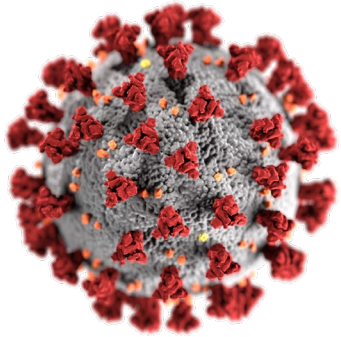
DIPARTIMENTO DI SCIENZE
CARDIO-TORACO-VASCOLARI
E SANITA' PUBBLICA

UNIVERSITÀ
DEGLI STUDI
DI PADOVA

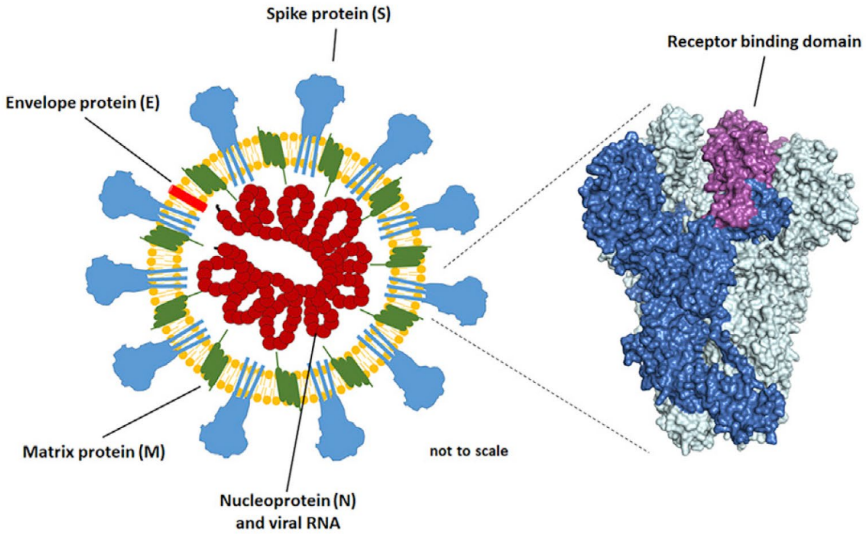
Il Vaccino a mRNA: caratteristiche, efficacia, sicurezza

Vincenzo Baldo

SARS-CoV-2



- Virus a RNA a filamento positivo
- Classica forma a corona

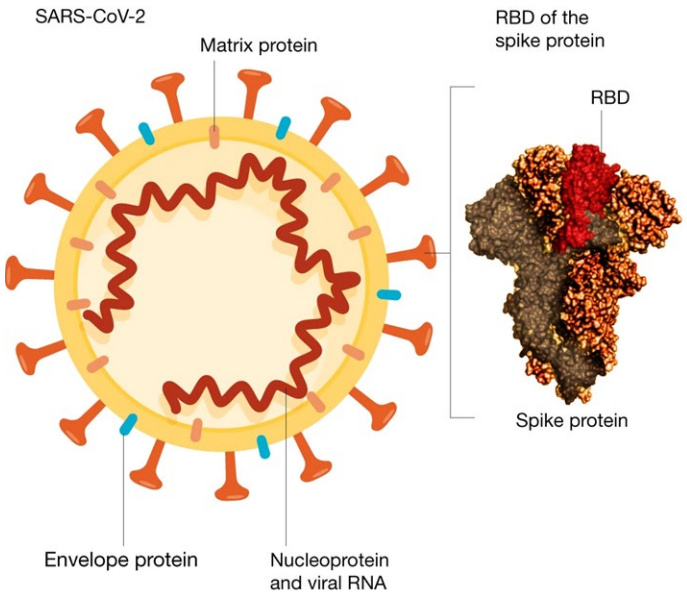


Quale proteina bersaglio?

- In SARS-CoV-1 e SARS-CoV-2, questa proteina interagisce con il recettore ACE2
- La proteina S sulla superficie del virus è un bersaglio ideale per un vaccino.

Wu et al., 2020; Zhou et al., 2020; Zhu et al., 2020

Quali piattaforme



Inactivated vaccines contain SARS-CoV-2 that is grown in cell culture and then chemically inactivated

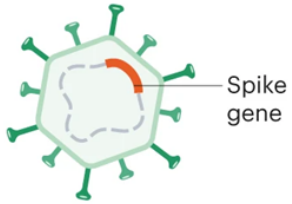
Live attenuated vaccines are made of genetically weakened versions of SARS-CoV-2 that is grown in cell culture

VLPs carry no genome but display the spike protein on their surface

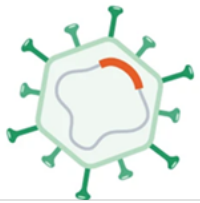
Recombinant spike-protein-based vaccines

Recombinant RBD-based vaccines

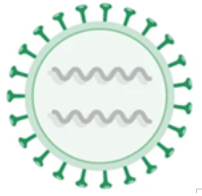
Replication-incompetent vector vaccines cannot propagate in the cells of the vaccinated individual but express the spike protein within them



Replication-competent vector vaccines can propagate to some extent in the cells of the vaccinated individual and express the spike protein within them

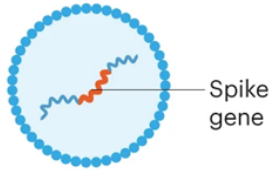


Inactivated virus vector vaccines carry copies of the spike protein on their surface but have been chemically inactivated



DNA vaccines consist of plasmid DNA encoding the spike gene under a mammalian promoter

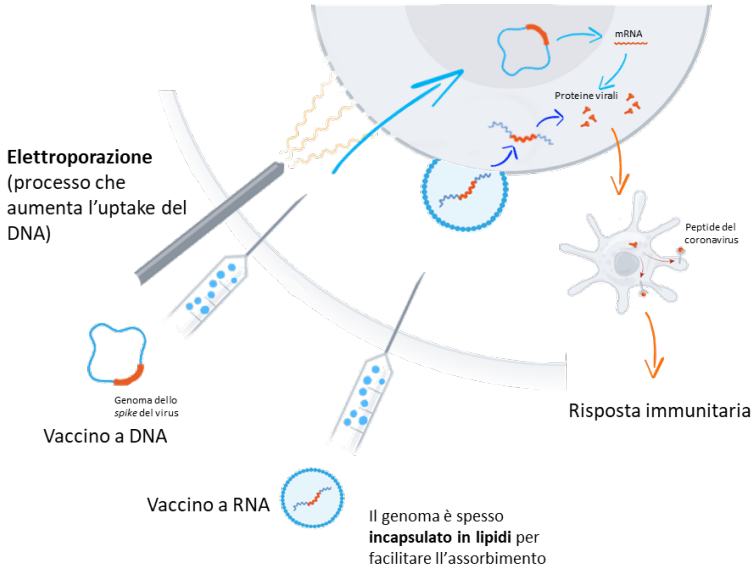
RNA vaccines consist of RNA encoding the spike protein and are typically packaged in LNPs

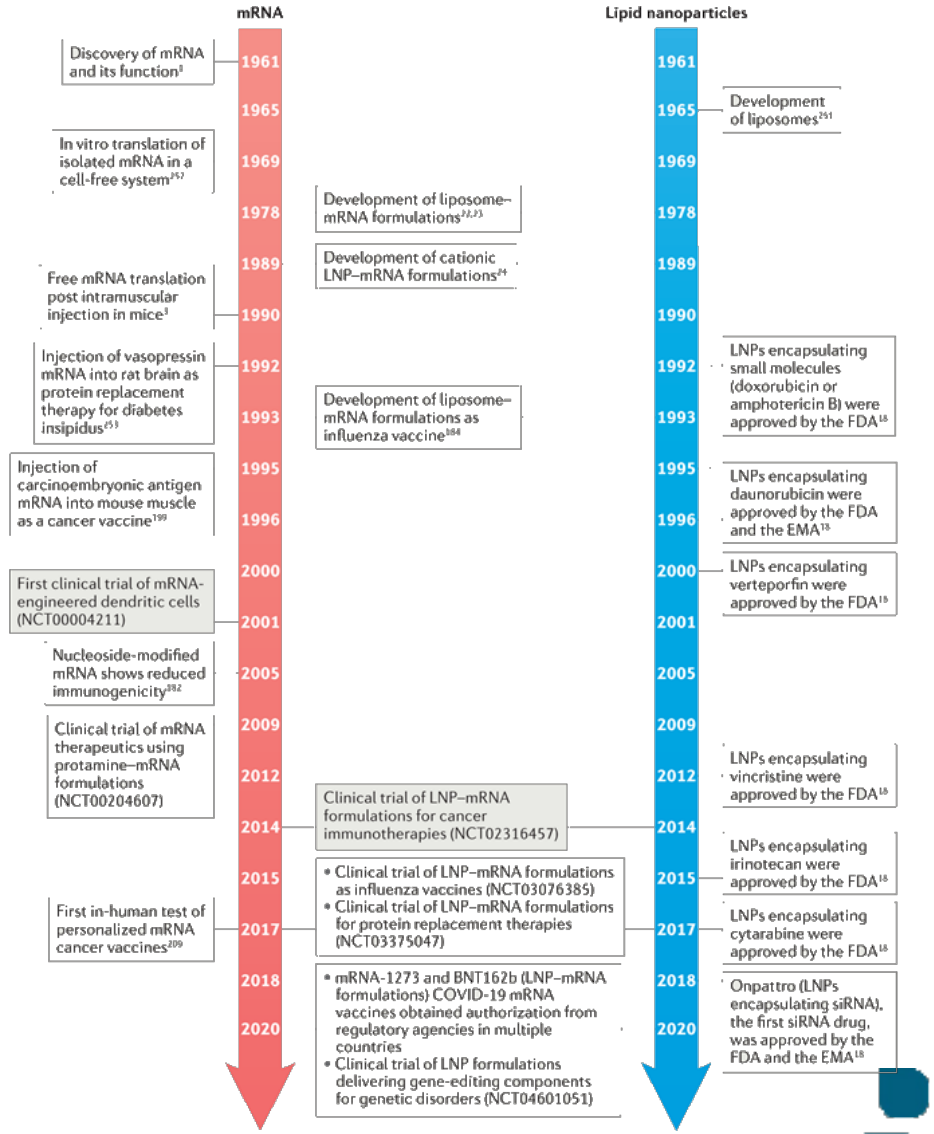


Nature 586, 516–527 (2020)

Vaccini ad Acidi nucleici

- Utilizzo delle **informazioni genetiche**
- L'acido nucleico viene **in trasferito nelle cellule umane**
- Permette la codifica per la proteina degli *spike* del virus.
- **Non si produce il virus**, semplicità di produzione
- **Fino ad oggi nessun vaccino era stato autorizzato utilizza questa tecnologia**





Nature 586, 516–527 (2020)

Studi fase 1

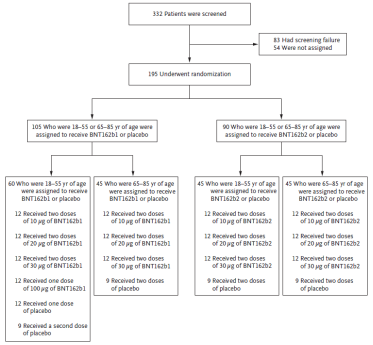
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates

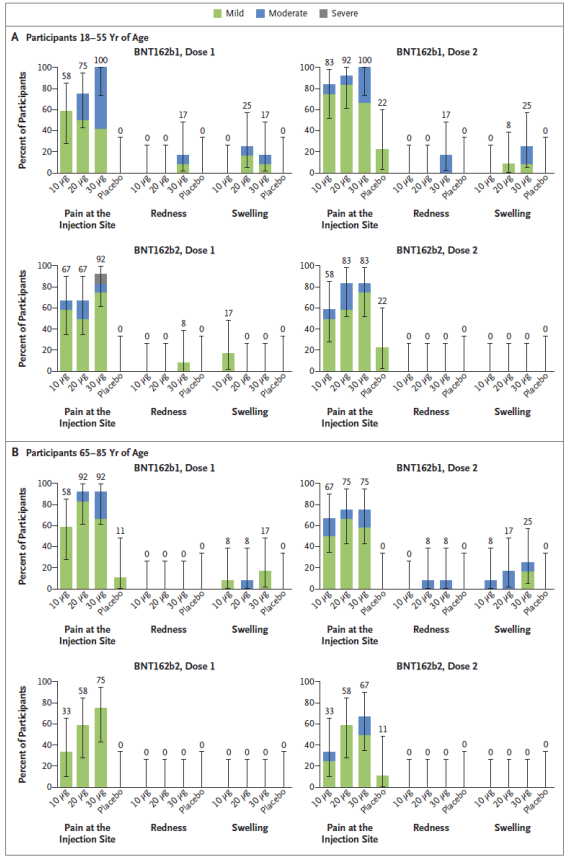
This article was published on October 14, 2020, at NEJM.org.

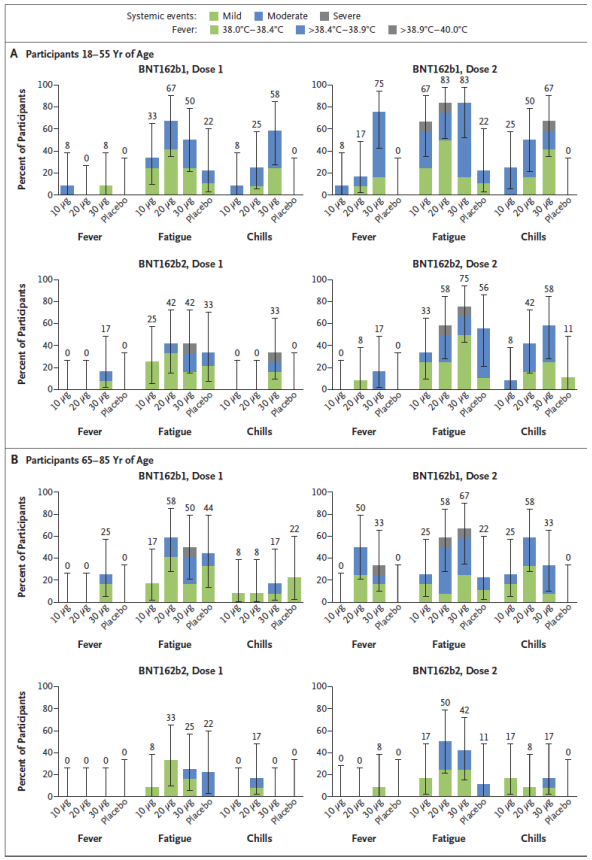
N Engl J Med 2020;383:2439-50.
DOI: 10.1056/NEJMoa2027906

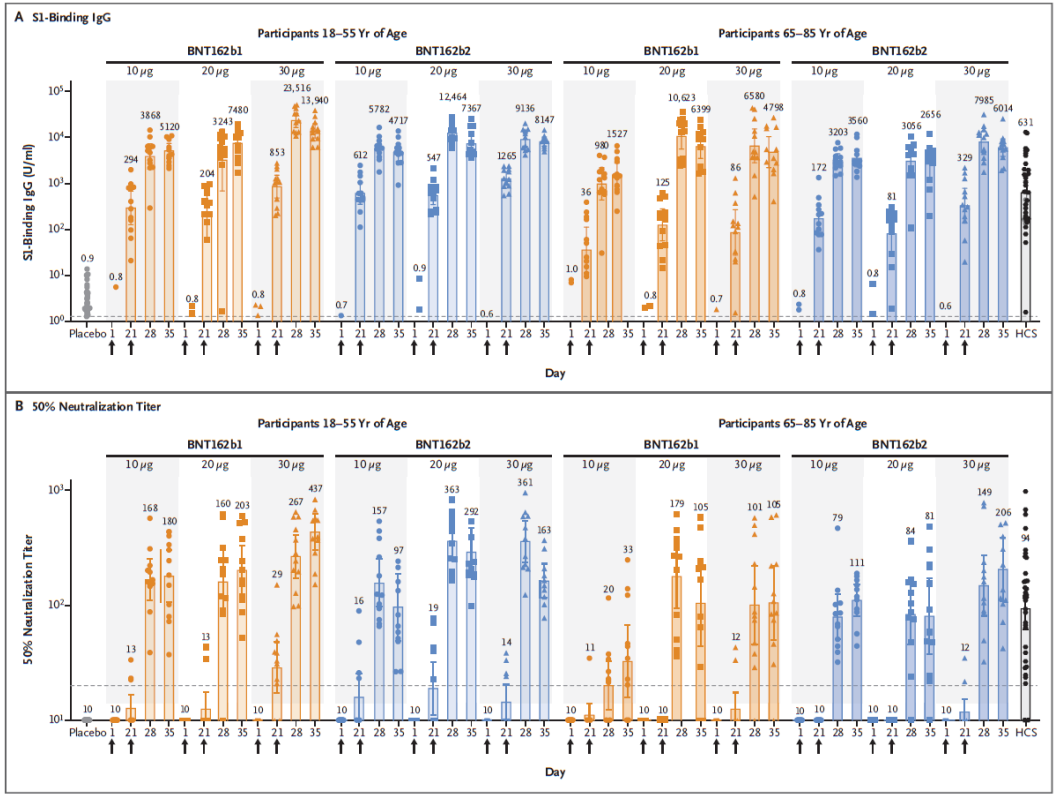


CONCLUSIONS

The safety and immunogenicity data from this U.S. phase 1 trial of two vaccine candidates in younger and older adults, added to earlier interim safety and immunogenicity data regarding BNT162b1 in younger adults from trials in Germany and the United States, support the selection of BNT162b2 for advancement to a pivotal phase 2–3 safety and efficacy evaluation. ClinicalTrials.gov number, NCT04368728.





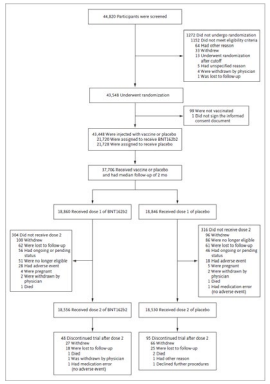


BNT162b2

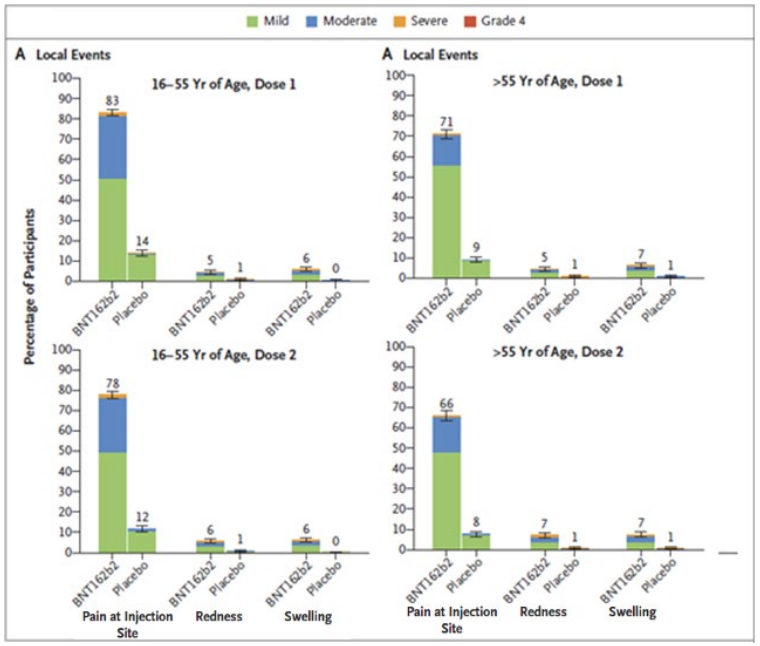
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 31, 2020 VOL. 383 NO. 27

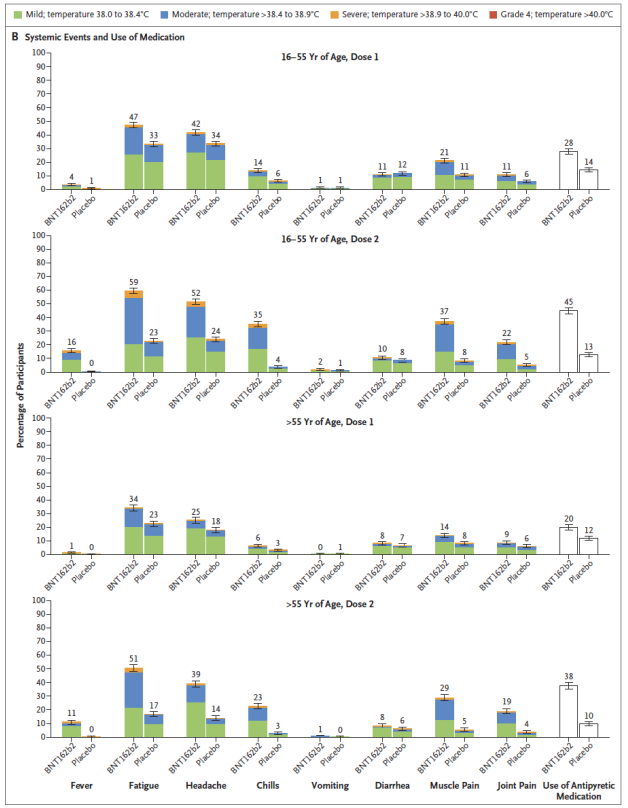
Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

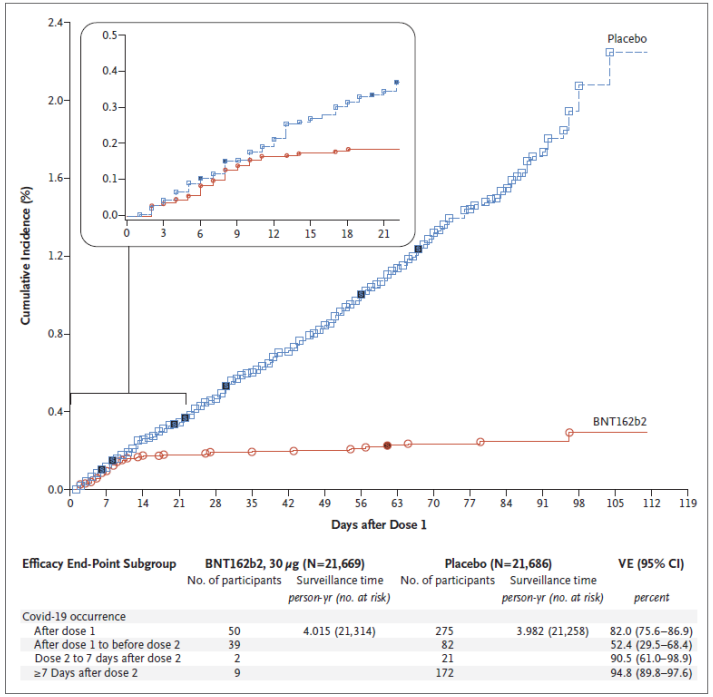
- 44.820 soggetti
- Doppio cieco



Efficacy End Point	BNT162b2 No. of Cases	BNT162b2 Surveillance Time (n)†	Placebo No. of Cases	Placebo Surveillance Time (n)†	Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
		(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







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

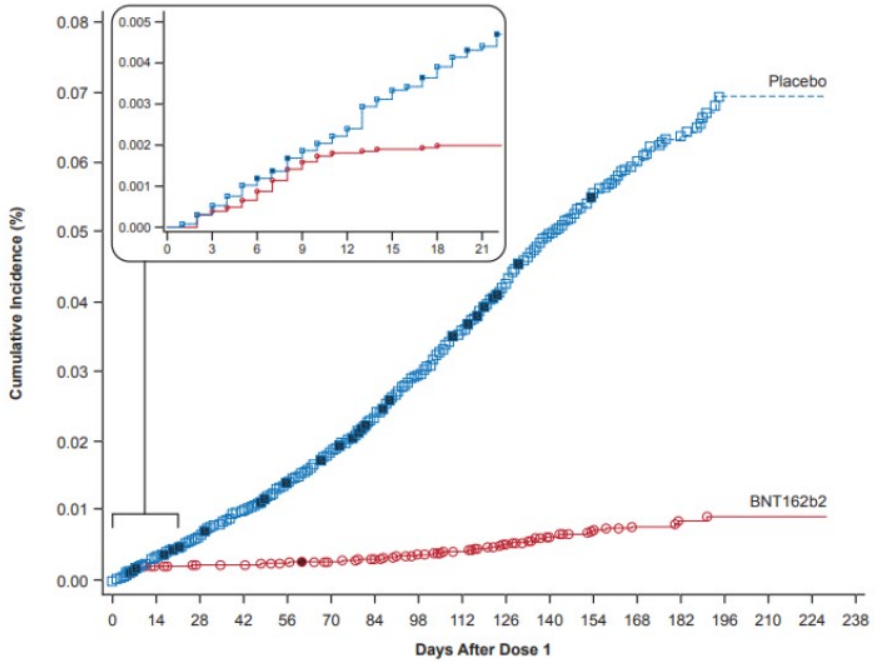
CONCLUSIONS

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 ClinicalTrials.gov number, NCT04368728.)

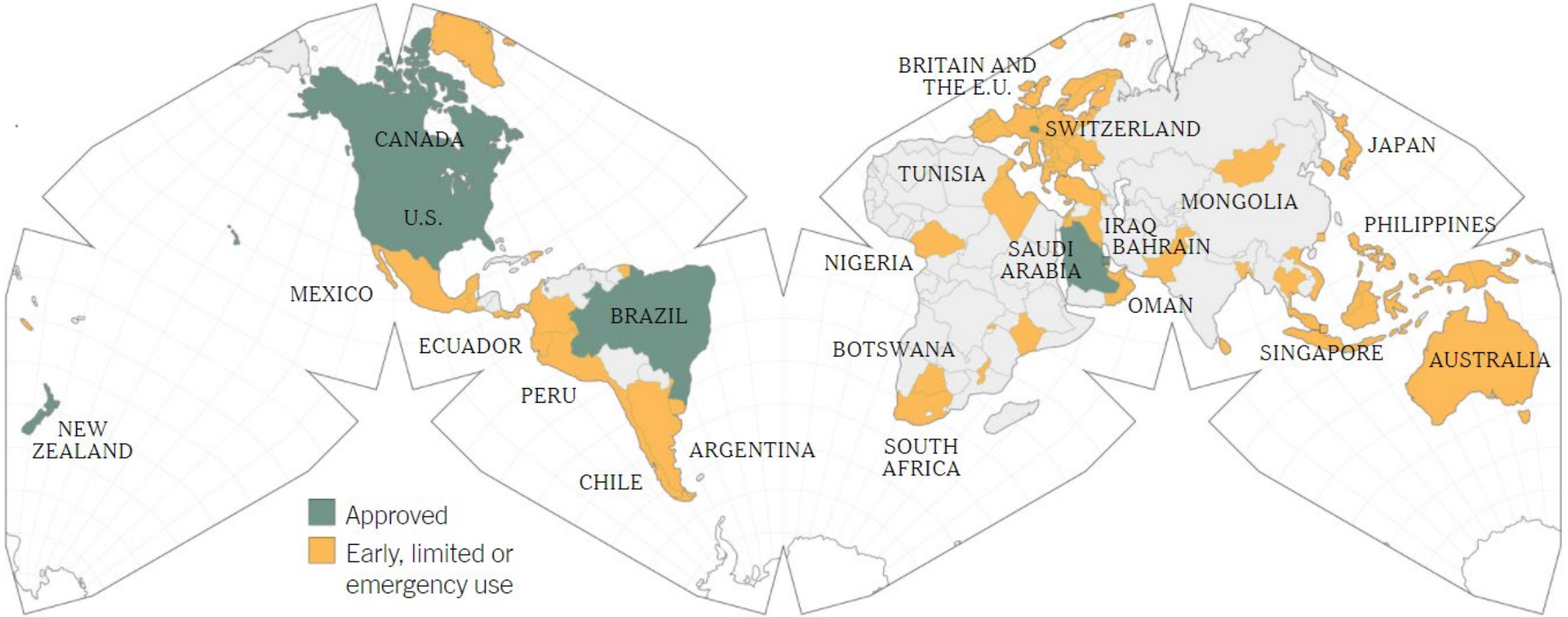
BNT162b2: dati a sei mesi

Six Month Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine

	BNT162b2		Placebo				
Efficacy Endpoint	**n1[a]**	**Surveillance Time[b] (n2[c])**	**n1[a]**	**Surveillance Time[b] (n2[c])**	**VE (%)**	**(95% CI[d])**	**Posterior Probability (VE >30% | data)[e]**
		(N[f]=20,998)		**(N[f]=21,096)**			
COVID-19 occurrence from 7 days after dose 2 in participants without prior evidence of infection	77	6.247 (20,712)	850	6.003 (20,713)	91.3	(89.0, 93.2)	>0.9999
		(N[f]=22,166)		**(N[f]=22,320)**			
COVID-19 occurrence from 7 days after dose 2 in participants with and those without prior evidence of infection	81	6.509 (21,642)	873	6.274 (21,689)	91.1	(88.8, 93.0)	>0.9999



BNT162b2


CANADA
U.S.
MEXICO
BRAZIL
ECUADOR
PERU
CHILE
ARGENTINA
NEW ZEALAND
BRITAIN AND THE E.U.
SWITZERLAND
TUNISIA
NIGERIA
SAUDI ARABIA
IRAQ
BAHRAIN
OMAN
MONGOLIA
JAPAN
PHILIPPINES
SINGAPORE
AUSTRALIA
BOTSWANA
SOUTH AFRICA
Approved
Early, limited or emergency use

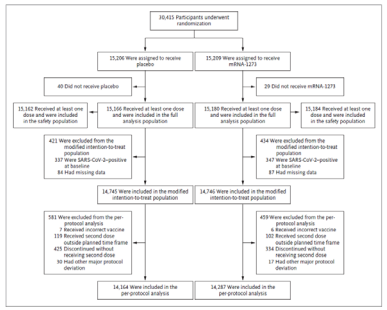
mRNA-1273

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase

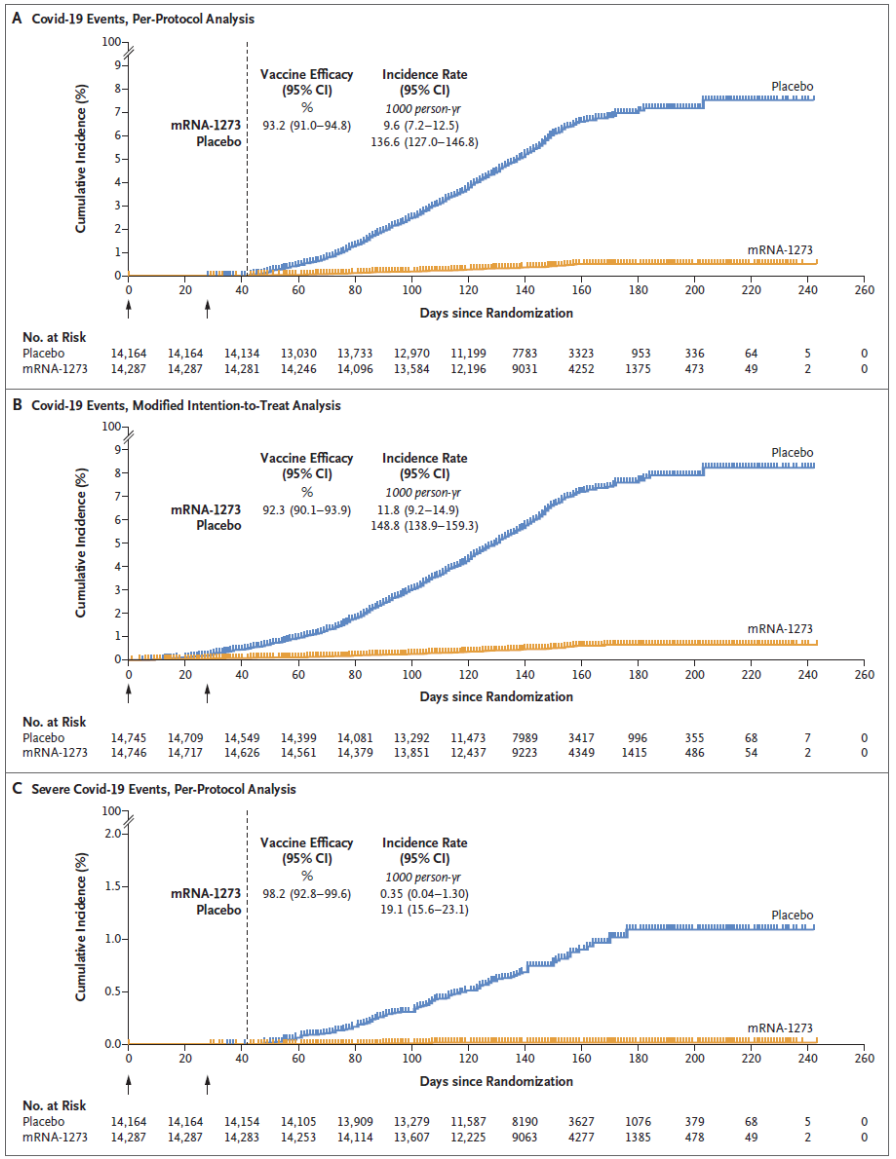
- 30.415 soggetti
- Doppio cieco



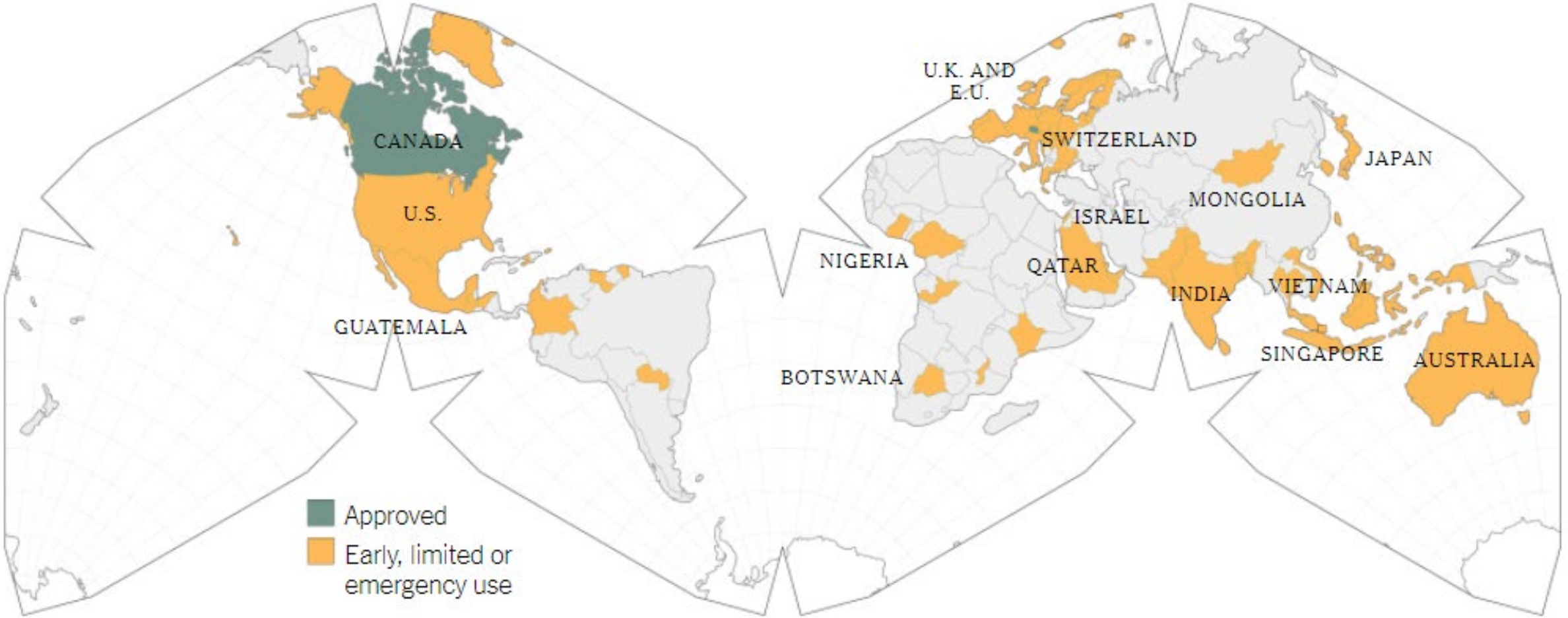
Subgroup	Placebo (N=14,164)	mRNA-1273 (N=14,287)	Vaccine Efficacy (95% CI)
	number of events		percent
Covid-19	744	55	93.2 (91.0–94.8)
Severe Covid-19	106	2	98.2 (92.8–99.6)
Covid-19 (secondary definition)	807	58	93.4 (91.4–94.9)
Death from Covid-19	3	0	100.0 (NE–100.0)
Covid-19 ≥14 days after first injection	769	56	93.3 (91.1–94.9)
Covid-19 regardless of previous SARS-CoV-2 status	754	58	92.8 (90.6–94.5)
Asymptomatic	498	214	63.0 (56.6–68.5)
Asymptomatic seroconversion	306	48	—
SARS-CoV-2 infection	1339	280	82.0 (79.5–84.2)

CONCLUSIONS

The mRNA-1273 vaccine continued to be efficacious in preventing Covid-19 illness and severe disease at more than 5 months, with an acceptable safety profile, and protection against asymptomatic infection was observed. (Funded by the Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases; COVE ClinicalTrials.gov number, NCT04470427.)



mRNA-1273


CANADA
U.S.
GUATEMALA
U.K. AND E.U.
SWITZERLAND
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MONGOLIA
ISRAEL
NIGERIA
QATAR
INDIA
VIETNAM
SINGAPORE
AUSTRALIA
BOTSWANA
Approved
Early, limited or emergency use

Autorizzazioni

BNT162b2

- **02 dicembre 2020**: Gran Bretagna
- **21 dicembre 2020**: EMA autorizza
- **22 dicembre 2020**: AIFA (≥16 anni)
- **28 Maggio 2021**: EMA estende ≥12 anni
- **31 Maggio 2021**: AIFA estende ≥12 anni
- **20 settembre 2021**: **risultati per bambini 5–11 anni (dosaggio ridotto)**

mRNA-1273

- **06 gennaio 2021**: EMA raccomanda immissione in commercio ≥18 anni
- **07 gennaio 2021**: AIFA (≥18 anni)
- **08 gennaio 2021**: approvato in Gran Bretagna
- **23 luglio 2021**: EMA estende ≥12 anni
- **28 luglio 2021**: AIFA estende ≥12 anni
- **In corso studi su bambini a partire dai 5 anni e autorizzazione terza dose (dosaggio ridotto)**

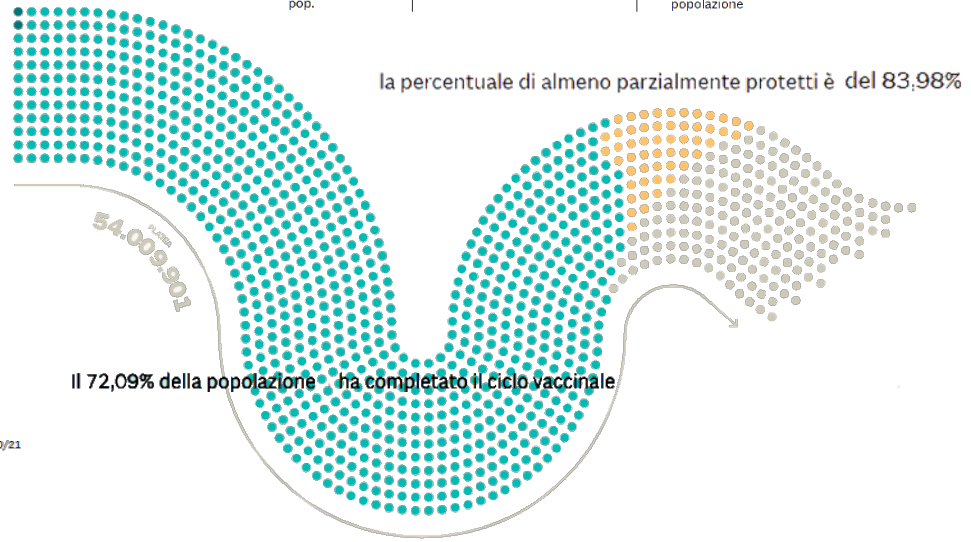
PERSONE VACCINATE
42.721.583
72,09% della popolazione

DI CUI VACCINO MONODOSE
1.476.846
2,49% della pop.

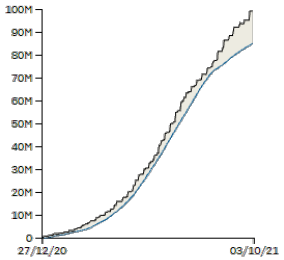
DI CUI PREGRESSA INFEZIONE
1.546.419
2,61% della pop.

IN ATTESA SECONDA DOSE
4,45% della popolazione

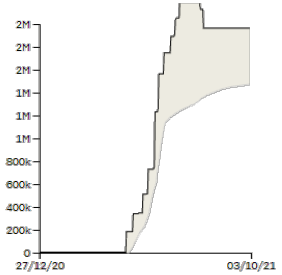
TERZA DOSE
95.300
10,23% della platea
0,16% della popolazione



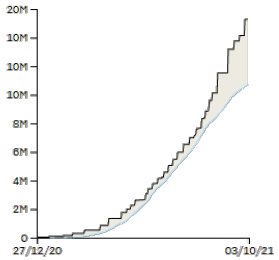
Pfizer
98.881.230
Somministrate 85.056.272
86%



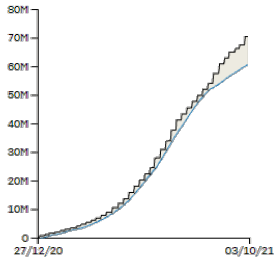
Ad26
1.958.893
Somministrate 1.476.847
75%



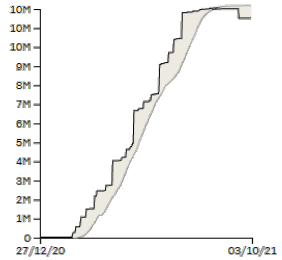
mRNA-1273
15.235.743
Somministrate 10.723.421
70%



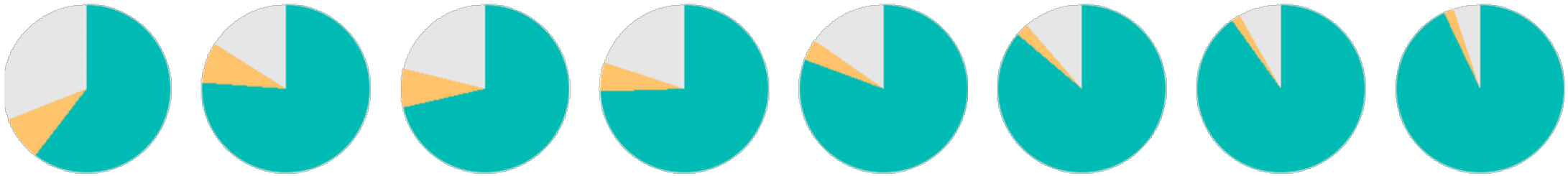
BNT162b2
70.143.221
Somministrate 60.707.128
87%



ChAdOx1
11.543.373
Somministrate 12.148.876
105%



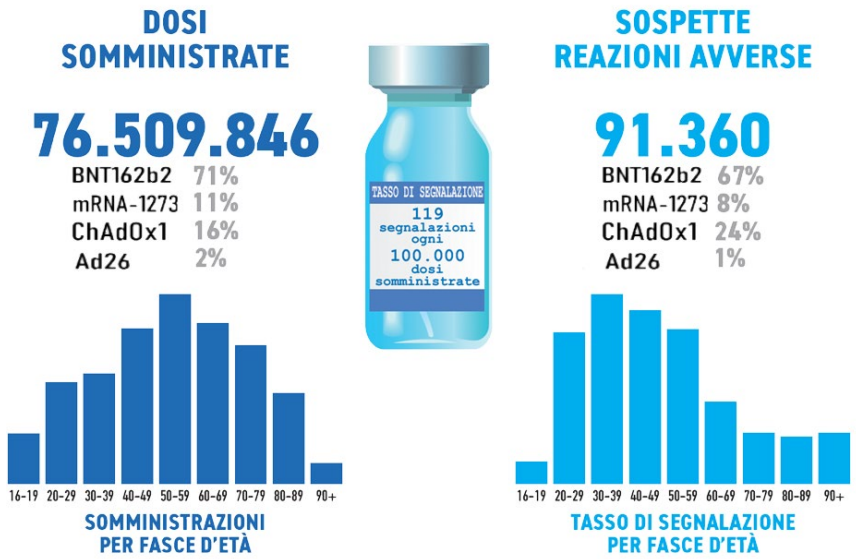
12-19	20-29	30-39	40-49	50-59	60-69	70-79	80+
60,41% (0,86%)	76,15% (2,02%)	71,41% (2,05%)	74,47% (2,26%)	80,62% (3,89%)	86,18% (5,80%)	90,07% (2,50%)	92,91% (0,30%)
8,59%	7,81%	7,46%	5,55%	4,07%	2,47%	1,77%	1,95%
31,00%	16,05%	21,14%	19,98%	15,31%	11,35%	8,16%	5,14%



Il Sole 24 ORE

Sicurezza

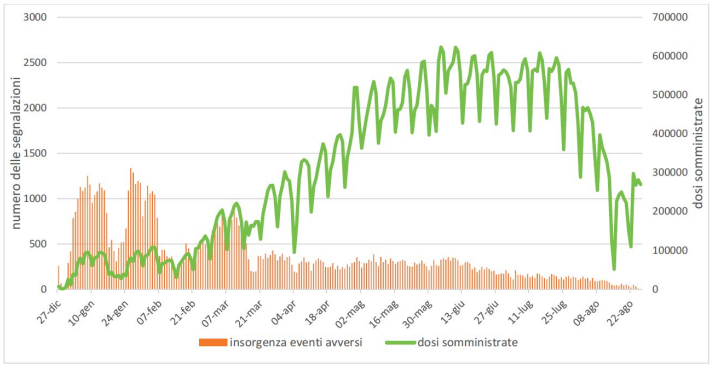
SOSPETTE REAZIONI AVVERSE A VACCINI COVID-19

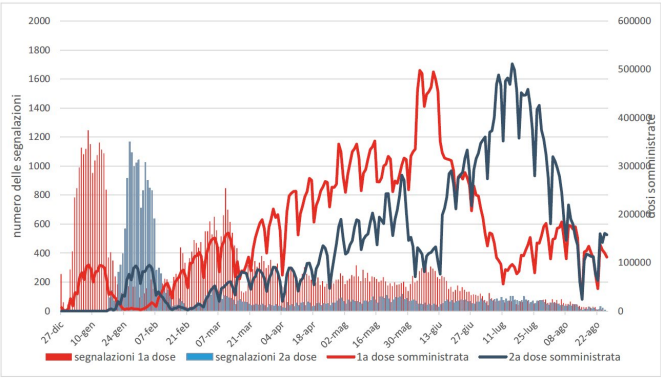


Vaccino COVID-19	Segnalazioni al 26/08/2021	Dosi somministrate al 26/08/2021	Tasso di segnalazione (per 100.000 dosi somministrate)	Intervallo di Confidenza al 95%
BNT162b2	61.281	54.226.752	***113***	***112-114***
mRNA-1273	7.056	8.762.697	***80***	***78-82***
Principio attivo mRNA	17			
ChAdOx1	21.790	12.093.073	***180***	***178-182***
Ad26	1.224	1.427.324	***85***	***80-90***
Totale	**91.368***	**76.509.846**	***119***	***118-120***

**il numero totale delle segnalazioni per vaccino commerciale non corrisponde al totale delle schede presenti nella RNF ma è maggiore in quanto in otto schede sono indicati due vaccini sospetti (dopo vaccinazione eterologa)*

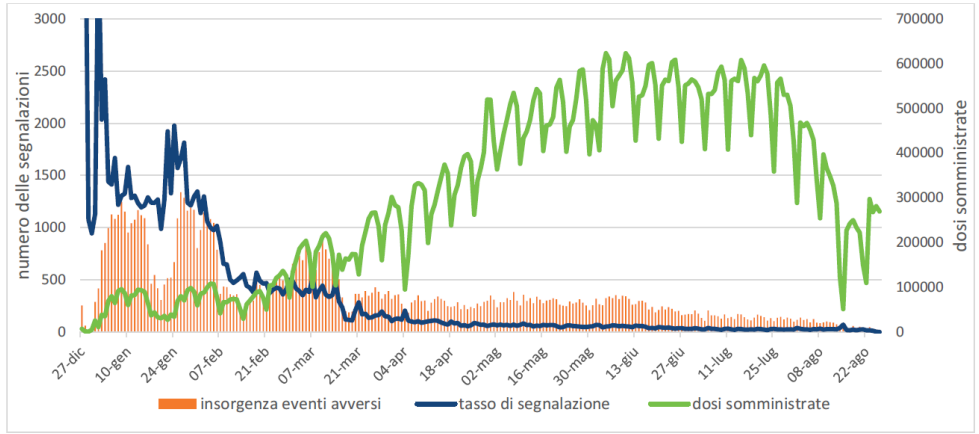
Al 26 agosto 2021 sono state inserite **119 segnalazioni ogni 100.000** dosi somministrate, indipendentemente dal vaccino e dalla dose somministrata.



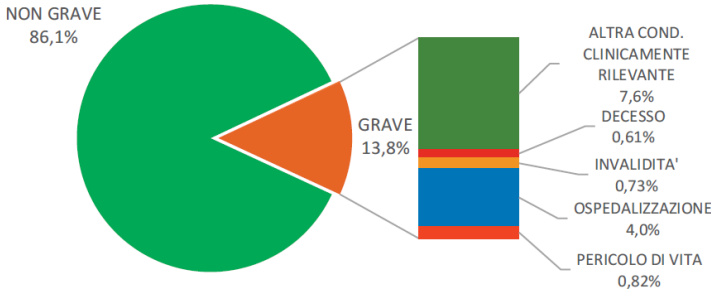


AGENZIA ITALIANA DEL FARMACO

Sicurezza



- Per tutti i vaccini, gli eventi avversi più segnalati sono febbre, stanchezza, cefalea, dolori muscolari/articolari, dolore in sede di iniezione, brividi e nausea

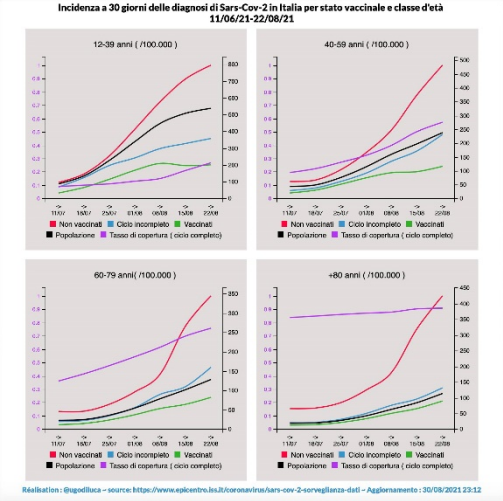


- La maggior parte degli eventi avversi segnalati sono classificati come non gravi (86,1% circa) che si risolvono completamente e solo in minor misura come gravi (13,8%), con esito in risoluzione completa o miglioramento nella maggior parte dei casi

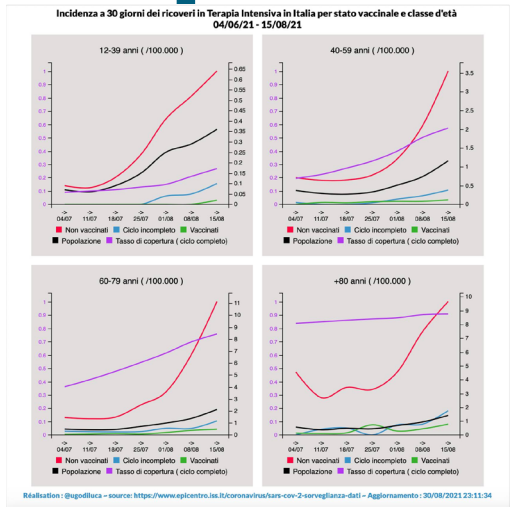
- Schedula mista è di **41 segnalazioni ogni 100.000 dosi somministrate**
- Il tasso di segnalazione tra i 12 e i 19 anni è di **22 eventi avversi ogni 100.000** dosi somministrate, con tipologia equivalente alle altre fascie di età

Efficacia sul campo

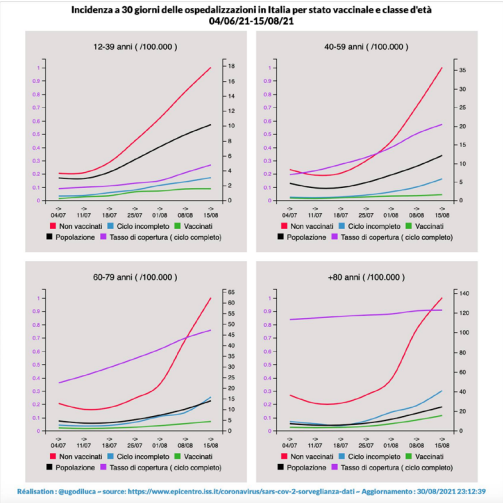
INFEZIONI



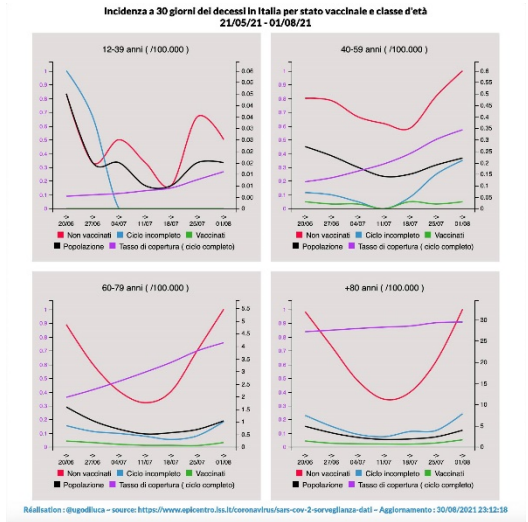
OSPEDALIZZAZIONI



TERAPIA INTENSIVA



DECESSI



- La linea rossa soggetti non vaccinati
- La linea verde soggetti vaccinati (completo)
- La linea viola tasso di copertura
- I tutte le età considerate il rischio è notevolmente inferiore
- Il rischio nei vaccinati è correlato con l'età.

Quale effetto sul viral load?

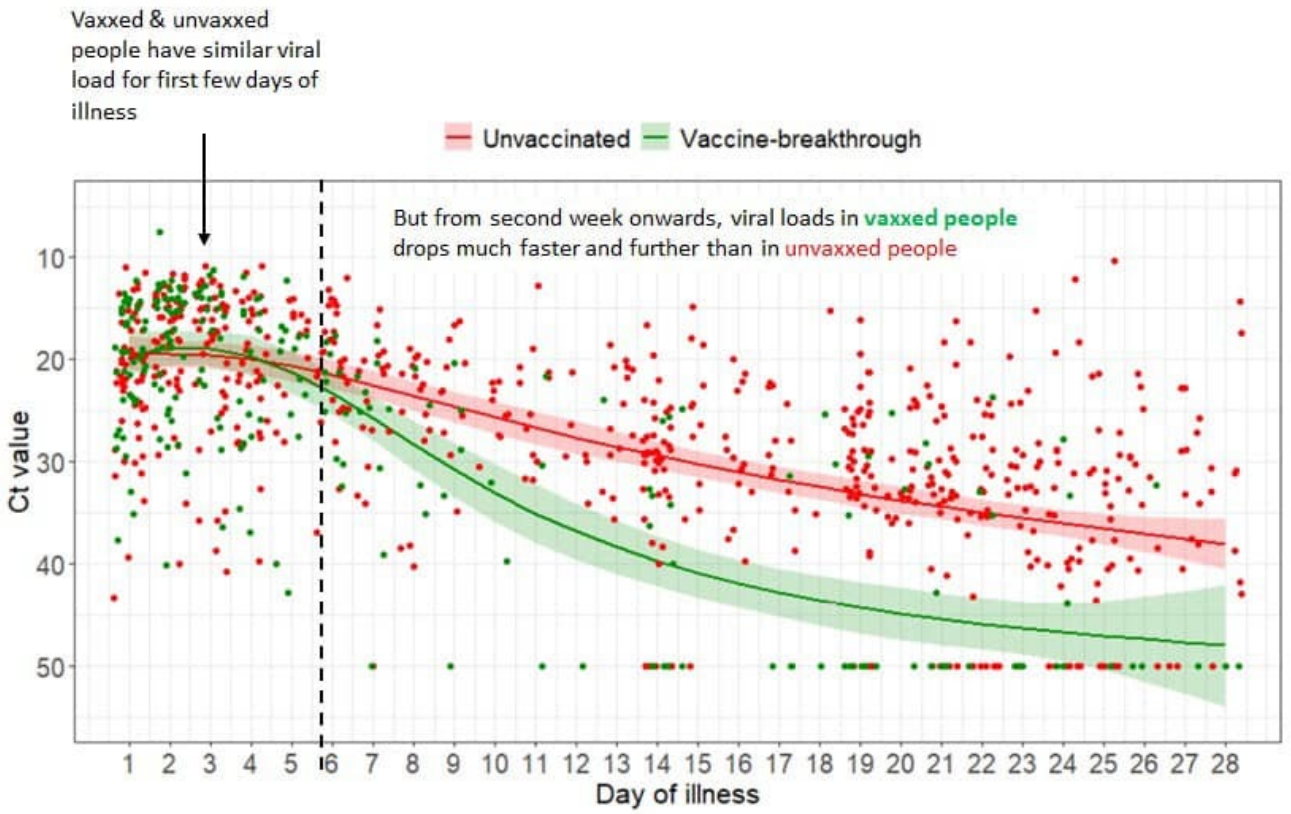


Chart from https://www.medrxiv.org/content/10.1101/2021.07.28.21261295v1.full.pdf

- Nella fase iniziale (6 giorni) **simile carica virale nei vaccinati e non vaccinati**
- **si riduce molto più rapidamente nei vaccinati a partire dalla** seconda settimana
- **Nei soggetti positivi alti livelli di anticorpi neutralizzanti**

Frequenza di genotipizzazione per variante del virus SARS-CoV-2, Italia, 28 dicembre 2020 – 16 agosto 2021

Nomenclatura OMS	Lignaggio	Numero casi (cumulativi)*	% (cumulativi)*	Numero casi (ultimi 45 gg)**	% ultimi 45 gg**
Alfa	B.1.1.7	27.188	57,9	779	7,9
	B.1.1.7 + E484K	70	0,1	6	0,1
Beta[a]	B.1.351	283	0,6	8	0,1
Gamma[b]	P.1	2.801	6,0	176	1,8
Delta[c]	B.1.617.2	10.281	21,9	8.111	82,4
Eta	B.1.525	424	0,9	7	0,1
Kappa	B.1.617.1	191	0,4	133	1,3
ND[d]	B.1.617.3	6	<0,1	5	0,1
ND[d,e]	P.2	5	<0,1	0	0,0
	Altro lignaggio /non indicato[f]	5.703	12,1	617	6,2
Totale		46.952	100	9.842	100

** periodo 28 dicembre 2020 – 16 agosto 2021; ** periodo 3 luglio – 16 agosto 2021*
a: la variante beta include i sottolignaggi B.1.351.2, B.1.351.3
b: la variante gamma include i sottolignaggi P.1.1, P.1.2.
c: la variante delta include i sottolignaggi AY.1, AY.2, AY.3
d: non disponibile
e: precedentemente "zeta"
f: si intende un caso genotipizzato appartenente ad altro lignaggio oppure ad un lignaggio non indicato dalle Regioni/PA.

Dal 30 luglio 2021

Effectiveness variante alfa

60,1% 1 dose
56,5% completa

	Vaccine effectiveness*		
	Age ≥65 years	Age ≥75 years	Age ≥85 years
SARS-CoV-2 infection†	94·8% (93·9–95·5)	95·1% (93·9–96·0)	94·1% (91·9–95·7)
Asymptomatic SARS-CoV-2 infection	88·5% (86·4–90·3)	87·5% (84·2–90·1)	83·2% (76·3–88·1)
Symptomatic COVID-19	96·4% (95·9–97·0)	96·7% (95·9–97·4)	96·6% (95·2–97·6)
COVID-19-related hospitalisation	96·8% (96·2–97·3)	97·0% (96·2–97·7)	96·9% (95·5 –97·9)
Severe or critical COVID-19-related hospitalisation	97·3% (96·8–97·8)	97·6% (96·8–98·1)	97·4% (95·9 –98·3)
COVID-19-related death	96·9% (96·0–97·6)	97·1% (96·0–97·9)	97·0% (94·9–98·3)

Estimates are % (95% CI). *Model is adjusted for age group (16–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years), sex, and calendar week. †Includes asymptomatic and symptomatic infections, as well as cases with positive SARS-CoV-2 tests for which the symptom interview portion of the epidemiological investigation was not completed.

***Table 3*: Estimated effectiveness of two doses of BNT162b2 (≥7 days after the second dose) against laboratory-confirmed SARS-CoV-2 outcomes in the oldest age groups (Jan 24 to April 3, 2021)**

46,7% 1 dose
34,3% completa

Interpretation Two doses of BNT162b2 are highly effective across all age groups (≥16 years, including older adults aged ≥85 years) in preventing symptomatic and asymptomatic SARS-CoV-2 infections and COVID-19-related hospitalisations, severe disease, and death, including those caused by the B.1.1.7 SARS-CoV-2 variant. There were marked and sustained declines in SARS-CoV-2 incidence corresponding to increasing vaccine coverage. These findings suggest that COVID-19 vaccination can help to control the pandemic.

THE LANCET

Table 1. Vaccine Effectiveness against Infection and against Disease in Qatar.

Type of Infection or Disease	PCR-Positive Persons		PCR-Negative Persons		Effectiveness (95% CI)*
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
	number of persons				*percent*
Infection					
PCR-confirmed infection with the B.1.1.7 variant†					
After one dose	892	18,075	1241	17,726	29.5 (22.9–35.5)
≥14 days after second dose	50	16,354	465	15,939	89.5 (85.9–92.3)
PCR-confirmed infection with the B.1.351 variant‡					
After one dose	1329	20,177	1580	19,926	16.9 (10.4–23.0)
≥14 days after second dose	179	19,396	698	18,877	75.0 (70.5–78.9)
Disease§					
Severe, critical, or fatal disease caused by the B.1.1.7 variant					
After one dose	30	468	61	437	54.1 (26.1–71.9)
≥14 days after second dose	0	401	20	381	100.0 (81.7–100.0)
Severe, critical, or fatal disease caused by the B.1.351 variant					
After one dose	45	348	35	358	0.0 (0.0–19.0)
≥14 days after second dose	0	300	14	286	100.0 (73.7–100.0)
Severe, critical, or fatal disease caused by any SARS-CoV-2					
After one dose	139	1,966	220	1,885	39.4 (24.0–51.8)
≥14 days after second dose	3	1,692	109	1,586	97.4 (92.2–99.5)

* Vaccine effectiveness was estimated with the use of a test-negative case–control study design,[2] with persons found positive by polymerase-chain-reaction (PCR) testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serving as cases in the analysis and those found negative by PCR serving as controls. PCR-positive and PCR-negative persons were matched one to one according to age, sex, nationality, and reason for PCR testing. Vaccine effectiveness was calculated as described by Jackson and Nelson[2] (see the Supplementary Appendix).

† A B.1.1.7 infection was identified as an S gene "target failure" in an analysis conducted with the TaqPath COVID-19 Combo Kit platform (Thermo Fisher Scientific), with the criteria of a PCR cycle threshold value no higher than 30 for the genes encoding both the nucleocapsid protein (N) and ORF1ab but a negative outcome for the gene encoding the spike protein (S) applied. The median date of vaccination was March 1 for PCR-positive persons and February 28 for the matched PCR-negative persons.

‡ Because only B.1.351 and B.1.1.7 viruses were identified in viral genome sequencing in Qatar after March 7, 2021, the criteria used to identify a B.1.351 infection involved the complement of the criterion for S that was used to identify a B.1.1.7 infection — that is, any infection with a cycle threshold value no higher than 30 for the genes encoding N, ORF1ab, and S between March 8 and March 31 was regarded as a B.1.351 infection. The median date of vaccination was March 7 for the PCR-positive persons and March 1 for the matched PCR-negative persons.

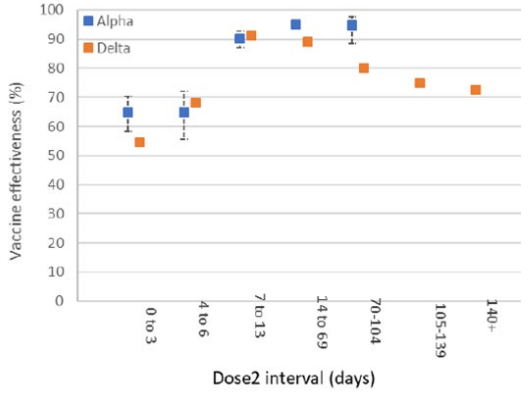
§ Effectiveness against severe, critical, or fatal disease caused by PCR-confirmed SARS-CoV-2 infection was analyzed. The B.1.1.7 and B.1.351 variants were dominant in Qatar during the study period. Severe, critical, and fatal coronavirus disease 2019 (Covid-19) were defined on the basis of the World Health Organization criteria[3] for classifying SARS-CoV-2 infection severity and Covid-19–related death.

The NEW ENGLAND JOURNAL of MEDICINE

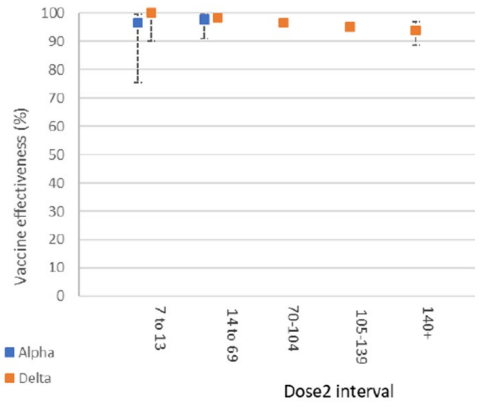
Effectiveness varianti alfa e delta

Public Health England

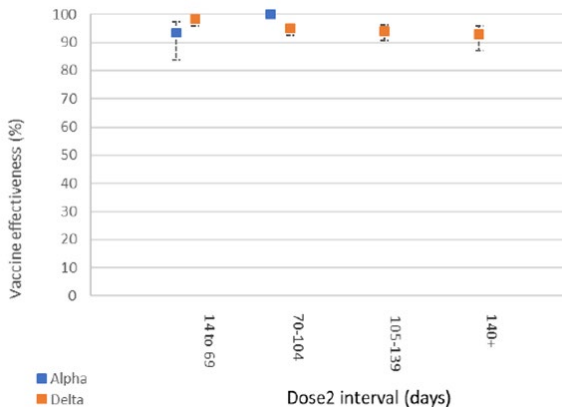
Malattia sintomatica



Ospedalizzazione

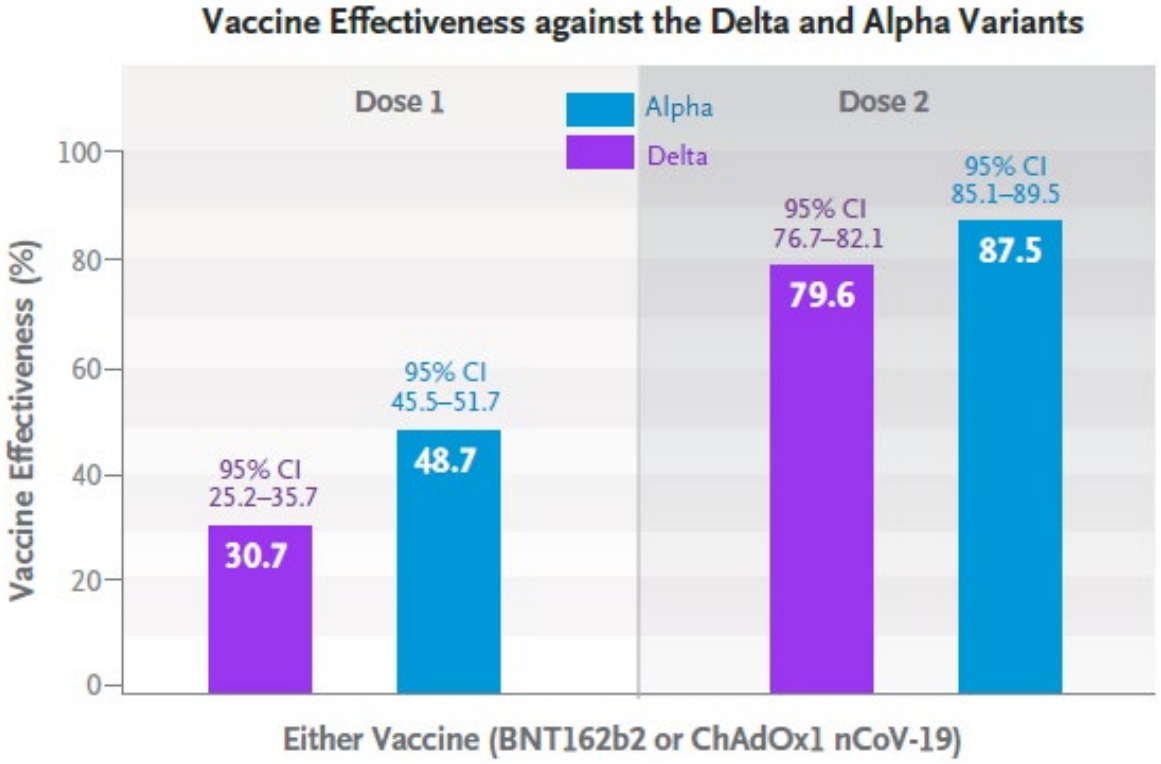


Mortalità



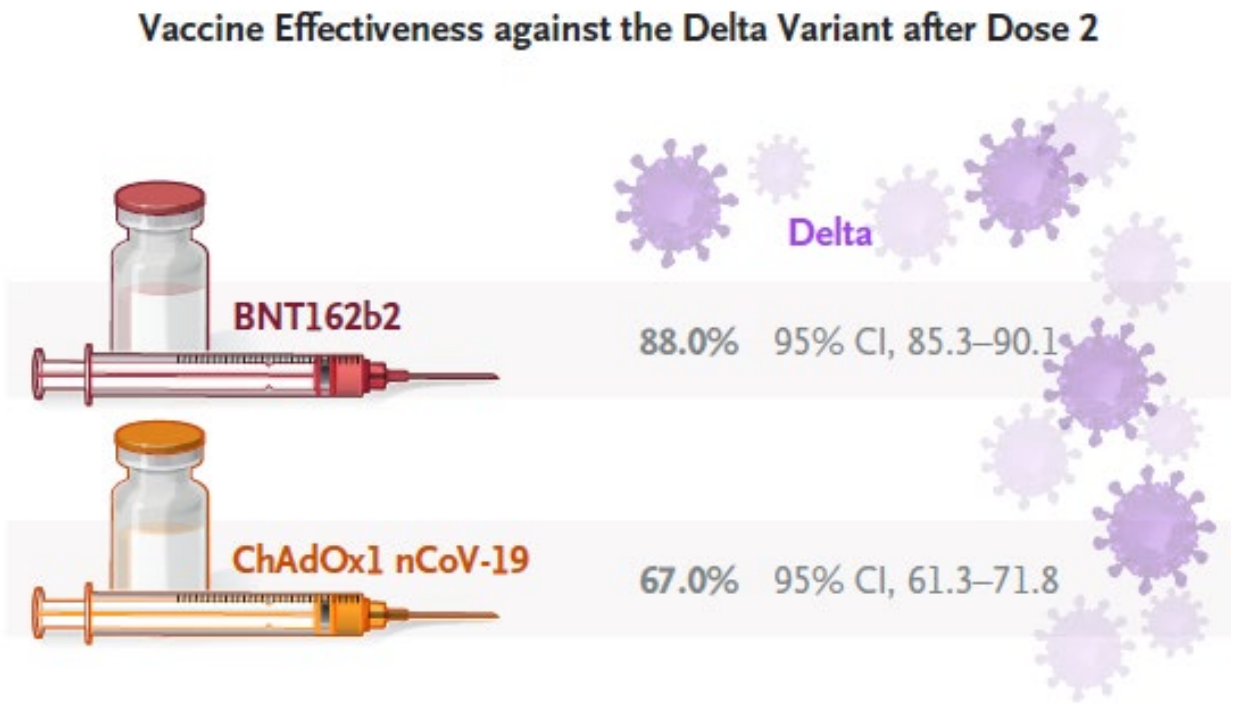
- **Diminuzione dell'efficacia del vaccino** nelle persone che hanno ricevuto due dosi di vaccino COVID-19
- Riduzione a 10 settimane dopo la somministrazione dei vaccini BNT162b2 e ChAdOx1, **più evidente negli anziani**
- La protezione **contro il ricovero è diminuita leggermente 15 settimane dopo la seconda dose**, in particolare per il vaccino ChAdOx1 e principalmente nei gruppi a rischio.
- Le persone anziane che hanno avuto un **intervallo di tempo più breve tra le due dosi** presentano una maggior riduzione rispetto a coloro che hanno avuto intervalli più lunghi.

Effectiveness varianti delta



Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant

Lopez Bernal J et al. DOI: 10.1056/NEJMoa2108891

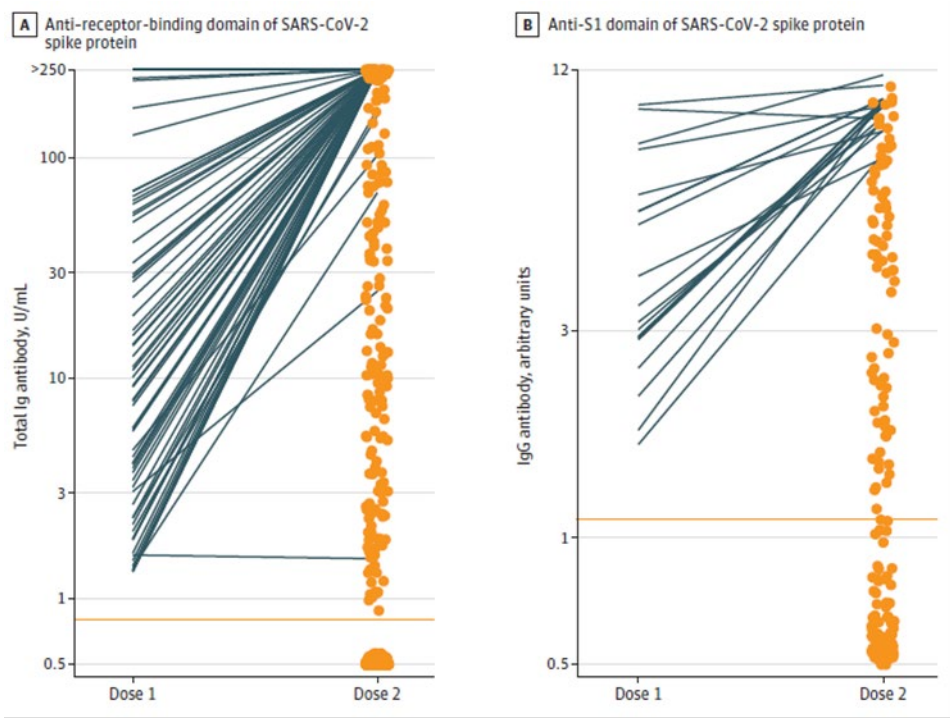


CONCLUSIONS

Two doses of the BNT162b2 or ChAdOx1 nCoV-19 vaccine were highly effective against the delta variant of SARS-CoV-2, although slightly less so than against the alpha variant.

Dose booster

- In alcuni casi, **i booster potrebbero essere giustificati**, le evidenze suggeriscono che deve essere presa in considerazione
  - Quando si sono **utilizzati vaccini inattivati** (ad esempio in Indonesia molti operatori sanitari completamente vaccinato aumento dei casi e utilizzo «scheda eterologa»)
  - nei soggetti **trapiantati immunosoppressi**: il 50% non aveva anticorpi dopo due dosi di vaccini mRNA



B. J. Boyarsky et al. JAMA 325, 2204-2206; 2021

The lines beginning at dose 1 reflect the antibody trajectory of participants who had detectable antibody after dose 1. Orange dots represent the antibody levels of participants who had undetectable antibody after dose 1.

I dati sono in continua evoluzione

Vaccinazione eterologa

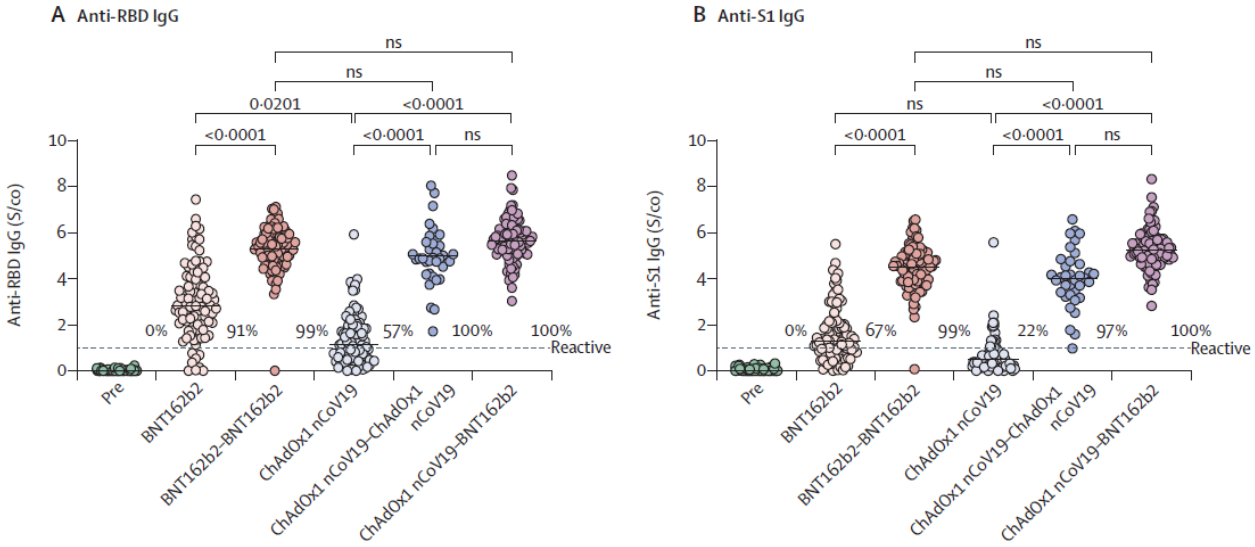
Lancet Respir Med 2021
Published Online
August 12, 2021
https://doi.org/10.1016/
S2213-2600(21)00357-X

Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: a prospective cohort study

David Hillus, Tatjana Schwarz*, Pinkus Tober-Lau, Kanika Vanshylla, Hana Hastor, Charlotte Thibeault, Stefanie Jentzsch, Elisa T Helbig, Lena J Lippert, Patricia Tscheak, Marie Luisa Schmidt, Johanna Riege, André Solarek, Christof von Kalle, Chantip Dang-Heine, Henning Gruell, Piotr Kopankiewicz, Norbert Suttorp, Christian Drosten, Harald Bias, Joachim Seybold, EICOV/COVIM Study Group†, Florian Klein, Florian Kurth‡, Victor Max Corman‡, Leif Erik Sander‡*

Background Heterologous vaccine regimens have been widely discussed as a way to mitigate intermittent supply shortages and to improve immunogenicity and safety of COVID-19 vaccines. We aimed to assess the reactogenicity and immunogenicity of heterologous immunisations with ChAdOx1 nCov-19 and BNT162b2 compared with homologous BNT162b2 and ChAdOx1 nCov-19 immunisation.

Interpretation The heterologous ChAdOx1 nCov-19–BNT162b2 immunisation with 10–12-week interval, recommended in Germany, is well tolerated and improves immunogenicity compared with homologous ChAdOx1 nCov-19 vaccination with 10–12-week interval and BNT162b2 vaccination with 3-week interval. Heterologous prime-boost immunisation strategies for COVID-19 might be generally applicable.



Studi preliminari utilizzando «schede eterologhe» suggeriscono risposte immunitarie più elevate, caratterizzate da alti livelli di anticorpi e cellule T.

COVID vaccine boosters: punti importanti

- Le preoccupazioni per la diminuzione dell'immunità
- Varianti della SARS-Cov-2
- Mancanza di prove sufficienti sulla sua necessità

Ministero della Salute

DIREZIONE GENERALE DELLA PREVENZIONE SANITARIA

0041416-14/09/2021-DGPRE-DGPRE-P

Per **dose addizionale** si intende una dose aggiuntiva di vaccino a completamento del ciclo vaccinale primario, somministrata al fine di raggiungere un adeguato livello di risposta immunitaria.

Per **dose "booster"**, in questo contesto, si intende una dose di richiamo dopo il completamento del ciclo vaccinale primario, a distanza di un determinato intervallo temporale, somministrata al fine di mantenere nel tempo o ripristinare un adeguato livello di risposta immunitaria, in particolare in popolazioni connotate da un alto rischio, per condizioni di fragilità che si associano allo sviluppo di malattia grave, o addirittura fatale, o per esposizione professionale.

Data from Israel and the United States suggest vaccine protection against COVID-19 infection wanes approximately 6 to 8 months following the second dose

Data Source	Type	Result
Kaiser Permanente Southern California (KPSC)	Retrospective Cohort Study	• Reduction in VE is likely due to waning effectiveness rather than to Delta escaping vaccine protection
FDA requested analysis	Post-hoc	• Waning effectiveness over time
C4591001 substudy	RCT	• A booster dose of BNT162b2 has an acceptable safety profile and elicits robust immune responses
Israeli booster vaccination program	RWE	• Reactogenicity profile similar or better to that seen after the second primary series dose • Restores high levels of protection against COVID-19 outcomes

I trial autorizzatori per la terza dose indicano

- Profilo di **sicurezza simile o migliore** rispetto a quello della seconda dose
- Risposte immunitarie **simili** a quelle suscitate contro risposte **wild-type** e non inferiori alle risposte osservate **dopo la seconda dose**
- **Soddisfano** i criteri indicati dagli enti regolatori
- Dimostrano **un'elevata efficacia (>90%)** contro COVID-19 e sicurezza

14 settembre 2021

Ministero della Salute
DIREZIONE GENERALE DELLA PREVENZIONE SANITARIA
0041416-14/09/2021-DGPRE-DGPRE-P

- In base alle indicazioni del CTS, si considera prioritaria la somministrazione della **dose addizionale** nei soggetti trapiantati e immunocompromessi
- Ferma restando la **priorità del raggiungimento di un'elevata copertura vaccinale con il completamento dei cicli attualmente autorizzati**
- Sarà definita **la strategia di somministrazione di una dose "*booster*"** di vaccino a mRNA in favore di ulteriori gruppi *target* tenendo conto delle evidenze scientifiche e dell'evoluzione dello scenario epidemiologico

In particolare sono incluse le seguenti condizioni:

- trapianto di organo solido in terapia immunosoppressiva
- trapianto di cellule staminali ematopoietiche (entro 2 anni dal trapianto o in terapia immunosoppressiva per malattia del trapianto contro l'ospite cronica)
- attesa di trapianto d'organo;
- terapie a base di cellule T esprimenti un Recettore Chimerico Antigenico (cellule CAR-T)
- patologia oncologica o onco-ematologica in trattamento con farmaci immunosoppressivi, mielosoppressivi o a meno di 6 mesi dalla sospensione delle cure
- immunodeficienze primitive (es. sindrome di DiGeorge, sindrome di Wiskott-Aldrich, immunodeficienza comune variabile etc.);
- immunodeficienze secondarie a trattamento farmacologico (es: terapia corticosteroidea ad alto dosaggio protratta nel tempo, farmaci immunosoppressori, farmaci biologici con rilevante impatto sulla funzionalità del sistema immunitario etc.)dialisi e insufficienza renale cronica grave;
- pregressa splenectomia
- sindrome da immunodeficienza acquisita (AIDS) con conta dei linfociti T CD4+ < 200cellule/µl o sulla base di giudizio clinico.

- sarà possibile utilizzare come dose addizionale uno qualsiasi dei vaccini a **mRNA autorizzati**
- La dose addizionale va somministrata dopo almeno **28 giorni dall'ultima dose**

27 settembre 2021

Avvio della somministrazione di dosi "*booster*" nell'ambito della campagna di vaccinazione anti SARS-CoV-2/COVID-19.

Ministero della Salute
DIREZIONE GENERALE DELLA PREVENZIONE SANITARIA
0043604-27/09/2021-DGPRE-DGPRE-P

- Facendo seguito alla circolare prot. n° 41416 del 14/09/2021, tenuto conto della determina AIFA n° 1067/2021 del 10 settembre 2021, ed in linea con il parere espresso dal Comitato Tecnico Scientifico di cui all'Ordinanza del Capo Dipartimento della Protezione Civile n. 751 (CTS),
- Ferma restando la priorità del raggiungimento di un'elevata copertura vaccinale dei cicli attualmente autorizzati,
- Somministrazione di dosi "*booster*" di vaccino anti SARS-CoV-2/COVID-19
  - soggetti di età ≥ 80;
  - personale e ospiti dei presidi residenziali per anziani
- In un momento successivo, una dose booster potrà essere altresì offerta agli esercenti le professioni sanitarie e operatori di interesse sanitario che svolgono le loro attività nelle strutture sanitarie, sociosanitarie e socio-assistenziali, pubbliche e private, nelle farmacie, parafarmacie e negli studi professionali, a partire dai soggetti di età ≥60 anni o con patologia concomitante tale da renderli vulnerabili a forme di COVID-19 grave o con elevato livello di esposizione all'infezione.
- Uno qualsiasi dei due vaccini a m-RNA autorizzati in Italia
- La dose "*booster*" va somministrata dopo almeno sei mesi dal completamento del ciclo vaccinale primario.

04 ottobre 2021

- EMA autorizzazione terza dose in immunoddepressi e in soggetti ≥18 anni
- Differenzia
  - dose aggiuntiva (dopo 28 giorni)
  - dose booster (dopo 6 mesi)
- Da mandato ai Paesi su adozione in relazione alla situazione epidemiologica

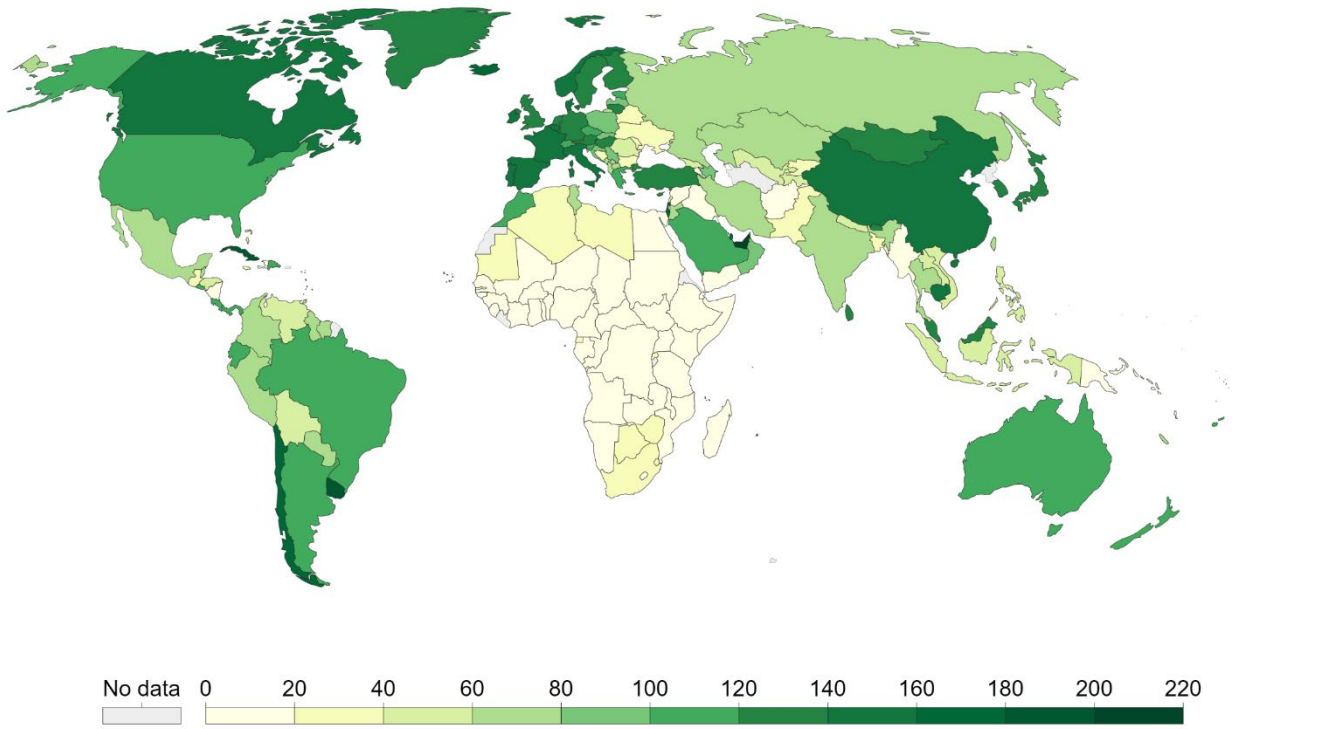
The international journal of science / 19 August 2021

nature

The WHO is right to call for delay to vaccine boosters

Richer countries must supply COVID-19 vaccines to the billions waiting for a first dose.

- Raggiungimento del 10% della popolazione di tutti i paesi prima di una dose extra
  - >60% dei Paesi ad alto reddito ha ricevuto almeno una dose di vaccino
  - Nei Paesi a basso reddito 1,3%
- Non ancora sufficienti evidenze
- La maggior parte dei vaccini COVID-19 attualmente in uso rimane estremamente efficace 12 mesi dopo la somministrazione, in particolare contro la malattia grave e la morte.



- 45.6% of the world population has received at least one dose of a COVID-19 vaccine.
- 6.31 billion doses have been administered globally, and 26.1 million are now administered each day.
- Only 2.3% of people in low-income countries have received at least one dose.

Bambini 5-11 anni

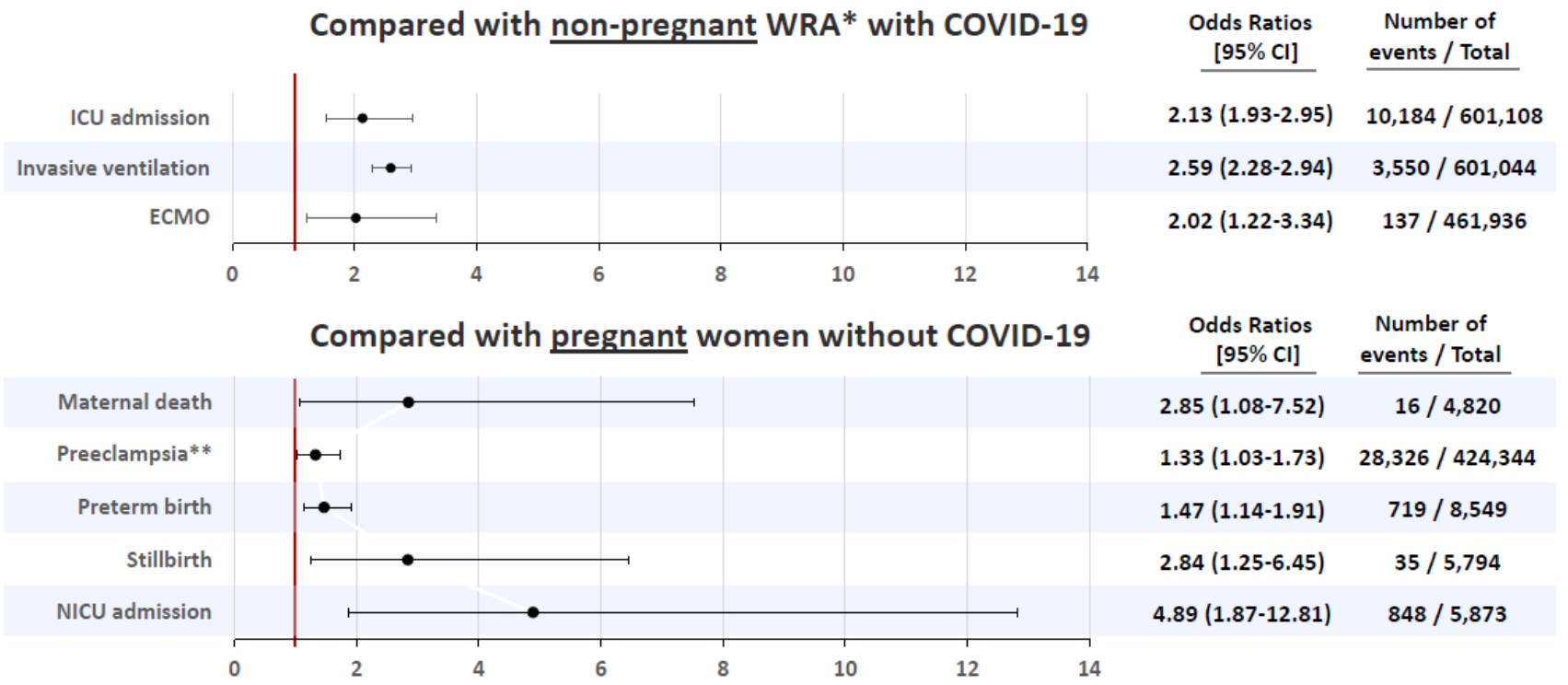
ANNOUNCE POSITIVE TOPLINE RESULTS FROM PIVOTAL TRIAL OF COVID-19 VACCINE IN CHILDREN 5 TO 11 YEARS

Monday, September 20, 2021 - 06:45am

- *Results are the first from a pivotal trial of any COVID-19 vaccine in children under 12 years of age*
- *In participants 5 to 11 years of age, the vaccine was safe, well tolerated and showed robust neutralizing antibody responses*
- *Companies plan to submit these data to the FDA, EMA and other regulatory agencies around the world as soon as possible*
- *Results in children under 5 years of age are expected as soon as later this year*

NEW YORK AND MAINZ, Germany--(BUSINESS WIRE)-- today announced results from a Phase 2/3 trial showing a favorable safety profile and robust neutralizing antibody responses in children 5 to 11 years of age using a two-dose regimen of 10 µg administered 21 days apart, a smaller dose than the 30 µg dose used for people 12 and older. The antibody responses in the participants given 10 µg doses were comparable to those recorded in a previous study in people 16 to 25 years of age immunized with 30 µg doses. The 10 µg dose was carefully selected as the preferred dose for safety, tolerability and immunogenicity in children 5 to 11 years of age. These are the first results from a pivotal trial of a COVID-19 vaccine in this age group.

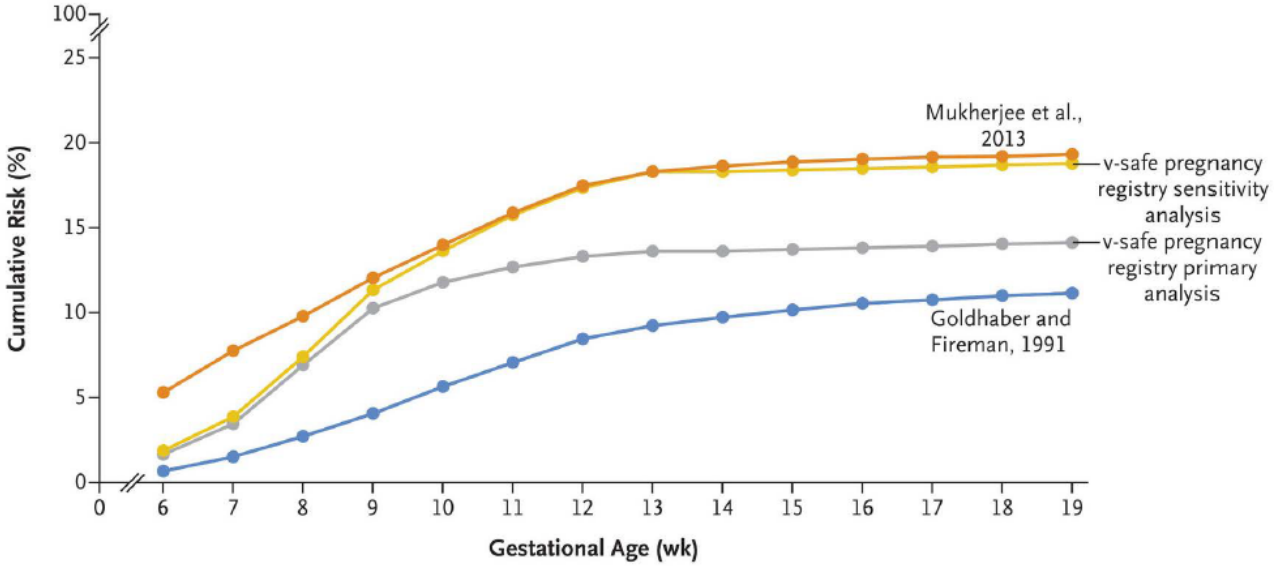
Gravidanza e COVID-19



Data from Allotey, J et al. unless otherwise noted; *Women of reproductive age; ** Preeclampsia data from Wei et al.; ECMO: Extracorporeal membrane oxygenation

Sicurezza in gravidanza

- Rischio cumulativo grezzo di aborto spontaneo di SAB dopo la vaccinazione con mRNA COVID-19 è del 14,1%
- Rischio cumulativo standardizzato per età di aborto spontaneo
  - 12,8% (IC 95%: 10,8%–14,8%)
  - Simile alle stime di base di aborto spontaneo precedentemente pubblicate (11%–22%)
- la vaccinazione contro l'mRNA COVID-19 durante la gravidanza non è associata ad aborto spontaneo SAB



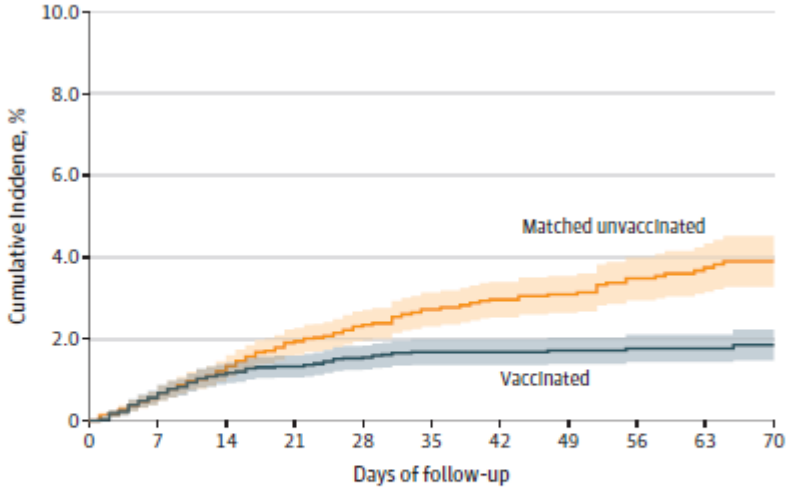
Zauche et al. N EnglJ Med. 2021 Sep 8. doi: 10.1056/NEJMc2113891.

Efficacia in gravidanza

JAMA | Original Investigation

Association Between BNT162b2 Vaccination and Incidence of SARS-CoV-2 Infection in Pregnant Women

Inbal Goldshtein, PhD; Daniel Nevo, PhD; David M. Steinberg, PhD; Ran S. Rotem, ScD; Malka Gorfine, PhD; Gabriel Chodick, PhD; Yaakov Segal, MD



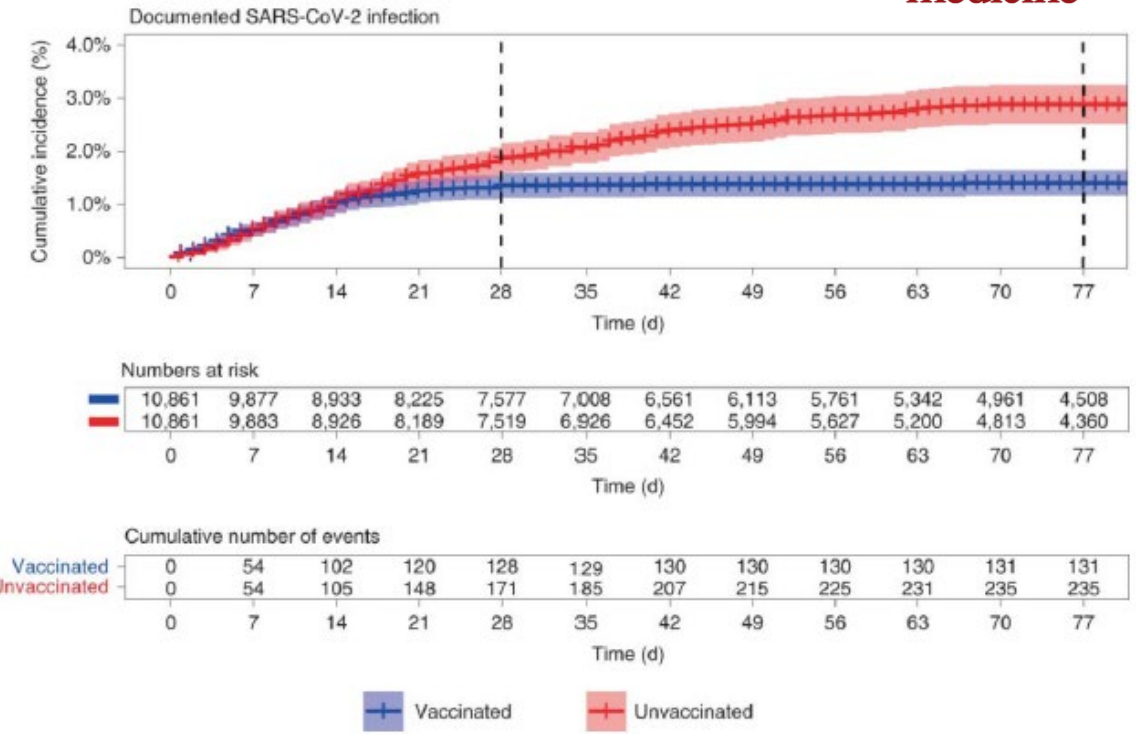
No. at risk											
Matched unvaccinated	7530	7446	6825	5661	4788	4023	3376	2327	1748	1295	955
Vaccinated	7530	7446	6825	5661	4788	4023	3376	2327	1748	1295	955
Cumulative No. of events											
Matched unvaccinated	0	51	99	137	158	175	184	188	196	200	202
Vaccinated	0	51	87	97	109	115	115	116	117	117	118

Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy

Noa Dagan[1,2,3,4,14], Noam Barda[1,2,3,4,14], Tal Biron-Shental[5,6], Maya Makov-Assif[1], Calanit Key[7], Isaac S. Kohane[3,4], Miguel A. Hernán[8,9], Marc Lipsitch[10], Sonia Hernandez-Diaz[8], Ben Y. Reis[4,11,12] and Ran D. Balicer[1,4,13] ✉

Cumulative incidence of SARS-CoV-2 infection over time (Time since 2nd dose)

nature medicine



I dati suggeriscono che ricevere il vaccino in gravidanza riduce il rischio di infezione

Altri benefici in gravidanza

- La vaccinazione COVID-19 mRNA induce una **importante risposta anticorpale in donne in gravidanza o in allattamento**
- **Immunogenicità e reattogenicità** sono simili a quelle osservate a donne non in gravidanza
- Gli anticorpi vengono **trasferiti** al neonato e si ritrovano nel **latte materno**

OBSTETRICS

Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study

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Concludendo...

- Stiamo aumentando le conoscenze in termini "temporali"
- Stimolazione "esogena" nei vaccinati e effetto "paradosso"
- Schedule "mixate"
- Vaccinazione bambini
- Problematica variant da monitorare

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Grazie per l'attenzione!

Vincenzo Baldo