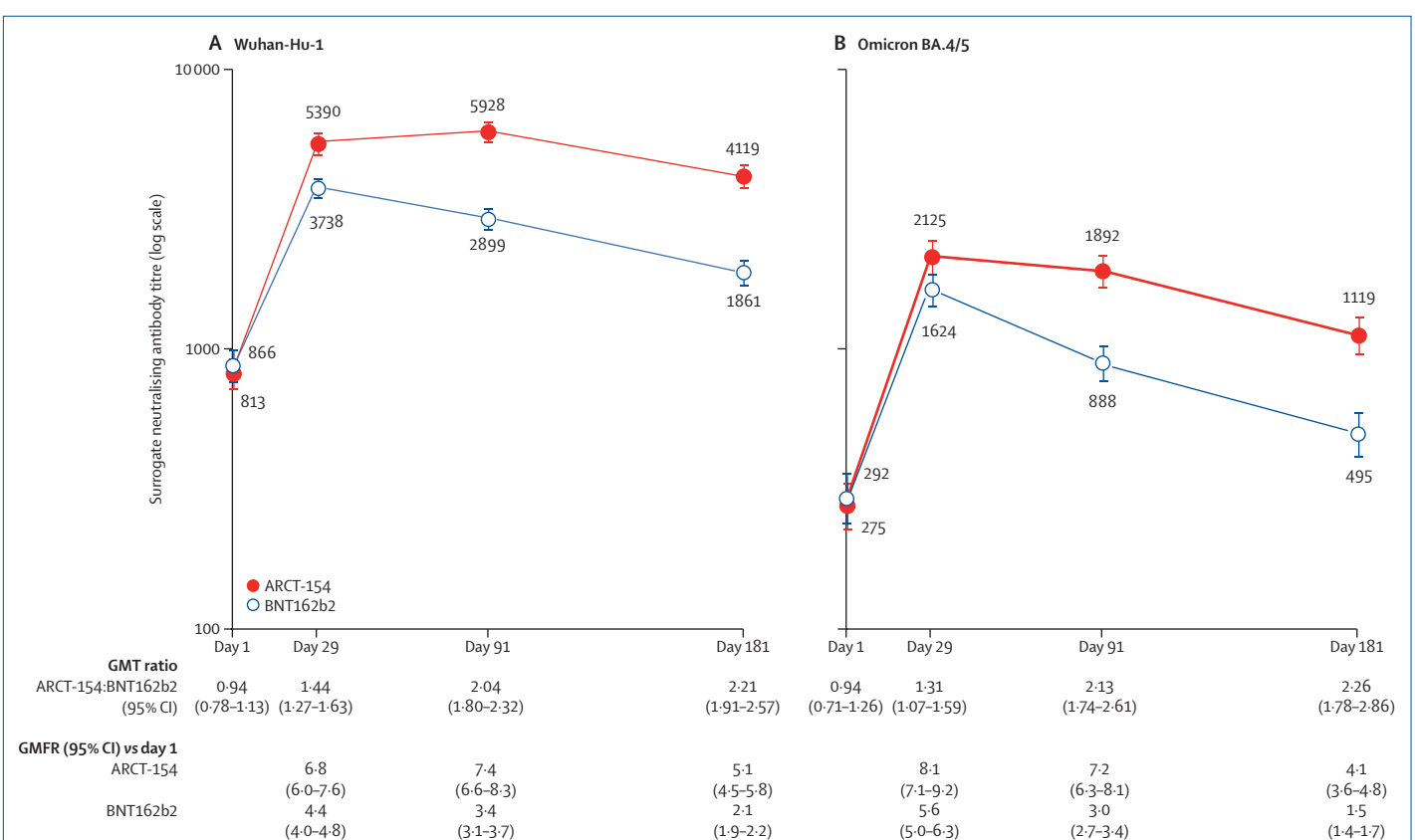
Persistence of immune responses of a self-amplifying RNA COVID-19 vaccine (ARCT-154) versus BNT162b2

Lancet Infect Dis 2024
Published Online
February 1, 2024
https://doi.org/10.1016/S1473-3099(24)00060-4

Of the many effective vaccines developed to combat the COVID-19 pandemic, the most notable were novel mRNA vaccines. Despite their high efficacy against the original Wuhan-Hu-1 strain and early SARS-CoV-2 variants, mRNA vaccines elicit a relatively short duration of immunity, exacerbated by immune evasion by variants leading to lower efficacy;[1] for example, mRNA vaccine effectiveness against omicron declined to below 20% within 6 months of vaccination.[2] Additionally, new variants are continuing to emerge,[3] so the ongoing risk of COVID-19 outbreaks due to persistent viral circulation necessitates ongoing development of new vaccines to prolong vaccine-induced immunity, ideally for at least 1 year to meet new annual immunisation recommendations.[3] We recently reported that a booster dose of the novel mRNA vaccine, ARCT-154 (Arcturus Therapeutics Holdings, San Diego, CA, USA), a self-amplifying mRNA (saRNA) vaccine based on the SARS-CoV-2 D614G variant (B.1), induced superior immunogenicity than BNT162b2 (Comirnaty; Pfizer–BioNTech) in BNT162b2-primed adults 1 month after administration.[4] Commenting on our Article, Herfst and de Vries[5] noted that "whether this [improvement in RNA vaccine technology] leads to better and longer-lasting immunity warrants further investigation". In response, we present available ARCT-154 and BNT162b2 immunogenicity data at 3-months and 6-months post-booster until data showing responses at 12 months becomes available.



	Wuhan-Hu-1				Omicron BA.4/5			
GMT ratio								
ARCT-154:BNT162b2	0·94	1·44	2·04	2·21	0·94	1·31	2·13	2·26
(95% CI)	(0·78–1·13)	(1·27–1·63)	(1·80–2·32)	(1·91–2·57)	(0·71–1·26)	(1·07–1·59)	(1·74–2·61)	(1·78–2·86)
GMFR (95% CI) *vs* day 1								
ARCT-154		6·8 (6·0–7·6)	7·4 (6·6–8·3)	5·1 (4·5–5·8)		8·1 (7·1–9·2)	7·2 (6·3–8·1)	4·1 (3·6–4·8)
BNT162b2		4·4 (4·0–4·8)	3·4 (3·1–3·7)	2·1 (1·9–2·2)		5·6 (5·0–6·3)	3·0 (2·7–3·4)	1·5 (1·4–1·7)

Figure: **Geometric mean titres (with 95% CIs) of surrogate neutralising antibodies against the SARS-CoV-2 Wuhan-Hu-1 (A) and Omicron BA.4/5 (B) strains up to 6 months after vaccination with one booster dose of either ARCT-154 or BNT162b2**
GMT ratios (95% CI) for ARCT-154:BNT162b2 are shown for days 1, 29, 91, and 181 and GMFR (95% CI) are shown for each group at days 29, 91 and 181. GMFR=geometric mean-fold rises over baseline. GMT=geometric mean titre.

In our study, Japanese adults who had been primed with two doses of mRNA vaccine and a booster dose of BNT162b2 at least 3 months earlier were randomly assigned equally to receive a second booster of either ARCT-154 (n=420) or BNT162b2 (n=408).[4] In this extension analysis, we progressively excluded any participant who displayed seropositivity on days 1, 29, 91, or 181 for SARS-CoV-2 N-protein, considered to be indicative of COVID-19 infection, leaving 332 in the ARCT-154 group and 313 participants in the BNT162b2 group eligible for inclusion at the 6-month timepoint (appendix).

See Online for appendix

Both groups had similar geometric mean surrogate virus neutralising titres (GMT) at baseline (GMT ratios were 0·94 for both Wuhan-Hu-1 and Omicron BA.4/5 SARS-CoV-2 variants). 1 month post-booster, the ARCT-154 group had the previously reported superior immunogenicity against both strains (figure A); GMTs against Wuhan-Hu-1 in the ARCT-154 group was 5390 (95% CI 4899–5931, n=378) and in the BNT162b2 group was 3738 (3442–4060, n=367), with a GMT ratio of 1·44 (95% CI 1·27–1·64). 3 months post-booster GMTs were 5928 (5414–6491, n=369) in the ARCT-154 group and 2899 (2648–3175, n=356) in the BNT162b2 group, a higher GMT ratio of 2·04 (1·80–2·32). Day 91 titres were equal to or greater than day 29 titres in 205 of 369 (55·6% [95% CI 50·3–60·7]) ARCT-154 recipients, but in only 108 of 356 (30·3% [25·6–35·4]) BNT162b2 recipients. Due to different rates of antibody waning by day 181 GMTs were 4119 (95% CI 3723–4557, n=332) in the ARCT-154 group and 1861 (1667–2078, n=313) in the BNT162b2 group, maintaining a GMT ratio of 2·21 (1·91–2·57) between vaccine groups. GMTs against Wuhan-Hu-1 remained higher 180 days after ARCT-154 than GMTs observed 28 days after the BNT162b2 booster.

We observed the same pattern of superior immunogenicity and slower decline in omicron BA.4/5 neutralising antibodies (figure B): GMTs increased to 2125 (95% CI 1841–2453) after ARCT-154 versus 1624 (1418–1858) after BNT162b2 at day 29, then waned to 1892 (1646–2175) after ARCT-154 and 888 (764–1031) after BNT162b2 at day 91. Between days 29 and 91 titres were stable or increased in 128 of 369 (34·7% [95% CI 29·8–39·8]) ARCT-154 recipients, compared with 36 of 356 (10·1% [7·2–13·7]) BNT162b2 recipients. The difference in neutralising activity against omicron BA.4/5 was maintained to day 181 when GMTs were 1119 (95% CI 960–1305) in the ARCT-154 group and 495 (413–595) in the BNT162b2 group, with a GMT ratio of 2·26 (1·78–2·86) in favour of ARCT-154.

These data demonstrate the extended persistence of neutralising antibodies after the saRNA vaccine compared with conventional mRNA vaccine in the clinical setting, confirming the longer-lasting immunity questioned by Herfst and deVries.[5] Because neutralising antibodies have been shown to be the main indicator of protective immunity,[6] these results suggest a longer duration of protection by the saRNA vaccine. The previously demonstrated superior immunogenicity against the omicron BA.4/5 sublineage,[4] confirmed here, suggests an improved breadth of response. Given that vaccines are being reformulated to target current predominant SARS-CoV-2 variants, notably omicron XBB.1.5 and BA.2.86 sublineages (including JN.1),[7] further evaluation of responses to these sublineages will be best done using these new vaccines. Finally, ARCT-154 contains 5 µg of mRNA, as compared with 30 µg in BNT162b2, suggesting potential dose sparing with saRNA vaccines. We anticipate that the advantages of saRNA vaccine in new formulations could provide superior protective immunity against future emergent variants.

TK is a board member and stockholder of Meiji Seika Pharma. YO, MK, YI, IO, TM, and YY are full-time employees of Meiji Seika Pharma. YK received consulting fees from Meiji Seika Pharma. PC and YZ are full-time employees with stock options in Arcturus Therapeutics. JLW received consulting fees from Arcturus Therapeutics.

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