AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

COVID-19 Vaccine
Intervallo tra le dosi

04/03/2021

International strategies and recommendations for COVID-19 immunization program roll-out in the context of limited vaccine supply (I/II)

Organization	Strategy - Recommendation
Strategic Advisory Group of Experts on Immunization (SAGE, World Health Organization) https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1	• COVID-19 vaccines **should be given according to recommended intervals** unless exceptional circumstances of vaccine supply constraints and epidemiologic settings warrant a delay in the second dose.
CDC (United States) https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html	• The second dose of authorized COVID-19 mRNA vaccines **should be administered as close as possible to the recommended interval** within a grace period of < 4 days from the recommended date for the second dose to be considered valid.
FDA (United States) https://www.fda.gov/news-events/press-announcements/fda-statement-following-authorized-dosing-schedules-covid-19-vaccines	Changes to the authorized dosing or schedules of COVID-19 vaccines at this time is "premature and not rooted solidly in the available evidence. Without appropriate data supporting such changes…we run a significant risk of placing public health at risk."

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

COVID-19 Vaccine AstraZeneca è indicato per l'immunizzazione attiva nella prevenzione di COVID-19, malattia causata dal virus SARS-CoV-2, in soggetti di età pari o superiore a 18 anni.

L'uso di questo vaccino deve essere conforme alle raccomandazioni ufficiali.

4.2 Posologia e modo di somministrazione

Posologia

Soggetti di età pari o superiore a 18 anni
Il ciclo di vaccinazione con COVID-19 Vaccine AstraZeneca consiste in due dosi separate da 0,5 mL ciascuna. La seconda dose deve essere somministrata da 4 a 12 settimane (da 28 a 84 giorni) dopo la prima dose (vedere paragrafo 5.1).

Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials

Methods

- Data from three single-blind randomised controlled trials in the UK (**COV001/COV002**), Brazil (**COV003**), and one double-blind study in South Africa (**COV005**) are included in this exploratory analysis as all four trials now meet the required criteria for inclusion of having at least 5 primary outcome cases.

- The data cut-off date for cases to be included in the current report was **December 7, 2020**.

- 17.178 participants included in the efficacy analysis (8.597 ChAdOx1 nCoV-19 and 8.581 control participants): 8948 from UK, 6753 from Brazil and 1477 from South Africa

Objectivs

- To provide exploratory analyses of the impact on immunogenicity and efficacy of extending the interval between priming and booster doses.

- To show the immunogenicity and protection afforded by the first dose, before a booster dose has been offered

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Limitations

- **Studies were not designed to determine if vaccine efficacy differed by dose interval** and the presence of data of varying intervals arose due to the logistics of running large-scale clinical trials in a pandemic setting
- **Post-hoc exploratory analyses only** with potential for multiple sources of bias, and were not pre-specified.
- **Limited length of follow-up after the second dose** and follow-up tends to be longer in those who were boosted early and thus have shorter prime-boost intervals
- Participants who contribute to the analysis of single dose efficacy are a mixture of participants with events occurring prior to their boost dose, and participants who did not receive a boost dose. These two cohorts differ in some key characteristics.

Voysey M, et al. Lancet Preprint

Overview of ChAdOx1 nCoV-19 clinical trials

Element	COV001	COV002	COV003	COV005
Identifier	NCT04324606; EudraCT 2020-001072-15	NCT04400838; EudraCT 2020-001228-32	ISRCTN89951424	NCT04444674
Region	United Kingdom	United Kingdom	Brazil	South Africa
Phase	I/II	II/III	III	I/II
Period	23Apr2020-ongoing	29 May2020-ongoing	Jun2020-ongoing	Jun2020-ongoing
Design	FIH, participant blind, randomised, controlled	Participant blind, randomised, controlled	Participant blind, randomised, controlled	Double blind, randomised, placebo-controlled, adaptive
Study population	Healthy adults aged 18-55 years	Healthy adults aged ≥18 years Priority given to health professionals and adults with high potential for exposure to SARS-CoV-2 Safety and immunogenicity substudies: Healthy children aged 5 to 12 years, inclusive HIV+ adults aged 18 - 55 years	Health professionals and adults with high potential for exposure to SARS-CoV-2, aged ≥18 years	Adults aged 18-65 years, living with and without HIV
Primary efficacy endpoints	Virologically-confirmed symptomatic cases of COVID-19	Virologically-confirmed symptomatic cases of COVID-19	COVID-19 virologically-confirmed symptomatic cases	Virologically-confirmed COVID-19 cases occurring in participants that were COVID-19 naïve at the time of randomization and who received at least two doses of ChAdOx1 nCoV-19 or placebo. Events included if they occurred ≥ 14 days after the booster dose.
Planned total enrolment	1090	12390	10000	2070
Control	MenACWY	MenACWY	MenACWY	Saline
Number of doses	One or two (based on study group)	One or two (based on study group)	Two	Two
AZD1222 dose	Standard and Low	Standard and Low	Standard and standard	Standard and Low
Prophylactic treatment	Paracetamol for a portion of participants	Paracetamol for a portion of participants	Paracetamol systematically	As clinically needed

Efficacy of ChAdOx1 nCoV-19 more than 14 days after a second dose

	Total cases	ChAdOx1 nCoV-19	Control	Vaccine efficacy (95% CI)*
Prespecified analyses				
Cases more than 14 days after second dose				
Primary symptomatic COVID-19	332	84/8597 (1·0%)	248/8581 (2·9%)	66·7% (57·4 to 74·0)
Two standard doses	271	74/7201 (1·0%)	197/7179 (2·7%)	63·1% (51·8 to 71·7)†
Low dose plus standard dose	61	10/1396 (0·7%)	51/1402 (3·6%)	80·7% (62·1 to 90·2)
Asymptomatic or unknown infection (COV002 UK only)	130	57/4071 (1·4%)	73/4136 (1·8%)	22·2% (–9·9 to 45·0)
Two standard doses	83	41/2692 (1·5%)	42/2751 (1·5%)	2·0% (–50·7 to 36·2)
Low dose plus standard dose	47	16/1379 (1·2%)	31/1385 (2·2%)	49·3% (7·4 to 72·2)
Any NAAT positive	507	161/8597 (1·9%)	346/8581 (4·0%)	54·1% (44·7 to 61·9)
Two standard doses	390	132/7201 (1·8%)	258/7179 (3·6%)	49·5% (37·7 to 59·0)
Low dose plus standard dose	117	29/1396 (2·1%)	88/1402 (6·3%)	67·6% (50·8 to 78·7)

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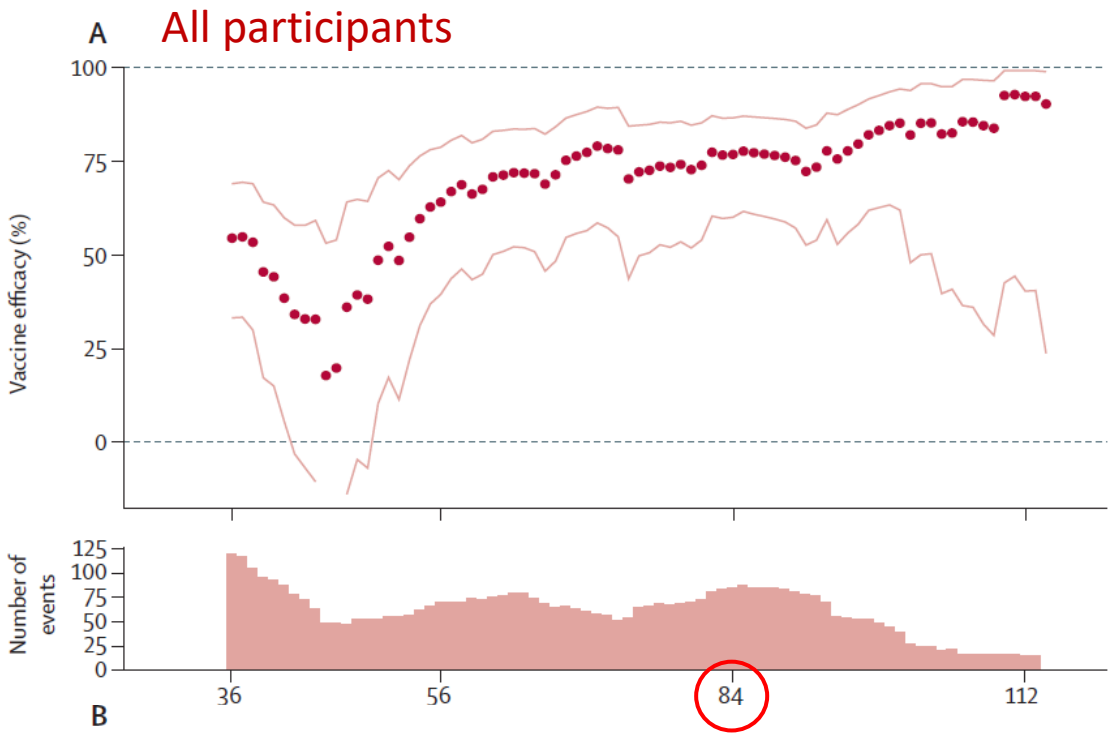
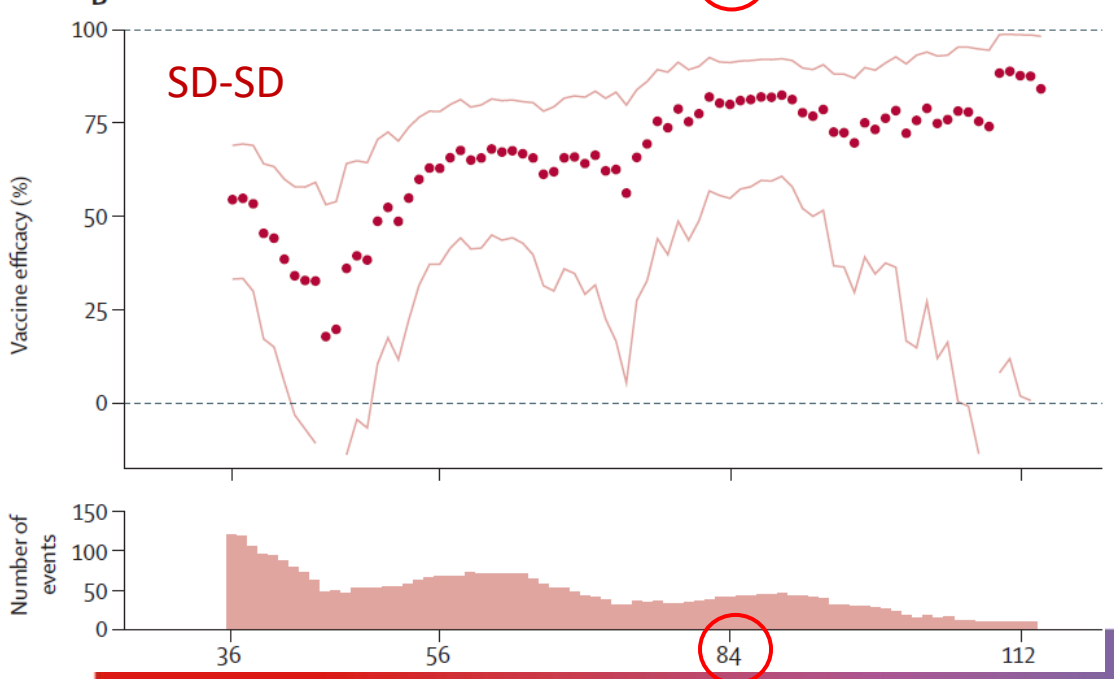
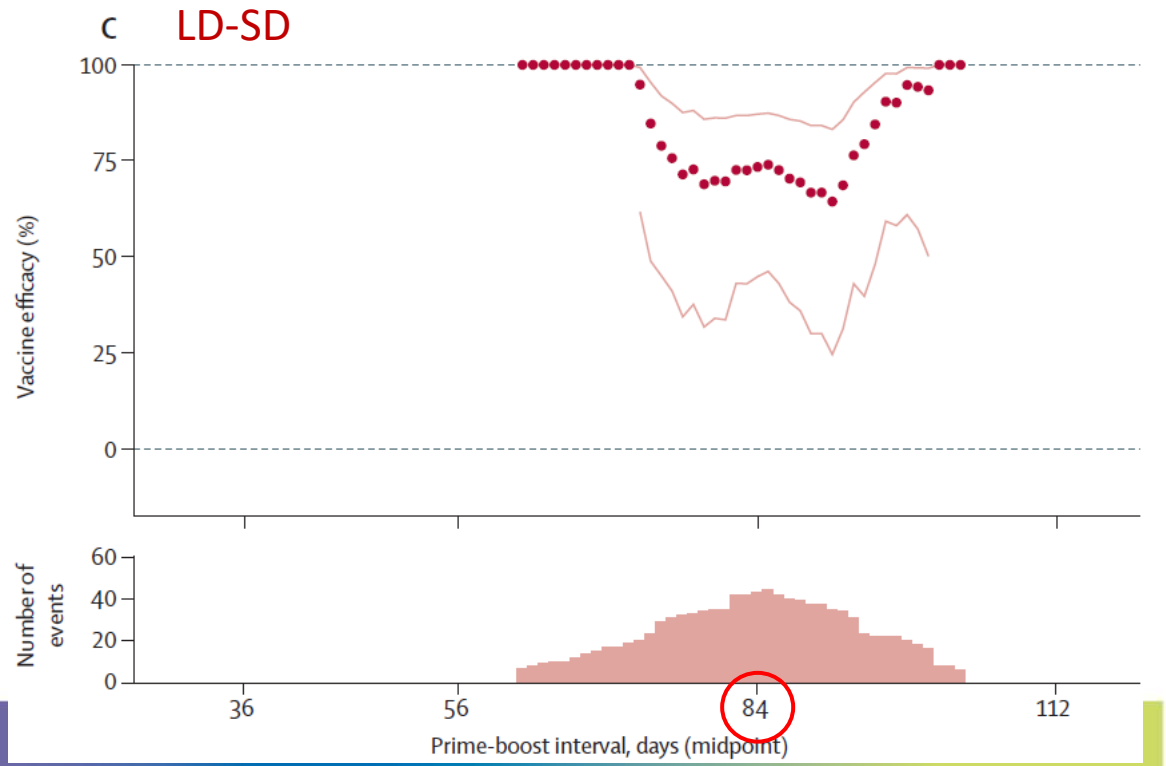
Exploratory analysis of vaccine efficacy against primary symptomatic COVID-19 more than 14 days after a booster dose, by prime-boost interval







Vaccine efficacy by dose interval

	Total cases	ChAdOx1 nCoV-19	Control	Vaccine efficacy (95% CI)*
Exploratory analyses by prime-boost interval				
Primary symptomatic COVID-19 cases more than 14 days after second dose				
Prime-boost interval (two standard doses)				
<6 weeks	111	35/3890 (0·9%)	76/3856 (2·0%)	55·1% (33·0 to 69·9)
6–8 weeks	64	20/1112 (1·8%)	44/1009 (4·4%)	59·9% (32·0 to 76·4)
9–11 weeks	43	11/906 (1·2%)	32/958 (3·3%)	63·7% (28·0 to 81·7)
≥12 weeks	53	8/1293 (0·6%)	45/1356 (3·3%)	81·3% (60·3 to 91·2)
Prime-boost interval (two standard doses or low dose plus standard dose)				
<6 weeks	111	35/3905 (0·9%)	76/3871 (2·0%)	55·1% (33·0 to 69·9)
6–8 weeks	64	20/1124 (1·8%)	44/1023 (4·3%)	59·7% (31·7 to 76·3)
9–11 weeks	66	14/1530 (0·9%)	52/1594 (3·3%)	72·2% (50·0 to 84·6)
≥12 weeks	91	15/2038 (0·7%)	76/2093 (3·6%)	80·0% (65·2 to 88·5)

A longer interval provides better protection post-boost

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Immunogenicity results by dose interval

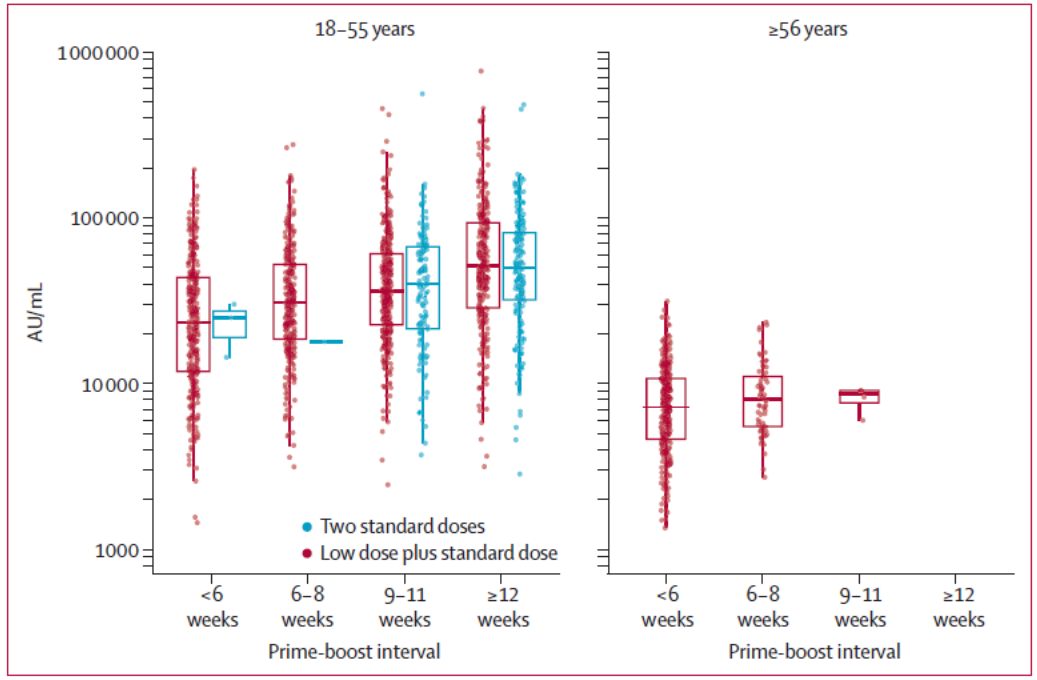

Figure 3: Anti-SARS-CoV-2 spike IgG responses by multiplex immunoassay at 28 days after the second dose in participants receiving two standard doses or low dose plus standard dose, by prime-boost interval (n=3337)

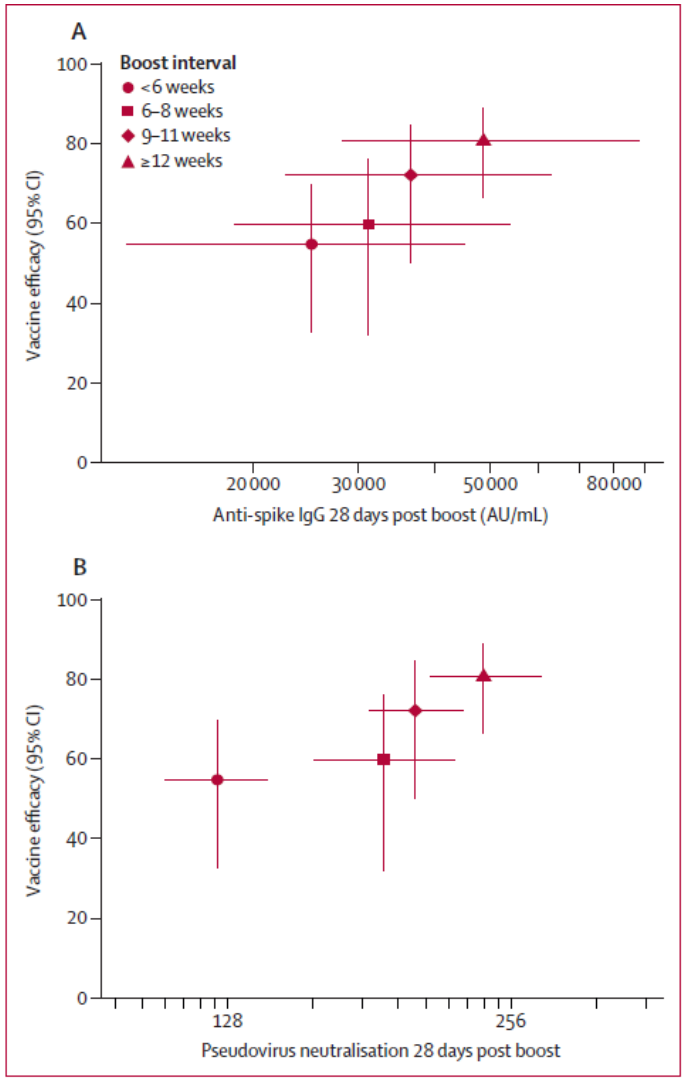

Figure 4: Relationship between binding and neutralising antibody 28 days after second dose, and vaccine efficacy against primary symptomatic COVID-19

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Vaccine efficacy and persistence of anti-SARS-CoV-2 spike IgG after single dose

Exploratory analysis of vaccine efficacy over time from 22 days after a single standard dose ChAdOx1 nCoV-19 (A)

Exploratory analysis of persistence of anti-SARS-CoV-2 spike IgG by standardised ELISA antibody after a single dose of either standard-dose or low-dose vaccine (B)

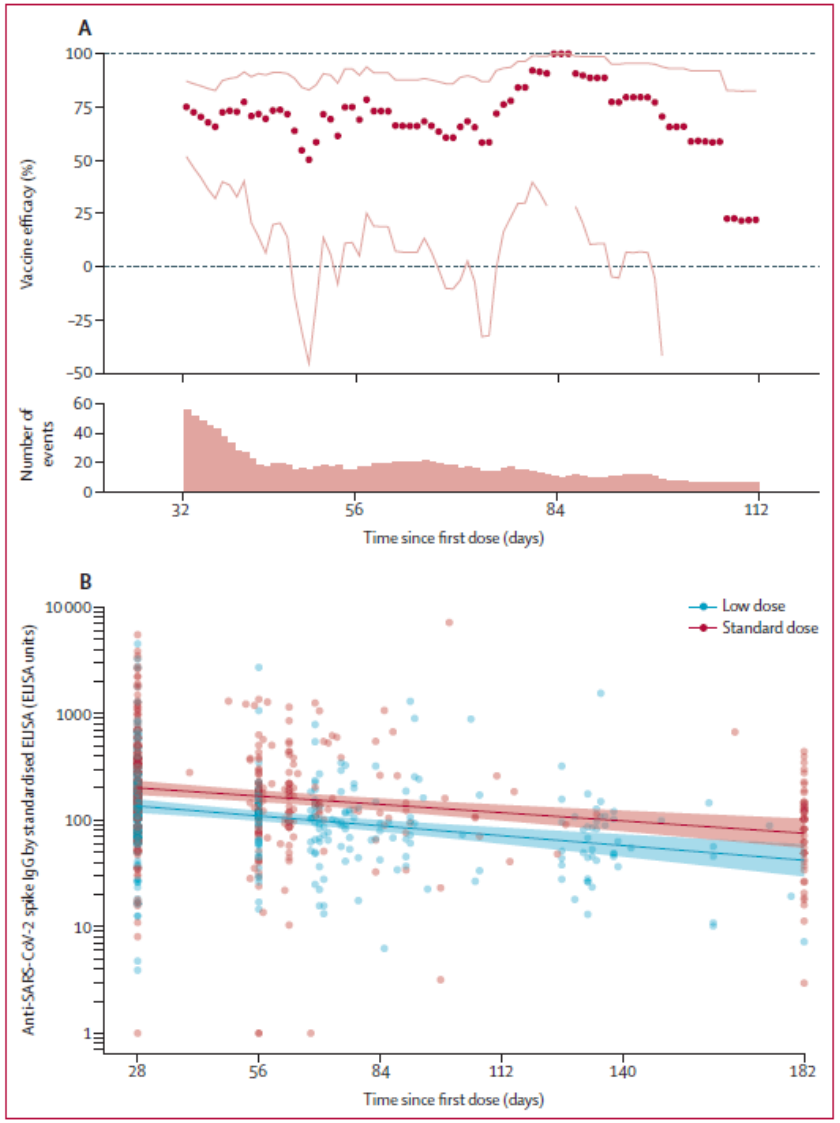

Figure 2: Exploratory analysis of vaccine efficacy over time from 22 days after a single standard dose ChAdOx1 nCoV-19 (A) and persistence of anti-SARS-CoV-2 spike IgG by standardised ELISA antibody after a single dose of either standard-dose or low-dose vaccine (B)

	Total cases	ChAdOx1 nCoV-19	Control	Vaccine efficacy (95% CI)
Primary symptomatic COVID-19 cases more than 21 days after a single standard dose				
Time since first standard dose				
22 to 30 days	37	7/9257 (0·1%)	30/9237 (0·3%)	76·7% (47·0 to 89·8)
31 to 60 days	28	6/7147 (0·1%)	22/7110 (0·3%)	72·8% (32·9 to 89·0)
61 to 90 days	23	4/2885 (0·1%)	19/2974 (0·6%)	78·3% (36·4 to 92·6)
91 to 120 days	10	4/1369 (0·3%)	6/1404 (0·4%)	31·6% (−141·8 to 80·7)
22 to 90 days	88	17/9257 (0·2%)	71/9237 (0·8%)	76·0% (59·3 to 85·9)
Asymptomatic COVID-19 infections more than 21 days after a single standard dose (UK COV002 only)				
Time since first dose				
22 to 30 days	6	3/3236 (0·1%)	3/3239 (0·1%)	−0·1% (−395·4 to 79·8)
31 to 60 days	6	4/2703 (0·1%)	2/2687 (0·1%)	−100·1% (−992·2 to 63·3)
61 to 90 days	1	0/1843 (0·0%)	1/1891 (0·1%)	..
91 to 120 days	4	1/780 (0·1%)	3/765 (0·4%)	67·6% (−210·8 to 96·6)
22 to 90 days	13	7/3236 (0·2%)	6/3239 (0·2%)	−17·2% (−248·6 to 60·6)
Any NAAT-positive COVID-19 infections more than 21 days after a single standard dose				
Time since first dose				
22 to 30 days	51	14/9257 (0·2%)	37/9237 (0·4%)	62·3% (30·2 to 79·6)
31 to 60 days	46	14/7147 (0·2%)	32/7110 (0·5%)	56·3% (18·2 to 76·7)
61 to 90 days	24	4/2885 (0·1%)	20/2974 (0·7%)	79·4% (39·8 to 93·0)
91 to 120 days	17	7/1369 (0·5%)	10/1404 (0·7%)	28·2% (−88·1 to 72·6)
22 to 90 days	121	32/9257 (0·3%)	89/9237 (1·0%)	63·9% (46·0 to 75·9)

Efficacy of ChAdOx1 nCoV-19 more than 21 days after a single dose

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Conclusioni

L'analisi esplorativa sulla durata dell'intervallo tra le due dosi, pur con tutte le limitazioni metodologiche, mostra:

- Un intervallo maggiore tra le due dosi evoca, dopo la somministrazione della seconda dose, una risposta anticorpale più accentuata e una protezione vaccinale più efficace (≥12 settimane 81,3% *vs* <6 settimane 55,1%)
- Dopo la prima dose il titolo degli anticorpi neutralizzanti sembra declinare solo modestamente con un'efficacia vaccinale stabilmente >73%. Complessivamente per il periodo dal giorno 22-90 risulta del 76% (IC95%: 59-86%)
- In generale, la risposta immunologica (umorale e T-cellulare) è evocata principalmente dalla prima dose, ma la dose booster ne rafforza l'entità e verosimilmente la durata
- Nell'ambito dell'intervallo tra le dosi approvato (4-12 settimane), l'intervallo di 9-11 settimane mostra una efficacia vaccinale del 63,7% (IC95%: 28,0-81,7%) e si associa ad una protezione dopo la prima dose pari al 76%
- Un intervallo >12 settimane, sebbene apparentemente associato ad una efficacia vaccinale maggiore, non garantisce una protezione adeguata dopo la prima dose e i risultati sono gravati da limiti interpretativi (*bias:* LD/SD, follow-up, etc). In ogni caso **tale tempistica non rientra nell'intervallo approvato per il farmaco**

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AIFA raccomanda che la seconda dose del vaccino Astrazeneca dovrebbe essere somministrata idealmente **nel corso della 12° settimana** (da 78 a 84 giorni) e comunque ad una distanza di **almeno 10 settimane** (63 giorni) dalla prima dose