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Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

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BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μ g per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

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*A complete list of investigators in the C4591001 Clinical Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Polack and Thomas contributed equally to this article.

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Generalities

- Population
 - What is the population
 - Limitations on the conclusions
- Sample
 - Sampling strategy
 - Observational/experimental
 - Other relevant features
- Are there any issue related to sampling in this case?

CORONAVIRUS DISEASE 2019 (COVID-19) has affected tens of millions of people globally¹ since it was declared a pandemic by the World Health Organization on March 11, 2020.² Older adults, persons with certain coexisting conditions, and front-line workers are at highest risk for Covid-19 and its complications. Recent data show increasing rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 in other populations, including younger adults.³ Safe and effective prophylactic vaccines are urgently needed to contain the pandemic, which has had devastating medical, economic, and social consequences.

We previously reported phase 1 safety and immunogenicity results from clinical trials of the vaccine candidate BNT162b2,⁴ a lipid nanoparticle-formulated,⁵ nucleoside-modified RNA (modRNA)⁶ encoding the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation.⁷ Findings from studies conducted in the United States and Germany among healthy men and women showed that two 30- μ g doses of BNT162b2 elicited high SARS-CoV-2 neutralizing antibody titers and robust antigen-specific CD8+ and Th1-type CD4+ T-cell responses.⁸ The 50% neutralizing geometric mean titers elicited by 30 μ g of BNT162b2 in older and younger adults exceeded the geometric mean titer measured in a human convalescent serum panel, despite a lower neutralizing response in older adults than in younger adults. In addition, the reactogenicity profile of BNT162b2 represented mainly short-term local (i.e., injection site) and systemic responses. These findings supported progression of the BNT162b2 vaccine candidate into phase 3.

Here, we report safety and efficacy findings from the phase 2/3 part of a global phase 1/2/3 trial evaluating the safety, immunogenicity, and efficacy of 30 μ g of BNT162b2 in preventing Covid-19 in persons 16 years of age or older. This data set and these trial results are the basis for an application for emergency use authorization.⁹ Collection of phase 2/3 data on vaccine immunogenicity and the durability of the immune response to immunization is ongoing, and those data are not reported here.

METHODS

TRIAL OBJECTIVES, PARTICIPANTS AND OVERSIGHT
We assessed the safety and efficacy of two 30- μ g doses of BNT162b2, administered intramuscu-

larly 21 days apart, as compared with placebo. Adults 16 years of age or older who were healthy or had stable chronic medical conditions, including but not limited to human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus infection, were eligible for participation in the trial. Key exclusion criteria included a medical history of Covid-19, treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition.

Pfizer was responsible for the design and conduct of the trial, data collection, data analysis, data interpretation, and the writing of the manuscript. BioNTech was the sponsor of the trial, manufactured the BNT162b2 clinical trial material, and contributed to the interpretation of the data and the writing of the manuscript. All the trial data were available to all the authors, who vouch for its accuracy and completeness and for adherence of the trial to the protocol, which is available with the full text of this article at NEJM.org. An independent data and safety monitoring board reviewed efficacy and unblinded safety data.

TRIAL PROCEDURES

With the use of an interactive Web-based system, participants in the trial were randomly assigned in a 1:1 ratio to receive 30 μ g of BNT162b2 (0.3 ml volume per dose) or saline placebo. Participants received two injections, 21 days apart, of either BNT162b2 or placebo, delivered in the deltoid muscle. Site staff who were responsible for safety evaluation and were unaware of group assignments observed participants for 30 minutes after vaccination for any acute reactions.

SAFETY

The primary end points of this trial were solicited, specific local or systemic adverse events and use of antipyretic or pain medication within 7 days after the receipt of each dose of vaccine or placebo, as prompted by and recorded in an electronic diary in a subset of participants (the reactogenicity subset), and unsolicited adverse events (those reported by the participants without prompts from the electronic diary) through 1 month after the second dose and unsolicited serious adverse events through 6 months after the second dose. Adverse event data through approximately 14 weeks after the second dose are included in this report. In this report, safety

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POPULATION

DATA

RANDOM ASSIGNMENT TREATMENT PLACEBO

DOUBLE BLIND

POPULATION

RANDOM ASSIGNMENT TREATMENT PLACEBO

DOUBLE BLIND

the occurrence of adverse events more than 2 to 3.5 months after the second dose and more comprehensive information on the duration of protection remain to be determined. Although the study was designed to follow participants for safety and efficacy for 2 years after the second dose, given the high vaccine efficacy, ethical and practical barriers prevent following placebo recipients for 2 years without offering active immunization, once the vaccine is approved by regulators and recommended by public health authorities. Assessment of long-term safety and efficacy for this vaccine will occur, but it cannot be in the context of maintaining a placebo group for the planned follow-up period of 2 years after the second dose. These data do not address whether vaccination prevents asymptomatic infection; a serologic end point that can detect a history of infection regardless of whether symptoms were present (SARS-CoV-2 N-binding antibody) will be reported later. Furthermore, given the high vaccine efficacy and the low number of vaccine breakthrough cases, potential establish-

ment of a correlate of protection has not been feasible at the time of this report.

This report does not address the prevention of Covid-19 in other populations, such as younger adolescents, children, and pregnant women. Safety and immune response data from this trial after immunization of adolescents 12 to 15 years of age will be reported subsequently, and additional studies are planned to evaluate BNT162b2 in pregnant women, children younger than 12 years, and those in special risk groups, such as immunocompromised persons. Although the vaccine can be stored for up to 5 days at standard refrigerator temperatures once ready for use, very cold temperatures are required for shipping and longer storage. The current cold storage requirement may be alleviated by ongoing stability studies and formulation optimization, which may also be described in subsequent reports.

The data presented in this report have significance beyond the performance of this vaccine candidate. The results demonstrate that Covid-19 can be prevented by immunization, provide proof of concept that RNA-based vaccines are a promising new approach for protecting humans against infectious diseases, and demonstrate the speed with which an RNA-based vaccine can be developed with a sufficient investment of resources. The development of

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Generalities

- Population

- What is the population

- «Adults 16 years of age or older who were healthy or had stable chronic medical conditions, including but not limited to human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus infection, were eligible for participation in the trial. Key exclusion criteria included a medical history of Covid-19, treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition.»

- «This report does not address the prevention of Covid-19 in other populations, such as younger adolescents, children, and pregnant women.»

Generalities

- Sample

- «With the use of an interactive Web-based system, participants in the trial were randomly assigned in a 1:1 ratio to receive 30 µg of BNT162b2 (0.3 ml volume per dose) or saline placebo. Participants received two injections, 21 days apart, of either BNT162b2 or placebo, delivered in the deltoid muscle. Site staff who were responsible for safety evaluation and were unaware of group assignments observed participants for 30 minutes after vaccination for any acute reactions.»
- Sampling strategy: **random assignment**
- Observational/**experimental**
- Other relevant features: **double blind**

- Are there any issue related to sampling in this case?

familywise type 1 error rate at 2.5%. Descriptive analyses (estimates of vaccine efficacy and 95% confidence intervals) are provided for key subgroups.

RESULTS

PARTICIPANTS

Between July 27, 2020, and November 14, 2020, a total of 44,820 persons were screened, and 43,548 persons 16 years of age or older underwent randomization at 152 sites worldwide (United States, 130 sites; Argentina, 1; Brazil, 2; South Africa, 4; Germany, 6; and Turkey, 9) in the phase 2/3 portion of the trial. A total of 43,448 participants received injections: 21,720 received BNT162b2 and 21,728 received placebo (Fig. 1). At the data cut-off date of October 9, a total of 37,706 participants had a median of at least 2 months of safety data available after the second dose and contributed to the main safety data set. Among these 37,706 participants, 49% were female, 83% were White, 9% were Black or African American, 28% were Hispanic or Latinx, 35% were obese (body mass index [the weight in kilograms divided by the square of the height in meters] of at least 30.0), and 21% had at least one coexisting condition. The median age was 52 years, and 42% of participants were older than 55 years of age (Table 1 and Table S2).

RESULTS

Between July 27, 2020, and November 14, 2020, 44,820 persons were screened, and 43,548 persons 16 years of age or older underwent randomization at 152 sites worldwide (United States, 130 sites; Argentina, 1; Brazil, 2; South Africa, 4; Germany, 6; and Turkey, 9) in the phase 2/3 portion of the trial. A total of 43,448 participants received injections: 21,720 received BNT162b2 and 21,728 received placebo. At the data cut-off date of October 9, a total of 37,706 participants had a median of at least 2 months of safety data available after the second dose and contributed to the main safety data set. Among these 37,706 participants, 49% were female, 83% were White, 9% were Black or African American, 28% were Hispanic or Latinx, 35% were obese (body mass index [the weight in kilograms divided by the square of the height in meters] of at least 30.0), and 21% had at least one coexisting condition. The median age was 52 years, and 42% of participants were older than 55 years of age (Table 1 and Table S2).

Systemic Reactogenicity

The reactogenicity subset included 8183 participants: 4111 BNT162b2 recipients reported more systemic events than placebo recipients. Among vaccine recipients, mild-to-moderate pain at the injection site within 7 days after an injection was the most commonly reported local reaction, occurring in 1% of participants across all age groups. Severe pain (Fig. 2). Pain was reported more frequently among participants older than 55 years of age (71% reported pain after the first dose; 66% after the second dose) than among younger participants (83% after the first dose; 78% after the second dose). A noticeably lower percentage of participants reported injection-site redness or swelling. The proportion of participants reporting local reactions did not increase after the second dose (Fig. 2A), and no

Figure 1 (facing page). Enrollment and Randomization.

The diagram represents all enrolled participants through November 14, 2020. The safety subset (those with a median of 2 months of follow-up, in accordance with application requirements for Emergency Use Authorization) is based on an October 9, 2020, data cut-off date. The further procedures that one participant in the placebo group declined after dose 2 (lower right corner of the diagram) were those involving collection of blood and nasal swab samples.

participant reported a grade 4 local reaction. In general, local reactions were mostly mild-to-moderate in severity and resolved within 1 to 2 days.

Systemic Reactogenicity

Systemic events were reported more often by younger vaccine recipients (16 to 55 years of age) than by older vaccine recipients (more than 55 years of age) in the reactogenicity subset and more often after dose 2 than dose 1 (Fig. 2B). The most commonly reported systemic events were fatigue and headache (59% and 52%, respectively, after the second dose, among younger vaccine recipients; 51% and 39% among older recipients), although fatigue and headache were also reported by many placebo recipients (23% and 24%, respectively, after the second dose, among younger vaccine recipients; 17% and 14% among older recipients). The frequency of any severe systemic event after the first dose was 0.9% or less. Severe systemic events were reported in less than 2% of vaccine recipients after either dose, except for fatigue (in 3.8%) and headache (in 2.0%) after the second dose.

Fever (temperature, $\geq 38^{\circ}\text{C}$) was reported after the second dose by 16% of younger vaccine recipients and by 11% of older recipients. Only 0.2% of vaccine recipients and 0.1% of placebo recipients reported fever (temperature, 38.9 to 40°C) after the first dose, as compared with 0.8% and 0.1%, respectively, after the second dose. Two participants each in the vaccine and placebo groups reported temperatures above 40.0°C . Younger vaccine recipients were more likely to use antipyretic or pain medication (28% after dose 1; 45% after dose 2) than older vaccine recipients (20% after dose 1; 38% after dose 2), and placebo recipients were less likely (10 to 14%) than vaccine recipients to use the medications,

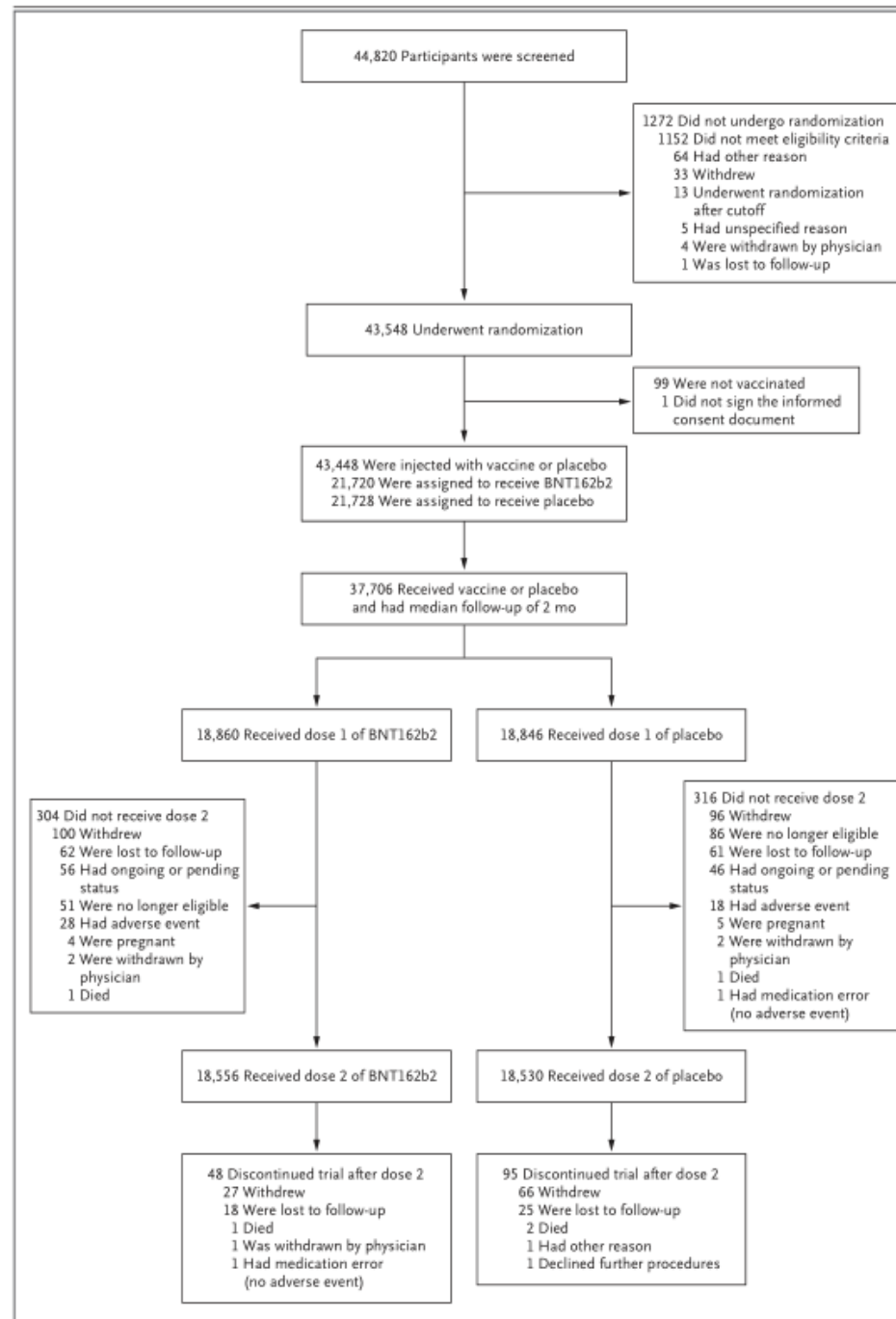


Table 1. Demographic Characteristics of the Participants in the Main Safety Population.*

Characteristic	BNT162b2 (N=18,860)	Placebo (N=18,846)	Total (N=37,706)
Sex — no. (%)			
Male	9,639 (51.1)	9,436 (50.1)	19,075 (50.6)
Female	9,221 (48.9)	9,410 (49.9)	18,631 (49.4)
Race or ethnic group — no. (%)†			
White	15,636 (82.9)	15,630 (82.9)	31,266 (82.9)
Black or African American	1,729 (9.2)	1,763 (9.4)	3,492 (9.3)
Asian	801 (4.2)	807 (4.3)	1,608 (4.3)
Native American or Alaska Native	102 (0.5)	99 (0.5)	201 (0.5)
Native Hawaiian or other Pacific Islander	50 (0.3)	26 (0.1)	76 (0.2)
Multiracial	449 (2.4)	406 (2.2)	855 (2.3)
Not reported	93 (0.5)	115 (0.6)	208 (0.6)
Hispanic or Latinx	5,266 (27.9)	5,277 (28.0)	10,543 (28.0)
Country — no. (%)			
Argentina	2,883 (15.3)	2,881 (15.3)	5,764 (15.3)
Brazil	1,145 (6.1)	1,139 (6.0)	2,284 (6.1)
South Africa	372 (2.0)	372 (2.0)	744 (2.0)
United States	14,460 (76.7)	14,454 (76.7)	28,914 (76.7)
Age group — no. (%)			
16–55 yr	10,889 (57.7)	10,896 (57.8)	21,785 (57.8)
>55 yr	7,971 (42.3)	7,950 (42.2)	15,921 (42.2)
Age at vaccination — yr			
Median	52.0	52.0	52.0
Range	16–89	16–91	16–91
Body-mass index‡			
≥30.0: obese	6,556 (34.8)	6,662 (35.3)	13,218 (35.1)

* Percentages may not total 100 because of rounding.

† Race or ethnic group was reported by the participants.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Outcome measure – endpoint(s)

Outcome measure

For clinical trials, a planned measurement described in the protocol that is used to determine the effect of an intervention/treatment on participants. For observational studies, a measurement or observation that is used to describe patterns of diseases or traits, or associations with exposures, risk factors, or treatment. Types of outcome measures include primary outcome measure and secondary outcome measure.

When there are many endpoints prespecified in a clinical trial, they are usually classified into three families: primary, secondary, and exploratory.

- The set of primary endpoints consists of the outcome or outcomes (based on the drug's expected effects) that establish the effectiveness, and/or safety features, of the drug in order to support regulatory action. When there is more than one primary endpoint and success on any one alone could be considered sufficient to demonstrate the drug's effectiveness, the rate of falsely concluding the drug is effective is increased due to multiple comparisons (see section II.E).
- Secondary endpoints may be selected to demonstrate additional effects after success on the primary endpoint. For instance, a drug may demonstrate effectiveness on the primary endpoint of survival, after which the data regarding an effect on a secondary endpoint, such as functional status, would be tested. Secondary endpoints may also provide evidence that a particular mechanism underlies a demonstrated clinical effect (e.g., a drug for osteoporosis with fractures as the primary endpoint, and improved bone density as a secondary endpoint).
- All other endpoints are referred to as exploratory in this document (see section III.A).

data are reported for all participants who provided informed consent and received at least one dose of vaccine or placebo. Per protocol, safety results for participants infected with HIV (196 patients) will be analyzed separately and are not included here.

During the phase 2/3 portion of the study, a stopping rule for the theoretical concern of vaccine-enhanced disease was to be triggered if the one-sided probability of observing the same or a more unfavorable adverse severe case split (a split with a greater proportion of severe cases in vaccine recipients) was 5% or less, given the same true incidence for vaccine and placebo recipients. Alert criteria were to be triggered if this probability was less than 11%.

EFFICACY

The first primary end point was the efficacy of BNT162b2 against confirmed Covid-19 with onset at least 7 days after the second dose in participants who had been without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose; the second primary end point was efficacy in participants with and participants without evidence of prior infection. Confirmed Covid-19 was defined according to the Food and Drug Administration (FDA) criteria as the presence of at least one of the following symptoms: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was positive for SARS-CoV-2 by nucleic acid amplification-based testing, either at the central laboratory or at a local testing facility (using a protocol-defined acceptable test).

Major secondary end points included the efficacy of BNT162b2 against severe Covid-19. Severe Covid-19 is defined by the FDA as confirmed Covid-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death. Details are provided in the protocol.

An explanation of the various denominator values for use in assessing the results of the trial is provided in Table S1 in the Supplementary Appendix, available at NEJM.org. In brief,

the safety population includes persons 16 years of age or older; a total of 43,448 participants constituted the population of enrolled persons injected with the vaccine or placebo. The main safety subset as defined by the FDA, with a median of 2 months of follow-up as of October 9, 2020, consisted of 37,706 persons, and the reactogenicity subset consisted of 8183 persons. The modified intention-to-treat (mITT) efficacy population includes all age groups 12 years of age or older (43,355 persons; 100 participants who were 12 to 15 years of age contributed to person-time years but included no cases). The number of persons who could be evaluated for efficacy 7 days after the second dose and who had no evidence of prior infection was 36,523, and the number of persons who could be evaluated 7 days after the second dose with or without evidence of prior infection was 40,137.

STATISTICAL ANALYSIS

The safety analyses included all participants who received at least one dose of BNT162b2 or placebo. The findings are descriptive in nature and not based on formal statistical hypothesis testing. Safety analyses are presented as counts, percentages, and associated Clopper-Pearson 95% confidence intervals for local reactions, systemic events, and any adverse events after vaccination, according to terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.1, for each vaccine group.

Analysis of the first primary efficacy end point included participants who received the vaccine or placebo as randomly assigned, had no evidence of infection within 7 days after the second dose, and had no major protocol deviations (the population that could be evaluated). Vaccine efficacy was estimated by $100 \times (1 - \text{IRR})$, 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 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%. Moreover, primary and secondary efficacy end points are evaluated sequentially to control the

Soglia al 30% (ipotesi nulla $VE \leq 30\%$) è usata anche nei trial di Moderna e AstraZeneca

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SYMPTOMATIC
CASES ARE
CONFIRMED

Statistical model

- A parametric statistical model is a triplet
 - Sample space
 - Parameter space
 - Distribution family
- A Bayesian model also requires a prior distribution

(Hints: look for possible reparametrizations/ nuisance parameters/ sufficient statistics.)

	CASES	NON CASES	
Vaccinated	n_{v1}	n_{v2}	$N_v = n_{v1} + n_{v2}$
Controls	n_{c1}	n_{c2}	$N_c = n_{c1} + n_{c2}$
	$n_1 = n_{v1} + n_{c1}$	$n_2 = n_{v2} + n_{c2}$	N

$$n_{v1} \sim \text{Binomial}(N_v, \pi_v)$$

$$\pi_v = P(\text{infection} | \text{vaccine}) \quad \hat{\pi}_v = \frac{n_{v1}}{n_{v1} + n_{v2}}$$

$$n_{c1} \sim \text{Binomial}(N_c, \pi_c)$$

$$\pi_c = P(\text{infection} | \text{control}) \quad \hat{\pi}_c = \frac{n_{c1}}{n_{c1} + n_{c2}}$$

N is fixed (total sample size)

The incidence rate ratio (IRR) is the incidence rate for the treated divided by the incidence rate for the control.

$$IRR = \frac{\pi_v}{\pi_c} \quad \widehat{IRR} = \frac{\hat{\pi}_v}{\hat{\pi}_c}$$

Vaccine and controls are randomly assigned with a 1:1 ratio, so

$$N_v = N_c = N/2$$

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

$$\widehat{IRR} = \frac{\hat{\pi}_v}{\hat{\pi}_c} = \frac{n_{v1}}{n_{c1}}$$

Vaccine efficacy was estimated by $100 \times (1 - IRR)$

$$VE = 1 - IRR$$

$$\widehat{VE} = 1 - \widehat{IRR}$$

	CASES	NON CASES	
Vaccinated	n_{v1}	n_{v2}	$N_v = n_{v1} + n_{v2}$
Controls	n_{c1}	n_{c2}	$N_c = n_{c1} + n_{c2}$
	$n_1 = n_{v1} + n_{c1}$	$n_2 = n_{v2} + n_{c2}$	N

$$n_{v1} | n_1 \sim \text{Binomial}(n_1, \theta)$$

$$\theta = P(\text{Vacc} | \text{Inf})$$

$$n_1 \sim \text{Binomial}(N, \pi)$$

$$\pi = \frac{1}{2} \pi_v + \frac{1}{2} \pi_c$$

We consider the parameter

$$\theta = P(\text{Vacc} | \text{Inf}) = \frac{P(\text{Vacc})P(\text{Inf} | \text{Vacc})}{P(\text{Inf})} = \frac{\frac{1}{2} \pi_v}{\frac{1}{2} \pi_v + \frac{1}{2} \pi_c} = \frac{\pi_v}{\pi_v + \pi_c}$$

This is a reparametrization where

$$\theta = \frac{IRR}{IRR + 1} = \frac{1 - VE}{2 - VE}$$

So inference on VE can be based on inference on θ .

The two parametrizations/likelihoods

With respect to the (π_v, π_c) parametrization we are using the new parametrization (θ, π) where

$$\theta = \frac{\pi_v}{\pi_v + \pi_c}; \quad \pi = \frac{1}{2}\pi_v + \frac{1}{2}\pi_c$$

The inverse transformation is

$$\pi_v = 2\theta\pi; \quad \pi_c = 2(1 - \theta)\pi$$

$$n_{v1} \sim \text{Binomial}(N_v, \pi_v)$$

$$n_{c1} \sim \text{Binomial}(N_c, \pi_c)$$

$$p(n_{v1}, n_{c1}; \pi_v, \pi_c) = p(n_{v1}; \pi_v)p(n_{c1}; \pi_c)$$

The sampling distribution is obtained as the joint distribution of n_{v1} and n_{c1} independent binomial variables.

$$n_{v1} | n_1 \sim \text{Binomial}(n_1, \theta)$$

$$n_1 \sim \text{Binomial}(N, \pi)$$

$$p(n_{v1}, n_1; \theta, \pi) = p(n_{v1} | n_1; \theta)p(n_1; \pi)$$

The sampling distribution is obtained as the joint distribution of n_{v1} and $n_1 = n_{v1} + n_{c1}$ which is the product of the conditional distribution of $n_{v1} | n_1$ and the marginal of n_1 . The latter does not depend on θ .

Likelihood

We consider the observation that out of n cases n_v are from vaccinated individuals, then

$$n_v | n \sim \text{Binomial}(\theta, n)$$

where

$$\theta = P(\text{Vacc} | \text{Inf}) = \frac{\pi_v}{\pi_v + \pi_c}$$

Prior

We need a prior on θ , the following is used (SM)

$$\theta \sim \text{Beta}(0.700102, 1)$$

Which corresponds to

$$E(\theta) = 0.4118 \leftrightarrow E(VE) = 30\%$$

or, in terms of 95% intervals

$$\theta \in [0.005, 0.964] \leftrightarrow VE \in [-26.2, 0.995]$$

See:

<https://statmodeling.stat.columbia.edu/2020/11/13/pfizer-beta-prior-vaccine-effect/>

	CASES
Vaccinated	n_v
Controls	$n - n_v$
	n

$$\pi_v = P(\text{infection} | \text{vaccine})$$

$$\pi_c = P(\text{infection} | \text{control})$$

$$\theta = \frac{IRR}{IRR + 1} = \frac{1 - VE}{2 - VE}$$

$$VE = \frac{1 - 2\theta}{1 - \theta} \quad IRR = \frac{\theta}{1 - \theta}$$

EFFICACY

Among 36,523 participants who had no evidence of existing or prior SARS-CoV-2 infection, 8 cases of Covid-19 with onset at least 7 days after the second dose were observed among vaccine recipients and 162 among placebo recipients. This case split corresponds to 95.0% vaccine efficacy (95% confidence interval [CI], 90.3 to 97.6; Table 2). Among participants with and those without evidence of prior SARS CoV-2 infection, 9 cases of Covid-19 at least 7 days after the second dose were observed among vaccine recipients and 169 among placebo recipients, corresponding to 94.6% vaccine efficacy (95% CI, 89.9 to 97.3). Supplemental analyses indicated that vaccine efficacy among subgroups defined by age, sex, race, ethnicity, obesity, and presence of a coexisting condition was generally consistent with that observed in the overall population (Table 3 and Table S4). Vaccine efficacy among participants with hypertension was analyzed separately but was consistent with the other subgroup analyses (vaccine efficacy, 94.6%; 95% CI, 68.7 to 99.9; case split: BNT162b2, 2 cases; placebo, 44 cases). Figure 3 shows cases of Covid-19 or severe Covid-19 with onset at any time after the first dose (mITT population) (additional data on severe Covid-19 are available in Table S5). Between the first dose and the second dose, 39 cases in the BNT162b2 group and 82 cases in the placebo group were observed, resulting in a vaccine efficacy of 52% (95% CI, 29.5 to 68.4) during this interval and indicating early protection by the vaccine, starting as soon as 12 days after the first dose.

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.

† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.

‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

	CASES
Vaccinated	$n_v = 8$
Controls	$n - n_v = 162$
	$n = 170$

$$\theta \sim \text{Beta}(0.700102, 1)$$



$$\theta | \text{Data} \sim \text{Beta}(0.700102 + 8, 1 + 162)$$

EFFICACY

Among 36,523 participants who had no evidence of existing or prior SARS-CoV-2 infection, 8 cases of Covid-19 with onset at least 7 days after the second dose were observed among vaccine recipients and 162 among placebo recipients. This case split corresponds to 95.0% vaccine efficacy (95% confidence interval [CI], 90.3 to 97.6; Table 2). Among participants with and those without evidence of prior SARS CoV-2 infection, 9 cases of Covid-19 at least 7 days after the second dose were observed among vaccine recipients and 169 among placebo recipients, corresponding to 94.6% vaccine efficacy (95% CI, 89.9 to 97.3). Supplemental analyses indicated that vaccine efficacy among subgroups defined by age, sex, race, ethnicity, obesity, and presence of a coexisting condition was generally consistent with that observed in the overall population (Table 3 and Table S4). Vaccine efficacy among participants with hypertension was analyzed separately but was consistent with the other subgroup analyses (vaccine efficacy, 94.6%; 95% CI, 68.7 to 99.9; case split: BNT162b2, 2 cases; placebo, 44 cases). Figure 3 shows cases of Covid-19 or severe Covid-19 with onset at any time after the first dose (mITT population) (additional data on severe Covid-19 are available in Table S5). Between the first dose and the second dose, 39 cases in the BNT162b2 group and 82 cases in the placebo group were observed, resulting in a vaccine efficacy of 52% (95% CI, 29.5 to 68.4) during this interval and indicating early protection by the vaccine, starting as soon as 12 days after the first dose.

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§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

	CASES
Vaccinated	$n_v = 8$
Controls	$n - n_v = 162$
	$n = 170$

$$\theta | Data \sim Beta(8.700102, 163)$$

$$E(\theta | Data) = \frac{8.700102}{8.700102 + 163} = 0.0506$$

$$E(VE | Data) = 0.9467$$

EFFICACY

Among 36,523 participants who had no evidence of existing or prior SARS-CoV-2 infection, 8 cases of Covid-19 with onset at least 7 days after the second dose were observed among vaccine recipients and 162 among placebo recipients. This case split corresponds to 95.0% vaccine efficacy (95% confidence interval [CI], 90.3 to 97.6; Table 2). Among participants with and those without evidence of prior SARS CoV-2 infection, 9 cases of Covid-19 at least 7 days after the second dose were observed among vaccine recipients and 169 among placebo recipients, corresponding to 94.6% vaccine efficacy (95% CI, 89.9 to 97.3). Supplemental analyses indicated that vaccine efficacy among subgroups defined by age, sex, race, ethnicity, obesity, and presence of a coexisting condition was generally consistent with that observed in the overall population (Table 3 and Table S4). Vaccine efficacy among participants with hypertension was analyzed separately but was consistent with the other subgroup analyses (vaccine efficacy, 94.6%; 95% CI, 68.7 to 99.9; case split: BNT162b2, 2 cases; placebo, 44 cases). Figure 3 shows cases of Covid-19 or severe Covid-19 with onset at any time after the first dose (mITT population) (additional data on severe Covid-19 are available in Table S5). Between the first dose and the second dose, 39 cases in the BNT162b2 group and 82 cases in the placebo group were observed, resulting in a vaccine efficacy of 52% (95% CI, 29.5 to 68.4) during this interval and indicating early protection by the vaccine, starting as soon as 12 days after the first dose.

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‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

	CASES
Vaccinated	$n_v = 8$
Controls	$n - n_v = 162$
	$n = 170$

$$\theta | \text{Data} \sim \text{Beta}(8.700102, 163)$$

$$\text{Me}(\theta | \text{Data}) = 0.04893$$

$$\text{Me}(\text{VE} | \text{Data}) = 0.9485$$

EFFICACY

Among 36,523 participants who had no evidence of existing or prior SARS-CoV-2 infection, 8 cases of Covid-19 with onset at least 7 days after the second dose were observed among vaccine recipients and 162 among placebo recipients. This case split corresponds to 95.0% vaccine efficacy (95% confidence interval [CI], 90.3 to 97.6; Table 2). Among participants with and those without evidence of prior SARS CoV-2 infection, 9 cases of Covid-19 at least 7 days after the second dose were observed among vaccine recipients and 169 among placebo recipients, corresponding to 94.6% vaccine efficacy (95% CI, 89.9 to 97.3). Supplemental analyses indicated that vaccine efficacy among subgroups defined by age, sex, race, ethnicity, obesity, and presence of a coexisting condition was generally consistent with that observed in the overall population (Table 3 and Table S4). Vaccine efficacy among participants with hypertension was analyzed separately but was consistent with the other subgroup analyses (vaccine efficacy, 94.6%; 95% CI, 68.7 to 99.9; case split: BNT162b2, 2 cases; placebo, 44 cases). Figure 3 shows cases of Covid-19 or severe Covid-19 with onset at any time after the first dose (mITT population) (additional data on severe Covid-19 are available in Table S5). Between the first dose and the second dose, 39 cases in the BNT162b2 group and 82 cases in the placebo group were observed, resulting in a vaccine efficacy of 52% (95% CI, 29.5 to 68.4) during this interval and indicating early protection by the vaccine, starting as soon as 12 days after the first dose.

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* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.

† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.

‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

	CASES
Vaccinated	$n_v = 8$
Controls	$n - n_v = 162$
	$n = 170$

$$\theta | \text{Data} \sim \text{Beta}(8.700102, 155)$$

Credibility intervals (2.5%, 97.5% quantiles)

$$\theta \in [0.02319, 0.08799]$$

$$VE \in [0.9035, 0.9762]$$

Conclusion

- What is the final criterion to decide on the efficacy of the vaccine?

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

Success: $P(VE > 30\%|Data) \geq 0.986$

To

- 1) compensate for interim analysis
- 2) Control overall type I error rate at 2.5%

2) Type I error rate is a frequentist concept, so here we are **assessing a frequentist property of a Bayesian procedure**.

How does it work?

Forget interim analysis for now, assume the decision rule for rejecting the null hypotheses

$$H_0: VE \leq 30\% \quad (\theta \geq 0.4118)$$

is

$$P(VE > 30\%|Data) \geq 0.986$$

Checked at $n = 164$, that is, the condition is

$$n_v \leq 53$$

(since $P(\theta < 0.4118|n_v = 54) = 0.985$ and $P(\theta < 0.4118|n_v = 53) = 0.99$), then the type I error occurs if

$$n_v \leq 53 | \theta > 0.4118$$

Which has probability at most

$$P(n_v \leq 53 | \theta = 0.4118) = 0.0122$$

The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%. Moreover, primary and secondary efficacy end points are evaluated sequentially to control the familywise type 1 error rate at 2.5%. Descriptive analyses (estimates of vaccine efficacy and 95% confidence intervals) are provided for key subgroups.

$P(VE > 30 | Data)$
POSTERIOR
PROBAB.

	CASES
Vaccinated	n_v
Controls	$n - n_v$
	n

$$\pi_v = P(\text{infection} | \text{vaccine})$$

$$\pi_c = P(\text{infection} | \text{control})$$

$$IRR = \frac{\pi_v}{\pi_c}$$

$$VE = 1 - IRR$$

Success: $P(VE > 30\%|Data) \geq 0.986$

To

- 1) compensate for interim analysis
- 2) Control overall type I error rate at 2.5%

1)

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, $P[VE > 30\%|data]$) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.
- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is $< 5\%$. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.
- Efficacy and futility boundaries will be applied in a nonbinding way.

The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%. Moreover, primary and secondary efficacy end points are evaluated sequentially to control the familywise type 1 error rate at 2.5%. Descriptive analyses (estimates of vaccine efficacy and 95% confidence intervals) are provided for key subgroups.

$P(VE > 30 | Data)$
POSTERIOR
PROBAB.

	CASES
Vaccinated	n_v
Controls	$n - n_v$
	n

$$\pi_v = P(\text{infection} | \text{vaccine})$$

$$\pi_c = P(\text{infection} | \text{control})$$

$$IRR = \frac{\pi_v}{\pi_c}$$

$$VE = 1 - IRR$$

Success: $P(VE > 30\%|Data) \geq 0.986$

To

- 1) compensate for interim analysis
- 2) Control overall type I error rate at 2.5%

- 1) This means that the actual stopping rule was to end declaring efficacy if at any of the following # of infected observed the number of vaccinated among them were below the threshold

	Vacc (threshold)	Cases
	6	32
	15	62
	25	92
	35	120

The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%. Moreover, primary and secondary efficacy end points are evaluated sequentially to control the familywise type 1 error rate at 2.5%. Descriptive analyses (estimates of vaccine efficacy and 95% confidence intervals) are provided for key subgroups.

$P(VE > 30 | Data)$
POSTERIOR
PROBAB.

	CASES
Vaccinated	n_v
Controls	$n - n_v$
	n

$$\pi_v = P(\text{infection}|\text{vaccine})$$

$$\pi_c = P(\text{infection}|\text{control})$$

$$IRR = \frac{\pi_v}{\pi_c}$$

$$VE = 1 - IRR$$

Success: $P(VE > 30\%|Data) \geq 0.986$

To

- 1) compensate for interim analysis
- 2) Control overall type I error rate at 2.5%

- 1) This means that the actual stopping rule was to end declaring efficacy if at any of the following # of infected observed the number of vaccinated among them were below the threshold

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria ^a	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.

Note: Case split = vaccine : placebo.

a. Interim efficacy claim: $P(VE > 30\%|data) > 0.995$; success at the final analysis: $P(VE > 30\%|data) > 0.986$.

The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%. Moreover, primary and secondary efficacy end points are evaluated sequentially to control the familywise type 1 error rate at 2.5%. Descriptive analyses (estimates of vaccine efficacy and 95% confidence intervals) are provided for key subgroups.

$P(VE > 30 | Data)$
POSTERIOR
PROBAB.

	CASES
Vaccinated	n_v
Controls	$n - n_v$
	n

$$\pi_v = P(\text{infection}|\text{vaccine})$$

$$\pi_c = P(\text{infection}|\text{control})$$

$$IRR = \frac{\pi_v}{\pi_c}$$

$$VE = 1 - IRR$$

Success: $P(VE > 30\%|Data) \geq 0.986$

To

- 1) compensate for interim analysis
- 2) Control overall type I error rate at 2.5%

Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤ 6)	Probability of Failure (Cases in Vaccine Group ≥ 15)	Probability of Success (Cases in Vaccine Group ≤ 15)	Probability of Failure (Cases in Vaccine Group ≥ 26)	Probability of Success (Cases in Vaccine Group ≤ 25)	Probability of Failure (Cases in Vaccine Group ≥ 35)	Probability of Success (Cases in Vaccine Group ≤ 35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤ 53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%. Moreover, primary and secondary efficacy end points are evaluated sequentially to control the familywise type 1 error rate at 2.5%. Descriptive analyses (estimates of vaccine efficacy and 95% confidence intervals) are provided for key sub-groups.

$P(VE > 30 | Data)$
POSTERIOR PROBABILITY

	CASES
Vaccinated	n_v
Controls	$n - n_v$
	n

$$\pi_v = P(\text{infection} | \text{vaccine})$$

$$\pi_c = P(\text{infection} | \text{control})$$

$$IRR = \frac{\pi_v}{\pi_c}$$

$$VE = 1 - IRR$$

Conclusion

DISCUSSION

A two-dose regimen of BNT162b2 (30 μg per dose, given 21 days apart) was found to be safe and 95% effective against Covid-19. The vaccine met both primary efficacy end points, with more than a 99.99% probability of a true vaccine efficacy greater than 30%. These results met our prespecified success criteria, which were to establish a probability above 98.6% of true vaccine efficacy being greater than 30%, and greatly exceeded the minimum FDA criteria for authorization.⁹ Although the study was not powered to definitively assess efficacy by subgroup, the point estimates of efficacy for subgroups based on age, sex, race, ethnicity, body-mass index, or the presence of an underlying condition associated with a high risk of Covid-19 complications are also high. For all analyzed subgroups in which more than 10 cases of Covid-19 occurred, the lower limit of the 95% confidence interval for efficacy was more than 30%.

	CASES
Vaccinated	$n_v = 8$
Controls	$n - n_v = 162$
	$n = 170$

$$\theta \sim \text{Beta}(0, 700102, 1)$$

$$\theta | \text{Data} \sim \text{Beta}(0, 700102 + 8, 1 + 162)$$

$$E(\theta | \text{Data}) = \frac{8.700102}{8.700102 + 163} = 0.0506$$

$$E(\text{VE} | \text{Data}) = 0.9467$$

Credibility intervals
(2.5%, 97.5% quantiles)
 $\theta \in [0.02319, 0.08799]$
 $\text{VE} \in [0.9035, 0.9762]$

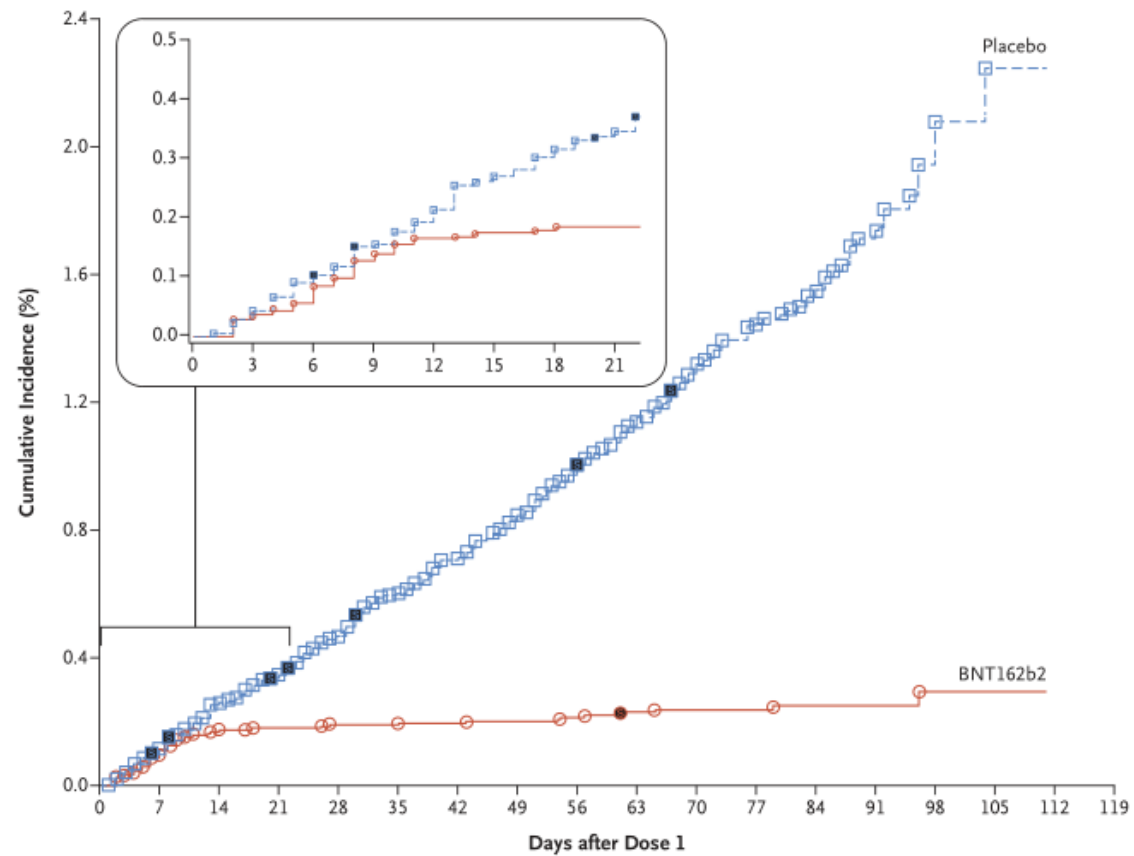
Table 3. Vaccine Efficacy Overall and by Subgroup in Participants without Evidence of Infection before 7 Days after Dose 2.

Efficacy End-Point Subgroup	BNT162b2 (N=18,198)		Placebo (N=18,325)		Vaccine Efficacy, % (95% CI) [†]
	No. of Cases	Surveillance Time (No. at Risk)*	No. of Cases	Surveillance Time (No. at Risk)*	
Overall	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.0–97.9)
Age group					
16 to 55 yr	5	1.234 (9,897)	114	1.239 (9,955)	95.6 (89.4–98.6)
>55 yr	3	0.980 (7,500)	48	0.983 (7,543)	93.7 (80.6–98.8)
≥65 yr	1	0.508 (3,848)	19	0.511 (3,880)	94.7 (66.7–99.9)
≥75 yr	0	0.102 (774)	5	0.106 (785)	100.0 (–13.1–100.0)
Sex					
Male	3	1.124 (8,875)	81	1.108 (8,762)	96.4 (88.9–99.3)
Female	5	1.090 (8,536)	81	1.114 (8,749)	93.7 (84.7–98.0)
Race or ethnic group [‡]					
White	7	1.889 (14,504)	146	1.903 (14,670)	95.2 (89.8–98.1)
Black or African American	0	0.165 (1,502)	7	0.164 (1,486)	100.0 (31.2–100.0)
All others	1	0.160 (1,405)	9	0.155 (1,355)	89.3 (22.6–99.8)
Hispanic or Latinx	3	0.605 (4,764)	53	0.600 (4,746)	94.4 (82.7–98.9)
Non-Hispanic, non-Latinx	5	1.596 (12,548)	109	1.608 (12,661)	95.4 (88.9–98.5)
Country					
Argentina	1	0.351 (2,545)	35	0.346 (2,521)	97.2 (83.3–99.9)
Brazil	1	0.119 (1,129)	8	0.117 (1,121)	87.7 (8.1–99.7)
United States	6	1.732 (13,359)	119	1.747 (13,506)	94.9 (88.6–98.2)

* Surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.

[†] The confidence interval (CI) for vaccine efficacy is derived according to the Clopper–Pearson method, adjusted for surveillance time.

[‡] Race or ethnic group was reported by the participants. “All others” included the following categories: American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported.



Efficacy End-Point Subgroup	BNT162b2, 30 µg (N=21,669)		Placebo (N=21,686)		VE (95% CI) percent
	No. of participants	Surveillance time person-yr (no. at risk)	No. of participants	Surveillance time person-yr (no. at risk)	
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Figure 3. Efficacy of BNT162b2 against Covid-19 after the First Dose.

Shown is the cumulative incidence of Covid-19 after the first dose (modified intention-to-treat population). Each symbol represents Covid-19 cases starting on a given day; filled symbols represent severe Covid-19 cases. Some symbols represent more than one case, owing to overlapping dates. The inset shows the same data on an enlarged y axis, through 21 days. Surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from the first dose to the end of the surveillance period. The confidence interval (CI) for vaccine efficacy (VE) is derived according to the Clopper–Pearson method.

Efficacy Endpoint Subgroup	BNT162b2 (30 µg) (N ^a =21669)		Placebo (N ^a =21686)		VE (%)	(95% CI ^e)
	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b	Surveillance Time ^c (n2 ^d)		
Severe COVID-19 occurrence after Dose 1	1	4.021 (21314)	9	4.006 (21259)	88.9	(20.1, 99.7)
After Dose 1 to before Dose 2	0		4		100.0	(-51.5, 100.0)
Dose 2 to 7 days after Dose 2	0		1		100.0	(-3800.0, 100.0)
≥7 Days after Dose 2	1		4		75.0	(-152.6, 99.5)

Table S5 | Vaccine Efficacy of Severe COVID-19 Occurrence after Dose 1 (Modified Intention-to-Treat). a. N = number of participants in the specified group. b. n1 = Number of participants meeting the endpoint definition. c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period. d. n2 = Number of participants at risk for the endpoint. e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).

http://skranz.github.io//r/2020/11/11/CovidVaccineBayesian.html?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+skranz_R+%28Economics+and+R+%28R+Posts%29%29