ChAdOx1 COVID-19 vaccine

5.1.2e

5.1.2e

An agency of the European Union

ChAdOX1 COVID-19 vaccine

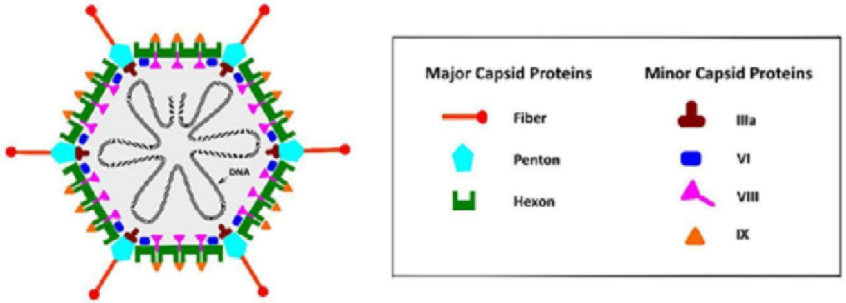
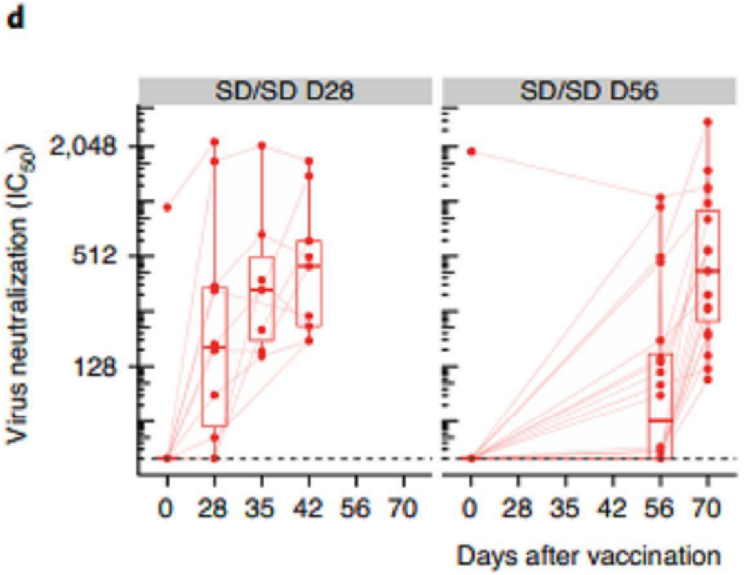
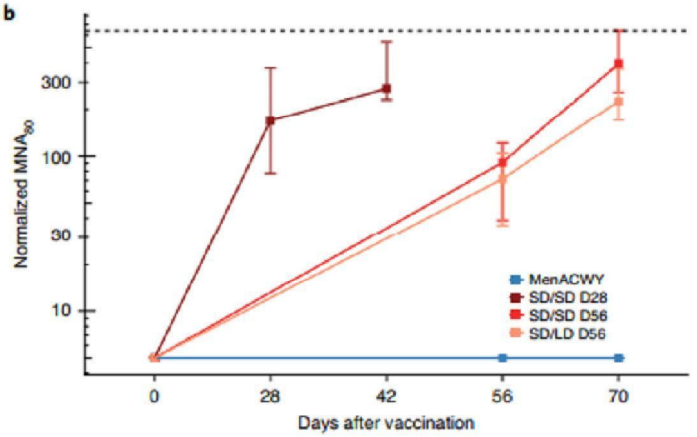


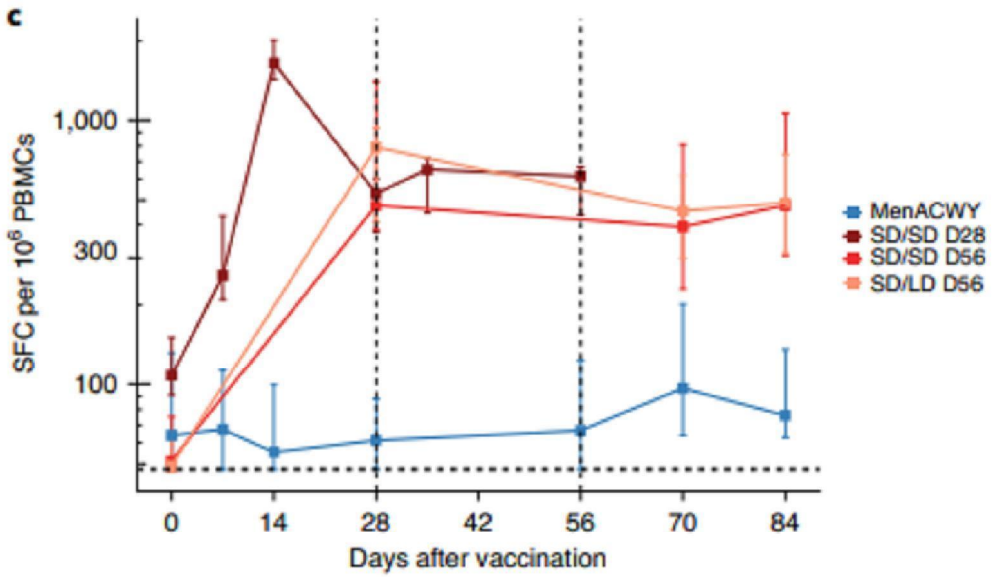
Figure 2 Structure of the nCOV-19 spike protein gene expression cassette (6214 bp)

ChadOX1 vaccine - Neutralising antibodies after homologous prime-boost





ChadOX1 vaccine – T cell responses after homologous prime-boost



ChAdOX1 vaccine - immunogencity

Subgroup	Timepoint	Statistic	SD/SD	
			Control	AZD1222
	Baseline	n /N[sub]	515 / 994	551 / 1104
		GMT	**20.36**	**20.10**
		(95% CI)	(20.00, 20.71)	(19.90, 20.31)
Age 18-64	Post Dose 1	n/N[sub]	522/994	500/1104
		GMT	**20.37**	**59.03**
		(95% CI)	(19.99, 20.76)	(52.87, 65.90)
	Post Dose 2	n/N[sub]	501/994	497/1104
		GMT	**21.49**	**173.71**
		(95% CI)	(20.67, 22.33)	(156.52, 192.78)
Age ≥65	Baseline	n /N[sub]	81 / 172	78 / 216
		GMT	**20.00**	**20.00**
		(95% CI)	(NE, NE)	(NE, NE)
	Post Dose 1	n/N[sub]	77/172	75/216
		GMT	**21.11**	**37.10**
		(95% CI)	(18.96, 23.49)	(29.26, 47.05)
	Post Dose 2	n/N[sub]	193/380	192/394
		GMT	**21.07**	**109.21**
		(95% CI)	(18.98, 23.38)	(77.58, 153.73)

Validated PSVNA50 age and interval

Visit Window	Statistic	SDSD AZD1222			
		< 6 wks	6-8 wks	9-11 wks	≥ 12 wks
		N=677	N=239	N=169	N=235
Baseline	N	246	131	100	152
	GMT	**20.000**	**20.434**	**20.000**	**20.000**
	95% CI for GMT	(NE, NE)	(19.58, 21.32)	(NE, NE)	(NE, NE)
	Min, Max	20.00, 20.00	20.00, 333.72	20.00, 20.00	20.00, 20.00
Day 28 post the first dose	N	243	109	91	132
	GMT	**50.565**	**53.040**	**59.106**	**65.783**
	95% CI for GMT	(43.44, 58.86)	(42.00, 66.97)	(45.64, 76.55)	(52.67, 82.17)
	Min, Max	20.00, 5440.37	20.00, 2061.91	20.00, 1961.43	20.00, 1634.36
Day 28 post the second dose	N	202	112	94	141
	GMT	**105.373**	**177.862**	**199.164**	**268.381**
	95% CI for GMT	(88.67, 125.22)	(145.13, 217.97)	(165.55, 239.60)	(221.71, 324.87)
	Min, Max	20.00, 6863.67	20.00, 2350.68	20.00, 2142.76	20.00, 7725.75

ChAdOx1 vaccine – pooled analysis for efficacy

Exposure to Study Intervention at the time of data cut-off (4nov2020)

Parameter		Any Dose for Safety Analysis Set		SD/SD + LD/SD Seronegative for Efficacy Analysis Set	
		AZD1222 (N = 12021)	**Control (N = 11724)**	**AZD1222 (N = 5807)**	**Control (N = 5829)**
Dose level [a], n (%)	LD/SD	1516 (12.6)	1472 (12.6)	1367 (23.5)	1374 (23.6)
	LD/LD	127 (1.1)	69 (0.6)	0	0
	SD/SD	6568 (54.6)	6472 (55.2)	4440 (76.5)	4455 (76.4)
	SD/LD	55 (0.5)	36 (0.3)	0	0
	LD	305 (2.5)	281 (2.4)	0	0
	SD	3450 (28.7)	3394 (28.9)	0	0
	Total	12021	11724	5807	5829

ChAdOX1 vaccine – pooled analysis for efficacy

Selected Population Characteristics for LD/SD and SD/SD Seronegative Analysis Sets by Country

Parameter	Statistic	LD/SD – UK		SD/SD – UK		SD/SD - Brazil	
		AZD1222 (N = 1367)	Control (N = 1374)	AZD1222 (N = 2377)	Control (N = 2430)	AZD1222 (N = 2063)	Control (N = 2025)
Age (years) at screening	Median	40.0	40.0	44.00	44.00	37.0	36.0
	≥ 65 years, n (%)	0	0	277 (11.7)	279 (11.5)	64 (3.1)	40 (2.0)
Race, n (%)	White	1261 (92.2)	1296 (94.3)	2189 (92.1)	2238 (92.1)	1357 (65.8)	1366 (67.5)
¥	Other	8 (0.6)	7 (0.5)	14 (0.6)	12 (0.5)	260 (12.6)	260 (12.8)
Comorbidity, n (%)	Yes	459 (33.6)	463 (33.7)	852 (35.8)	935 (38.5)	759 (36.8)	735 (36.3)
	No	908 (66.4)	909 (66.2)	1524 (64.1)	1492 (61.4)	1301 (63.1)	1282 (63.3)
Dose interval (weeks)	Median	12	12	10	10	5	5
Dose interval n(%)	< 6 weeks	0	0	453 (19.1)	454 (18.7)	1249 (60.5)	1244 (61.4)
	6-8 weeks	6 (0.4)	6 (0.4)	317 (13.3)	277 (11.4)	245 (11.9)	244 (12.0)
	9-11 weeks	388 (28.4)	378 (27.5)	653 (27.5)	718 (29.5)	403 (19.5)	392 (19.4)
	≥ 12 weeks	973 (71.2)	990 (72.1)	954 (40.1)	981 (40.4)	166 (8.0)	145 (7.2)

Table 2 COVID-19 Vaccine AstraZeneca efficacy against COVID-19[a]

Population	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (95% CI)[b]
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
Licensing regimen					
4 – 12 weeks (28 to 84 days)	5,258	64 (1.2)	5,210	154 (3.0)	59.5 (45.8, 69.7)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval;

[a] Efficacy endpoint was based on confirmed COVID-19 cases in subjects aged 18 years and over who were seronegative at baseline, who had received two doses and were on-study ≥15 days post second dose.

[b] CI not adjusted for multiplicity.

Vaccine efficacy was 62.6% (95% CI: 50.9; 71.5) in participants receiving two recommended doses with any dose interval (ranging from 3 to 23 weeks), in a pre-specified analysis.

ChAdOX1 vaccine – pooled analysis for efficacy – efficacy per interval

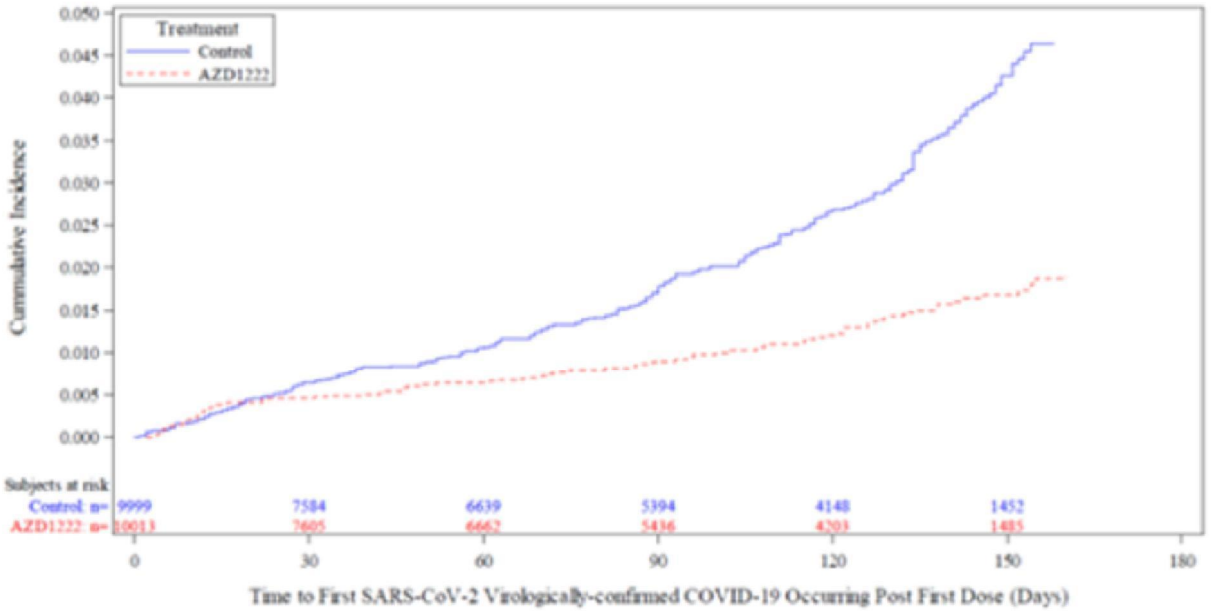
Vaccine Efficacy for Incidence of First SARSCoV2 Virologically Confirmed Symptomatic COVID19 Occurring ≥ 15 Days Post Second Dose by Dose Interval (SDSD Seronegative for Efficacy Analysis Set): 4–8 Weeks, 9–12 Weeks, > 12 Weeks, and 4-12 Weeks (Data cut-off: 07 December 2020)

Study Dose interval	Participants with events, n (%) AZD1222 n / N (%)	 Control n / N (%)	VE (%)	95% CI (%)
COV002 (UK)				
4–8 weeks	11 /1228 (0.90)	20 / 1180 (1.69)	49.37	-5.49, 75.70
9–12 weeks	6 / 728 (0.82)	29 / 798 (3.63)	77.50	45.82, 90.66
> 12 weeks	6 / 708 (0.85)	27 / 744 (3.63)	77.02	44.28, 90.52
4-12 weeks	17 / 1956 (0.87)	49 / 1978 (2.48)	65.49	40.14, 80.11
Any interval	23 / 2692 (0.85)	77 / 2751 (2.80)	70.02	52.56, 81.18

Study Dose interval	Participants with events, n (%) AZD1222 n / N (%)	 Control n / N (%)	VE (%)	95% CI (%)
COV003 (Brazil)				
4–8 weeks	42 / 2981 (1.41)	95 / 2934 (3.24)	56.96	38.13, 70.05
9–12 weeks	5 / 321 (1.56)	10 / 298 (3.36)	54.33	-33.12, 84.33
> 12 weeks	2 / 99 (2.02)	6 / 84 (7.14)	72.80	-33.86, 94.47
4-12 weeks	47 / 3302 (1.42)	105 / 3232 (3.25)	56.75	39.03, 69.32
Any interval	49 /3414 (1.44)	112 / 3339 (3.35)	57.61	40.73, 69.68

ChAdOx1 vaccine – pooled analysis for efficacy – efficacy after first dose

Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Occurring Post First Dose (Any Dose for Efficacy Analysis Set, Any Serostatus)



ChAdOx1 vaccine – pooled analysis for efficacy – efficacy after first dose

Study Time Period	Participants with events, n (%) AZD1222 n / N (%)	Control n / N (%)	VE (%)	95% [a] or 97.5% [b] CI (%)
COV002 (UK)				
Post Dose 1	31 / 3217 (0.96)	64 / 3216 (1.99)	51.6	25.9, 68.5
Post Dose 1 – before Dose 2	11 / 3217 (0.34)	18 / 3216 (0.56)	39.4	-28.3, 71.3
Dose 1 + 21 days – Dose 2 [c]	5 / 3067 (0.16)	9 / 3068 (0.29)	44.1	-66.8, 81.3
COV003 (Brazil)				
Post Dose 1	61 / 4791 (1.27)	121 / 4797 (2.52)	50.0	31.9, 63.2
Post Dose 1 – before Dose 2	44 / 4791 (0.92)	78 / 4797 (1.63)	43.6	18.3, 61.0
Dose 1 + 21 days – Dose 2 [c]	7 / 3343 (0.21)	35 / 3324 (1.05)	80.2	55.3, 91.2
Pooled (COV002 + COV003)				
Post Dose 1	92 / 8008 (1.15)	185 / 8013 (2.31)	50.5	36.5, 61.5
Post Dose 1 – before Dose 2	55 / 8008 (0.69)	96 / 8013 (1.20)	42.8	20.3, 59.0
Dose 1 + 21 days – Dose 2 [c]	12 / 6410 (0.19)	44 / 6392 (0.69)	73.0	48.9, 85.8

a) VE of AZD1222 versus control, the 95% CI, and p-value were estimated based on Poisson regression with robust variance including the term of treatment, as well as the log of the follow-up time as an offset. VE was defined as 1 - (incidence of infection from the AZD1222 arm / incidence of infection from the control arm) expressed as a percentage, where the risk ratio was derived from the Poisson regression model with robust variance. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.

b) The maximum likelihood estimate of VE of AZD1222 versus control, the exact 97.5% one-sided CI and p-value were estimated based on stratified Poisson regression with Exact Conditional Method including treatment as factor, study code, and age group at screening (18-55, 56-69, and ≥ 70 years) as strata factors, as well as the log of total number of participants for each combination of treatment and strata. VE was defined as 1 - (incidence of infection from the AZD1222 arm / incidence of infection from the control arm) expressed as a percentage, where the risk ratio was derived from stratified Poisson regression with Exact Conditional Method. The 97.5% one-sided CI for the VE was obtained by taking 1 minus the 97.5% one-sided CI of the risk ratio derived from the model.

c) Censored at 12 weeks post Dose 1.

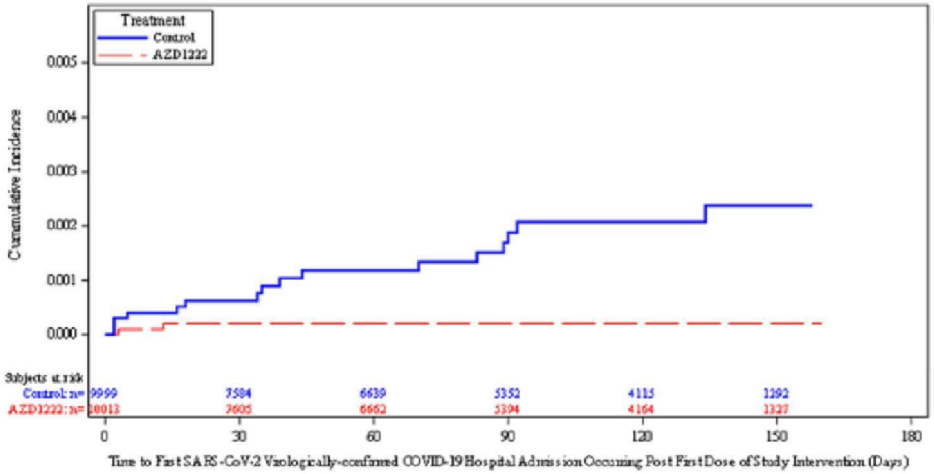
Data cut-off date: 04 NOV 2020.

ChAdOx1 vaccine – severe disease

SmPC

there were 0 (0.0%; N=5,258) cases of COVID-19 hospitalisation in participants who received two doses of COVID-19 Vaccine AstraZeneca (≥15 days post dose 2) as compared to 8 (0.2%; N=5,210) for control, including one severe case (WHO Severity grading ≥6), reported for control. In all participants who received at least one dose, as from 22 days post dose 1, there were 0 (0.0%, N=8,032) cases of COVID-19 hospitalisation in participants who received COVID-19 Vaccine AstraZeneca, as compared to 14 (0.2%, N=8,026), including one fatality, reported for control.

Cumulative Incidence Plot for Time to First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Hospital Admission Occurring Post First Dose (Any Dose for Efficacy Analysis Set, Any Serostatus)



The time to first SARS-CoV-2 virologically confirmed COVID-19 occurring post first dose of study intervention, in days, has been calculated as follows: Date of SARS-CoV-2 virologically confirmed test – (date of first dose of study intervention + 1. For censored participants, the censoring time is from date of first dose of study intervention to last observed time during the analysis period.

The observation period for the endpoint was post first dose up to 1 year in study.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ChAdOx1 vaccine – prevention of asymptomatic infection

Table 4 **Vaccine Efficacy for Incidence of First Asymptomatic SARS-CoV-2 Infection Occurring ≥ 15 Days Post Second Dose of Study Intervention Using Poisson Regression with Robust Variance (COV002 Only), DCO2 (07 December 2020)**

Analysis set Event	Participants with events AZD1222 n / N (%)	 Control n / N (%)	VE (%)	95% CI (%)	P-value
SDSD seronegative for efficacy analysis set, 4 to 12 weeks dosing interval (COV002 only)					
Asymptomatic SARS-CoV-2 Infection	13 / 1956 (0.66)	14 / 1978 (0.71)	7.66	(-96.25, 56.55)	0.836

Asymptomatic infection was assessed in COV002 only.
Data cut-off: DCO2 (07 December 2020)
VE of AZD1222 versus control, the 95% CI and p value were estimated based on Poisson regression with robust variance including the term of treatment as well as the log of the follow-up time as an offset.
VE is defined as 1-(incidence from the AZD1222 arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from Poisson regression with robust variance.
The 95% CI for the VE is obtained by taking 1 minus the 95% CI of the risk ratio derived from the model. The observation period for the endpoint was 15 days post second dose up to 1 year in study.
Asymptomatic SARS-CoV-2 infections are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test.
The 4 to 12 weeks dosing interval range corresponds to > 28 days to < 84 days.

ChAdOx1 vaccine - safety

The most frequently reported solicited systemic AEs after any dose SD of AZD1222 were fatigue (62.3% vs 48.0% in subjects who received MenACWY) and headache (57.5% vs 42.4% in control); other frequently reported systemic solicited AEs were muscle pain (48.6%), and malaise (44.2%). Pyrexia was reported in 9.2% participants who received any dose of AZD1222 (vs 0.5% in subjects who received MenACWY).

Most of the systemic AEs following AZD1222 were mild or moderate and self-limiting with a mean duration of 2.8 days following the first dose and 2.7 days following the second dose. However, 9.3% of subjects experienced grade 3 systemic AEs, being malaise, chills and feverishness the most frequently grade 3 solicited systemic AE reported.

Only ≤0,1% participants reported a SAE considered treatment-related, 2 in the AZD1222 group (pyrexia and myelitis transverse) and 2 in the control group (autoimmune haemolytic anaemia and myelitis).

Other serious adverse events with a neuro-inflammatory aetiology have been observed in the safety database for which causality to the vaccine cannot be excluded at this stage: a single event of facial spasm and a case of multiple sclerosis.

three events with a potential neuro-inflammatory aetiology in ongoing studies which were not part of the submission for CMA: an event of Sensory neuropathy, an event of Chronic Inflammatory Demyelinating Polyradiculopathy, and a case of acute encephalopathy

Conclusions

- Immunogenicity shows both humoral and cellular response boosted after second dose – interval has some impact on booster response (trending better if later)
- Elderly showed similar levels of immune response, e.g. neutralising antibodies
- Efficacy around 60% after second dose shown in pooled analysis covering UK and Brazil studies and 4-12 weeks (approx 12000 subjects)
- 13% participants were aged 65 or older and 2.8% aged 75 or older; total of 2,068 (39.3%) participants had at least one pre-existing comorbidity (defined as a BMI ≥30 kg/m2, cardiovascular disorder, respiratory disease or diabetes). Median follow up time post-dose 2 was 78 days
- Efficacy is seen after first dose but not possible to quantify precisely up to 12 weeks.
- Efficacy against hospitalisation and severe disease seen after first dose
- No apparent effect on asymptomatic infection but data are limited
- Safety profile is acceptable with more reactogenicity in adults than in elderly