Bezpečnost a účinnost vakcíny BNT162b2 mRNA Covid-19

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- Článek
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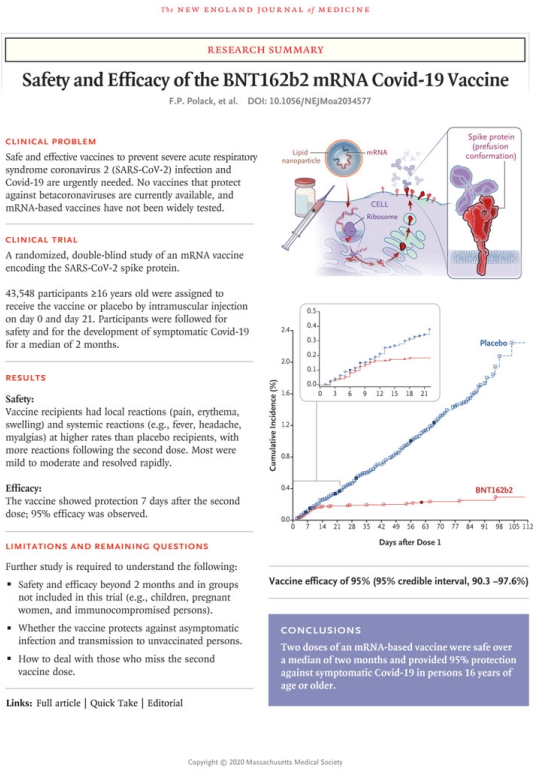
Metriky

Abstraktní

Pozadí

Infekce těžkým akutním respiračním syndromem coronavirem 2 (SARS-CoV-2) a následná koronavirová nemoc 2019 (Covid-19) postihly v celosvětové pandemii desítky milionů lidí. Bezpečné a účinné vakcíny jsou naléhavě potřeba.

Metody



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RESEARCH SUMMARY

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

F.P. Polack, et al. DOI: 10.1056/NEJMoa2034577

CLINICAL PROBLEM

Safe and effective vaccines to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 are urgently needed. No vaccines that protect against betacoronaviruses are currently available, and mRNA-based vaccines have not been widely tested.

CLINICAL TRIAL

A randomized, double-blind study of an mRNA vaccine encoding the SARS-CoV-2 spike protein.

43,548 participants ≥16 years old were assigned to receive the vaccine or placebo by intramuscular injection on day 0 and day 21. Participants were followed for safety and for the development of symptomatic Covid-19 for a median of 2 months.

RESULTS

Safety:
Vaccine recipients had local reactions (pain, erythema, swelling) and systemic reactions (e.g., fever, headache, myalgias) at higher rates than placebo recipients, with more reactions following the second dose. Most were mild to moderate and resolved rapidly.

Efficacy:
The vaccine showed protection 7 days after the second dose; 95% efficacy was observed.

LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- Safety and efficacy beyond 2 months and in groups not included in this trial (e.g., children, pregnant women, and immunocompromised persons).
- Whether the vaccine protects against asymptomatic infection and transmission to unvaccinated persons.
- How to deal with those who miss the second vaccine dose.

Links: Full article | Quick Take | Editorial

Vaccine efficacy of 95% (95% credible interval, 90.3 –97.6%)

CONCLUSIONS

Two doses of an mRNA-based vaccine were safe over a median of two months and provided 95% protection against symptomatic Covid-19 in persons 16 years of age or older.

V probíhající nadnárodní, placebem kontrolované, pozorovatelem zaslepené, klíčové studii účinnosti jsme náhodně přidělili osoby ve věku 16 let nebo starší v poměru 1:1, aby dostaly dvě dávky placeba nebo kandidáta na vakcínu BNT162b2 s odstupem 21 dnů. (30 μg na dávku). BNT162b2 je nukleosidy modifikovaná RNA vakcína formulovaná na lipidových nanočásticích, která kóduje prefúzně stabilizovaný, membránou ukotvený celodélkový vrcholový protein SARS-CoV-2. Primárními cílovými body byla účinnost vakcíny proti laboratorně potvrzenému Covid-19 a bezpečnost.

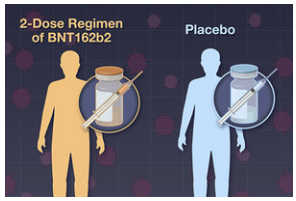
Výsledek

Randomizaci podstoupilo celkem 43 548 účastníků, z nichž 43 448 dostalo injekce: 21 720 s BNT162b2 a 21 728 s placebem. Mezi účastníky, kteří dostávali BNT162b2, bylo 8 případů Covid-19 s nástupem nejméně 7 dní po druhé dávce a 162 případů mezi těmi, kteří dostávali placebo; BNT162b2 byl 95% účinný v prevenci Covid-19 (95% důvěryhodný interval, 90,3 až 97,6). Podobná účinnost vakcíny (obecně 90 až 100 %) byla pozorována u podskupin definovaných věkem, pohlavím, rasou, etnickým původem, výchozím indexem tělesné hmotnosti a přítomností souběžných onemocnění. Z 10 případů závažného onemocnění Covid-19 s nástupem po první dávce se 9 vyskytlo u příjemců placeba a 1 u příjemce BNT162b2. Bezpečnostní profil BNT162b2 byl charakterizován krátkodobou, mírnou až střední bolestí v místě vpichu, únavou a bolestí hlavy.

Závěry

Dvoudávkový režim BNT162b2 poskytl 95% ochranu proti Covid-19 osobám ve věku 16 let nebo starším. Bezpečnost po mediánu 2 měsíců byla podobná jako u jiných virových vakcín. (Financováno společnostmi BioNTech a Pfizer; číslo ClinicalTrials.gov, NCT04368728.)

- RYCHLÝ ODBĚR**Bezpečnost a účinnost vakcíny BNT162b2 Covid-19** *03:00*



Coronavirová nemoc 2019 (Covid-19) zasáhla desítky milionů lidí na celém světě [1] od té doby, co byla 11. března 2020 Světovou zdravotnickou organizací vyhlášena pandemií. [2] Starší dospělí, osoby s určitými souběžnými onemocněními a pracovníci v první linii jsou s nejvyšším rizikem Covid-19 a jeho komplikací. Nedávné údaje ukazují, že se zvyšuje míra infekce koronavirem 2 (SARS-CoV-2) a Covid-19 u jiných populací, včetně mladších dospělých. [3] Bezpečné a účinné profylaktické vakcíny jsou naléhavě potřeba k potlačení pandemie, která má zničující lékařské, ekonomické a sociální důsledky.

Již dříve jsme uvedli výsledky fáze 1 bezpečnosti a imunogenicity z klinických studií kandidáta na vakcínu BNT162b2, [4] lipidové nanočástice formulované, [5] nukleosidy modifikované RNA (modRNA) [6] kódující SARS-CoV-2 plné délky, modifikované dvěma prolinem mutace k uzamčení v prefuzní konformaci. [7] Poznatky ze studií provedených ve Spojených státech a v Německu mezi zdravými muži a ženami ukázaly, že dvě 30μg dávky BNT162b2 vyvolaly vysoké titry neutralizačních protilátek SARS-CoV-2 a robustní antigen-specifické CD8+ a Th1-typové CD4+ T-buněčné odpovědi. . [8]50% neutralizační průměr geometrických titrů vyvolaných 30 μg BNT162b2 u starších a mladších dospělých překročil geometrický průměr titru naměřený na panelu lidského rekonvalescentního séra, a to navzdory nižší neutralizační reakci u starších dospělých než u mladších dospělých. Kromě toho profil reaktogenity BNT162b2 představoval hlavně krátkodobé lokální (tj. místo vpichu) a systémové reakce. Tato zjištění podpořila progresi kandidátní vakcíny BNT162b2 do fáze 3.

Zde uvádíme zjištění bezpečnosti a účinnosti z části 2/3 globální studie fáze 1/2/3 hodnotící bezpečnost, imunogenicitu a účinnost 30 μg BNT162b2 v prevenci Covid-19 u osob ve věku 16 let nebo starší. Tento soubor údajů a tyto výsledky zkoušek jsou základem pro žádost

o povolení nouzového použití. [9] Sběr údajů fáze 2/3 o imunogenicitě vakcíny a trvanlivosti imunitní odpovědi na imunizaci probíhá a tato data zde nejsou uvedena.

Metody

Cíle zkoušky, účastníci a dohled

Hodnotili jsme bezpečnost a účinnost dvou 30 μg dávek BNT162b2 podaných intramuskulárně s odstupem 21 dnů ve srovnání s placebem. Dospělí ve věku 16 let nebo starší, kteří byli zdraví nebo měli stabilní chronické zdravotní stavy, včetně, ale bez omezení na ně, virem lidské imunodeficience (HIV), virem hepatitidy B nebo virem hepatitidy C, byli způsobilí k účasti ve studii. Klíčová vylučovací kritéria zahrnovala anamnézu Covid-19, léčbu imunosupresivní terapií nebo diagnózu imunokompromitujícího stavu.

Společnost Pfizer byla zodpovědná za návrh a provedení studie, sběr dat, analýzu dat, interpretaci dat a napsání rukopisu. BioNTech byl sponzorem studie, vyrobil materiál pro klinickou studii BNT162b2 a přispěl k interpretaci dat a napsání rukopisu. Všechna data ze studie byla k dispozici všem autorům, kteří ručí za jejich přesnost a úplnost a za dodržování protokolu, který je k dispozici s plným textem tohoto článku na NEJM.org. Nezávislý výbor pro monitorování údajů a bezpečnosti přezkoumal účinnost a nezaslepené údaje o bezpečnosti.

Zkušební postupy

S použitím interaktivního webového systému byli účastníci studie náhodně rozděleni v poměru 1:1, aby dostali 30 μg BNT162b2 (0,3 ml objem na dávku) nebo fyziologické placebo. Účastníci obdrželi dvě injekce s odstupem 21 dnů buď BNT162b2 nebo placeba do deltového svalu. Zaměstnanci místa, kteří byli zodpovědní za hodnocení bezpečnosti a nevěděli o skupinových přiřazeních, pozorovali účastníky po dobu 30 minut po vakcinaci kvůli jakékoli akutní reakci.

Bezpečnost

Primárními cílovými body této studie byly vyžádané, specifické lokální nebo systémové nežádoucí příhody a použití antipyretik nebo léků proti bolesti během 7 dnů po obdržení každé dávky vakcíny nebo placeba, jak bylo vybídnuto a zaznamenáno v elektronickém deníku v podskupině účastníky (podskupina reaktogenity) a nevyžádané nežádoucí příhody (ty hlášené účastníky bez výzvy z elektronického deníku) po dobu 1 měsíce po druhé dávce a nevyžádané závažné nežádoucí účinky po dobu 6 měsíců po druhé dávce. V této zprávě jsou zahrnuty údaje o nežádoucích účincích za období přibližně 14 týdnů po druhé dávce. V této zprávě jsou uvedeny bezpečnostní údaje pro všechny účastníky, kteří poskytli informovaný souhlas a dostali alespoň jednu dávku vakcíny nebo placeba. Podle protokolu,

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

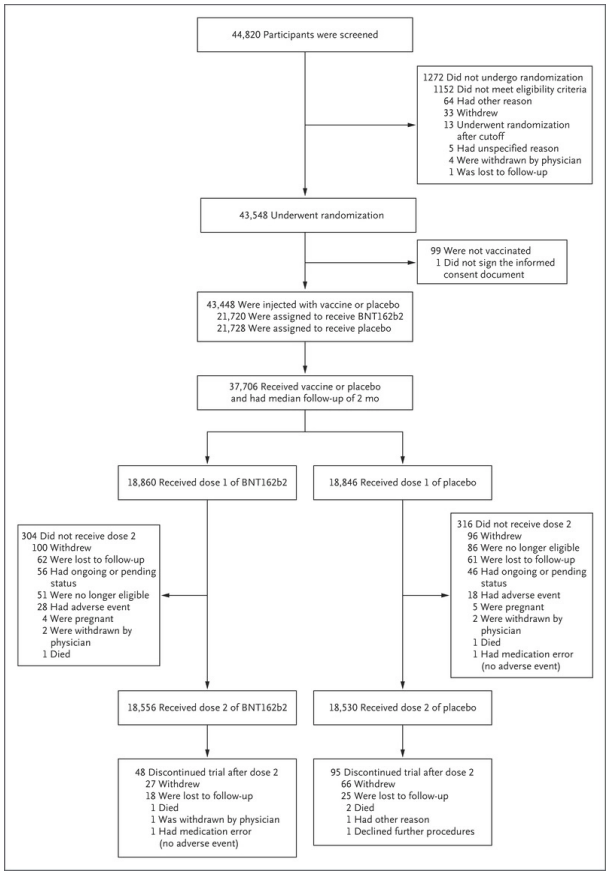
analyses are presented as counts, percentages, and associated Clopper–Pearson 95% confidence intervals for local reactions, systemic events, and any adverse events after vaccination, according to terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.1, for each vaccine group.

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×(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 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.

Results

Participants

Enrollment and Randomization.



Demographic Characteristics of the Participants in the Main Safety Population.

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.

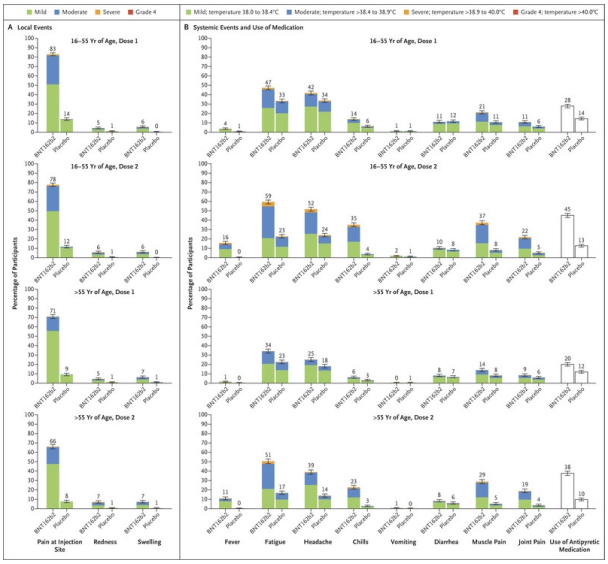
Between July 27, 2020, and November 14, 2020, a total of 44,820 persons were screened, and 43,548 persons 16 years of age or older underwent randomization at 152 sites worldwide (United States, 130 sites; Argentina, 1; Brazil, 2; South Africa, 4; Germany, 6; and Turkey, 9) in the phase 2/3 portion of the trial. A total of 43,448 participants received injections: 21,720 received BNT162b2 and

21,728 received placebo (Figure 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).

Safety

Local Reactogenicity

Local and Systemic Reactions Reported within 7 Days after Injection of BNT162b2 or Placebo, According to Age Group.



The reactogenicity subset included 8183 participants. Overall, BNT162b2 recipients reported more local reactions than placebo recipients. Among BNT162b2 recipients, mild-to-moderate pain at the injection site within 7 days after an injection was the most commonly reported local reaction, with less than 1% of participants across all age groups reporting severe pain (Figure 2). Pain was reported less 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 (Figure 2A), and no 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 (Figure 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, ≥38°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, regardless of age or dose. Systemic events including fever and chills were observed within the first 1 to 2 days after vaccination and resolved shortly thereafter.

Daily use of the electronic diary ranged from 90 to 93% for each day after the first dose and from 75 to 83% for each day after the second dose. No difference was noted between the BNT162b2 group and the placebo group.

Adverse Events

Adverse event analyses are provided for all enrolled 43,252 participants, with variable follow-up time after dose 1 (Table S3). More BNT162b2 recipients than placebo recipients reported any adverse event (27% and 12%, respectively) or a related adverse event (21% and 5%). This distribution largely reflects the inclusion of transient reactogenicity events, which were reported as adverse events more commonly by vaccine recipients than by placebo recipients. Sixty-four vaccine recipients (0.3%) and 6 placebo recipients (<0.1%) reported lymphadenopathy. Few participants in either group had severe adverse events, serious adverse events, or adverse events leading to withdrawal from the trial. Four related serious adverse events were reported among BNT162b2 recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia). Two BNT162b2 recipients died (one from arteriosclerosis, one from cardiac arrest), as did four placebo recipients (two from unknown causes, one from hemorrhagic stroke, and one from myocardial infarction). No deaths were considered by the investigators to be related to the vaccine or placebo. No Covid-19–associated deaths were observed. No stopping rules were met during the reporting period. Safety monitoring will continue for 2 years after administration of the second dose of vaccine.

Efficacy

Vaccine Efficacy against Covid-19 at Least 7 days after the Second 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.

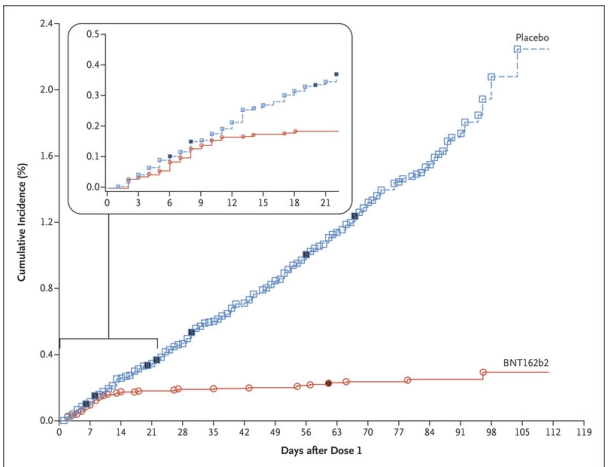
Vaccine Efficacy Overall and by Subgroup in Participants without Evidence of Infection before 7 Days after Dose 2.

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 of BNT162b2 against Covid-19 after the First Dose.



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
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)

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.

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%.

The cumulative incidence of Covid-19 cases over time among placebo and vaccine recipients begins to diverge by 12 days after the first dose, 7 days after the estimated median viral incubation period of 5 days,[10] indicating the early onset of a partially protective effect of immunization. The study was not designed to assess the efficacy of a single-dose regimen. Nevertheless, in the interval between the first and second doses, the observed vaccine efficacy against Covid-19 was 52%, and in the first 7 days after dose 2, it was 91%, reaching full efficacy against disease with onset at least 7 days after dose 2. Of the 10 cases of severe Covid-19 that were observed after the first dose, only 1 occurred in the vaccine group. This finding is consistent with overall high efficacy against all Covid-19 cases. The severe case split provides preliminary evidence of vaccine-mediated protection against severe disease, alleviating many of the theoretical concerns over vaccine-mediated disease enhancement.[11]

The favorable safety profile observed during phase 1 testing of BNT162b2[4,8] was confirmed in the phase 2/3 portion of the trial. As in phase 1, reactogenicity was generally mild or moderate, and reactions were less common and milder in older adults than in younger adults. Systemic reactogenicity was more common and severe after the second dose than after the first dose, although local reactogenicity was similar after the two doses. Severe fatigue was observed in approximately 4% of BNT162b2 recipients, which is higher than that observed in recipients of some vaccines recommended for older adults.[12] This rate of severe fatigue is also lower than that observed in recipients of another approved viral vaccine for older adults.[13] Overall, reactogenicity events were transient and resolved within a couple of days after onset. Lymphadenopathy, which generally resolved within 10 days, is likely

to have resulted from a robust vaccine-elicited immune response. The incidence of serious adverse events was similar in the vaccine and placebo groups (0.6% and 0.5%, respectively).

This trial and its preliminary report have several limitations. With approximately 19,000 participants per group in the subset of participants with a median follow-up time of 2 months after the second dose, the study has more than 83% probability of detecting at least one adverse event, if the true incidence is 0.01%, but it is not large enough to detect less common adverse events reliably. This report includes 2 months of follow-up after the second dose of vaccine for half the trial participants and up to 14 weeks' maximum follow-up for a smaller subset. Therefore, both 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 establishment 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 BNT162b2 was initiated on January 10, 2020, when the SARS-CoV-2 genetic sequence was released by the Chinese Center for Disease Control and Prevention and disseminated globally by the GISAID (Global Initiative on Sharing All Influenza Data) initiative. This rigorous demonstration of safety and efficacy less than 11 months later provides a practical demonstration that RNA-based vaccines, which require only viral genetic sequence information to initiate development, are a major new tool to combat pandemics and other infectious disease outbreaks. The continuous phase 1/2/3 trial design may provide a model to reduce the protracted development timelines that have delayed the availability of vaccines against other infectious diseases of medical importance. In the context of the current, still expanding pandemic, the BNT162b2 vaccine, if approved, can contribute, together with other public health measures, to reducing the devastating loss of health, life, and economic and social well-being that has resulted from the global spread of Covid-19.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Drs. Polack and Thomas contributed equally to this article.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Author Affiliations

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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.

Supplementary Material

Research Summary	PDF	3161KB
Protocol	PDF	4781KB
Supplementary Appendix	PDF	171KB
Disclosure Forms	PDF	559KB
Data Sharing Statement	PDF	71KB

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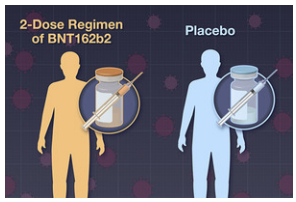
QUICK TAKE**Safety and Efficacy of the BNT162b2 Covid-19 Vaccine** *03:00*



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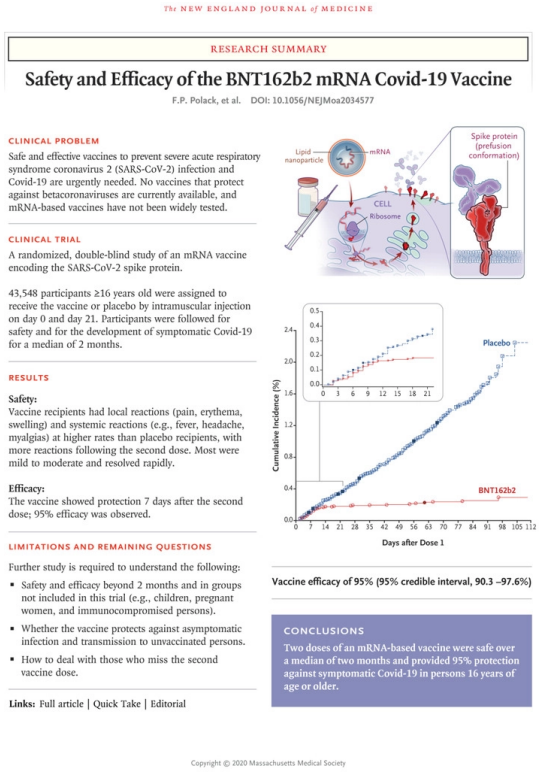


The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

F.P. Polack, et al. DOI: 10.1056/NEJMoa2034577

CLINICAL PROBLEM

Safe and effective vaccines to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 are urgently needed. No vaccines that protect against betacoronaviruses are currently available, and mRNA-based vaccines have not been widely tested.

CLINICAL TRIAL

A randomized, double-blind study of an mRNA vaccine encoding the SARS-CoV-2 spike protein.

43,548 participants ≥16 years old were assigned to receive the vaccine or placebo by intramuscular injection on day 0 and day 21. Participants were followed for safety and for the development of symptomatic Covid-19 for a median of 2 months.

RESULTS

Safety:
Vaccine recipients had local reactions (pain, erythema, swelling) and systemic reactions (e.g., fever, headache, myalgias) at higher rates than placebo recipients, with more reactions following the second dose. Most were mild to moderate and resolved rapidly.

Efficacy:
The vaccine showed protection 7 days after the second dose; 95% efficacy was observed.

LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- Safety and efficacy beyond 2 months and in groups not included in this trial (e.g., children, pregnant women, and immunocompromised persons).
- Whether the vaccine protects against asymptomatic infection and transmission to unvaccinated persons.
- How to deal with those who miss the second vaccine dose.

Links: Full article | Quick Take | Editorial

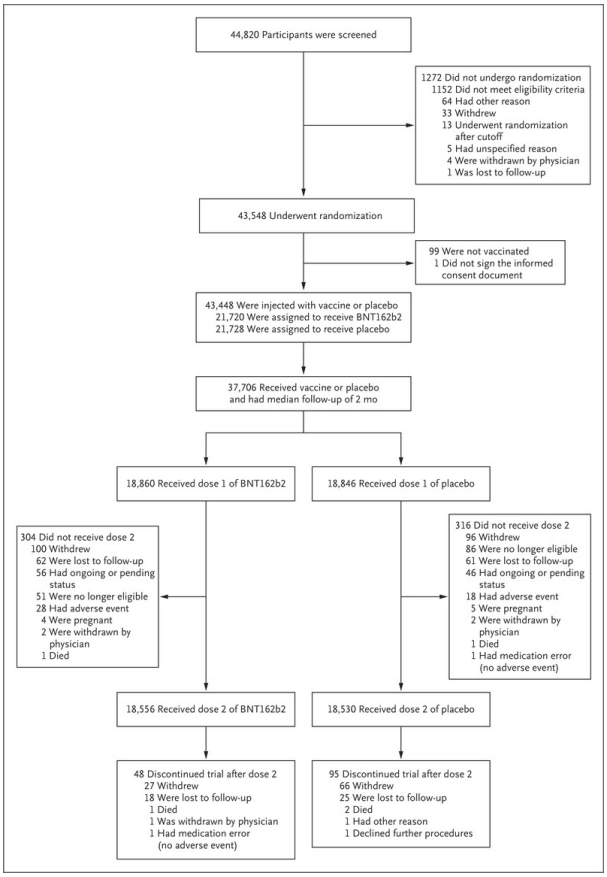
Vaccine efficacy of 95% (95% credible interval, 90.3 –97.6%)

CONCLUSIONS

Two doses of an mRNA-based vaccine were safe over a median of two months and provided 95% protection against symptomatic Covid-19 in persons 16 years of age or older.

Download a PDF of the Research Summary.

2. **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.

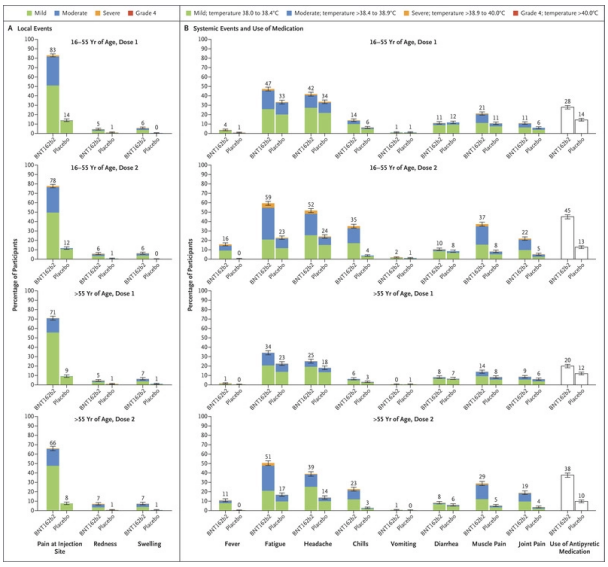
3. **Demographic Characteristics of the Participants in the Main Safety Population.***

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.

4. **Local and Systemic Reactions Reported within 7 Days after Injection of BNT162b2 or Placebo, According to Age Group.**
5. **Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.***
6. **Vaccine Efficacy Overall and by Subgroup in Participants without Evidence of Infection before 7 Days after Dose 2.**
7. **Efficacy of BNT162b2 against Covid-19 after the First Dose.**



Data on local and systemic reactions and use of medication were collected with electronic diaries from participants in the reactogenicity subset (8,183 participants) for 7 days after each vaccination. Solicited injection-site (local) reactions are shown in Panel A. Pain at the injection site was assessed according to the following scale: mild, does not interfere with activity; moderate, interferes with activity; severe, prevents daily activity; and grade 4, emergency department visit or hospitalization. Redness and swelling were measured according to the following scale: mild, 2.0 to 5.0 cm in diameter; moderate, >5.0 to 10.0 cm in diameter; severe, >10.0 cm in diameter; and grade 4, necrosis or exfoliative dermatitis (for redness) and necrosis (for swelling). Systemic events and medication use are shown in Panel B. Fever categories are designated in the key; medication use was not graded. Additional scales were as follows:

fatigue, headache, chills, new or worsened muscle pain, new or worsened joint pain (mild: does not interfere with activity; moderate: some interference with activity; or severe: prevents daily activity), vomiting (mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; or severe: requires intravenous hydration), and diarrhea (mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; or severe: 6 or more loose stools in 24 hours); grade 4 for all events indicated an emergency department visit or hospitalization. I bars represent 95% confidence intervals, and numbers above the I bars are the percentage of participants who reported the specified reaction.

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.

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)
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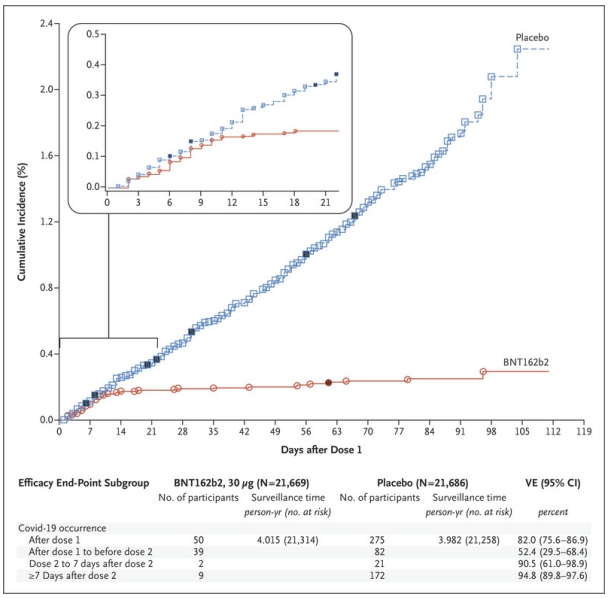
Country					
Argentina	1	0.351 (2,545)	35	0.346 (2,521)	97.2 (83.3–99.9)
Brazil	1	0.119 (1,129)	8	0.117 (1,121)	87.7 (8.1–99.7)
United States	6	1.732 (13,359)	119	1.747 (13,506)	94.9 (88.6–98.2)

* 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) No. of participants	Surveillance time person-yr (no. at risk)	Placebo (N=21,686) No. of participants	Surveillance time person-yr (no. at risk)	VE (95% CI) percent
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)

Je ukázán kumulativní výskyt Covid-19 po první dávce (upravená populace s úmyslem léčit). Každý symbol představuje případy Covid-19 začínající v daný den; plné symboly představují vážné případy Covid-19. Některé symboly představují více než jeden případ kvůli překrývajícím se datům. Vložená část ukazuje stejná data na zvětšené ose y v průběhu 21 dnů. Doba sledování je celková doba v 1000 osoborokech pro daný koncový bod napříč všemi účastníky v každé skupině ohrožené pro daný koncový bod. Časové období pro nárůst případů Covid-19 je od první dávky do konce období sledování. Interval spolehlivosti (CI) pro účinnost vakcíny (VE) je odvozen podle Clopper-Pearsonovy metody.

Více o

31. prosince 2020
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Čínský překlad

PRÁCE LÉKAŘE

24. listopadu 2022

Stockton, Kalifornie

Gastroenterologie

Gastroenterologický lékař
New York

Medicína kritické péče

Intenzivista – kardiologie
Miami na Floridě

Primární péče

Dvojjazyčný ambulantní lékař primární péče WellMed Miami FL
Tennessee

Interní lékařství

Geriatrie – nejlepší potenciál výdělku a možnosti vedení v Memphis, Tennessee
Brooklyn, New York

Psychiatrie

Ošetřující psychiatr – ambulantní – nemocnice Coney Island – Brooklyn, New York – plný úvazek
Los Angeles, Kalifornie

Psychiatrie

Psychiatr pro dospělé

Více z týdne od 31. prosince 2020

- Redakční **Zaměstnanci Massachusetts Medical Society v roce 2020** *EJ Rubin*

- Obrázky v klinické medicíně **Echinokokové cysty na nohou** *N. Akhtar a V. Kumar*
- Úhly pohledu **Březen – Rozmanitost tváří v tvář nepřízni osudu** *S. Jain, VM Arora a KD Manning*
- Recenze článku **Patofyziologie zánětlivých onemocnění střev** *JT Chang*
- Původní článek **Zkouška dexamethasonu pro chronický subdurální hematom** *PJ Hutchinson a další*
- Perspektivní **Whiteout** *EJ Rourke*
- Redakční **FDA a důležitost důvěry** *LR Baden a další*
- Redakční **Očkování proti SARS-CoV-2 – unce (ve skutečnosti mnohem méně) prevence** *EJ Rubin a DL Longo*
- Případové záznamy Všeobecné nemocnice v Massachusetts **Case 41-2020: A 62-Year-Old Man with Memory Loss and Odd Behavior** *B.H. Price and Others*
- Perspective **Medicaid and Child Health Equity** *J.M. Perrin, G.M. Kenney, and S. Rosenbaum*
- Original Article **Higher or Lower Hemoglobin Transfusion Thresholds for Preterm Infants** *H. Kirpalani and Others*
- Editorial **Audio Interview: A Look at Covid-19 Prevention and Care in 2020** *E.J. Rubin, L.R. Baden, and S. Morrissey*
- Perspective **Reentry** *R.E. Leiter*
- Perspective **Supporting Clinicians during Covid-19 and Beyond — Learning from Past Failures and Envisioning New Strategies** *J. Shapiro and T.B. McDonald*
- Perspective **Essential but Undefined — Reimagining How Policymakers Identify Safety-Net Hospitals** *P. Chatterjee, B.D. Sommers, and K.E. Joynt Maddox*
- Perspective **FDA Approval of Remdesivir — A Step in the Right Direction** *D. Rubin and Others*
- Images in Clinical Medicine **Acquired Hypertrichosis Lanuginosa** *T. Kovitwanichkanont and M. Darling*

- Editorial **Hiding in Plain Sight — Somatic Mutation in Human Disease** *E. Levy-Lahad and M.-C. King*
- Clinical Implications of Basic Research **Emergence of a Highly Fit SARS-CoV-2 Variant** *R.S. Baric*
- Editorial **Beneath a Tough Mother (Dura Mater) — Chronic Subdural Hematoma** *A.H. Ropper*
- Original Article **Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease** *D.B. Beck and Others*
- Editorial **Employees of the Massachusetts Medical Society in 2020** *E.J. Rubin*
- Images in Clinical Medicine **Echinococcal Cysts in the Leg** *N. Akhtar and V. Kumar*
- Points of View **March On — Diversity in the Face of Adversity** *S. Jain, V.M. Arora, and K.D. Manning*
- Review Article **Pathophysiology of Inflammatory Bowel Diseases** *J.T. Chang*
- Original Article **Trial of Dexamethasone for Chronic Subdural Hematoma** *P.J. Hutchinson and Others*
- Perspective **Whiteout** *E.J. Rourke*

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