



Preliminary Immune Correlates of Risk Analysis from the CVIA 061 Rotavirus Vaccine Trial

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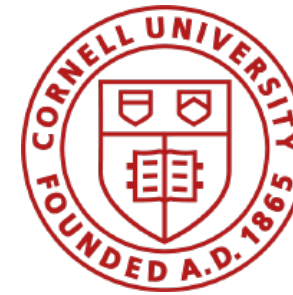
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Gates Foundation



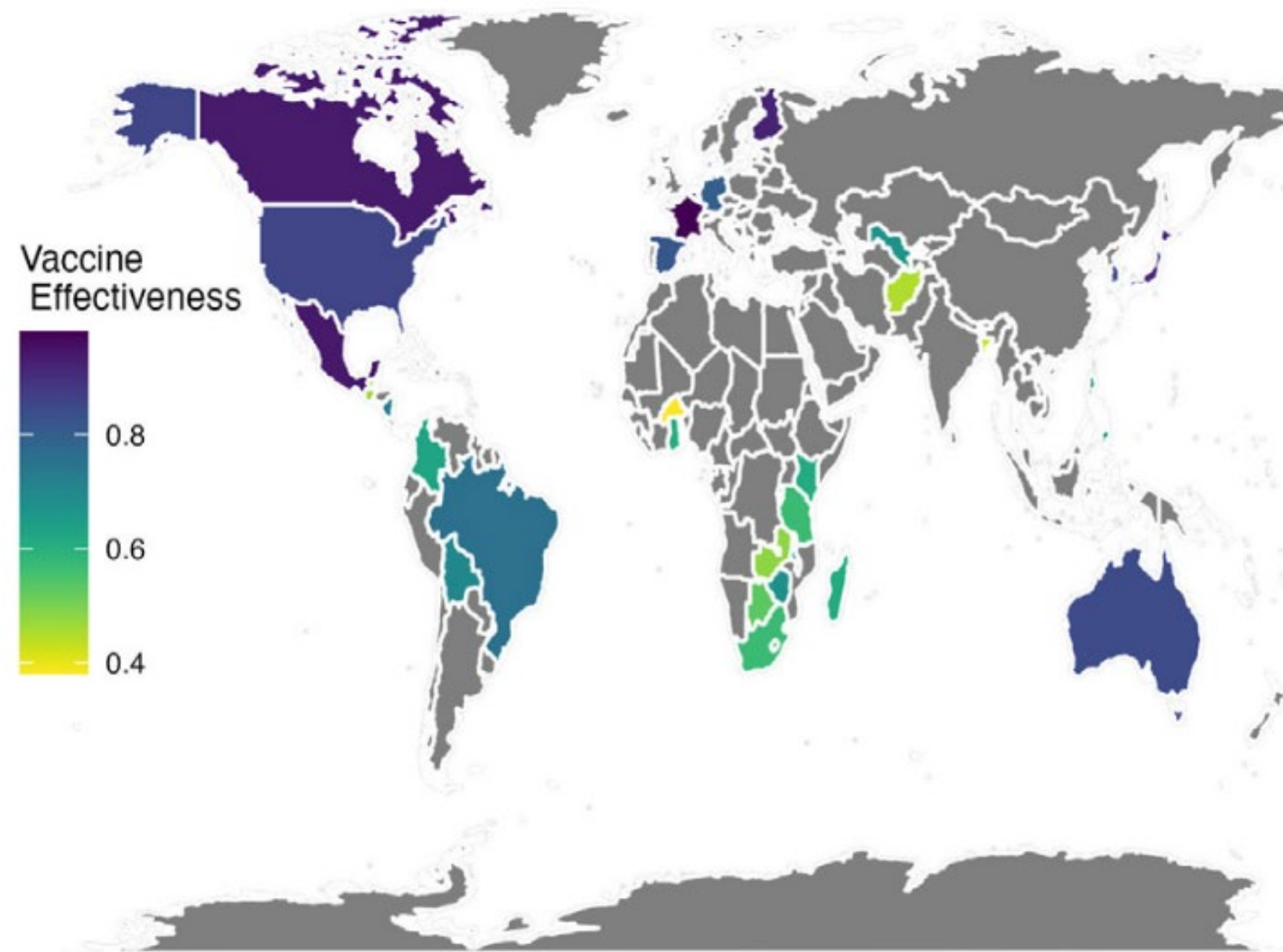
**CVIA061 study
participants and families!**

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Efficacy of live-attenuated oral rotavirus vaccines (LORVs) vary by income setting

- Efficacy is lowest in countries with highest incidence of RVGE
- Factors adversely affecting LORV efficacy may include: nutrition, microbiome, disease burden and elevated maternal antibodies
- There is great need for a more highly effective vaccine, or improved LORV regimens

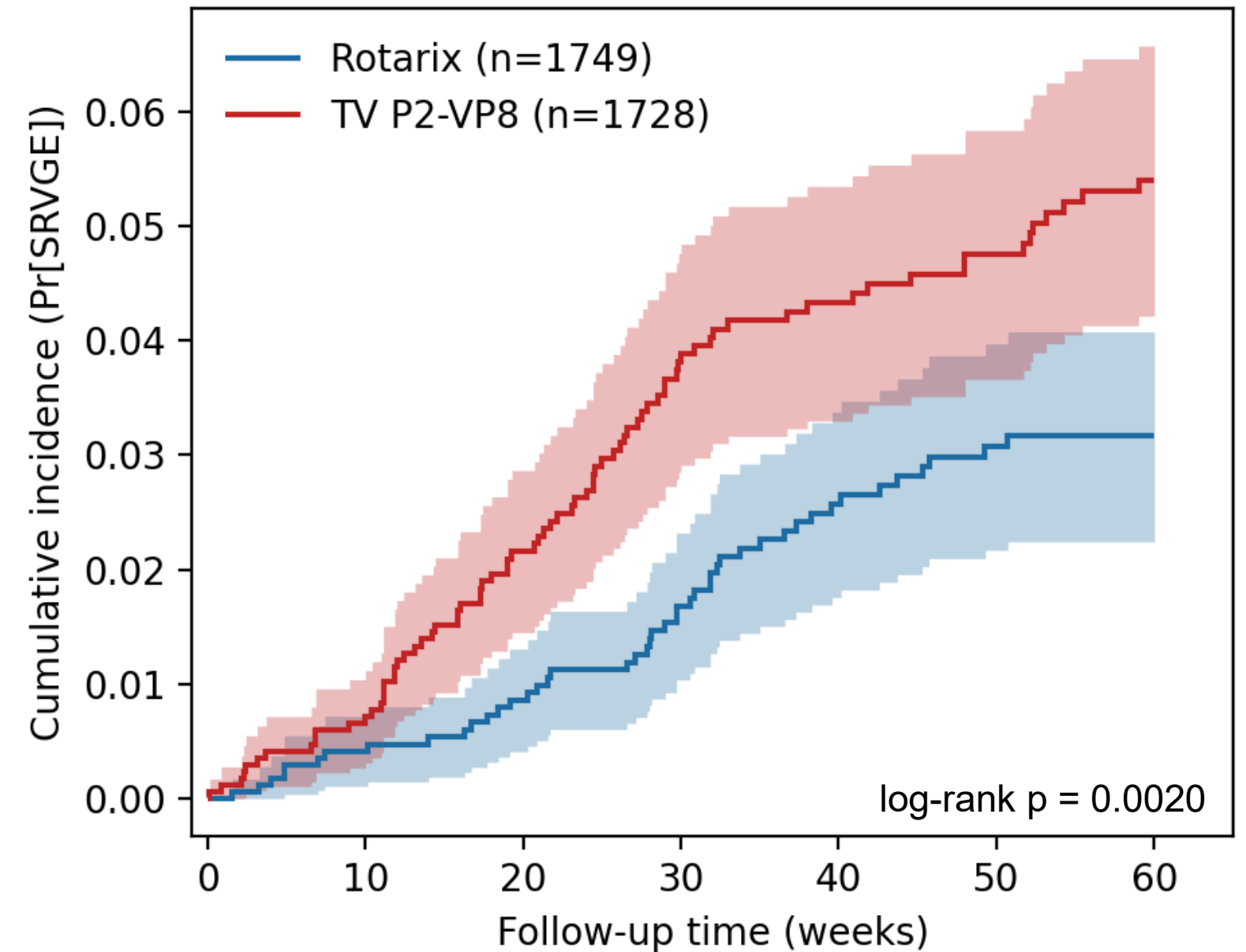
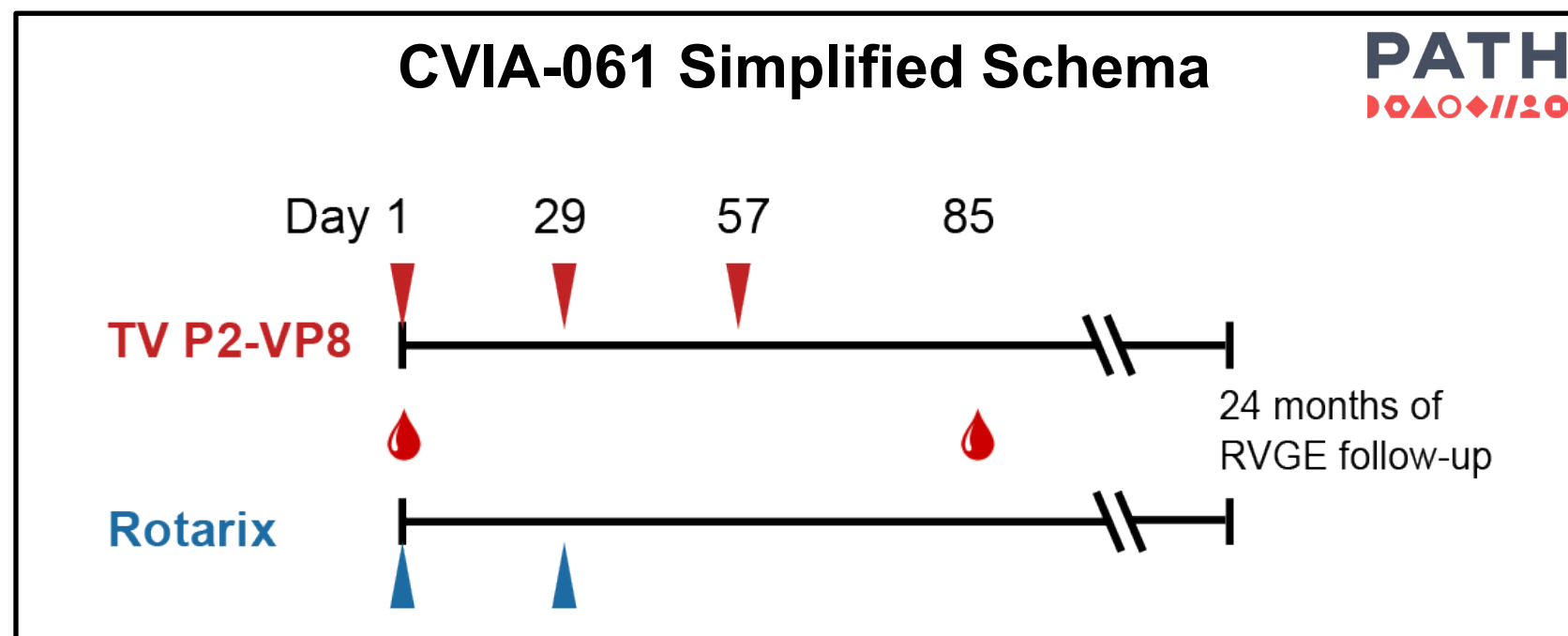
Observed Vaccine Effectiveness



Prunas et al., eClinical Medicine, 2025

Phase 3 Rotarix vs. TV P2-VP8 study: reduced SRVGE risk with Rotarix

- CVIA-061 was a phase 3 double-blind, randomized comparison of Rotarix vs. TV P2-VP8
- Enrolled 3,730 infants in Malawi, Zambia and Ghana
- First vaccination is at 6-8 weeks of age (Day 1)
- TV P2-VP8 was safe and well-tolerated
- Study halted for efficacy futility at interim analysis Aug 2022
- Absolute efficacies are unknown (no placebo group)
- Incidence of SRVGE was higher in TV P2-VP8 vs. Rotarix group



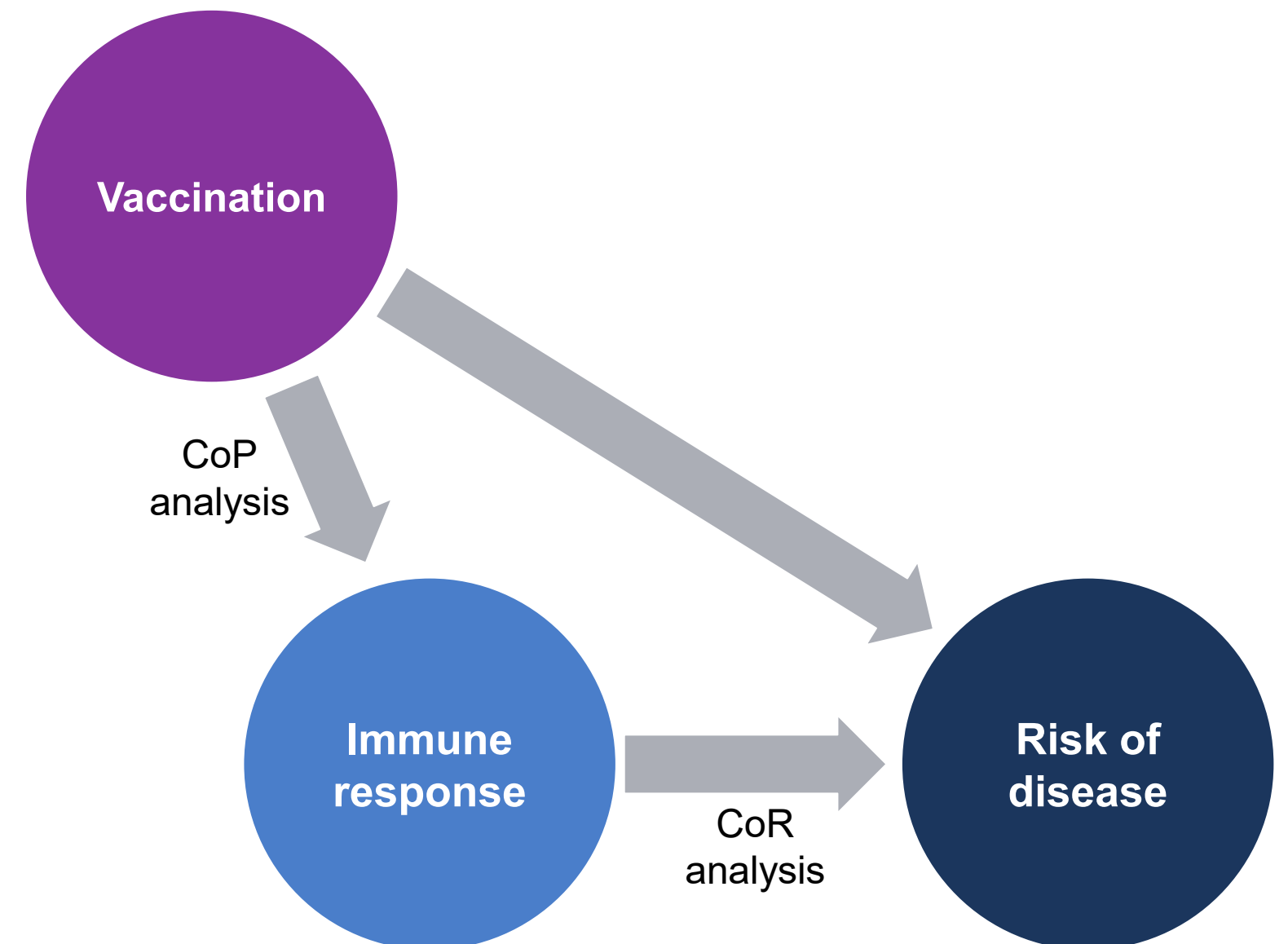
Tushar Tewari: "Safety, efficacy and immunogenicity of a parenteral trivalent rotavirus subunit vaccine candidate in Ghanaian, Zambian and Malawian infants" (10:55, Oct 1st)

Immune correlates of risk can accelerate vaccine development

- **Correlate of protection (CoP):** a biomarker correlated with vaccine efficacy (VE); a validated CoP can be used as a surrogate endpoint for vaccine development
- **Correlate of risk (CoR):** a biomarker associated with risk of a clinical endpoint (i.e., SRVGE)
- CoRs and CoPs are statistical analyses: not necessarily mechanisms

Correlates of risk (CoRs) help us:

- Identify protective immune responses: a potential benchmark for improving vaccines
- Identify antigen targets associated with reduced risk
- Better understand vaccines' mechanisms of protection
- Elucidate baseline factors that impact vaccine response



CVIA-061: Correlates of SRVGE Risk Study Design

- **Case definition:** Stool-positive for RV and severe GE (Vesikari score >11) (SRVGE)
- **Controls sampled:** RVGE negative, random stratified sampling (3:1) on treatment arm, country and age at vaccination
- **Samples:** serum assayed pre-vaccination (Day 1) and post-vaccination (Day 85). No stool samples were assayed.
- **Cox proportional-hazard models:** adjusted for sex and country, inverse-probability weighted (IPW) and model biomarkers as continuous (log-scale) and categorical (i.e., high, medium, low)

Nested case-cohort sampling plan

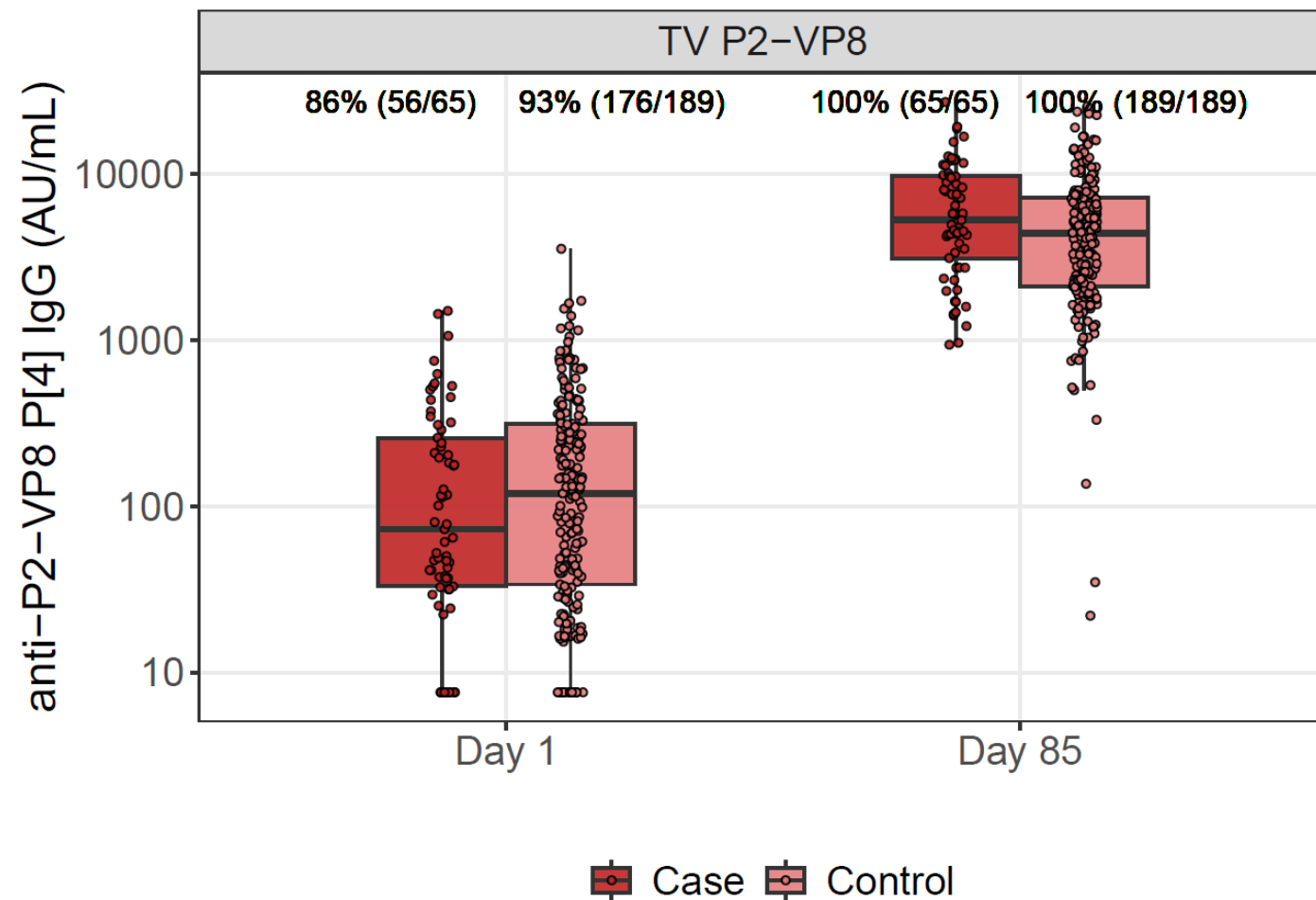
Treatment	Visits	SRVGE Cases	Sampled Controls	Analysis Cohort	Per Protocol Cohort
Rotarix	Day 1 & 85	39	115	154	1749
TV P2-VP8	Day 1 & 85	66	189	255	1728

Assay	Antigen (P-type/strain)	Rotarix	TV P2-VP8
ELISA IgA	Whole-virus (RV 89-12, G1P[8])	X	X
Intracellular neutralization (AMIN)	Rotarix	X	X
Neutralization	WA G1P[8]	X	X
Neutralization	1076 G4P[6]		X
Neutralization	DS-1 G2P[4]		X
ELISA IgG	VP8 (P[8])		X
ELISA IgG	VP8 (P[6])		X
ELISA IgG	VP8 (P[4])		X
ELISA IgA	VP8 (P[8])		X
ELISA IgA	VP8 (P[6])		X
ELISA IgA	VP8 (P[4])		X

* ELISA : Enzyme-Linked Immunosorbent Assay

TV P2-VP8 induces robust anti-VP8 IgG

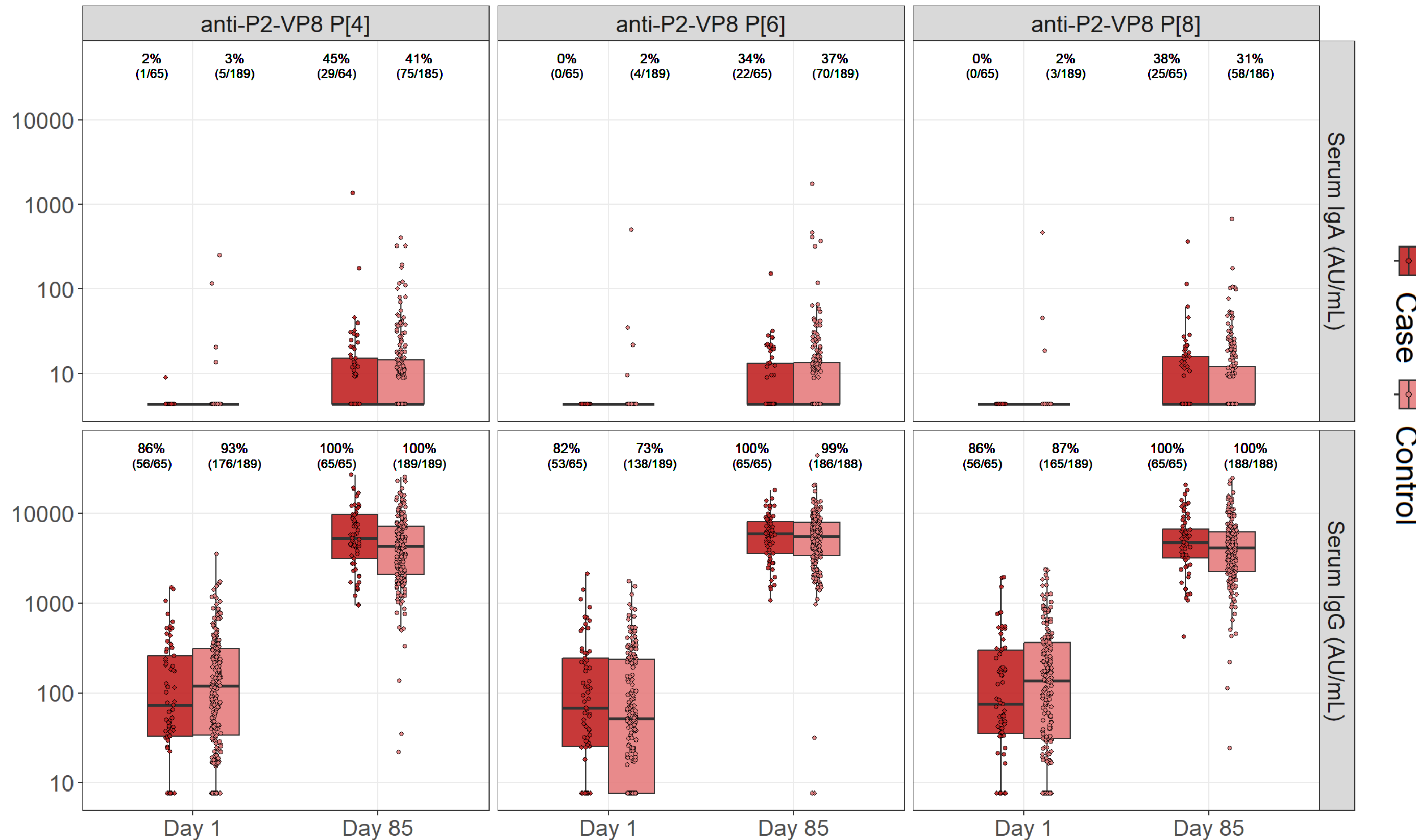
- Vaccine induced IgG and IgA in serum at Day 85
- Day 1 elevated IgG is a result of maternal antibodies
- *Day 1*: none of the biomarkers were associated with SRVGE risk
- *Day 85*: only anti-VP8 ELISA IgG P[4] was a statistically significant correlate of increased SRVGE risk (P[6] and P[8] were not).



Visit	Biomarker	Antigen/virus	HR (95% CI)	P-value
Day 1	Whole-virus IgA	RV 89-12 (G1P[8])	0.93 (0.19, 4.46)	0.925
		Wa P[8]	1.04 (0.59, 1.82)	0.903
		X1076 P[6] DS1 P[4]	1.29 (0.79, 2.13) 1.47 (0.85, 2.51)	0.311 0.166
	AMIN	Rotarix	0.88 (0.03, 24.42)	0.939
	anti-VP8 IgA	P[4]	<LLOQ	-
		P[6]	<LLOQ	-
		P[8]	<LLOQ	-
	anti-VP8 IgG	P[4]	0.77 (0.48, 1.23)	0.274
		P[6]	1.49 (0.95, 2.32)	0.081
		P[8]	0.82 (0.55, 1.22)	0.322
Day 85	Whole-virus IgA	RV 89-12 (G1P[8])	0.58 (0.23, 1.45)	0.242
		WA P[8]	2.23 (0.76, 6.61)	0.146
		X1076 P[6] DS1 P[4]	1.21 (0.54, 2.71) 1.38 (0.59, 3.22)	0.645 0.453
	AMIN	Rotarix	5.94 (0.71, 50.07)	0.101
	anti-VP8 IgA	P[4]	1.03 (0.57, 1.85)	0.927
		P[6]	0.71 (0.39, 1.31)	0.278
		P[8]	1.26 (0.67, 2.35)	0.478
	anti-VP8 IgG	P[4]	3.02 (1.31, 6.98)	0.009*
		P[6]	1.48 (0.72, 3.04)	0.290
		P[8]	1.91 (0.85, 4.26)	0.115

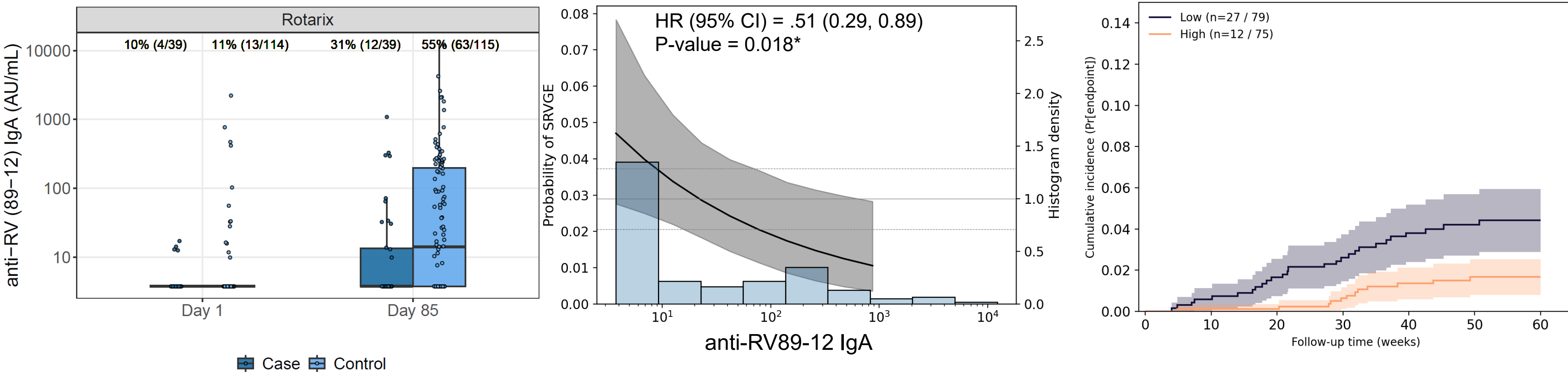
TV P2-VP8 induces robust anti-VP8 IgG and IgA across P-strains

- anti-VP8 ELISA IgG had similar trends from Day 1 to Day 85
- anti-VP8 ELISA IgA had similar trends from Day 1 to Day 85



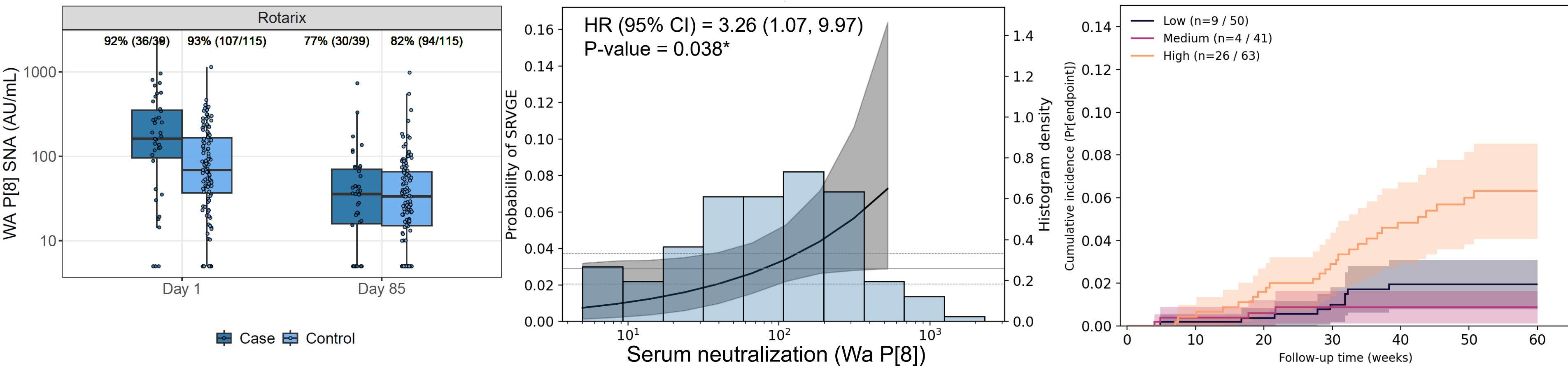
Post-vaccination serum IgA titers in Rotarix group associated with decreased risk of SRVGE

- Elevated Day 85 viral-lysate (RV89-12) IgA ELISA titers are a correlate of decreased risk in the Rotarix group
- Marginalized risk curve shows probability of SRVGE as a function of log-transformed serum IgA
- Categorical analysis showed higher cumulative incidence of SRVGE in infants with low Day 85 IgA
- Consistent with literature: viral-lysate IgA is a trial-level CoP for most LORVs



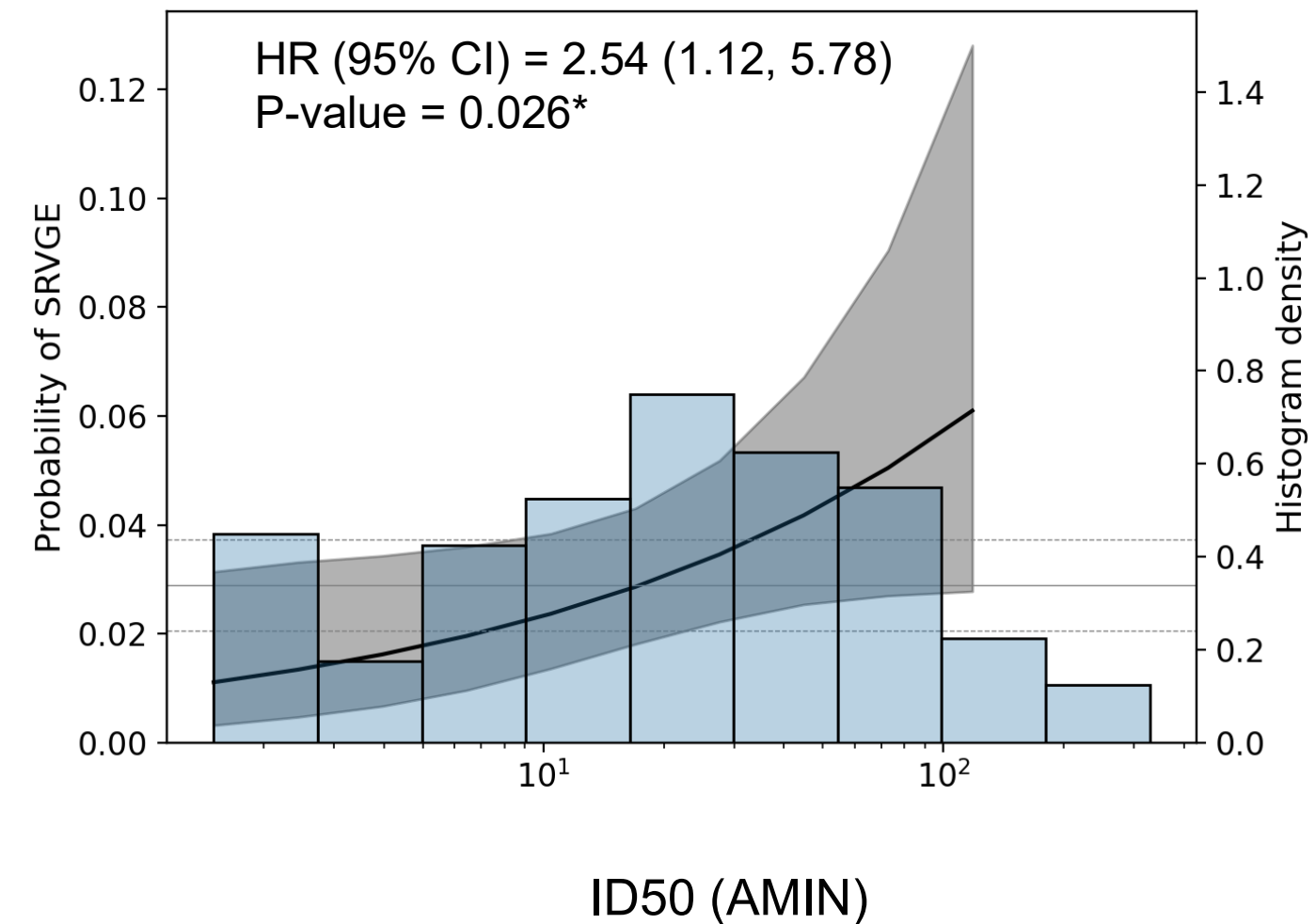
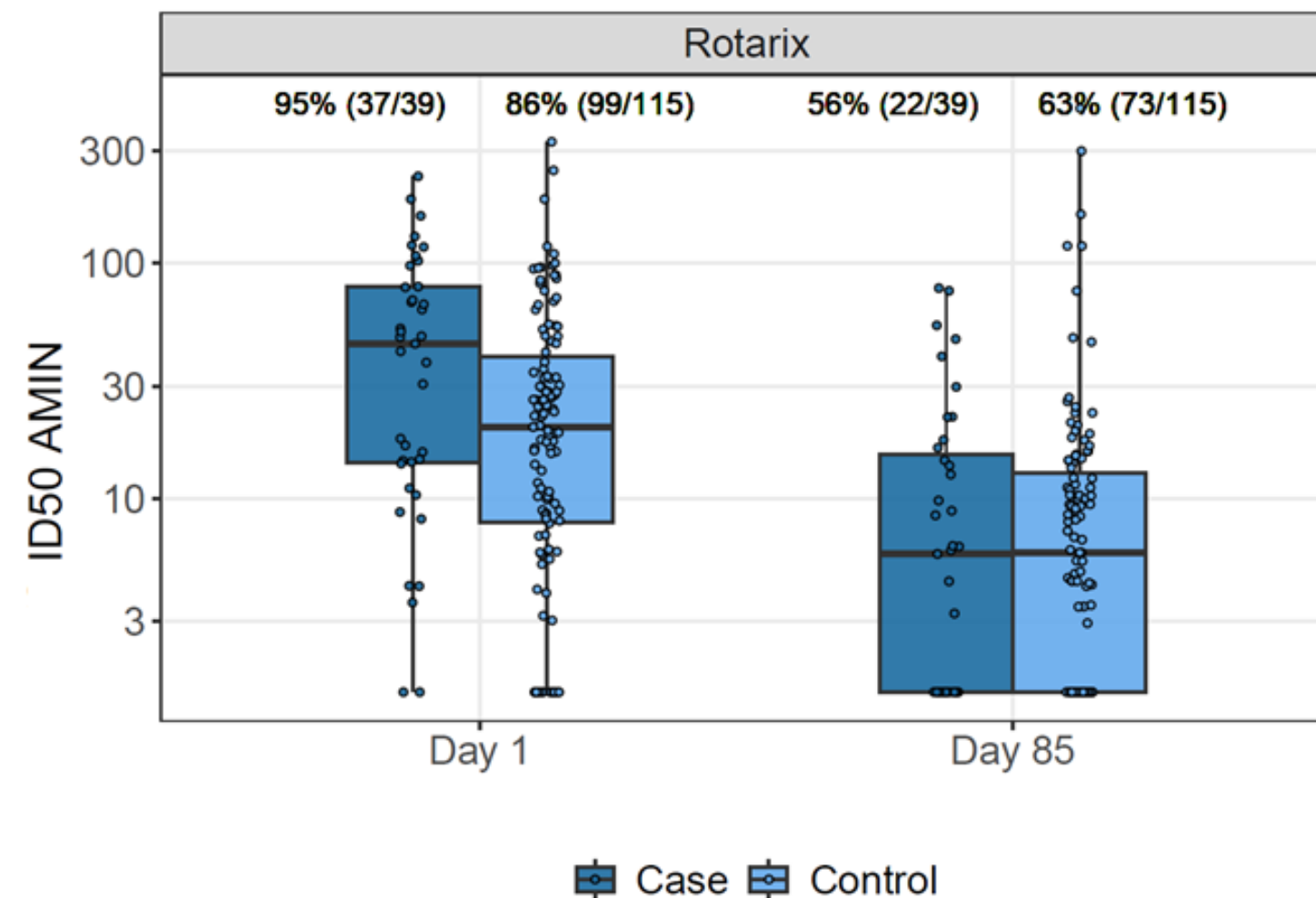
Pre-vaccination neutralizing antibody titers in Rotarix group associated with increased risk of disease

- Elevated pre-vaccination (Day 1) neutralizing antibody titers to Wa P[8] strain is associated with higher risk of SRVGE
- Categorical analysis showed infants with highest Day 1 neutralizing antibody titers had highest cumulative incidence of SRVGE



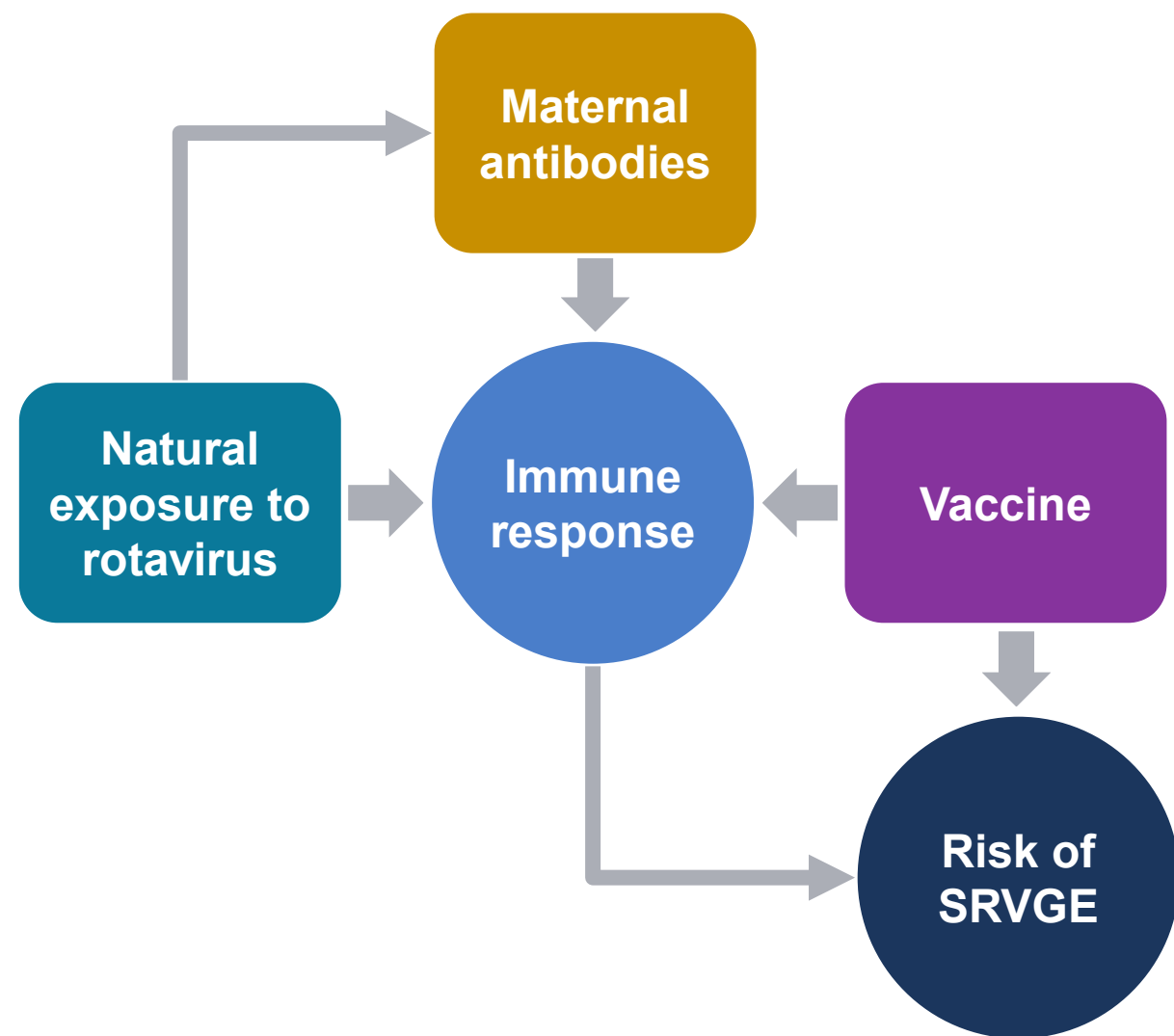
Pre-vaccination intracellular neutralizing antibody titers in the Rotarix group are also associated with increased risk of SRVGE

- Elevated Day 1 intracellular neutralizing antibody titers (AMIN) are a correlate of risk in the Rotarix group



Preliminary Conclusions

- Elevated serum IgA at Day 85 associated with lower risk of SRVGE in Rotarix group
- Elevated neutralizing antibody titers (SNA & AMIN) at Day 1 associated with higher risk of SRVGE in Rotarix group



Future Analyses

- Multivariate models including prediction of SRVGE for individuals
- Analysis of alternative GE outcomes: strain-specific, country-specific, very severe RVGE, hospitalizations
- Non-linear models to assess potential threshold effects

Thank you!

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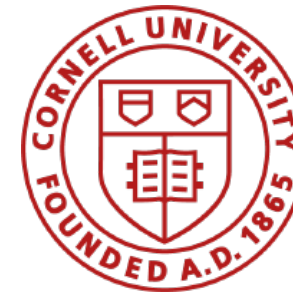
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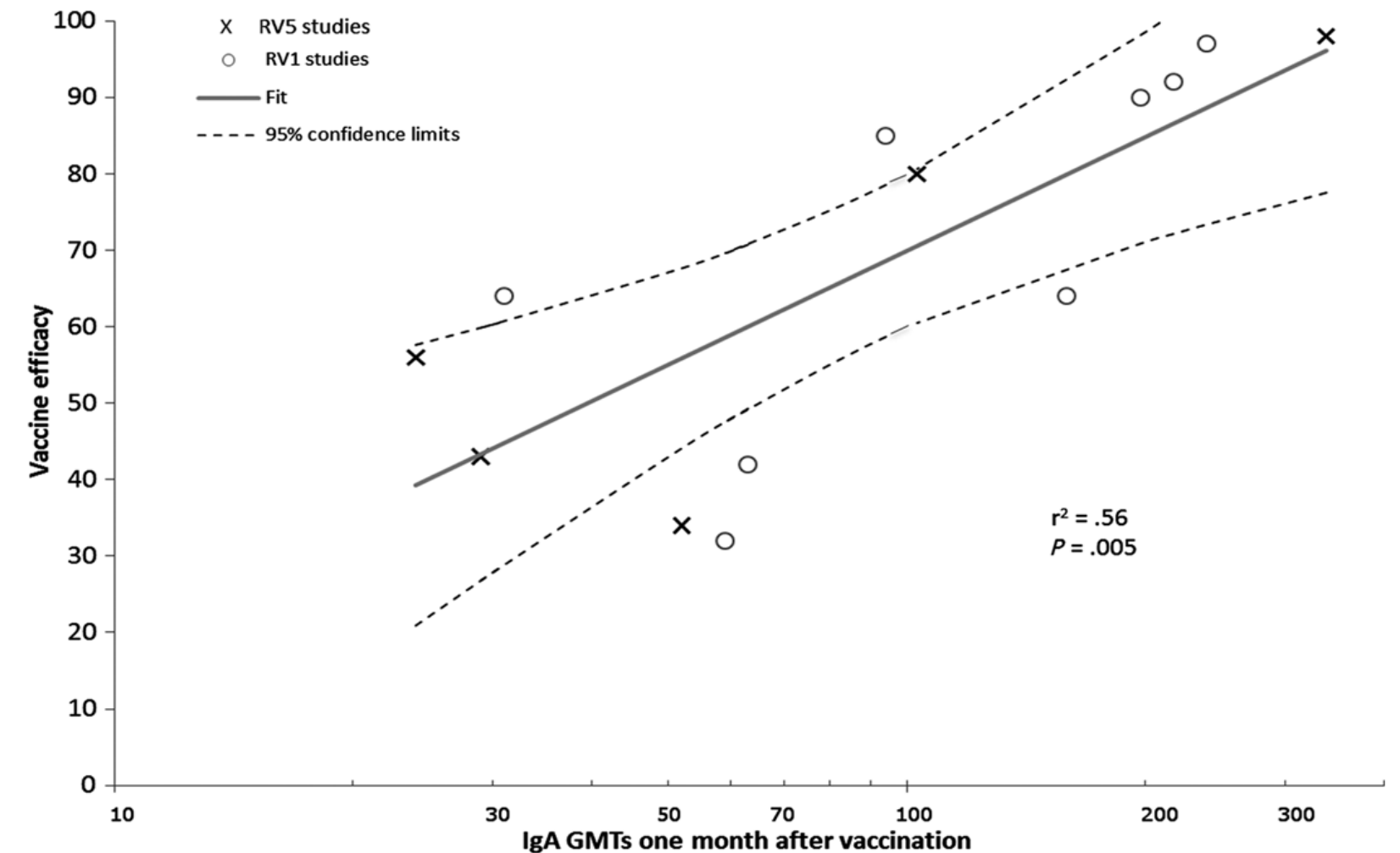
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Appendix 1: All Rotarix model results

Rotarix Correlates of Risk				
Visit	Biomarker	Antigen/virus	HR (95% CI)	P-value
Day 1	anti-viral-lysate IgA ELISA	RV 89-12 (G1P[8])	0.58 (0.24, 1.42)	0.237
	Neutralization	Wa [P8]	3.26 (1.07, 9.97)	0.038*
	AMIN	Wa P[8]	2.54 (1.12, 5.78)	0.026*
Day 85	anti-viral-lysate IgA ELISA	RV 89-12 (G1P[8])	0.51 (0.29, 0.89)	0.018*
	Neutralization	Wa [P8]	1.0 (0.45, 2.23)	0.994
	AMIN	Rotarix	0.89 (0.45, 1.75)	0.731

Appendix 2: Prior evidence suggests serum IgA is a CoP for most LORVs

- Post-LORV serum against RV viral-lysate IgA ELISA is associated with vaccine efficacy (VE)
- Higher IgA is associated with higher VE, in trial-level meta-analyses
- *Limitations:* RV lysate IgA is not mechanistic, antigen specificity is unknown, and no absolute threshold for protection
- CVIA061 Rotarix arm is consistent with prior evidence; will enable quantification of individual-level prediction



Patel et al. JID 2013