov/media/144246/download).
3. Vaccines and Related Biological Products Advisory Committee meeting. December 17, 2020. FDA briefing document: Moderna COVID-19 vaccine (https://www.fda.gov/media/144434/download).

DOI: 10.1056/NEJMc2036242

TO THE EDITOR: In their trial, Polack et al. found that the vaccine efficacy of the Covid-19 mRNA vaccine BNT162b2 was 95%. They reported similar efficacy across different subgroups. It is well known that subgroup analyses in randomized clinical trials are both important and challenging,[1] and the authors rightly pointed out that their trial was not powered to definitively assess efficacy according to subgroup.

In their article, however, questionable results are reported in Table 3. In each trial group, the sum of the number of cases across age groups (9 in the vaccine group and 186 in the placebo group) does not equal the overall number of cases (8 and 162, respectively). This discrepancy does not appear for any other variables in Table 3 and in Table S4 in the Supplementary Appendix.

The reasons for the discrepancy are not clearly explained in the article. This is all the more problematic because of the between-group difference in the extent of the discrepancy, which could be interpreted as an overestimation of the vaccine efficacy in the age groups. At a time when national public health programs are defining immunization policies that are age-sensitive,[2-4] it would be important to clarify these findings.

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

This letter was published on February 17, 2021, at NEJM.org.

1. Lagakos SW. The challenge of subgroup analyses — reporting without distorting. N Engl J Med 2006;354:1667-9.
2. World Health Organization. WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply. November 13, 2020 (https://www.who.int/publications/m/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines-in-the-context-of-limited-supply).
3. Centers for Disease Control and Prevention. COVID-19 vaccination program operational guidance. 2020 (https://www.cdc.gov/vaccines/covid-19/covid19-vaccination-guidance.html).
4. European Council, Council of the European Union. COVID-19: research and vaccines. 2020 (https://www.consilium.europa.eu/en/policies/coronavirus/covid-19-research-and-vaccines/).

DOI: 10.1056/NEJMc2036242

TO THE EDITOR: Polack et al. may have erroneously concluded that the differences in the absolute numbers of severe Covid-19 cases between the vaccine group and the placebo group provide preliminary evidence of protection against the development of severe Covid-19 illness. The percentage of Covid-19–positive patients in whom severe illness developed was 5.6% (9 of 162 patients) in the placebo group and 12.5% (1 of 8 patients) in the vaccine group — a difference of 6.9 percentage points (95% confidence interval [CI], 6.4 to 7.6) ($P<0.001$ by the chi-square test of proportions).[1] Thus, the preliminary data do not appear to support the conclusion that this vaccine offers protection against severe Covid-19 illness or alleviate the theoretical concern over vaccine-mediated disease enhancement, given that the percentage of Covid-19–positive patients in whom severe illness developed was significantly higher in the vaccine group than in the placebo group.

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

This letter was published on February 17, 2021, at NEJM.org.

1. Campbell I. Chi-squared and Fisher-Irwin tests of two-by-two tables with small sample recommendations. Stat Med 2007;26:3661-75.

DOI: 10.1056/NEJMc2036242

THE AUTHORS REPLY: In response to Skowronski and De Serres: we would like to emphasize that alternative dosing regimens of BNT162b2 have not been evaluated. The decision to implement alternative dosing regimens resides with health authorities; however, we at Pfizer believe that it is critical for health authorities to conduct surveillance on implemented alternative dosing schedules to ensure that vaccines provide the maximum possible protection.

Vergnes questions the results of the subgroup analyses in our article and notes that the total number of Covid-19 cases in the age groups exceeds the overall number of cases presented in Table 3. The author incorrectly summed the Covid-19 cases in the age groups. Among the participants who received the BNT162b2 vaccine, five cases occurred in the age group of 16 to 55 years and three cases in the age group of more than 55 years. The numbers of cases among the older age groups are listed for those 65 years of age and older (1 case) and for those 75 years of age and older (0 cases). Therefore, the author's assertion that the data overestimate vaccine efficacy in the age groups is unsubstantiated.

Wang suggests that, on the basis of an analysis that used a chi-square test of proportions, a vaccine efficacy of 95% was not demonstrated. We would like to clarify that it is not appropriate to use the proportion of Covid-19–positive patients in whom severe disease developed to assess vaccine protection against severe Covid-19. Protection against severe illness is an integrated effect of reducing the chance that any Covid-19 symptom will develop and reducing the risk that severe symptoms will develop after infection. The calculation provided by Wang considers only the second effect, and the estimate for the vaccine group is very imprecise owing to the small sample size (only 8 cases in this group). More importantly, the first effect was completely ignored. The estimation of vaccine efficacy against severe illness should be based on the incidence of severe illness in the total study population. After the first dose, vaccine efficacy against the development of severe Covid-19, calculated as $100 \times (1 - \mathrm{IRR})$, where IRR is the ratio of confirmed cases of severe Covid-19 illness per 1000 person-years of follow-up for the active vaccine group to the corresponding illness rate in the placebo group, was 88.9% (95% CI, 20.1 to 99.7). This result provides evidence of protection against severe Covid-19 illness, thereby alleviating concern about the potential for vaccine-enhanced disease.

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

This letter was published on February 17, 2021, at NEJM.org.

DOI: 10.1056/NEJMc2036242