Poster 1953

Immune responses, viral shedding, and COVID-19 symptom burden from breakthrough SARS-CoV-2 infection in a 2:1 randomized, double-blind, placebo-controlled Phase 3 study of AZD1222 (ChAdOx1 nCoV-19) vaccination

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Introduction

- AZD1222 primary series vaccination was 74% effective in preventing symptomatic COVID-19 in a 2:1 randomized, placebo-controlled, Phase 3 study in adult participants from US, Chile, and Peru (NCT04516746)[1]
- Primary series AZD1222 vaccination induces systemic anti-SARS-CoV-2 spike glycoprotein (spike), receptor-binding domain, and neutralizing antibody responses alongside polyfunctional T-helper 1 cell-dominated CD4+ and CD8+ cellular immune responses characterized by diverse T-cell receptors with broad coverage of spike epitopes[2–4]
- Breakthrough SARS-CoV-2 infection in COVID-19 vaccinees typically produces milder disease than infection in unvaccinated individuals[5,6]

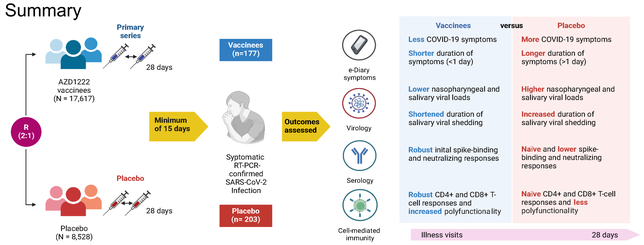
Objective

- We examined COVID-19 symptomology and immuno-virologic outcomes to symptomatic reverse transcription polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection in AZD1222 vaccinees and placebo recipients to explore disease attenuation and characterize crucial aspects of effective SARS-CoV-2 immunity (Data cut-off: July 30th 2021)[7]

Conclusions

- AZD1222 vaccinees had an overall lower incidence and shorter duration of COVID-19 symptoms, and displayed trends towards improved initial immuno-virological outcomes to symptomatic SARS-CoV-2 infection compared with placebo recipients
- These observations suggest that early high-quality robust recall responses to AZD1222 vaccination following symptom onset attenuate COVID-19 disease severity

Graphical Summary



Vaccines	versus	Placebo
Less COVID-19 symptoms		More COVID-19 symptoms
Shorter duration of symptoms (<1 day)		Longer duration of symptoms (>1 day)
Lower nasopharyngeal and salivary viral loads		Higher nasopharyngeal and salivary viral loads
Shortened duration of salivary viral shedding		Increased duration of salivary viral shedding
Robust inital spike-binding and neutralizing responses		Naive and lower spike-binding and neutralizing responses
Robust CD4+ and CD8+ T-cell responses and increased polyfunctionality		Naive CD4+ and CD8+ T-cell responses and less polyfunctionality

Illness visits 28 days

Supplementary Content

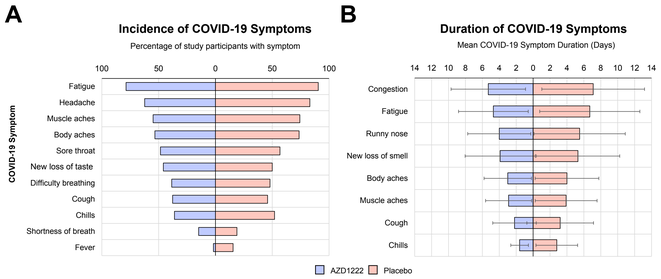
Mobile poster

Supplemental materials

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials. Alternatively, please click on the following link: https://bit.ly/3qVTugR

Results and interpretation

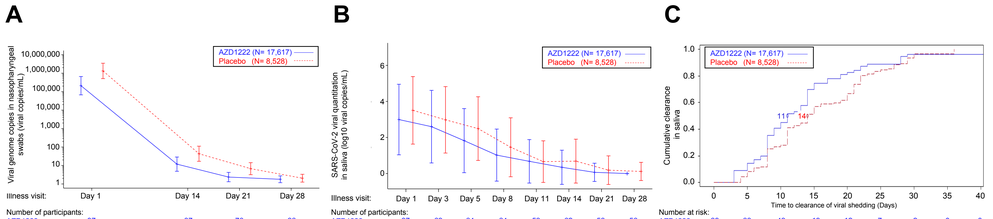
Figure 1: Participant illness e-Diary responses illustrate COVID-19 disease attenuation in vaccinees



(A) Symptoms with differences of ≤1.5% between arms were excluded from this plot. (B) Symptoms with differences in mean durations of ≤1 day between arms are excluded from this plot. Error bars depict standard deviation.

- Participant illness e-Diary responses illustrated that vaccinees had an overall lower incidence of COVID-19 symptoms **(Fig 1A)** and a trend towards shortened symptom duration **(Fig 1B)** compared with placebo recipients

Figure 2: Virologic outcomes to breakthrough infection are attenuated in vaccinees compared to unvaccinated



Number of participants:

	Day 1	Day 14	Day 21	Day 28
AZD1222:	97	87	76	86
Placebo:	104	82	78	82

Number of participants:

	Day 1	Day 3	Day 5	Day 8	Day 11	Day 14	Day 21	Day 28
AZD1222:	87	63	64	64	58	62	58	56
Placebo:	108	85	86	85	76	89	77	72

Number at risk:

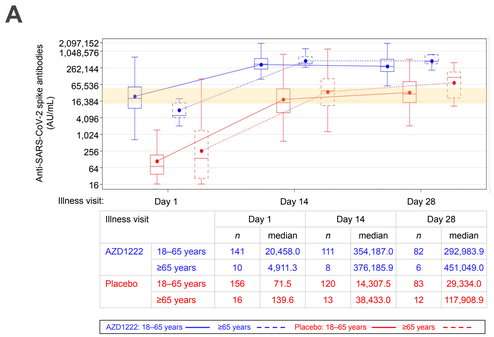
	0	5	10	15	20	25	30	35	40
AZD1222:	89	68	43	19	12	7	2	0	0
Placebo:	133	114	79	52	39	17	2	1	0

(A) Determined by quantitative(q) RT-PCR. Line plot with geometric means and 95% CI. Viral genome copies were imputed to 1 when the SARS-CoV-2 nasopharyngeal swab qualitative result was not detected. (B) SARS-CoV-2 quantitation (log10 viral copies/mL) in participant saliva over time. Line plot with mean ± SD. Not detected values of viral quantitation are treated as 0. (C) The median time to clearance of viral shedding for each group is marked by a circle. CI, confidence interval; qRT-PCR, quantitative reverse transcription polymerase chain reaction; SD, standard deviation.

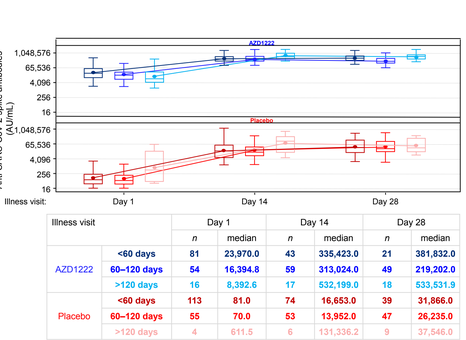
- Analyses of SARS-CoV-2 viral loads in nasopharyngeal swabs and saliva samples revealed a trend towards lower geometric mean titers (GMTs) and a shortened median duration of viral shedding in saliva samples in vaccinees compared with placebo recipients at all timepoints **(Fig 2A–C).**
- Among cases with sequence data at the first illness visit (ILL-D1), median overall viral loads in nasopharyngeal swabs and saliva samples were lower in vaccinees versus placebo recipients with consistent trends towards lowered viral loads observed for the ancestral virus and the Alpha variant **(Fig S1A–B)**

Figure 3: The kinetics and magnitude of anti-SARS-CoV-2 antibody responses are impacted by age and vaccination status

- Median ILL-D1 spike-binding **(Fig 3A)** and neutralizing **(Fig S2)** antibody titers were comparable to peak levels after second dose primary series and further increased throughout the illness visit period, with higher median titers in vaccinees than in placebo recipients at all time points
- At symptom onset (ILL-D1), median spike-binding titers differed with increased time since second dose of primary series vaccination **(Fig 3B)** – however, the overall magnitude of antibody response was similar across all subgroup intervals by the end of the illness period
- Nucleocapsid-specific antibodies displayed slower kinetics and lower magnitudes than anti-spike antibodies **(Fig S3)**



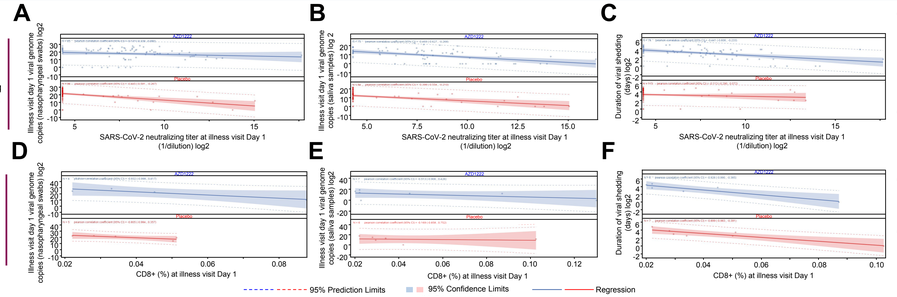
Illness visit		Day 1		Day 14		Day 28	
		n	median	*n*	median	*n*	median
AZD1222	18–65 years	141	20,458.0	111	354,187.0	82	292,983.9
	≥65 years	10	4,911.3	8	376,185.9	6	451,049.0
Placebo	18–65 years	156	71.5	120	14,307.5	83	29,334.0
	≥65 years	16	139.6	13	38,433.0	12	117,908.9



Illness visit		Day 1		Day 14		Day 28	
		n	median	*n*	median	*n*	median
AZD1222	<60 days	81	23,970.0	43	335,423.0	21	381,832.0
	60–120 days	54	16,394.8	59	313,024.0	49	219,202.0
	>120 days	16	8,392.6	17	532,199.0	18	533,531.9
Placebo	<60 days	113	81.0	74	16,653.0	39	31,866.0
	60–120 days	55	70.0	53	13,952.0	47	26,235.0
	>120 days	4	611.5	6	131,336.2	9	37,546.0

(A) Yellow shading denotes peak titers observed following second dose of AZD1222 primary series[1]
AU/mL, arbitrary units per milliliter.

Figure 4: Early neutralizing antibody and CD8+ T cell responses inversely correlate with virologic outcomes

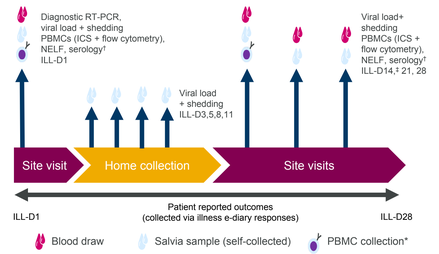


- ILL-D1 antibody responses inversely correlated with virologic outcomes with moderate correlations observed for neutralizing antibodies **(Fig 4A–C)** and low-moderate correlations observed for spike-binding antibodies **(Fig S5A–C)**
- Vaccinees had higher frequencies of spike-specific CD4+ and CD8+ T cells and a greater proportion of overall responders than placebo recipients at ILL-D1 **(Fig S4A–B)**
- Vaccinee ILL-D1 CD4+ and CD8+ T cells possessed a higher proportion of polyfunctional markers than placebo **(Fig S4C–D)**
- ILL-D1 T-cell responses inversely correlated with virologic endpoints with strong correlations observed for CD8+ T-cell responses **(Fig 4D–F)** and moderate-strong correlations observed for CD4+ T cells **(Fig S5D–F)**

Methods

- The analyses of SARS-CoV-2 infection in this poster are restricted to baseline-seronegative participants who remained on the study for ≥15 days after their second dose of primary series AZD1222 or placebo without infection **(Table S1)**
- Participants who experienced protocol-defined COVID-19 symptoms were requested to contact their local site for confirmatory RT-PCR testing and to initiate a 28-day series of illness visits **(Fig 5)**

Figure 5. Schedule of Illness Visits



*At sites with cell sorting capacity only, †Neutralizing antibodies were assessed using a SARS-CoV-2 pseudovirus assay, ‡PBMCs collected at ILL-D14 only.

ICS, intracellular cytokine staining; ILL-Dx, illness visit Day X; NELF, nasal epithelium lining fluid; PBMC, peripheral blood mononuclear cells.

Statistical methods

- In the box and whisker plots **(Fig 3, S1–4)** the bottom and top edges of the box indicate the first and third quartiles, the difference is the interquartile range (IQR), the line inside the box is the median, and the marker inside the box is the geometric mean. The whiskers that extend from the box indicate the minimum and maximum after removing outliers (i.e., datapoints >1.5 x IQR from the box)

Limitations

Data were obtained prior to and during a global SARS-CoV-2 Alpha variant wave and consequently there were no cases of Omicron within this dataset. However, we **(Fig S6A–B)** and others have observed CD4+ and CD8+ T cell responses to Omicron peptide stimulation suggesting minimal T-cell escape from variants of concern including Omicron BA.1[8]

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