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VACCINE

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Scientific update on COVID-19

Updated on December 21th 2020

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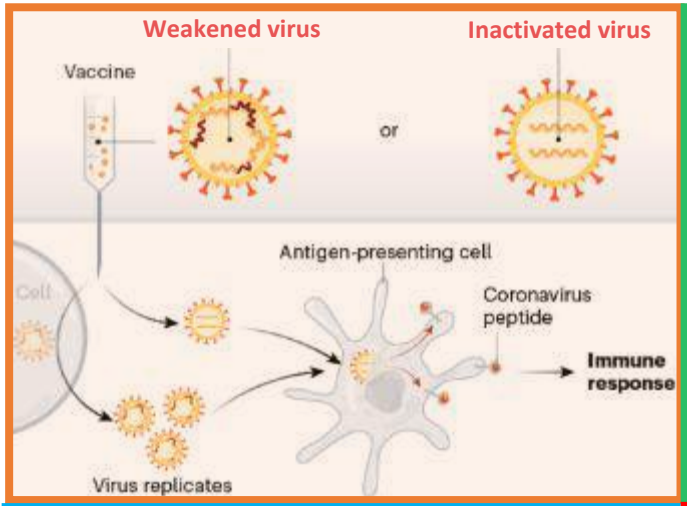
VACCINE

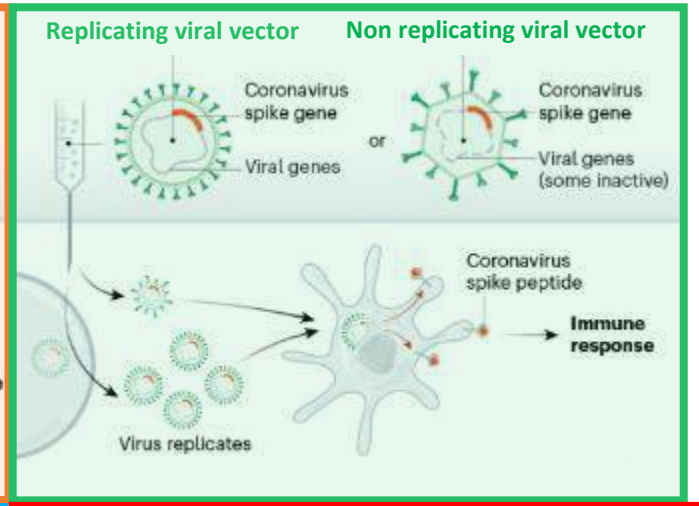
Question:

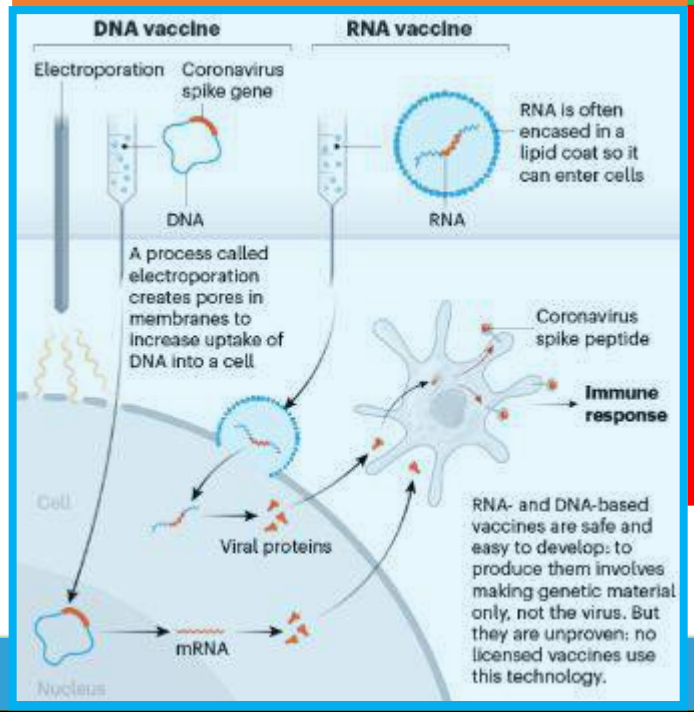
- What are the types of vaccines in clinical evaluation?

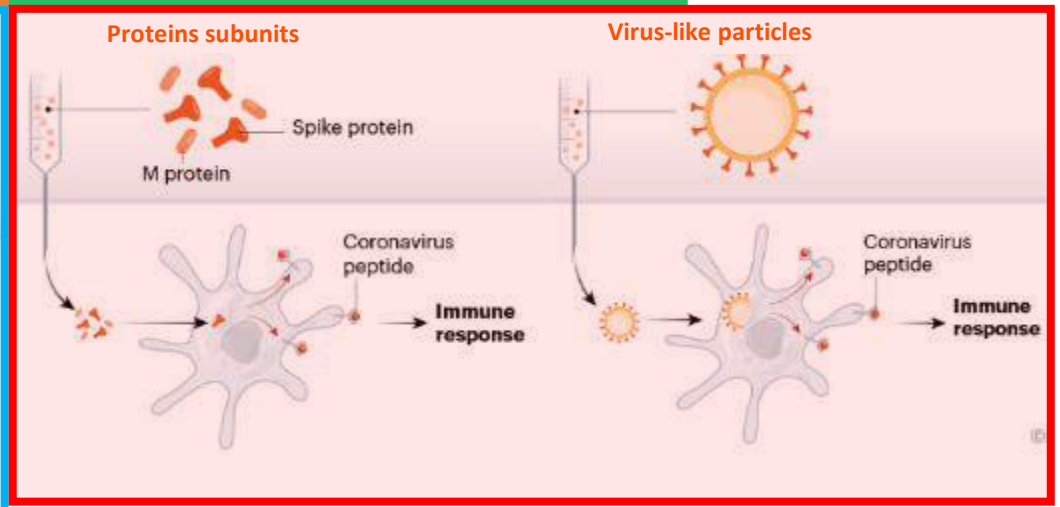
Vaccine

- **Vaccines aims**: expose the immune system to an antigen that won't cause disease, provoke an immune response (able to block/kill the virus)
- **Eight types of vaccines**:
  - virus (inactivated, weakened),
  - viral vector (replicating, non replicating)
  - nucleic acid (DNA, RNA)
  - protein based (protein subunit, virus like particles)









Callaway E. *Nature* Apr 2020

Vaccine

- **R&D landscape**: WHO lists more than 200 candidates in preclinical development, 48 candidate vaccines in clinical evaluation (November 25th); update available at :

  https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

		Preclinical	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Licensed
VIRUS	Inactivated	8		2	1		4	
	Weakened	3	1					
VIRAL VECTOR	Replicating	16	1	2	1			
	Non replicating	27	6				4	
NUCLEIC ACID	DNA	15	2	5				
	RNA	26	2	2	1		2	
PROTEIN BASED	Protein subunit	63	10	5	2			
	Virus-like Particles	14		1		1		
Other/unknown		31	3					

Phase III COVID-19 Vaccines (Nov 26th 2020)

Developer	Vaccine Platform	Description
BioNTech – Pfizer – Fosun Pharma	RNA	**BNT162b2*:** Lipid nanoparticle-formulated, nucleoside **modified mRNA** vaccine encoding **full-length spike (S) protein**
Moderna – NIAID	RNA	**mRNA-1273:** Lipid nanoparticle encapsulated, mRNA vaccine encoding **pre fusion spike (S) protein**
CureVac	RNA	**CVnCoV:** Lipid nanoparticle encapsulated, mRNA (non modified) vaccine encoding **pre fusion spike (S) protein**
Inovio-IVI	DNA	**INO-4800:** DNA plasmid vaccine with electroporation
Osaka University-Takara Bio	DNA	**AG0302-COVID19:** DNA plasmid vaccine + Adjuvant
CanSino Biologicals Inc – Beijing Institute of Biotechnology	Non replicating viral vector	**Ad5-nCoV:** Replication-deficient **Ad5** vector containing optimised **full-length spike (S) protein**
Gamaleya Research Institute	Non replicating viral vector	**Spoutnik V:** Recombinant **Ad26 (prime)** and recombinant **Ad5 (boost)** viruses expressing the gene for **spike (S) protein**
Janssen Pharmaceutical Companies – Beth Israel Deaconness Medical Center	Non replicating viral vector	**Ad26COVS1:** Recombinant adenovirus vaccine **(Ad26)** incorporating SARS-CoV-2 full stabilized **Spike (S)** protein
University of Oxford – AstraZeneca	Non replicating viral vector	**AZD1222:** Replication-deficient **simian adenovirus (ChAdOx1)** vector containing **codon-optimised spike (S) protein**

Licensed
Approved for limited use
Phase I/II data available (pre-print)
Phase I/II data available (peer reviewed)
Phase III data available (peer-reviewed)

Phase III COVID-19 Vaccines (Nov 26th 2020)

Developer	Vaccine Platform	Description
Novavax	Protein subunit	**NVX-COV2373:** Recombinant **nanoparticle** vaccine consisting of **full-length spike (S) protein**, with or without **Matrix-M1 adjuvant**
Medicago	Protein subunit	**CoVLP: Plant-derived** VLP **adjuvanted** with AS03
Anhui Zhifei Logcom Biopharmaceutical-Chinese Academy of Sciences	Protein subunit	**ZF2001: Adjuvanted** recombinant protein (**RBD-Dimer**) expressed in CHO cells
Sinovac – Institute Butantan	Inactivated	**CoronaVac: β-propiolactone inactivated** vaccine adiministered with **aluminium hydroxide adjuvant**
Beijing Institute of Biological Products – Sinophram	Inactivated	**BBIBP-CorV**: **β-propiolactone i**nactivated vaccine adiministered with **aluminium hydroxide adjuvant**
Wuhan Institute of Biological products– Sinopharm	Inactivated	**SARS-CoV-2 Vaccine: β-propiolactone inactivated** vaccine adsorbed to 0.5-mg **aluminum**
Bharat Biotech- ICMR- National Institut of Virology	Inactivated	**COVAXIN:** whole-virion inactivated vaccine

Approved for limited use

Phase I/II data available (pre-print)

Phase I/II data available (peer reviewed)

mRNA vaccine

BNT162 b2

IMMUNOGENICITY AND SAFETY DATA

BioNTech/Pfizer

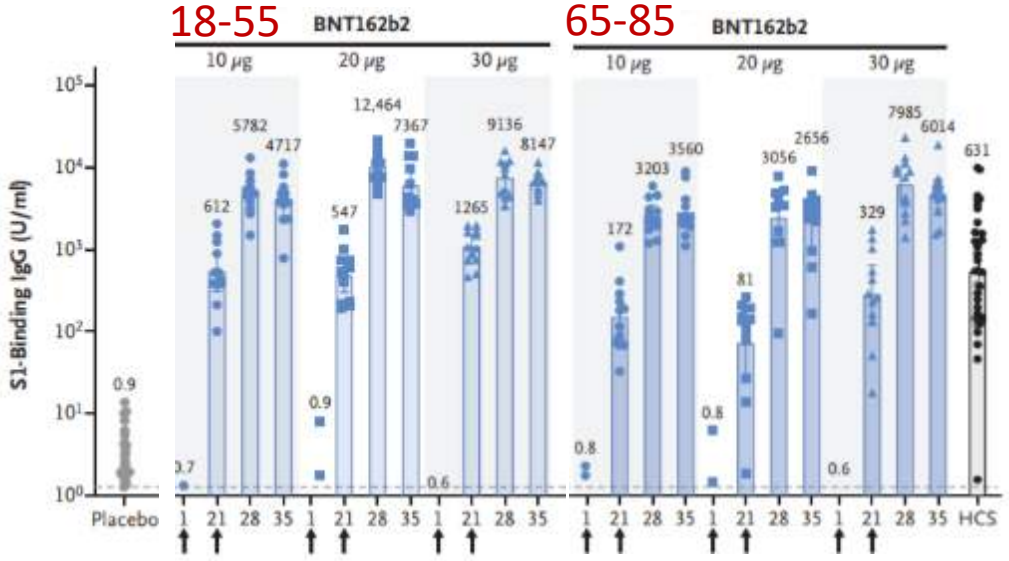
Phase I: NCT04368728

Study Designw	Phase I randomized controlled, dose-finding trial
Age range	18 – 55 or 65 – 85
Nb of participants	195
Nb of doses/route	2 (days 1/21)-IM
Vaccine groups	10 µg BNT162b2 (S) 18–55y (n = 12) 20 µg BNT162b2 (S) 18–55y (n = 12) 30 µg BNT162b2 (S) 18–55y (n = 12) 10 µg BNT162b2 (S) 65–85y (n = 12) 20 µg BNT162b2 (S) 65–85y (n = 12) 30 µg BNT162b2 (S) 65–85y (n = 12) *+BNT1621b (not used in Phase III)*
SAE	None
Local AE	Injection site pain, swelling
Systemic AE	Headache, fatigue, chills, muscle pain, fever, joint pain, diarrhoea

IMMUNOGENICITY 1/2

1. S1 specific binding responses

Assay: Luminex immunoassay
Units: Geometric mean concentration, U/mL (95% CI)



Antigen-binding IgG and virus-neutralizing responses to vaccination with 10 µg to 30 µg of BNT162b2 **boosted by the second dose** in both the younger adults and the older adults (**lower** antigen-binding **IgG in elderly** group)

mRNA vaccine

BNT162 b2

IMMUNOGENICITY AND SAFETY DATA

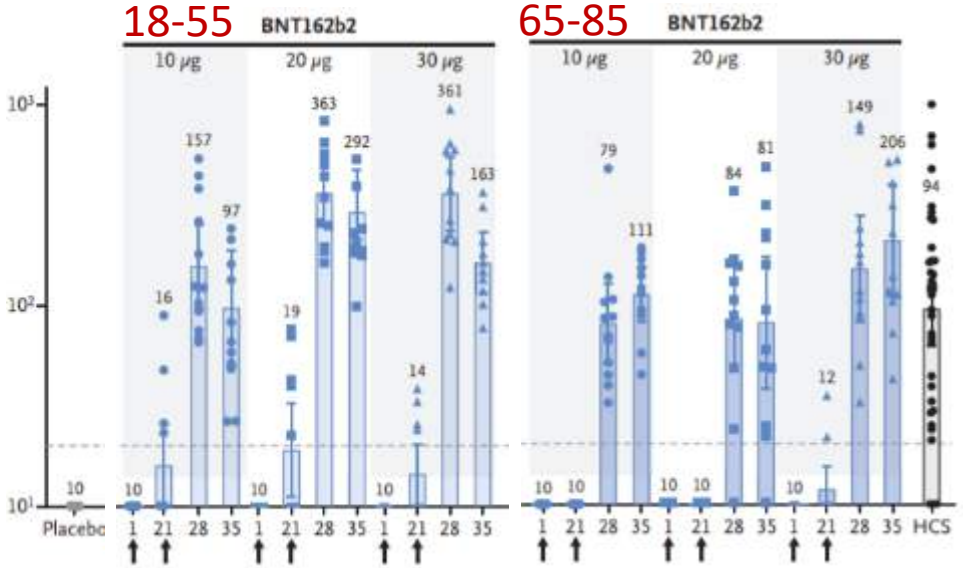
IMMUNOGENICITY 2/2

2. Neutralizing responses

Assay: SARS-CoV-2 virus neutralisation test (mNeonGreen reporter strain), 50% inhibitory dilution

Units: Geometric mean response, ID50 (95% CI)

The **50% neutralizing** at the 30-µg dose level on day 28 or day 35 ranged from **1.7 to 4.6 times the GMT of the convalescent serum panel** among participants **18 to 55** years of age and from 1.1 to 2.2 times the GMT of the convalescent serum panel among those **65 to 85** years of age.



Adenoviral vector vaccine

AZD1222

IMMUNOGENICITY AND SAFETY DATA

AstraZeneca-Oxford University

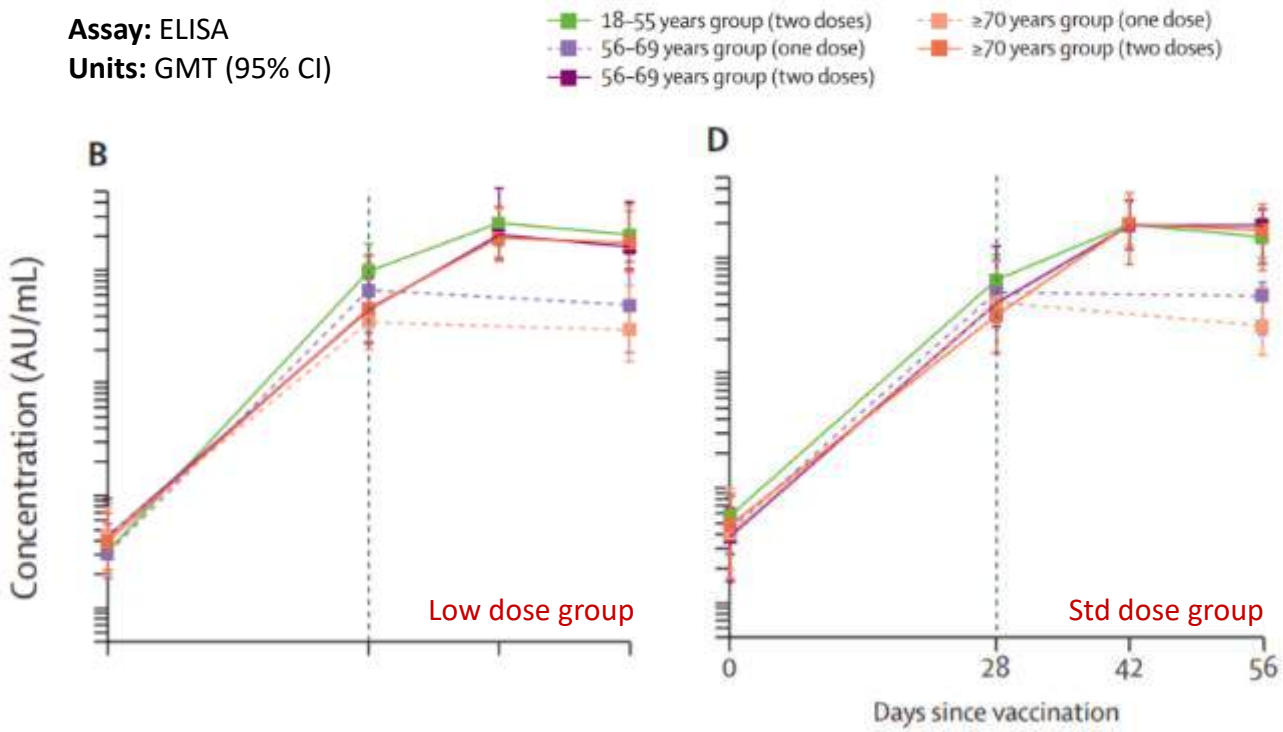
Phase II: NCT04400838

Study Design	Phase II randomised controlled trial
Age range	1: 18–55; 2: 56–69; 3: ≥70
Nb of participants	560
Nb of doses/route	1 (day 0) or 2 (days 0/28)- IM
Vaccine groups	18–55y: 2 x low dose (n = 50) 56–69y: 1 x low dose (n = 30) 56–69y: 2 x low dose (n = 30) ≥70y: 1 x low dose (n = 50) ≥70y: 2 x low dose (n = 50) 18–55y: 2 x std dose (n = 50) 56–69y: 1 x std dose (n = 30) 56–69y: 2 x std dose (n = 30) ≥70y: 1 x std dose (n = 50) ≥70y: 2 x std dose (n = 50) **Control group:** MenACWY (n = 534)
SAE	13 serious adverse events have occurred none of which are considered related to either study vaccine as assessed by the investigators *(Ph III trial suspended and resumed in Sep 2020 due to 2 cases of tranverse myelitis among participants, found not to be related to vaccination)*
Local AE	Tenderness, injection site pain; reported for participants who received 2 doses of vaccine; adverse events were less frequent in older adults (≥56y)
Systemic AE	Fatigue, headache, muscle ache, malaise, feverish, chills, joint pain; reported for participants who received 2 doses of vaccine; adverse events were less frequent in older adults (≥56y)

IMMUNOGENICITY 1/2

1. SARS-CoV-2 IgG response to spike protein

Assay: ELISA
Units: GMT (95% CI)



Total IgGs against the Spike protein **were similar in all age groups regardless the dose.** **Responses** at day 28 **decreased with increasing age** (low: 18–55 years, median 6439[AU]/mL; 56–69 years, 4553 AU/mL; ≥70 years, 3565 AU/mL. Std: 18–55 years, median 9807 AU/mL; 56–69 years, 5496 AU/mL; ≥70 years, 4156 AU/mL)

Adenoviral vector vaccine

AZD1222

IMMUNOGENICITY AND SAFETY DATA

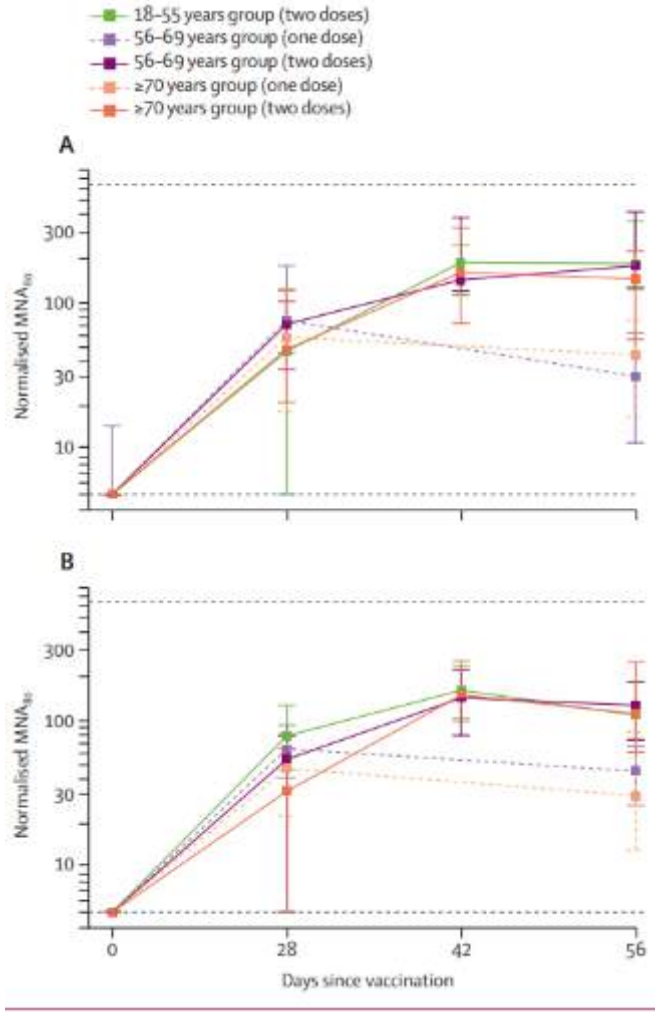
IMMUNOGENICITY 2/2

2. Live SARS-CoV-2 microneutralisation assay (MNA_{80})

Assay: Microneutralisation test (80% inhibitory dilution) tion)
Units: Median titre, ID80 (IQR)

Neutralizing antibody responses: Median titres peaked by day 42 in groups receiving two vaccinations.

There are **no significant differences** in normalized titers **between age groups at day 42** (low: 18–55 years, median 161; 56–69 years, 143; ≥70 years, 150. Std: 18–55 years, median 193; 56–69 years, 144; and ≥70 years, 161.



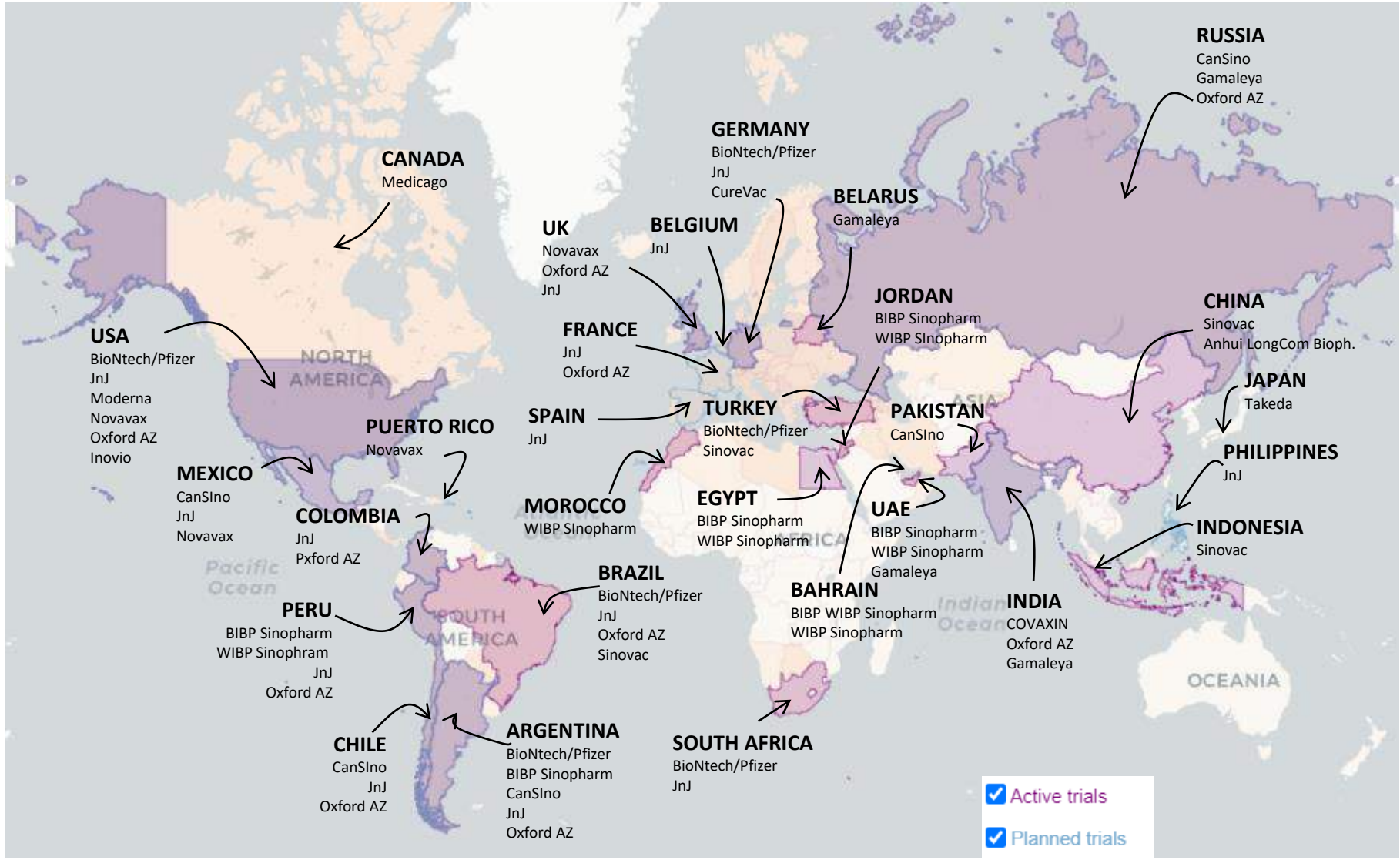
3. Induction of T cell responses and increase of IFN-γ expression

IFN-γ ELISpot responses against SARS-CoV-2 spike protein peaked 14 days after the prime vaccination

Summary of immunogenicity data

Vaccine & Developer	Phase III regimen	Specific IgG titers (14 - 28 days after 2nd dose) *as per Phase I or II published results*	NAb titers (14 - 28 days after 2nd dose) *as per Phase I or II published results*	Publication
BNT162b2 BioNTech – Pfizer – Fosun Pharma	2 doses (d1 and d22) 30µg/dose	8147 GMT *Test: Luminex anti S1 IgG*	163 GMT *Test: $wtVNA_{50}$*	*Walsh EE* et al. *NEJM* Oct 2020
mRNA-1273 Moderna – NIAID	2 doses (d1 and d29) 100µg/dose	782 719 GMT *Test: ELISA anti S IgG*	654.3 GMT *Test: $PRNT_{80}$*	*Jackson LA* et al. *NEJM* Jul 2020
Ad5-nCoV CanSino Biologicals Inc –Beijing Institute of Biotechnology	1 dose $5x10^{10}$ vp	571.0 GMT *Test: ELISA anti RBD IgG*	18.3 GMT *Test: WT virus neutralization*	*Zhu FC et al. Lancet* Jul 2020
SputnikV Gamaleya Research Institute	d1 0,5 mL rAd26 d21 0,5 mL rAd5	14 703 GMT *Test: ELISA anti RBD IgG*	49.25 GMT *Test: MNA_{50}*	*Logunov DY et al. Lancet* Sep 2020
Ad26COVS1 Janssen Pharmaceutical Companies Beth Israel Deaconness Medical Center	1 dose $1x10^{11}$ vp	Non published yet-preprint		
ChAdOx1 nCoV-19 University of Oxford – AstraZeneca	2 doses (d1 and d29) $5x10^{10}$ vp	639 EU *Test: ELISA anti S IgG*	136 MT *Test: MNA_{80}*	*Ramasay MN et al. Lancet Nov 2020*
NVX COV2373 Novavax	2 doses (d0 and d28) 25µg+Matrix M/ dose	47 521 GMEU *Test: ELISA anti S IgG*	3305 GMT *Test: MNA_{99}*	*Keech C et al. NEJM* Sep 2020
CoronaVac Sinovac – Institut Butantan	2 doses (d1 and d14)	1094,3 GMT *Test: ELISA anti RBD IgG*	27,6 GMT *Test: Micro cytopathic effect assay*	Zhang Y *et al. The Lancet Infect Dis* Nov 2020
BBIBP-CorV Beijing Inst. Biological Products –Sinophram	2 doses (d0 and d21)	*Not reported*	219,9 GMT *Test: MNA_{50}*	Xia S *et al. Lancet Infect Dis* Oct 2020
SARS-CoV-2 Vaccine Wuhan Inst. Biological products– Sinopharm	2 doses (d0 and d21)	215 GMT *Test: ELISA anti S IgG*	247 GMT *Test: $PRNT_{50}$*	Xia S *et al. JAMA* Sep 2020

Efficacy Trial Map (Nov 26th 2020)



Adapted from LSHTM COVID19 vaccine tracker https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/

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VACCINE EFFICACY DATA

Date	Company	Vaccine	Analysis
November 9th 2020	BioNTech/Pfizer	BNT162b2	1st interim analysis; 28 days after 1st dose 94 confirmed cases of COVID19 • **> 90% Efficacy**
November 11th 2020	Gamaleya	Spoutnik V	1st interim analysis; 21 days after 1st dose 20 confirmed cases of COVID19 • **> 92% Efficacy**
November 30th 2020	Moderna	mRNA 1273	1st interim analysis; 42 days after 1st dose 95 confirmed cases of COVID19 • **94.5% Efficacy**
November 18th 2020	BioNTech/Pfizer	BNT162b2	**Final analysis**; 28 days after 1st dose 170 confirmed cases of COVID19 • **95% Efficacy**
November 23rd 2020	AstraZenaca/Oxford	AZD1222	**1st interim analysis** 14 days after 2nd dose 131 confirmed cases of COVID19 • **90% Efficacy when given as half dose/full dose** • **62% Efficacy when given as full dose/full dose** • **Overall 70% efficacy**
November 24th 2020	Gamaleya	Spoutnik V	**2nd interim analysis**; 42 days after 1st dose 39 confirmed cases of COVID19 *(10 severe)* • **95% Efficacy**
November 30th 2020	Moderna	mRNA 1273	**Final analysis**; 42 days after 1st dose 196 confirmed cases of COVID19 *(30 severe)* • **94.1% Efficacy**

First data regarding vaccine efficacy has been made public by the means of press releases by pharmaceutical companies

mRNA vaccine

BNT162 b2

EFFICACY AND SAFETY DATA

- Efficacy data from ongoing double blind, randomized phase III trial across Argentina, Brazil, South Africa and USA (43 548 participants randomized 1:1)
- Two 30 µg doses of BNT162b2 vaccine, 21 days apart
- **Inclusion criteria:** healthy adults or stable chronic medical conditions, including HIV, HBV or HCV aged of 16y or more.
- **Exclusion criteria:** medical history of Covid-19, treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition
- Primary **efficacy** endpoint: efficacy of BNT162b2 against confirmed Covid-19 with onset at least 7 days after the second dose
- Primary **safety** end points: solicited, specific local or systemic adverse events and use of antipyretic or pain medication within 7 days after the receipt of each dose

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

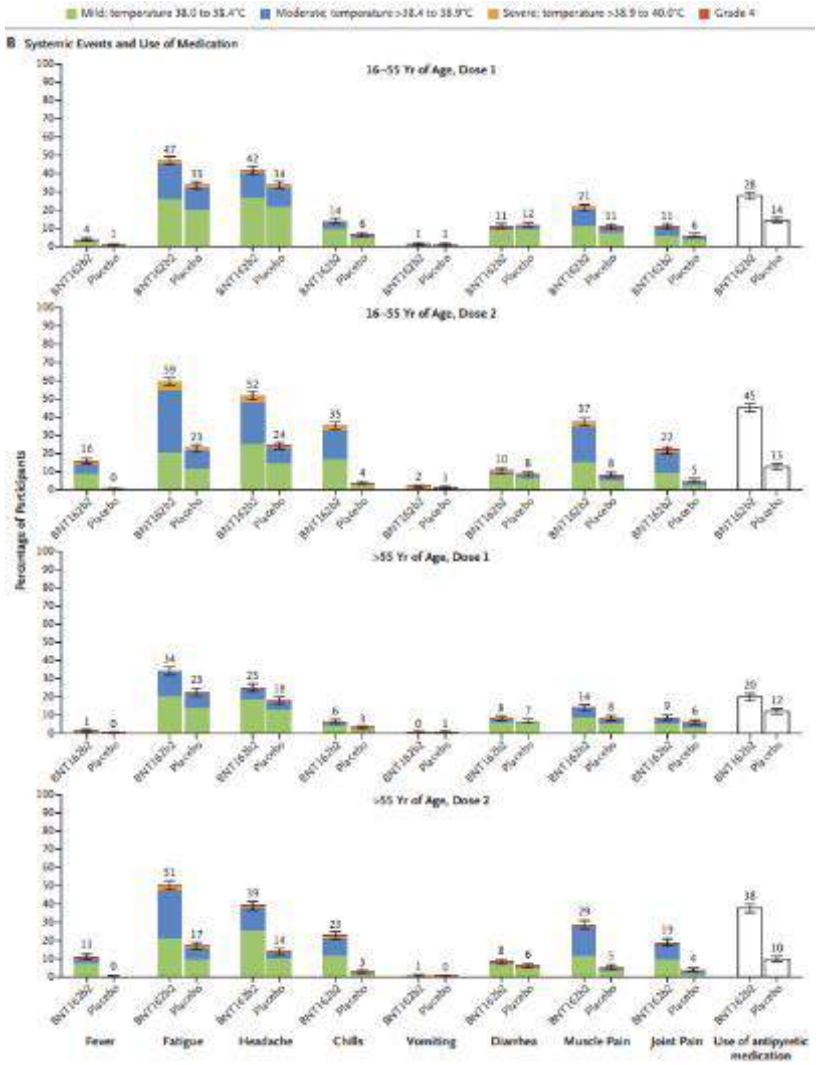
Characteristic	BNT162b2 (N=18,860)	Placebo (N=18,846)	Total (N=37,706)
Sex — no. (%)			
Male	9,639 (51.1)	9,436 (50.1)	19,075 (50.6)
Female	9,221 (48.9)	9,410 (49.9)	18,631 (49.4)
Race or ethnic group — no. (%)†			
White	15,636 (82.9)	15,630 (82.9)	31,266 (82.9)
Black or African American	1,729 (9.2)	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.

mRNA vaccine

BNT162 b2

EFFICACY
AND SAFETY DATA



- The BNT162b2 vaccine is reactogenic, but the side effects remain acceptable in all populations studied.
- The short-term safety profile of the BNT162b2 vaccine is characterized by mild to moderate pain at the injection site, fatigue and headache. These manifestations disappear after 24 to 48 hours.
- The only grade 3 adverse events with a frequency greater than 2% after the second vaccine administration are fatigue (97/2405 participants; 4.6%) and headache (7/2015; 3.2%).
- No grade 4 adverse side effects observed.

Six deaths were reported during the clinical trials, including four in the placebo group, but no relation with vaccination was found.

<u>Limits :</u>

Just 2 month follow up safety data

Data for over 75 is scarce and absent for children, pregnant women or immunocompromised

mRNA vaccine

BNT162 b2

EFFICACY AND SAFETY DATA

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 (1,7411)	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

TOTAL OF CASES: 170

- 8 in the BNT162b2 group/162 in the Control
- 10 severe cases, 9 within the Placebo group

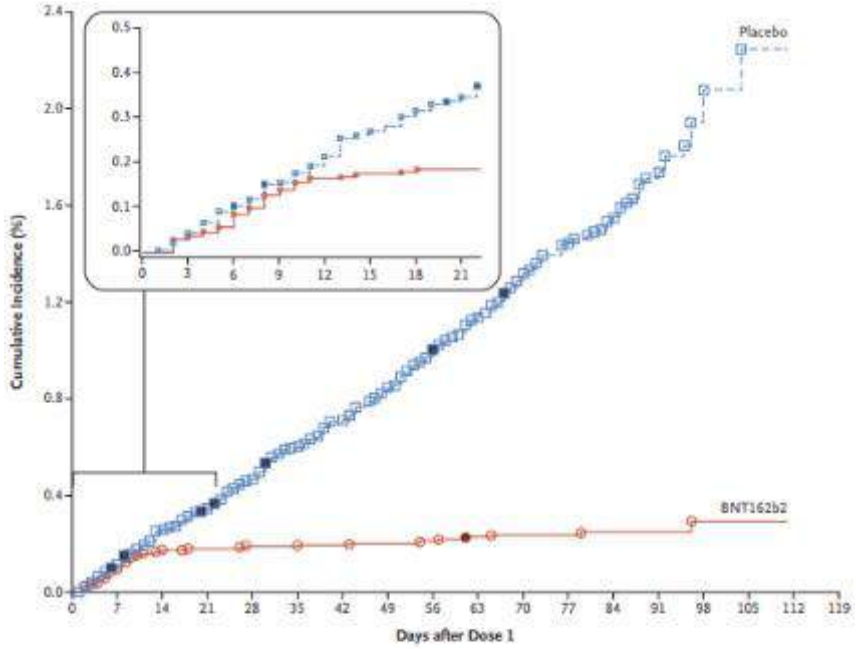
Vaccine efficacy: 95%

Limits:

Efficacy measured in symptomatic patients

No evidence of an potential effect against viral shedding

Protection occurs as early as the second week after the first vaccine administration, with an increase of protection level up to 95% after the second administration



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)

Adenoviral vector vaccine

AZD1222

EFFICACY AND SAFETY DATA

- Efficacy data from ongoing blinded, randomized, controlled trials across UK and Brazil
  - **COV 002:**Phase II/III study in UK. Two dosage groups:
    - LD/SD: prime **$2{,}2\times10^{10}$** vp; boost **5×10^{10}** vp at **28 days**
    - SD/SD: prime **5×10^{10}** vp; boost **5×10^{10}** vp at **28 days**
  - **COV 003:**Phase III study in Brazil. Dosage:
    - SD/SD: prime/boost **$3{\cdot}5–6{\cdot}5\times10^{10}$** vp up to **12 weeks** apart (target 4 weeks)
- **Inclusion criteria:** healthy adults aged of 18y or more.
  - **COV 002:** healthy adults
  - **COV 003:** healthy and stable pre-existing health conditions individuals
- **Main outcome**: virologically confirmed, symptomatic COVID-19 (positive swab combined with at least one qualifying symptom)
- The interim **efficacy** is assessed by **combining data from COV002 and COV003**

	COV002 (UK; LD/SD; N=2741)		COV002 (UK; SD/SD; N=4807)		COV003 (Brazil; all SD/SD; N=4088)	
	ChAdOx1 nCoV-19 (n=1367)	MenACWY (n=1374)	ChAdOx1 nCoV-19 (n=2377)	MenACWY (n=2430)	ChAdOx1 nCoV-19 (n=2063)	MenACWY plus saline (n=2025)
Age, years						
18–55	1367 (100·0%)	1374 (100·0%)	1879 (79·0%)	1922 (79·1%)	1843 (89·3%)	1833 (90·5%)
56–69	0	0	285 (12·0%)	293 (12·1%)	209 (10·1%)	187 (9·2%)
≥70	0	0	213 (9·0%)	215 (8·8%)	11 (0·5%)	5 (0·2%)
Sex						
Female	886 (64·8%)	927 (67·5%)	1378 (58·0%)	1437 (59·1%)	1261 (61·1%)	1156 (57·1%)
Male	481 (35·2%)	447 (32·5%)	999 (42·0%)	993 (40·9%)	802 (38·9%)	869 (42·9%)
BMI, kg/m²	25·2 (22·8–28·7)	25·3 (22·7–28·8)	25·4 (22·9–28·7)	25·5 (22·9–29·1)	25·6 (22·8–29·1)	25·6 (23·1–29·0)
Ethnicity						
White	1257 (92·0%)	1278 (93·0%)	2153 (90·6%)	2214 (91·1%)	1357 (65·8%)	1366 (67·5%)
Black	6 (0·4%)	2 (0·1%)	17 (0·7%)	14 (0·6%)	230 (11·1%)	210 (10·4%)
Asian	76 (5·6%)	59 (4·3%)	137 (5·8%)	138 (5·7%)	54 (2·6%)	53 (2·6%)
Mixed	19 (1·4%)	22 (1·6%)	48 (2·0%)	42 (1·7%)	410 (19·9%)	386 (19·1%)
Other	9 (0·7%)	13 (0·9%)	22 (0·9%)	22 (0·9%)	12 (0·6%)	10 (0·5%)
Health and social care setting workers	1236 (90·4%)	1253 (91·2%)	1441 (60·6%)	1513 (62·3%)	1833 (88·9%)	1775 (87·7%)
Comorbidities						
Cardiovascular disease	104 (7·6%)	92 (6·7%)	264 (11·1%)	266 (10·9%)	271 (13·1%)	244 (12·0%)
Respiratory disease	158 (11·6%)	176 (12·8%)	285 (12·0%)	316 (13·0%)	215 (10·4%)	210 (10·4%)
Diabetes	18 (1·3%)	15 (1·1%)	58 (2·4%)	60 (2·5%)	59 (2·9%)	60 (3·0%)

Data are n (%) or median (IQR). The primary efficacy population (LD/SD and SD/SD) includes randomly assigned participants who were seronegative at baseline and received LD/SD or SD/SD or were in the corresponding control group, and remained on study more than 14 days after their second dose without having had a previous virologically confirmed severe acute respiratory syndrome coronavirus 2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. MenACWY=meningococcal group A, C, W, and Y conjugate vaccine. BMI=body-mass index.

Table 1: **Baseline characteristics of participants included in the primary efficacy population, by study and dosing strategy**

Limits:

Immunocompromised volunteers not included in the trial

Elderly participants are low represented

Heterogenicity between trials (concentration and schedule)

Adenoviral vector vaccine

AZD1222

EFFICACY AND SAFETY DATA

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)
Other non-primary symptomatic COVID-19 disease¶	18	7/5807 (0·1%)	10·3 (248 299)	11/5829 (0·2%)	16·3 (247 228)	36·4% (−63·8 to 75·3)‡
Any symptomatic COVID-19 disease	149	37/5807 (0·6%)	54·4 (248 299)	112/5829 (1·9%)	165·5 (247 228)	67·1% (52·3 to 77·3)
Asymptomatic or symptoms unknown (COV002)	69	29/3288 (0·9%)	69·8 (151 673)	40/3350 (1·2%)	96·0 (152 138)	27·3% (−17·2 to 54·9)
LD/SD recipients	24	7/1120 (0·6%)	41·4 (61 782)	17/1127 (1·5%)	100·6 (61 730)	58·9% (1·0 to 82·9)‡
SD/SD recipients	45	22/2168 (1·0%)	89·4 (89 891)	23/2223 (1·0%)	92·9 (90 408)	3·8% (−72·4 to 46·3)
Any NAAT-positive swab	221	68/5807 (1·2%)	100·0 (248 299)	153/5829 (2·6%)	226·0 (247 228)	55·7% (41·1 to 66·7)

Vaccine efficacy was calculated from the robust Poisson model. The primary efficacy population (LD/SD and SD/SD) includes randomly assigned participants who were seronegative at baseline and received LD/SD or SD/SD or were in a corresponding control group, and remained on study more than 14 days after their second dose without having had a previous virologically confirmed SARS-CoV-2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. NAAT=nucleic acid amplification test. *CIs are 95% unless indicated otherwise. †95·8% CI used for primary analysis. ‡Vaccine efficacy calculated from a reduced robust Poisson model that was not adjusted for age. All other models included an adjustment for age. §p value for interaction term comparing LD/SD with SD/SD is p=0·010. ¶Other non-primary symptomatic COVID-19 disease includes cases who have symptoms other than the five main symptoms that are required for inclusion in the primary analysis (eg, a participant who has diarrhoea and malaise but no fever, cough, shortness of breath, anosmia, or ageusia).

Table 2: Efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population

Primary Efficacy Analysis: 2weeks after second dose

- 98 cases in the ***SD/SD*** group (2 trials)
  - 27 within the ChAdOx1 nCov19 group
  - 71 within the Control group
  - ***Vaccine Efficacy in SD/SD: 62,1%***
- 33 cases in the ***LD/SD*** group
  - 3 within the ChAdOx1 nCov19 group
  - 33 within the Control group
  - ***Vaccine Efficacy in LD/SD: 90%***

TOTAL OF CASES: 131
30 in the ChAdOx1 nCov /101 in the Control
Vaccine efficacy: 70,4%

Limits:

Is aggregation of SD/LD and SD/SD data for efficacy analysis possible? (different doses, different vaccination schedules schedules)

Adenoviral vector vaccine

AZD1222

EFFICACY AND SAFETY DATA

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (95% CI)
		n/N (%)	Incidence per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence per 1000 person-years (person-days of follow-up)	
COV002 (UK)	90	28/3060 (0·9%)	35·4 (288 955)	62/3064 (2·0%)	78·5 (288 395)	55·0% (29·7 to 71·1)
COV003 (Brazil)	102	23/3247 (0·7%)	46·7 (179 743)	79/3233 (2·4%)	162·4 (177 693)	71·2% (54·2 to 81·9)
Primary symptomatic COVID-19*	192	51/6307 (0·8%)	39·7 (468 698)	141/6297 (2·2%)	110·5 (466 088)	64·1% (50·5 to 73·9)
Other non-primary symptomatic COVID-19†	21	12/6307 (0·2%)	9·4 (468 698)	9/6297 (0·1%)	7·1 (466 088)	−32·8% (−214·8 to 44·0)‡
Any symptomatic COVID-19	213	63/6307 (1·0%)	49·1 (468 698)	150/6297 (2·4%)	117·5 (466 088)	58·3% (44·0 to 68·9)
Asymptomatic or symptoms unknown (COV002)	71	34/2751 (1·2%)	46·8 (265 142)	37/2760 (1·3%)	51·0 (264 994)	7·8% (−46·7 to 42·1)
Any NAAT-positive swab	291	102/6307 (1·6%)	79·5 (468 698)	189/6297 (3·0%)	148·1 (466 088)	46·3% (31·8 to 57·8)

Vaccine efficacy was calculated from the robust Poisson model. The first-standard-dose efficacy population includes participants seronegative at baseline who received only standard dose vaccines or were in the corresponding control group, and remained on study 22 days after their first dose without having had a previous virologically confirmed SARS-CoV-2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. NAAT=nucleic acid amplification test. *NAAT-positive swab plus at least one of cough, shortness of breath, fever higher than 37·8°C, anosmia, or ageusia. †Other non-primary symptomatic COVID-19 disease includes cases that have symptoms other than the five main symptoms required for inclusion in the primary analysis (eg, a participant who has diarrhoea and malaise but no fever, cough, shortness of breath, anosmia, or ageusia). ‡Vaccine efficacy was calculated from a reduced robust Poisson model (excluding the age group category due to the full model failing to converge). Participants with a low-dose prime were excluded.

Table 4: **Efficacy against SARS-CoV-2 more than 21 days after the first standard dose in seronegative participants who received only standard doses**

Primary Efficacy Analysis at more than 21 days after second dose

TOTAL OF CASES: 192
(only SD/SD group; two trials, *different vaccination schedules*)
51 in the ChAdOx1 nCov / 141 in the Control
Vaccine efficacy: 64,1%

Limits: No evidence of an potential effect against viral shedding

From 21 days after the first dose: there were ten cases hospitalized for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death

	ChAdOx1 nCoV-19 (n=12 021)	MenACWY or saline control (n=11 724)
Hospitalisation (WHO clinical progression score ≥4)		
≤21 days after the first dose	2*	6
>21 days after the first dose and ≤14 days after the second dose	0	5
>14 days after the second dose	0	5
Severe COVID-19 (WHO clinical progression score ≥6)		
≤21 days after the first dose	0	0
>21 days after the first dose and ≤14 days after the second dose	0	1
>14 days after the second dose	0	1

The safety population includes all randomisation participants who received at least one dose of vaccine. Severe COVID-19 (WHO score ≥6) is a subset of hospitalisations (WHO score ≥4). Cases were eligible for inclusion in efficacy if the first symptom or first NAAT-positive result was on or before the data cutoff date (Nov 4, 2020). Two cases appear in this table that do not appear in the table for serious adverse events in appendix 1 (pp 15–20) as the adverse event reporting date was after the data cutoff date. MenACWY=meningococcal group A, C, W, and Y conjugate vaccine. NAAT=nucleic acid amplification test. *One case on the day of the first vaccination and one case 10 days after the first dose.

Table 5: **Hospitalisation for COVID-19 and severe COVID-19 in the safety population**

VACCINE (December 21th 2020)

1. What are the types of vaccines in clinical evaluation?

- 48 candidates vaccines are in an ongoing clinical evaluation
- Published Phase I/II data suggests that vaccine candidates on trial are immunogenic and mostly well tolerated in young adults. Data is emerging on elderly, globally keeping the trend described in young adults
- Induced titers of NAb are variable depending on the vaccine candidate. Comparison of Nab titers among candidates should not be made at this stage
- No data on ADE risk on humans nor virus clearance in upper respiratory tract after human vaccination has been published yet
- 12 vaccines are already in Phase III for efficacy evaluation
- Data on vaccine efficacy has first being announced by the means of press releases with results of >94% for BNT162b2, mRNA 1273 and Spoutnik V vaccines. A mean efficacy of 70% has been announced for AZD1222 vaccine.
- AZD1222 and BNT16b2 efficacy data has been recently published confirming these results but leaving caveats regarding sterilization capacity and long term protection

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