Sicurezza ed efficacia del vaccino anti-CoViD: domande e risposte

Attualità sui vaccini e sicurezza

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Fase I: numero limitato di persone (alcune decine) per valutarne la tollerabilità, intesa come la frequenza e la gravità degli effetti collaterali del vaccino.

x 10

Fase II: possono coinvolgere anche centinaia di persone, il potenziale vaccino viene somministrato a dosi diverse e se ne studiano gli effetti, sia in termini di effetti tossici che di **immunogenicità**

$x\ 10^2$

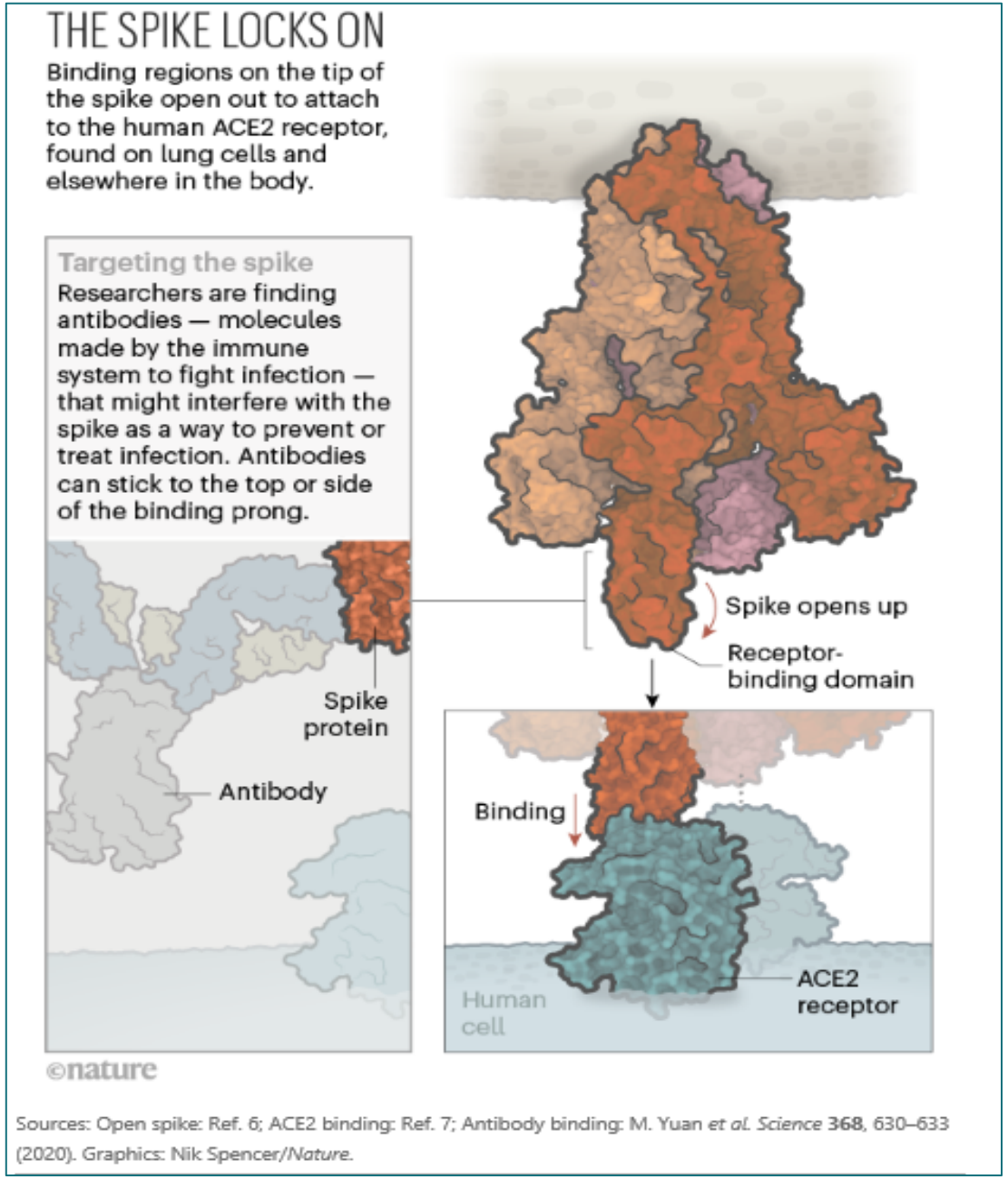
Fase III: prova di **efficacia** del vaccino su larga scala, in genere alcune migliaia di volontari soggetti di solito arruolati in più centri di ricerca

$x\ 10^3$

Fase IV: monitoraggio di sicurezza ed effetti secondari del vaccino negli anni e su una popolazione in costante aumento

$x\ 10^6$

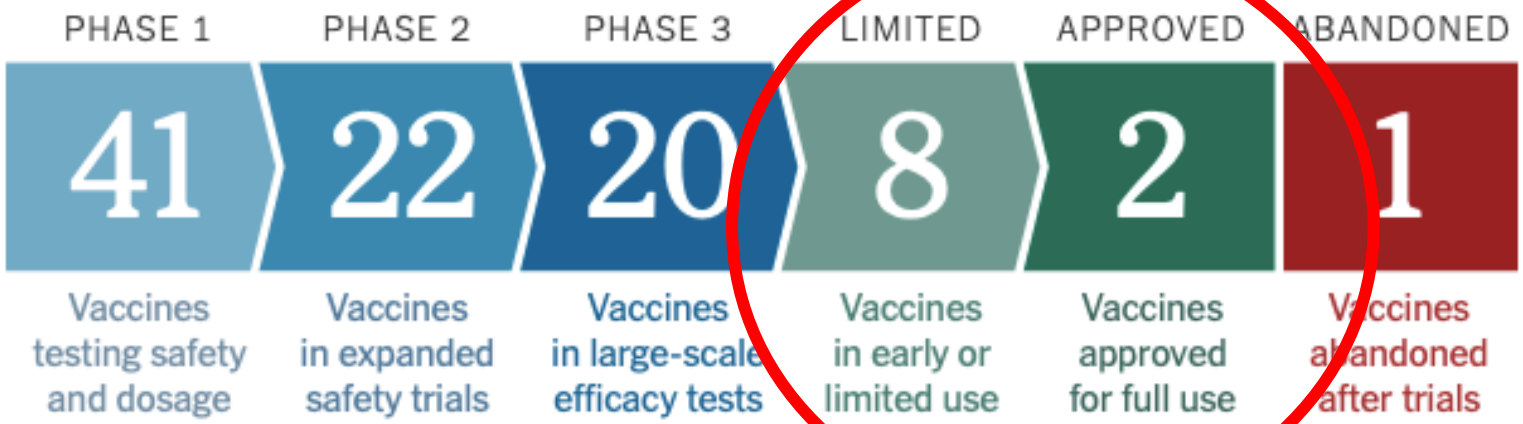
Vaccino SARS CoV2 : il target



https://www.nature.com/articles/d41586-020-01444-z

Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee Updated Jan. 14, 2021



Vaccines typically require years of research and testing before reaching the clinic, but in 2020, scientists embarked on a race to produce safe and effective coronavirus vaccines in record time. Researchers are currently testing **68 vaccines** in clinical trials on humans, and 20 have reached the final stages of testing. At least 90 preclinical vaccines are under active investigation in animals.

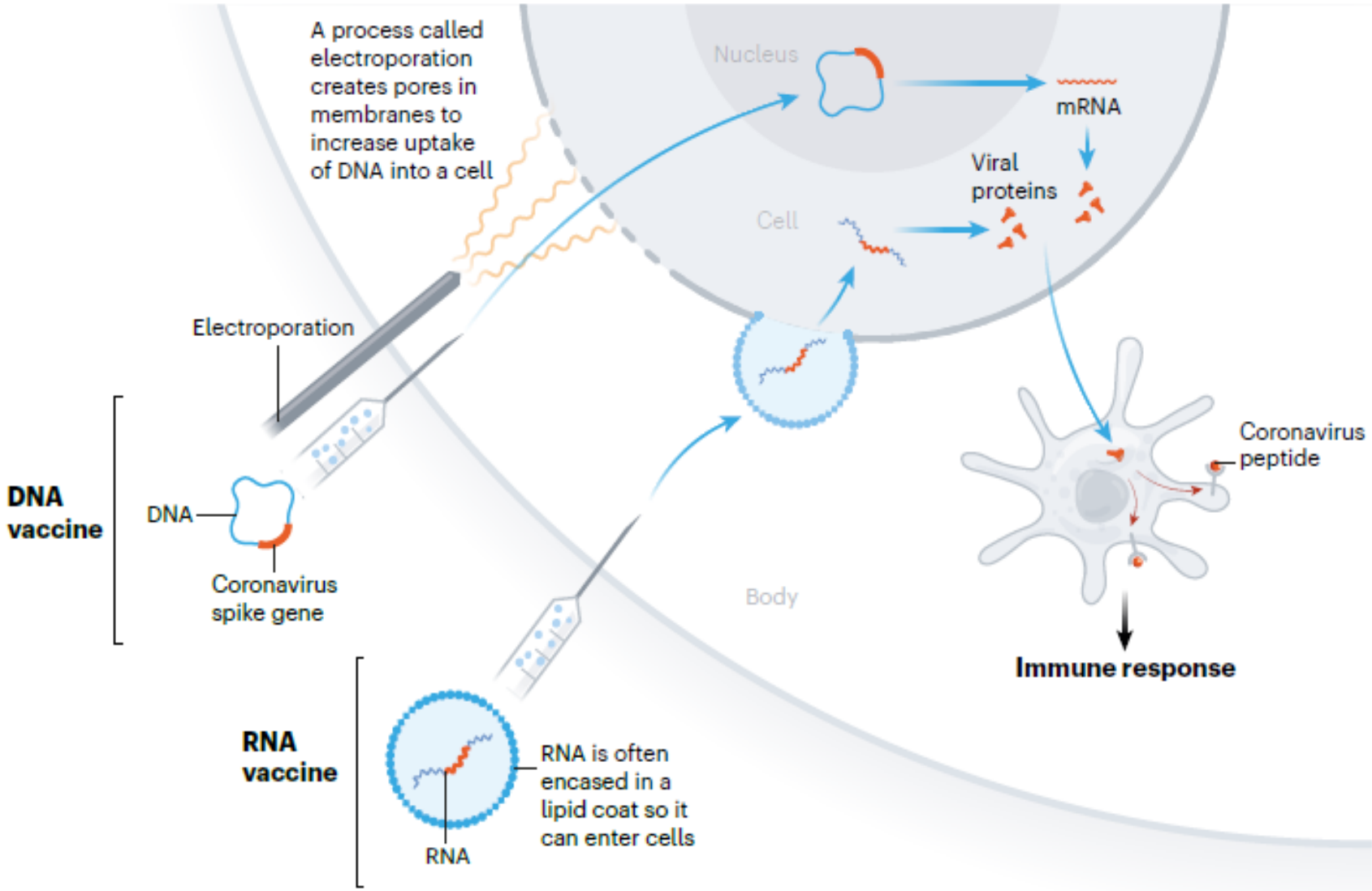
https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

Vaccini a RNA (e a DNA)

NUCLEIC-ACID VACCINES

At least 20 teams are aiming to use genetic instructions (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. The nucleic acid is inserted into human cells, which then churn out copies of the virus protein; most of these vaccines encode the virus's spike protein.

RNA- and DNA-based vaccines are safe and easy to develop: to produce them involves making genetic material only, not the virus. But they are unproven: no licensed vaccines use this technology.



Vaccini a mRNA

L'uso di mRNA ha diversi aspetti favorevoli:

- Sicurezza: dal momento che l'mRNA è una piattaforma non infettiva e non integrante, non vi è rischio potenziale di infezione o di mutagenesi inserzionale
- Efficacia: diverse modifiche tecnologiche rendono l'mRNA più stabile e altamente traducibile. Un efficiente rilascio *in vivo* può essere ottenuto formulando l'mRNA in molecule trasportatrici, che consentono una rapida captazione ed espressione nel citoplasma
- Produzione: I vaccini ad mRNA sono potenzialmente producibili in modo rapido, poco costoso e scalabile, soprattutto per l'alta resa *in vitro* delle reazioni di trascrizione

Problema: possibile necessità di una complessa catena del freddo

Fase 3 dei vaccini a RNA Pfizer e Moderna

- Sono studi di efficacy in doppio cieco
- Moderna include 30.000 partecipanti di cui la metà ricerveranno due dosi di vaccino con un intervallo di 4 settimane tra le dosi
- Pfizer include 44.000 soggetti di cui la metà riceveranno 2 dosi di vaccino con un intervallo tra le dosi di 3 settimane
- I partecipanti vengono costanetemente monitorati per valutare se sviluppano sintomi del Covid 19 e se risultano positivi al test.
- In aggiunta vengono monitorati eventuali segnali di sicurezza

Per determinare l'efficacia→ Moderna valuta i casi dei Covid19 che emergono ad almeno 2 settimane dopo la seconda dose, Pfizer almeno a 7 giorni dalla seconda dose.

L'FDA richiede una efficacia di almeno il 50% in termini di protezione dal Sars Cov 2.

(A total of 151 cases of Covid-19 from among the tens of thousands of people participating in the trial — spread between the vaccine and placebo groups — would be enough to determine whether the Moderna vaccine is 60 percent effective. Pfizer's case count for 60 percent efficacy is 164.)

https://www.nytimes.com/2020/09/17/health/covid-moderna-vaccine.html?smid=tw-share

Vaccino mRNA (Pfizer)

Risultati di clinica

Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
> 55 years and older	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >99.5% at the final analysis

[a] N = number of participants in the specified group.

[b] n1 = Number of participants meeting the endpoint definition.

[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

[d] n2 = Number of participants at risk for the endpoint.

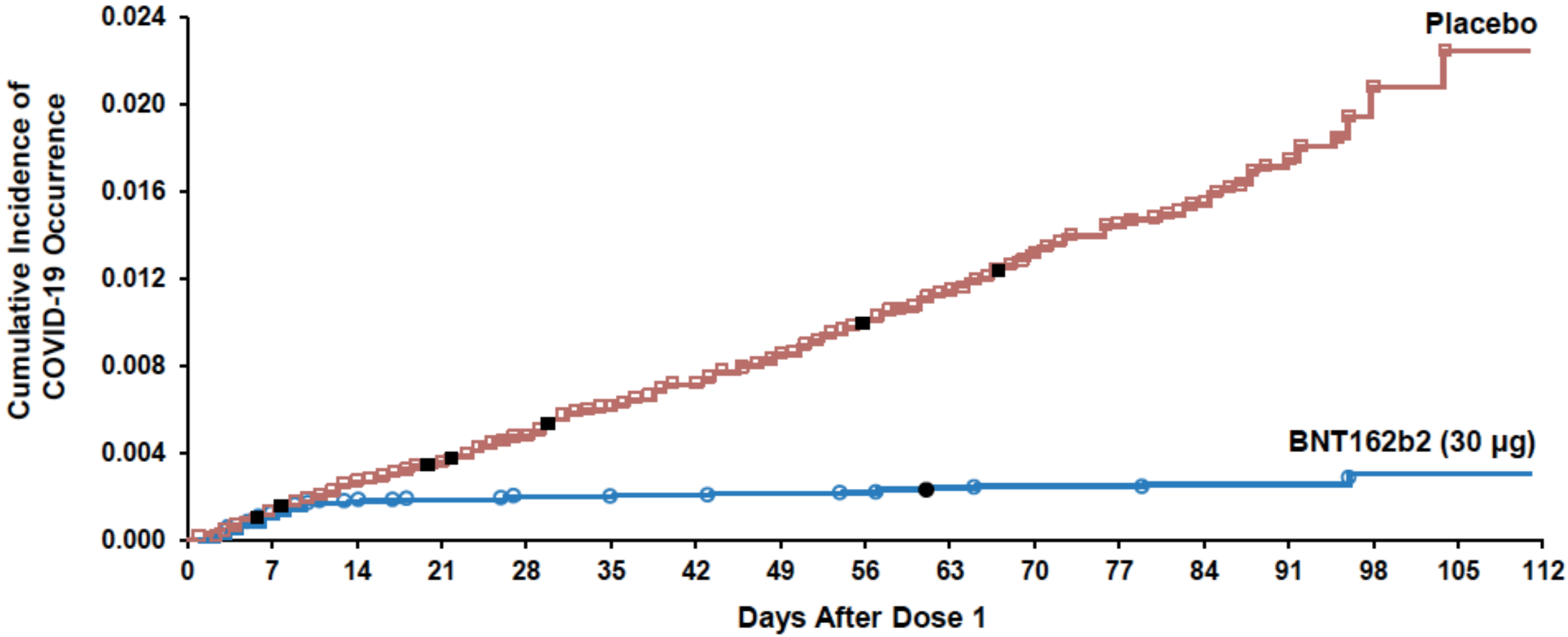
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.

[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

"Efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19"

https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-10-2020-meeting-announcement

Cumulative Incidence of COVID-19 After Dose 1



Solid fill marker indicates subjects with severe COVID-19

Pfizer-BioNTech (BNT162b2)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

December 10, 2020

Pfizer-BioNTech (BNT162b2)

The NEW ENGLAND JOURNAL of MEDICINE

Come è stata valutata la SICUREZZA

- 21.720 partecipanti ⟶ almeno una dose di vaccino
- 21.728 partecipanti ⟶ placebo

19.067 (9531 vaccino e 9536 placebo) ⟶ *SAFETY SUBSET*

8.183 partecipanti ⟶ *REACTOGENICITY SUBSET*

Reazioni locali "sollecitate"

REAZIONI LOCALI

- Reazioni locali più frequenti nei riceventi riceventi BNT162b2
- ++ dolore lieve-moderato nel sito di iniezione
- < 1% ha riportato dolore importante
- dolore meno frequente nei soggetti >55 anni
- nessuna reazione locale di grado 4
- *Tutte reazioni lievi-moderate e transitorie*

reazione lieve

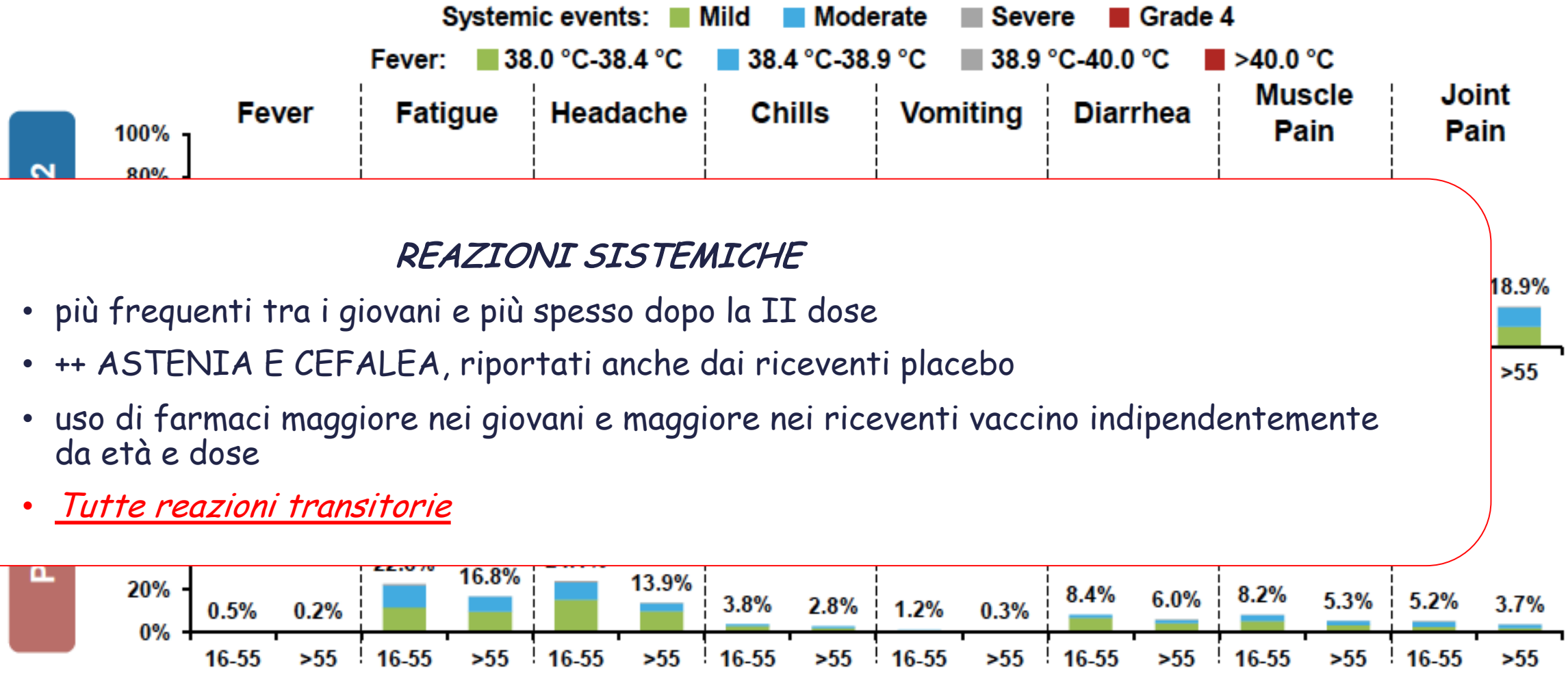
reazione moderata

reazione grave

reazione grado 4

The NEW ENGLAND JOURNAL of MEDICINE

eDiary: Systemic Events Within 7 Days From Dose 2 in 16-55 and >55 Year Olds (N=8,183)



REAZIONI SISTEMICHE

- più frequenti tra i giovani e più spesso dopo la II dose
- ++ ASTENIA E CEFALEA, riportati anche dai riceventi placebo
- uso di farmaci maggiore nei giovani e maggiore nei riceventi vaccino indipendentemente da età e dose
- *Tutte reazioni transitorie*

Fatigue, headache, chills, muscle pain, joint pain severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Vomiting severity definition: Mild=1-2 time in 24h; Moderate=>2times in 24h; Severe=Requires IV hydration; Grade 4=ER visit or hospitalization
Diarrhea severity definition: Mild=2-3 times in 24h; Moderate=4-5 times in 24h; Severe=6 or more times in 24h; Grade 4=ER visit or hospitalization
Dose 1: 18-55 yrs N=3529; 56-85 yrs N=3027 Dose 2: 18-55 yrs N=3345; 56-85 yrs N=2899

Serious Adverse Events by System Organ Class ≥0.1%
All Enrolled Subjects (N=43,448)

Vaccino a mRNA Pfizer-Biontech	BNT162b2 (30 µg) N=21621 n (%)	Placebo N=21631 n (%)
Any event	126 (0.6)	111 (0.5)
Infections and infestations	27 (0.1)	17 (0.1)
Cardiac disorders	18 (0.1)	18 (0.1)
Nervous system disorders	18 (0.1)	16 (0.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	11 (0.1)	8 (0.0)
Injury, poisoning and procedural complications	8 (0.0)	12 (0.1)

Vaccino mRNA (Moderna)

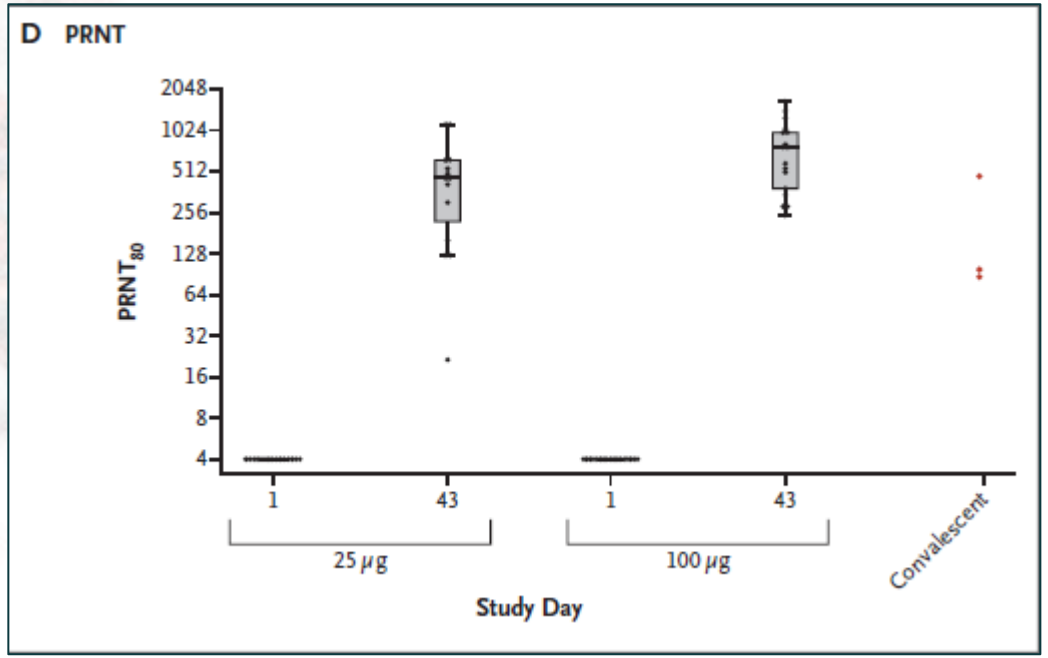
Risultati di clinica

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

- Risultati preliminari della fase 1 in 45 soggetti adulti sani; somministrate 2 dosi a un mese di distanza tra le dosi



Conclusioni

- Anticorpi neutralizzanti sono stati riscontrati in tutti i partecipanti
- Il profilo di sicurezza è stato considerato accettabile

This article was published on July 14, 2020, and updated on August 25, 2020, at NEJM.org.

Vaccino mRNA (Moderna)

Risultati di clinica

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults

CONCLUSIONS

In this small study involving older adults, adverse events associated with the mRNA-1273 vaccine were mainly mild or moderate. The 100-μg dose induced higher binding- and neutralizing-antibody titers than the 25-μg dose, which supports the use of the 100-μg dose in a phase 3 vaccine trial. (Funded by the National Institute of Allergy and Infectious Diseases and others; mRNA-1273 Study ClinicalTrials.gov number, NCT0428346

Vaccino mRNA Moderna

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

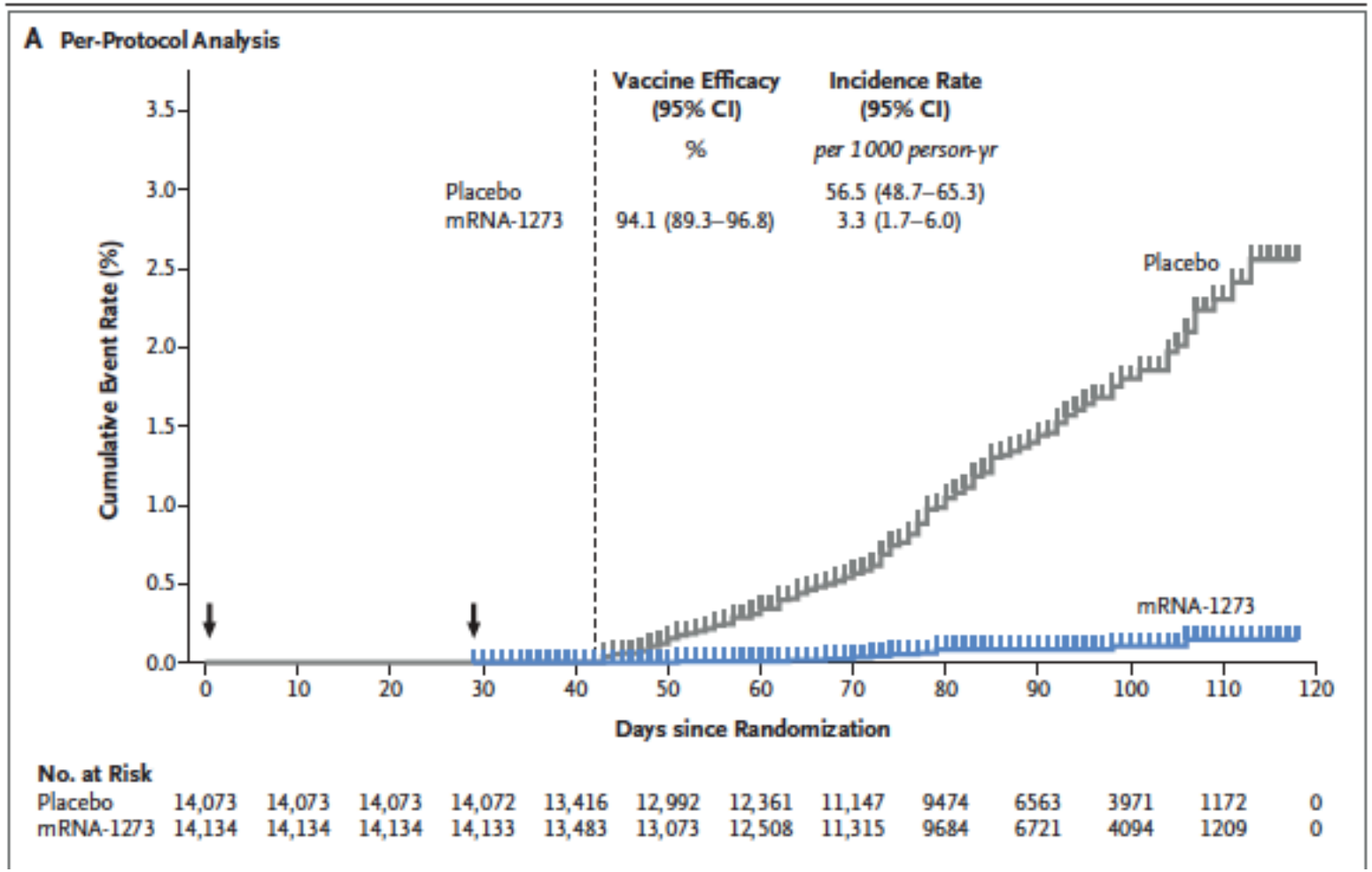
L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

RESULTS

The trial enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). More than 96% of participants received both injections, and 2.2% had evidence (serologic, virologic, or both) of SARS-CoV-2 infection at baseline. Symptomatic Covid-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001). Efficacy was similar across key secondary analyses, including assessment 14 days after the first dose, analyses that included participants who had evidence of SARS-CoV-2 infection at baseline, and analyses in participants 65 years of age or older. Severe Covid-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Moderate, transient reactogenicity after vaccination occurred more frequently in the mRNA-1273 group. Serious adverse events were rare, and the incidence was similar in the two groups.

CONCLUSIONS

The mRNA-1273 vaccine showed 94.1% efficacy at preventing Covid-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified. (Funded by the Biomedical Advanced Research


A Per-Protocol Analysis
Vaccine Efficacy (95% CI)
%
Incidence Rate (95% CI)
per 1000 person-yr
Placebo
56.5 (48.7–65.3)
mRNA-1273
94.1 (89.3–96.8)
3.3 (1.7–6.0)
Placebo
mRNA-1273
Cumulative Event Rate (%)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
0
10
20
30
40
50
60
70
80
90
100
110
120
Days since Randomization
No. at Risk
Placebo 14,073 14,073 14,073 14,072 13,416 12,992 12,361 11,147 9474 6563 3971 1172 0
mRNA-1273 14,134 14,134 14,134 14,133 13,483 13,073 12,508 11,315 9684 6721 4094 1209 0

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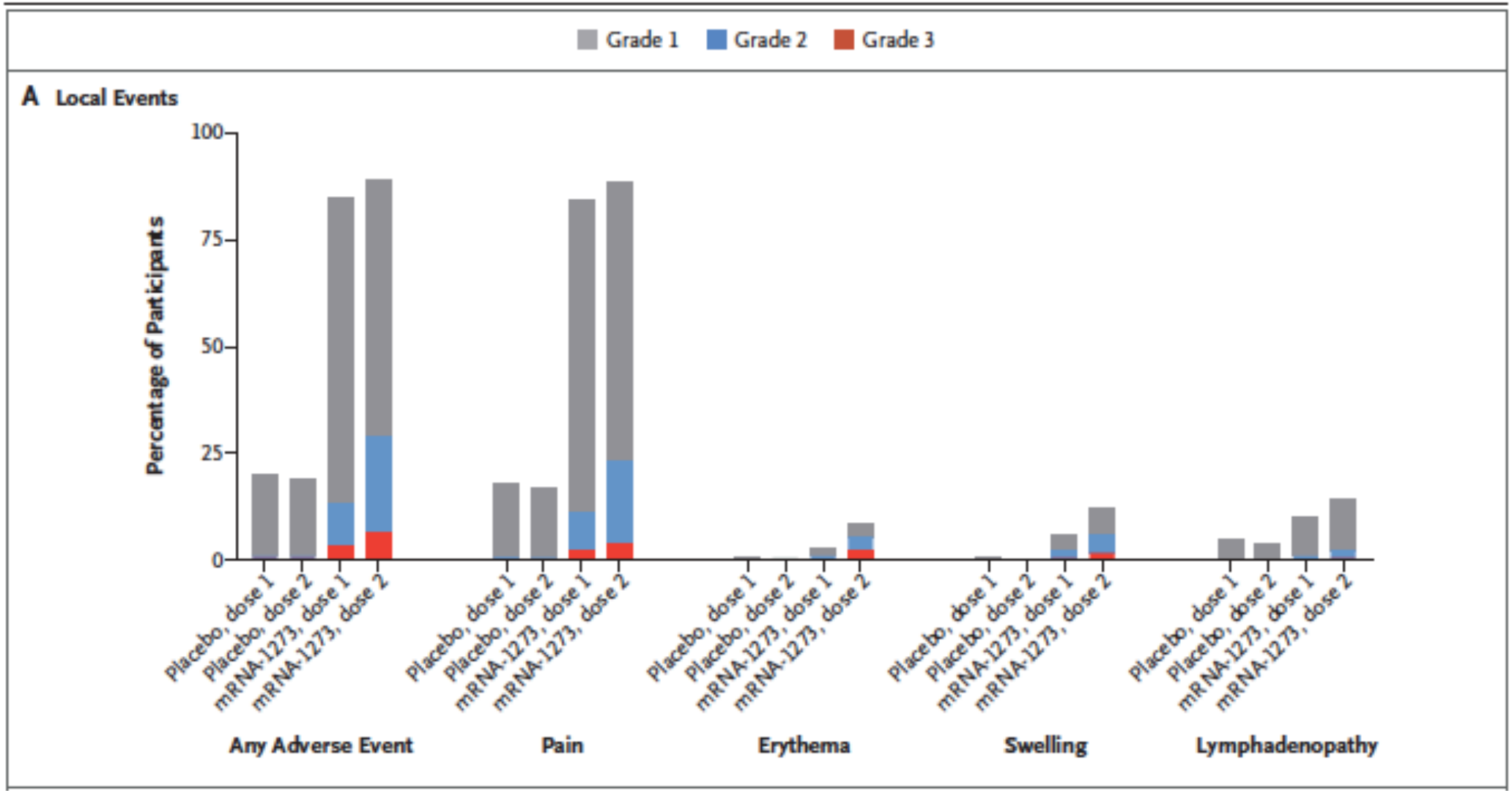
Vaccino mRNA Moderna: eventi avversi locali



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Vaccino mRNA Moderna: eventi avversi sistemici

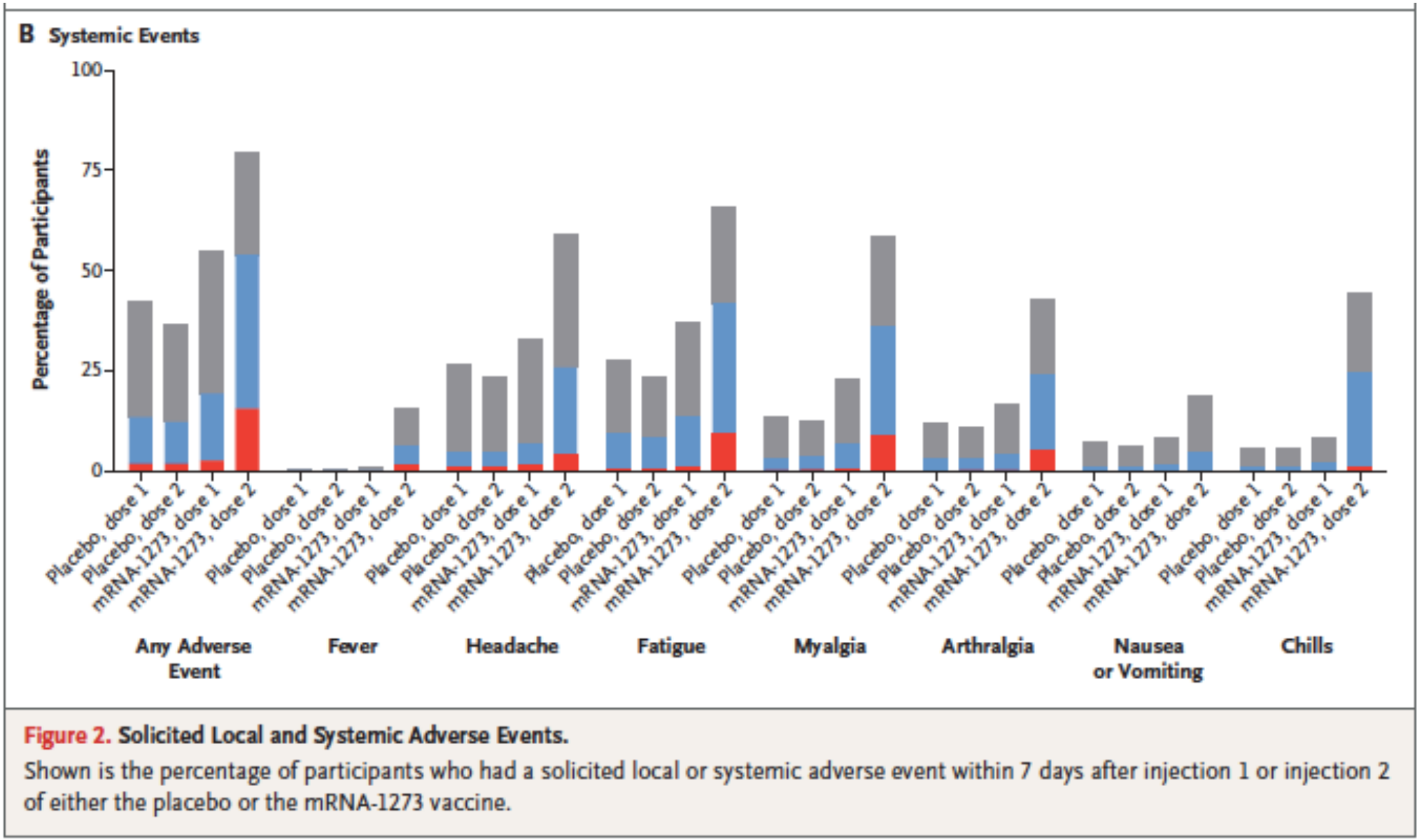
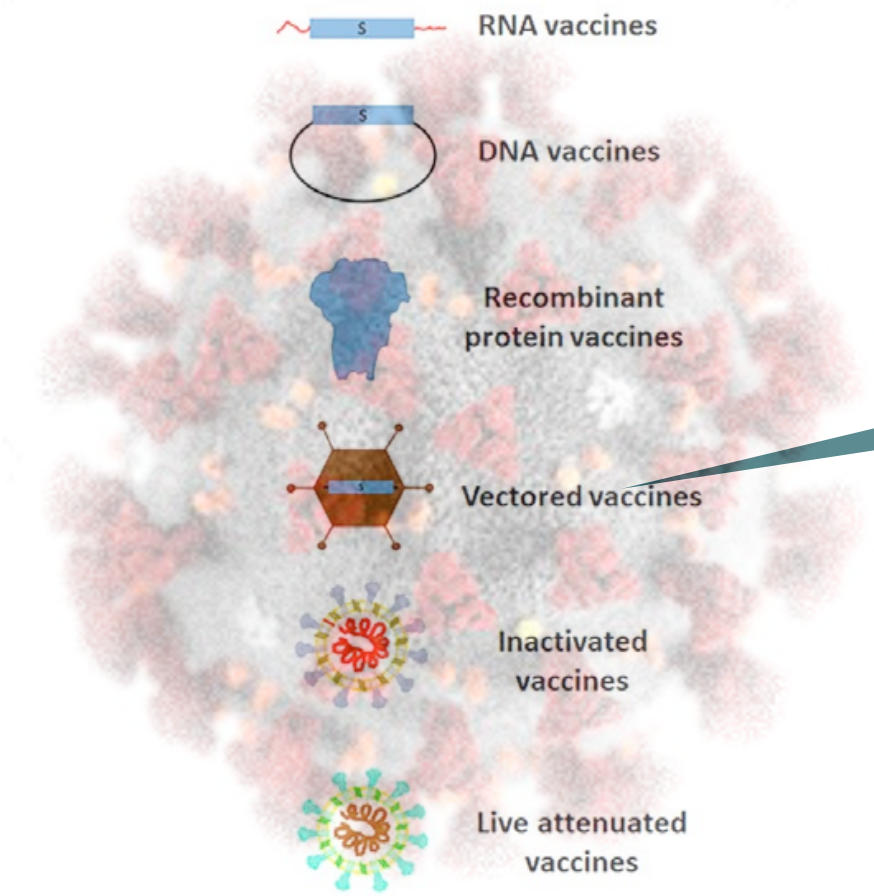


Figure 2. Solicited Local and Systemic Adverse Events.

Shown is the percentage of participants who had a solicited local or systemic adverse event within 7 days after injection 1 or injection 2 of either the placebo or the mRNA-1273 vaccine.

Vaccini a vettore virale

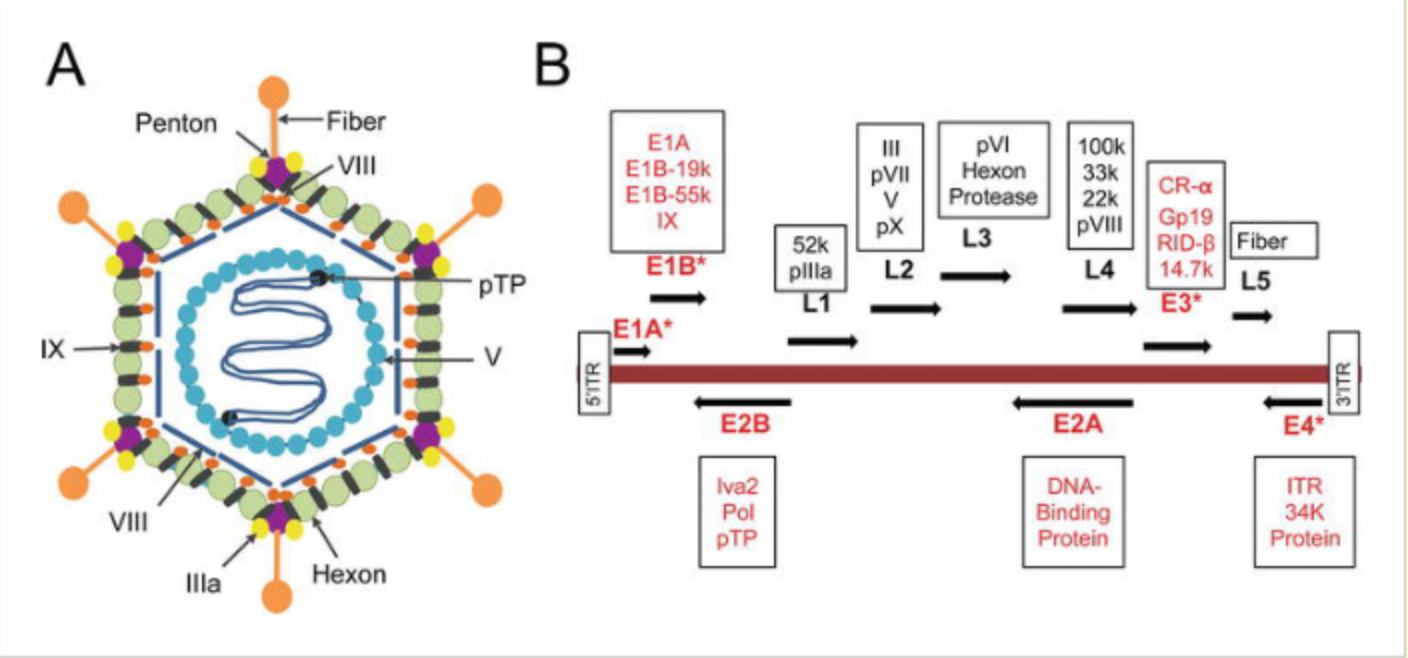


candidati a vettore adenovirale:

- ChAd5 sdi Astra Zeneca Fase III
- Ad26.COV2.S di Janseen in Fase III

Ad5-nCoV di CanSino Fase III

Vettore adenovirale



Vaccino adenovirale (Astra Zeneca)

Risultati di clinica

Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial

- Circa il 60% dei soggetti ha sieroconvertito in termini di anticorpi neutralizzanti
- Il profilo di sicurezza è buono, con sintomi usuali per i vaccini e prevalentemente di entità lieve e moderata

Conclusioni

- Una dose di vaccino a contenuto ridotto è immunogenica, ma ipotizzano un regime a due dosi nei soggetti target principale della vaccinazione
- Hanno riscontrato circa 50% dei partecipanti con anticorpi neutralizzanti contro il vettore
- I risultati di questo studio hanno portato il vaccino alla fase 3

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Lancet. 2021 Jan 9; 397(10269): 99–111.
doi: 10.1016/S0140-6736(20)32661-1: 10.1016/S0140-6736(20)32661-1

PMCID: PMC7723445
PMID: 33306989

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK

Merryn Voysey, DPhil,[a,*] Sue Ann Costa Clemens, PhD,[c,d,*] Shabir A Madhi, PhD,[f,*] Lily Y Weckx, PhD,[g,*] Pedro M Folegatti, MD,[b,*] Parvinder K Aley, PhD,[a] Brian Angus, MD,[b] Vicky L Baillie, PhD,[h] Shaun L Barnabas, PhD,[i] Qasim E Bhorat, MSc,[j] Sagida Bibi, PhD,[a] Carmen Briner, MBBCh,[k] Paola Cicconi, PhD,[b] Andrea M Collins, PhD,[m] Rachel Colin-Jones, MSc,[a] Clare L Cutland, PhD,[h] Thomas C Darton, DPhil,[n,o] Keertan Dheda, FRCPCH,[p,q] Christopher J A Duncan, DPhil,[r,s] Katherine R W Emary, BM BCh,[a] Katie J Ewer, PhD,[b] Lee Fairlie, FCPaeds,[l] Saul N Faust, PhD,[t,u] Shuo Feng, PhD,[a] Daniela M Ferreira, PhD,[m] Adam Finn, PhD,[v] Anna L Goodman, FRCP,[w,x] Catherine M Green, PhD,[e] Christopher A Green, DPhil,[y] Paul T Heath, FRCPCH,[z] Catherine Hill, BSc,[l] Helen Hill, PhD,[m] Ian Hirsch, PhD,[aa] Susanne H C Hodgson, DPhil,[b] Alane Izu, PhD,[ab] Susan Jackson, MRCP,[b] Daniel Jenkin, MRCP,[b] Carina C D Joe, PhD,[b] Simon Kerridge, MSc,[a] Anthonet Koen, MBChB,[ab] Gaurav Kwatra, PhD,[l] Rajeka Lazarus, DPhil,[ac] Alison M Lawrie, PhD,[b] Alice Lelliott, BMBS,[a] Vincenzo Libri, MD FRCP,[ad] Patrick J Lillie, PhD,[ae] Raburn Mallory, MD,[aa] Ana V A Mendes, MD,[af,ag] Eveline P Milan, MD,[ah] Angela M Minassian, DPhil,[b] Alastair McGregor, FRCPath,[ai] Hazel Morrison, MRCP,[b] Yama F Mujadidi, MSc,[a] Anusha Nana, MPharm,[k] Peter J O'Reilly, MBChBAO,[a] Sherman D Padayachee, MBChB,[aj] Ana Pittella, MD,[ak,al,am] Emma Plested,[a] Katrina M Pollock, PhD,[an] Maheshi N Ramasamy, DPhil,[a] Sarah Rhead, MBChB,[a] Alexandre V Schwarzbold, PhD,[ao] Nisha Singh, DPhil,[a] Andrew Smith, FRCPath,[ap] Rinn Song, MD,[a,aq] Matthew D Snape, MD,[a] Eduardo Sprinz, MD,[ar] Rebecca K Sutherland, FRCP,[as] Richard Tarrant, PhD,[e] Emma C Thomson, FRCP PhD,[at] M Estée Török, FRCP,[au,av] Mark Toshner, MD,[aw] David P J Turner, PhD,[ax] Johan Vekemans, MD,[aa] Tonya L Villafana, PhD,[aa] Marion E E Watson, PhD,[b] Christopher J Williams, FFPH,[ay,az] Alexander D Douglas, DPhil,[b,*] Adrian V S Hill, FMedSci,[b,*] Teresa Lambe, PhD,[b,*] Sarah C Gilbert, PhD,[b,*] Andrew J Pollard, FMedSci,[a,*,*] and Oxford COVID Vaccine Trial Group, on behalf of the

Findings

Between April 23 and Nov 4, 2020, 23 848 participants were enrolled and 11 636 participants (7548 in the UK, 4088 in Brazil) were included in the interim primary efficacy analysis. In participants who received two standard doses, vaccine efficacy was 62·1% (95% CI 41·0–75·7; 27 [0·6%] of 4440 in the ChAdOx1 nCoV-19 group *vs*71 [1·6%] of 4455 in the control group) and in participants who received a low dose followed by a standard dose, efficacy was 90·0% (67·4–97·0; three [0·2%] of 1367 *vs* 30 [2·2%] of 1374; $p_{interaction}$=0·010). Overall vaccine efficacy across both groups was 70·4% (95·8% CI 54·8–80·6; 30 [0·5%] of 5807 *vs* 101 [1·7%] of 5829). From 21 days after the first dose, there were ten cases hospitalised for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death. There were 74 341 person-months of safety follow-up (median 3·4 months, IQR 1·3–4·8): 175 severe adverse events occurred in 168 participants, 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group. Three events were classified as possibly related to a vaccine: one in the ChAdOx1 nCoV-19 group, one in the control group, and one in a participant who remains masked to group allocation.

Vaccino mRNA (Pfizer) e a vettore adenovirale di Astra Zeneca

Indicazioni dal Regno Unito

Dosing and schedule

Pfizer BioNTech COVID-19 vaccine*

The dose of Pfizer BioNTech COVID-19 vaccine is 30µg contained in 0.3ml of the diluted vaccine.

The vaccine should be administered in 2 doses, a minimum of 21 days apart.

AstraZeneca COVID-19 vaccine*

The dose of AstraZeneca COVID-19 vaccine is 0.5ml.

The vaccine should be administered in 2 doses, a minimum of 28 days apart.

For operational purposes, scheduling the second dose of COVID-19 vaccine from 28 days is recommended (although this would not preclude scheduling Pfizer BioNTech COVID-19 vaccine from 21 days where rapid protection is required). Using a consistent interval for all two-dose vaccines simplifies the messaging to the public and arrangements within clinic settings where alternative vaccines may be supplied at short notice.

If an interval longer than the recommended interval is left between doses, the second dose should still be given (preferably using the same vaccine as was given for the first dose if possible). The course does not need to be restarted.

Vaccino mRNA (Pfizer) e a vettore adenovirale di Astra Zeneca

Indicazioni dal Regno Unito

If the course is interrupted or delayed, it should be resumed using the same vaccine but the first dose should not be repeated. There is no evidence on the interchangeability of the COVID-19 vaccines although studies are underway (JCVI, 2020). Therefore, every effort should be made to determine which vaccine the individual received and to complete with the same vaccine. For individuals who started the schedule and who attend for vaccination at a site where the same vaccine is not available, or if the first product received is unknown, it is reasonable to offer a single dose of the locally available product. This option is preferred if the individual is likely to be at immediate high risk or is considered unlikely to attend again. In these circumstances, as both the vaccines are based on the spike protein, it is likely the second dose will help to boost the response to the first dose. For this reason, until additional information becomes available, further doses are not required.

Independent report

Priority groups for coronavirus (COVID-19) vaccination: advice from the JCVI, 2 December 2020

Updated 3 December 2020

Direct protection versus transmission reduction

JCVI has considered a number of different vaccination strategies, including those targeting transmission and those targeted at providing direct protection to persons most at risk.

In order to interrupt transmission, mathematical modelling indicates that we would need to vaccinate a large proportion of the population with a vaccine which is highly effective at preventing infection (transmission). At the start of the vaccination programme, good evidence on the effects of vaccination on transmission will not be available, and vaccine availability will be more limited. The best use of available vaccine will also, in part, be dependent on the point in the pandemic the UK is at.

Given the current epidemiological situation in the UK, all evidence indicates that the best option for preventing morbidity and mortality in the initial phase of the programme is to directly protect persons most at risk of morbidity and mortality.

https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-2-december-2020/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-2-december-2020#references

Vaccino adenovirale (Johnson and Johnson)

Layout table for study information	
Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	60000 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Prevention
Official Title:	A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older
Estimated Study Start Date :	September 5, 2020
Estimated Primary Completion Date :	March 10, 2023
Estimated Study Completion Date :	March 10, 2023

www.clinicaltrial.gov

Evento avverso

"Qualsiasi evento medico non desiderato che insorga in un paziente o in un soggetto incluso in uno studio clinico cui venga somministrato un farmaco/vaccino/placebo, e che non necessariamente abbia una relazione di causalità con il trattamento stesso"

Eventi avversi

- Incidenza di eventi avversi totali: 27% nei riceventi vaccino vs 12% nei riceventi placebo

- Incidenza di eventi avversi gravi è simile nei due gruppi (0.6% vaccino and 0.5% placebo)

- 4 "related serious adverse events" riportati nel gruppo BNT162b2:

danno alla spalla legato al vaccino, linfoadenopatia ascellare destra, aritmia ventricolare parossistica, parestesia gamba destra

Nessuna morte è stata considerata correlata a vaccino o placebo

- 2 morti nel gruppo BNT162b2 : aterosclerosi e arresto cardiaco
- 4 morti nel gruppo placebo: 2 causa ignota, 1 stroke emorragico, 1 infarto acuto del m

The NEW ENGLAND JOURNAL of MEDICINE

Centers for Disease Control and Prevention
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vaccini anti-COVID (mRNA) negli ALLERGICI

- Soggetti con storia di reazione allergica grave ad un qualunque componente del vaccino
- Reazione allergica grave dopo la I dose

- Soggetti con precedente reazione allergica grave a vaccino o farmaco: consulenza specifica

- Soggetti con storia di reazioni allergiche gravi ad altri allergeni (alimenti, inalanti, latice)
- Soggetti con storia di allergia a farmaci per os o storia familiare di allergia grave o precedenti reazioni moderate ad altri vaccini

Presidii e farmaci per emergenza
Operatori formati
Tempo di attesa adeguato

Centers for Disease Control and Prevention
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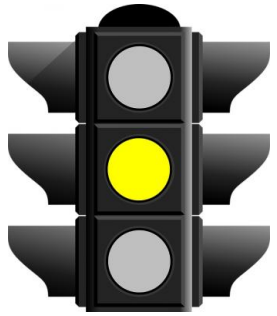
GRAVIDANZA e ALLATTAMENTO

- dati limitati su uso del vaccino durante la gravidanza e allattamento
- studi di laboratorio su **modelli animali** non hanno mostrato effetti dannosi in gravidanza.
- Non vi è motivo biologico per pensare che sia pericoloso
- L'infezione da Covid-19 può è essere rischiosa in gravidanza per la madre e per il feto, ++ se fattori di rischio associati

GRAVIDANZA E ALLATTAMENTO



- Non è raccomandato test di gravidanza prima del vaccino
- Non è raccomandato tempo di attesa prima di concepimento dopo la vaccinazione
- Valutare rapporto rischi/benefici in ogni singolo caso
- Non è noto alcun rischio che impedisca di continuare l'allattamento al seno

Centers for Disease Control and Prevention
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IMMUNODEPRESSIONE

- Le persone immunodepresse possono essere vaccinate in quanto potrebbero essere ad **alto rischio** di COVID-19

- NON vi sono controindicazioni

- Efficacia potrà essere inferiore → Continuare a proteggersi!

MALATTIE AUTOIMMUNI

- Soggetti con malattie autoimmuni possono essere vaccinati
- Non ancora disponibili dati su sicurezza ed efficacia del vaccino COVID-19 mRNA BNT162b2 nelle persone con malattie autoimmuni

- Durante gli studi clinici non osservate differenze nella comparsa di sintomi riconducibili a malattie autoimmuni o infiammatorie tra vaccinati e soggetti trattati con placebo

Moderna (mRNA-1273)

- Reattogenicità locale e sistemica frequente ma entità da lieve a moderata
- Reazioni avverse sistemiche più frequenti dopo la II dose e più frequenti e gravi nella fascia 18-64 anni
- Reazioni più comuni nei 1-2 giorni successivi e con risoluzione in 2-3 giorni
- Reazioni locali e sistemiche gravi (grado >= 3) più comuni nei riceventi vaccino (21.6% vs 4.4%).
- Frequenza di eventi avversi gravi 1.0% nel gruppo vaccino e 1.0% nel gruppo placebo

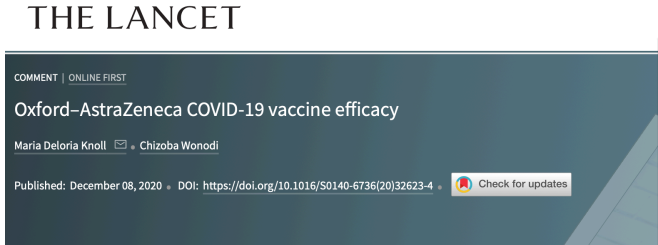
The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Moderna COVID-19 Vaccine — United States, December 2020
Early Release / December 20, 2020 / 69

AstraZeneca-Oxford University (ChAdOx1)

Eventi avversi gravi valutati in 12.174 soggetti vaccinati e 11.879 controlli

- 175 eventi avversi gravi:
  - **84 nel gruppo vaccino**
  - **91 nel gruppo controllo**

- Nessun evento avverso grave o morte associato al vaccino



Science

POLICY FORUM

Cite as: L. Corey *et al.*, *Science* 10.1126/science.abc5312 (2020).

A strategic approach to COVID-19 vaccine R&D

By **Lawrence Corey[1,2], John R. Mascola[3], Anthony S. Fauci[4], Francis S. Collins[5]**

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A public-private partnership and platform for harmonized clinical trials aims to accelerate licensure and distribution.

Quali sono le principali sfide per lo sviluppo di un vaccino contro SARS-CoV2

1. Definire cosa sia ‘immunità protettiva’ (correlato di protezione? durata immunità?)
2. Endpoint variabili: protezione da infezione vs riduzione replicazione virale / malattia
3. Ruolo di anticorpi neutralizzanti e cellule T
4. Difficile comprensione effettiva incidenza di infezioni (sintomatiche e asintomatiche)
5. Creazione di laboratori indipendenti con identici saggi sierologici validati per confrontare diversi candidati e differenti *clinical trials*
6. *Challenge trials* umani: sono utili ed eticamente accettabili?
7. Rischio Immunopotenziamento: i vaccini contro virus respiratori possono indurre una risposta immunitaria eccessiva che, in caso di infezione, anziché prevenire la malattia la aggrava, attaccando i tessuti stessi del malato → un vaccino candidato deve superare valutazioni approfondite di safety

L. Corey *et al.*, *Science* 10.1126/science.abc5312 (2020)

IO MI SONO VACCINATO

Gli operatori in prima linea

CONTRO LA COVID-19

RERUM COGNOSCERE CAUSAS

ItI

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