IgG and IgA antibody responses among Bangladeshi children after immunization with the Vi-TT vaccine

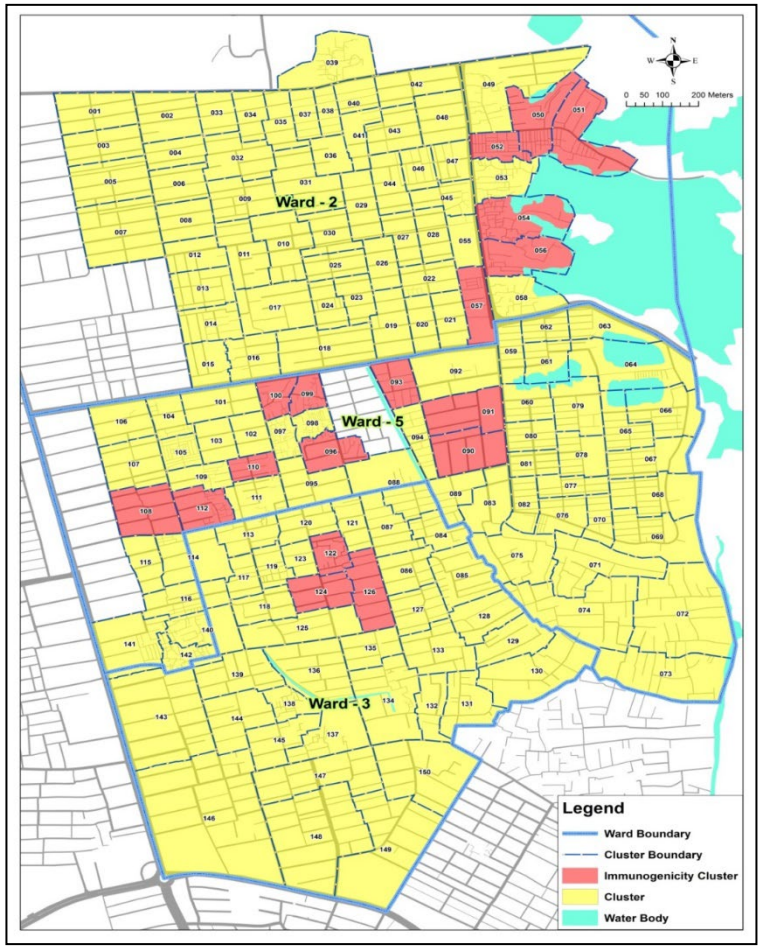
Farhana Khanam
icddr,b

Photo: PATH/Asad Zaidi

TyVAC Typhoid Vaccine Acceleration Consortium
CENTER FOR VACCINE DEVELOPMENT • OXFORD VACCINE GROUP • PATH

Key points of the TyVac Trial in Bangladesh

- Phase III, cluster-randomized trial to vaccinate Bangladeshi children aged 9 months to <16 years
- 150 clusters were randomized at a 1:1 ratio to allocate Vi-TT or JE vaccines
- 61,756 children were vaccinated during baseline and catch-up vaccination
- A subset of 18 clusters were randomly selected for the immunogenicity sub-study



Clusters (n=18) for the immunogenicity study

Immunogenicity study

- Participants of the immunogenicity study were selected on a 2:1 basis (Vi-TT vs JE clusters)
- Blood specimens were collected on day 0 prior to vaccination
- After vaccination, blood was collected on day 28, at 1.5 yrs, 2 yrs, 4 yrs, and 5 yrs (3 yrs missed)
- Immunization of children in the JE arm with the Vi-TT vaccine was carried out after 2.7 yrs of baseline vaccination as per protocol

Immunogenicity study (cont.)

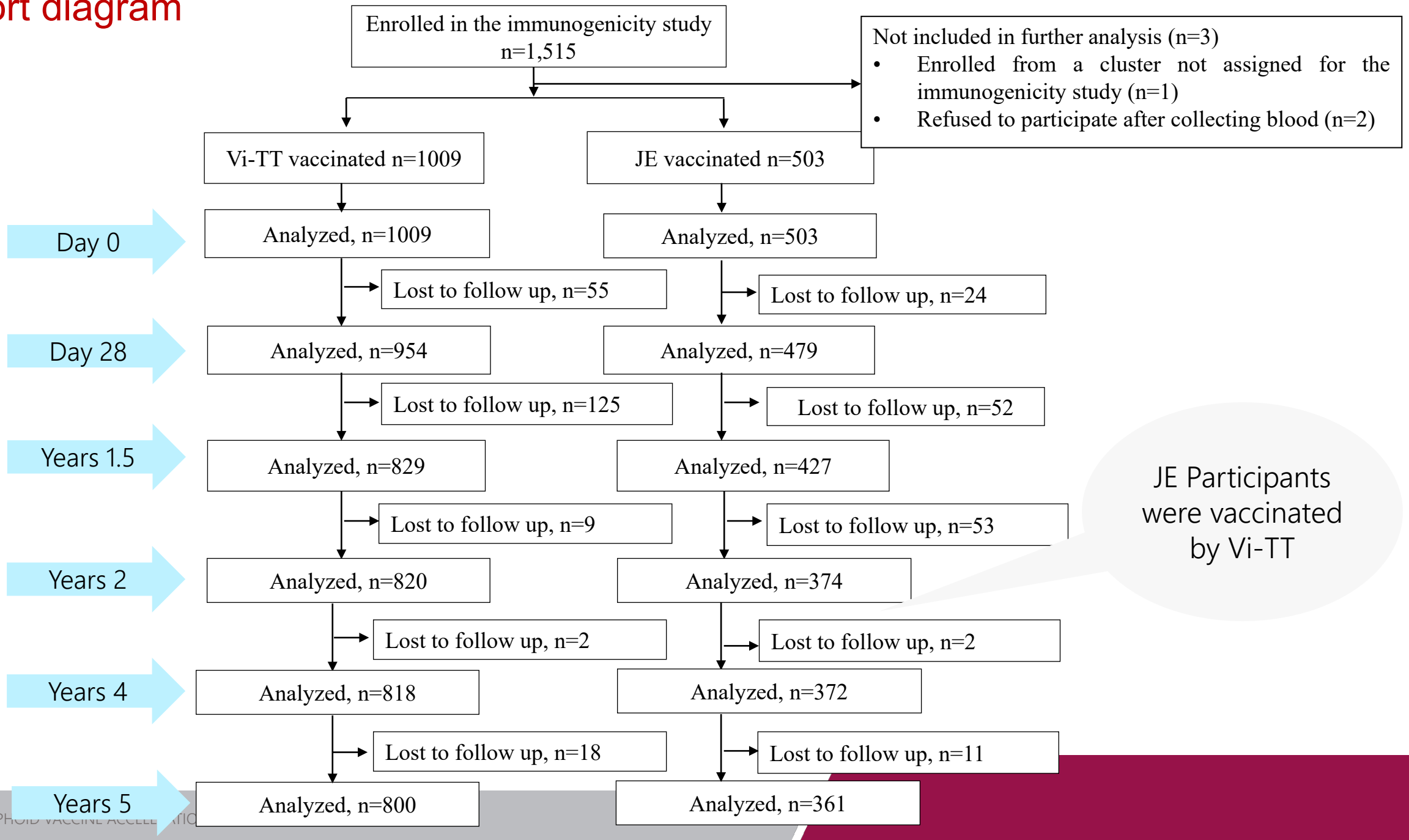
- There are no established assays for measuring functional antibodies that are considered true immunological correlates of protection against typhoid fever

- According to WHO, estimation of anti-Vi-IgG antibody responses by enzyme-linked immunosorbent assay (ELISA) is the key assessment tool to measure immune responses induced by the new typhoid conjugate vaccines

- IgA antibody plays a critical role in inducing mucosal immune response, it is important to determine whether IgA provides any protection at intestinal mucosa or IgA is a surrogate marker of protection against typhoid fever

Anti-Vi-IgG and IgA antibodies were measured in plasma following manufacturer's instruction using the VaccZyme kit from Binding Site

Consort diagram



Baseline characteristics of immunogenicity participants

Characteristics	Vi-TT (N = 1009)	JE (N = 503)	p-value
Age in years at enrollment (Mean ± SD)	6.1 ± 4.3	6.0 ± 4.3	0.683‖
Number of participants (%) were vaccinated by age groups			
<2 years	132 (13.1)	63 (12.5)	0.954¶
2-4 years	372 (36.9)	187 (37.2)	
≥5 years	505 (50.0)	253 (50.3)	
Gender			
Female n (%)	517 (51.2)	250 (49.7)	0.573¶
Body temperature (°C) (Mean ± SD)	36.30 ± 0.35	36.28 ± 0.36	0.327‖
Previous history of typhoid n (%)	57 (5.7)	25 (5.0)	0.583¶[a]

‖Two-sample t-test with equal variances
¶Pearson's chi-squared test
[a] Response of nine participants were "Unknown" and categorized them as "No" to perform the statistical test

Seroconversion rates for anti-Vi-IgG and anti-Vi-IgA antibody responses in Vi-TT and JE recipients

Responses	Time points	Vi-TT recipients	JE recipients
IgG	Day 28	99.6%	1.7%
	1.5 yrs	95.1%	5.6%
	2 yrs	91.2%	7.5%
IgA	Day 28	96.2%	3.6%
	1.5 yrs	75.9%	2.3%
	2 yrs	63.9%	4.8%

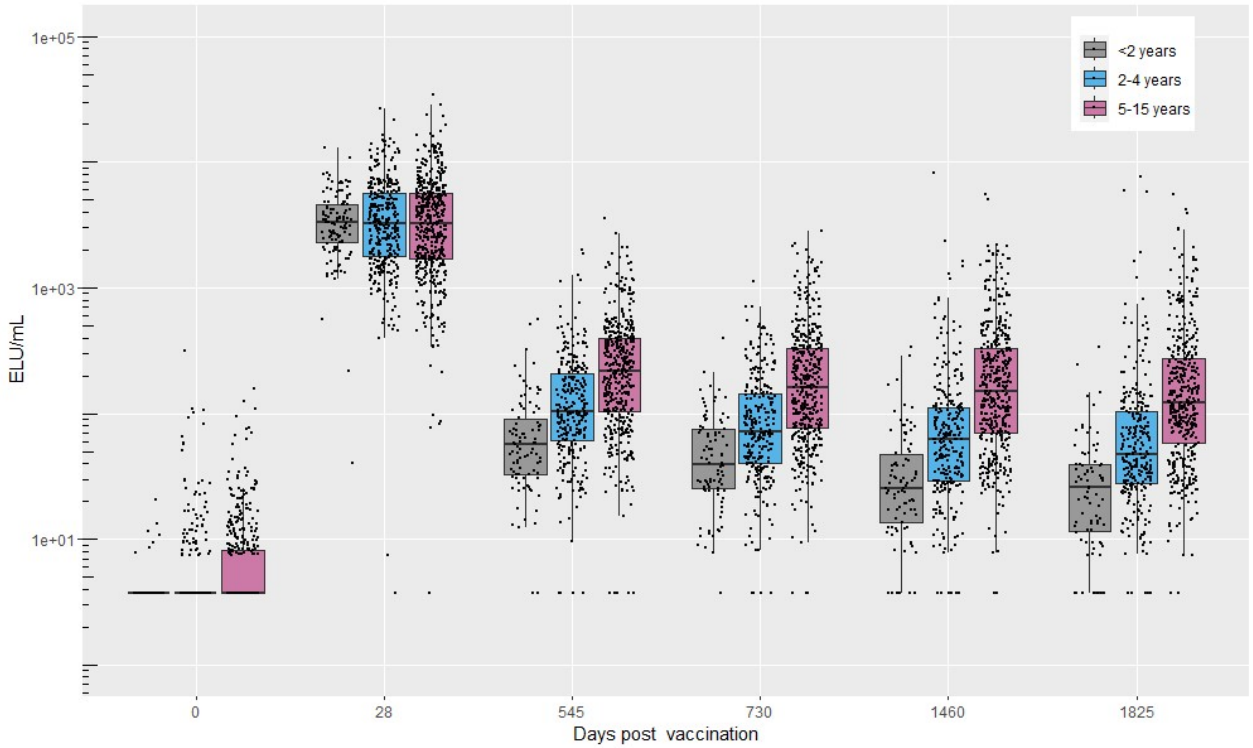
Seroconversion is defined as a ≥4-fold rise in antibody titres at different time points compared to baseline titres measured at day 0 prior to vaccination

The seroconversion rate is the proportion of participants who had seroconversion

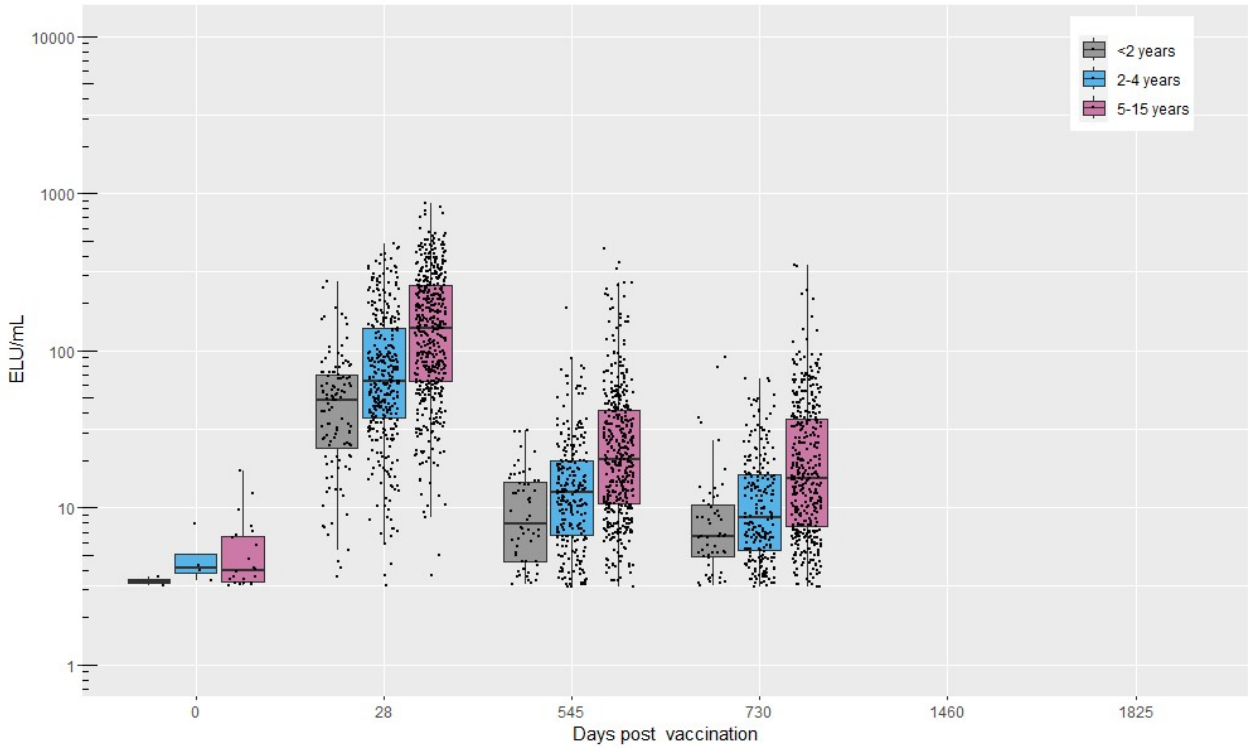
Anti-Vi-IgG and Anit-Vi-IgA antibody responses in Vi-TT recipients

Responses	Time points	Anti-Vi-IgG (overall)	Anti-Vi-IgA (overall)
GMT EU/mL (95% CI)	Day 0	5.03 (4.83-5.24)	1.61 (1.59-1.63)
	Day 28	2972 (2799-3155)	76.6 (70.97-82.75)
	1.5 years	138 (128-148.7)	13.0 (12.06-14.1)
	2 years	105.8 (97.84-114.3)	9.56 (8.83-10.35)
	4 years	91.19 (83.44-99.66)	Not done
	5 years	79.8 (72.82-87.44)	Not done
Fold rise over baseline GMT (95% CI)	Day 28	589.1 (550.7-630.3)	47.7 (44.4-51.5)
	1.5 years	27.1 (25.3-29.0)	8.08 (7.5-8.7)
	2 years	20.7 (19.2-22.2)	5.9 (5.5-6.4)
	4 years	18.1 (16.7-19.6)	Not done
	5 years	15.8 (14.5-17.1)	Not done

Kinetics of antibody responses in Vi-TT recipients



Anti-Vi IgG



Anti-Vi IgA

A cohort of ~1000 children was followed up at different time points post-vaccination

<2 years: N=132; 2-4 years: N=372; 5-15 years: N=505

Ratio of anti-Vi-IgG to anti-Vi-IgA fold-rise

Time point	Overall	Age: <2 years	Age: 2-4 years	Age: 5-16 years
Day 28	12.2 (11.2, 13.2)	39.3 (31.9, 48.4)	17.0 (14.9, 19.4)	7.1 (6.4, 7.9)
1.5 years	3.4 (3.2, 3.6)	5.0 (4.3, 5.8)	3.5 (3.2, 3.9)	3.0 (2.8, 3.3)
2 years	3.5 (3.3, 3.8)	4.2 (3.7, 4.8)	3.5 (3.1, 4.0)	3.4 (3.1, 3.7)

Breakthrough infection in two Vi-TT recipients of the immunogenicity sub-study

Participant 1: Fold rise with breakthrough infection on day 543 (1.5 yrs) post-vaccination

Antibody	D28	1.5 years	2 years	4 years	5 years
IgG	104	1.4	1.2	3.04	3.3
IgA	115	2.2	0.02	Not done	Not done

Participant 2: Fold rise with breakthrough infection on day 1436 (3.9 yrs) post-vaccination

Antibody	Day 28	1.5 years	2 years	4 years	5 years
IgG	1576	3.5	2.3	1.00	3.6
IgA	62	1.0	0.4	Not done	Not done

Summary

- The Vi-TT vaccine induced anti-Vi-IgG and anti-Vi-IgA responses in recipients of all age groups after one dose of Vi-TT vaccination compared to baseline antibody responses

- A decline in antibody levels was observed over time in IgG in the Vi-TT recipients of all age groups; however, the response was still present and there was a ≥4-fold rise in anti-Vi-IgG responses even after 5 yrs

- Age-dependent decline of antibody levels was observed over the study period; the highest decline was seen in the lower age group (<2 years of age) compared to children in the older age groups (2–4 years and ≥5 years) at later time points

- IgG showed a significantly higher fold-rise compared to IgA up to 2 yrs of follow-up

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