Potent Immune Responses to Norovirus G1.1 Evaluated in Elderly Subjects following Oral Tablet Delivery in a Phase 1 Placebo-Controlled Study

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Forward looking statement

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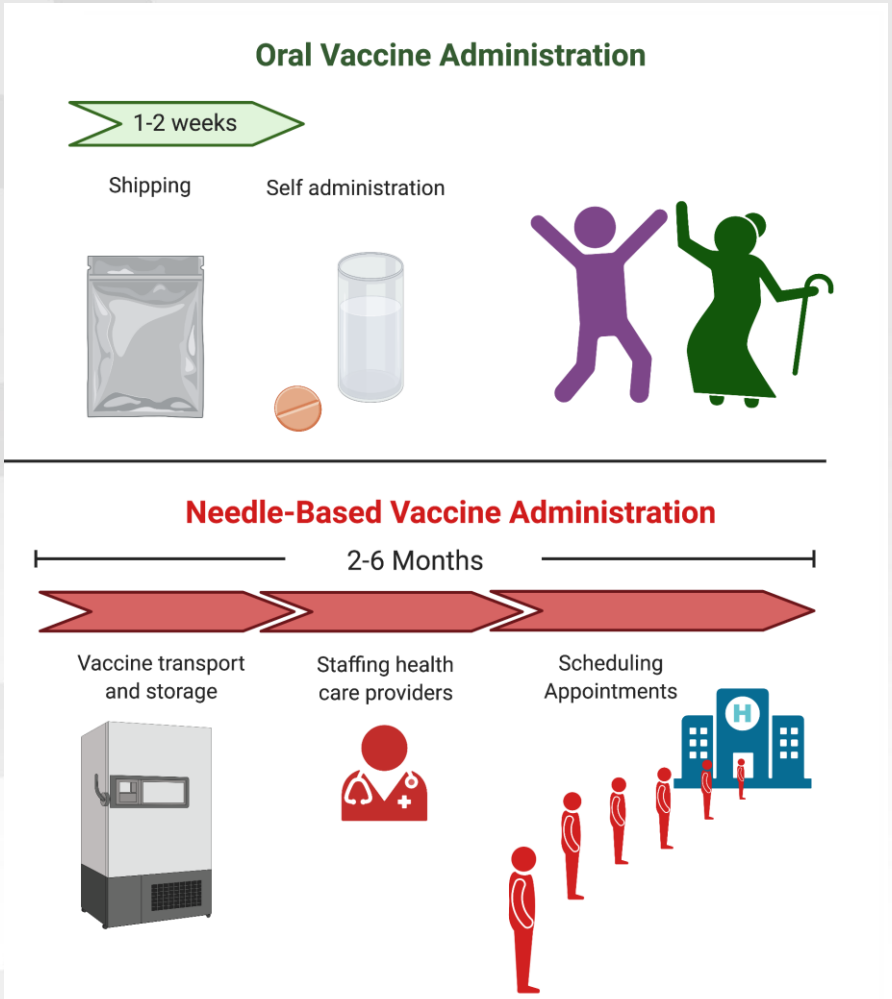
Benefits of Vaxart Vaccine platform



Distribution

- Temperature stable tablets
- Self administered
- Rapidly deployed in a pandemic or stockpiled

Safety

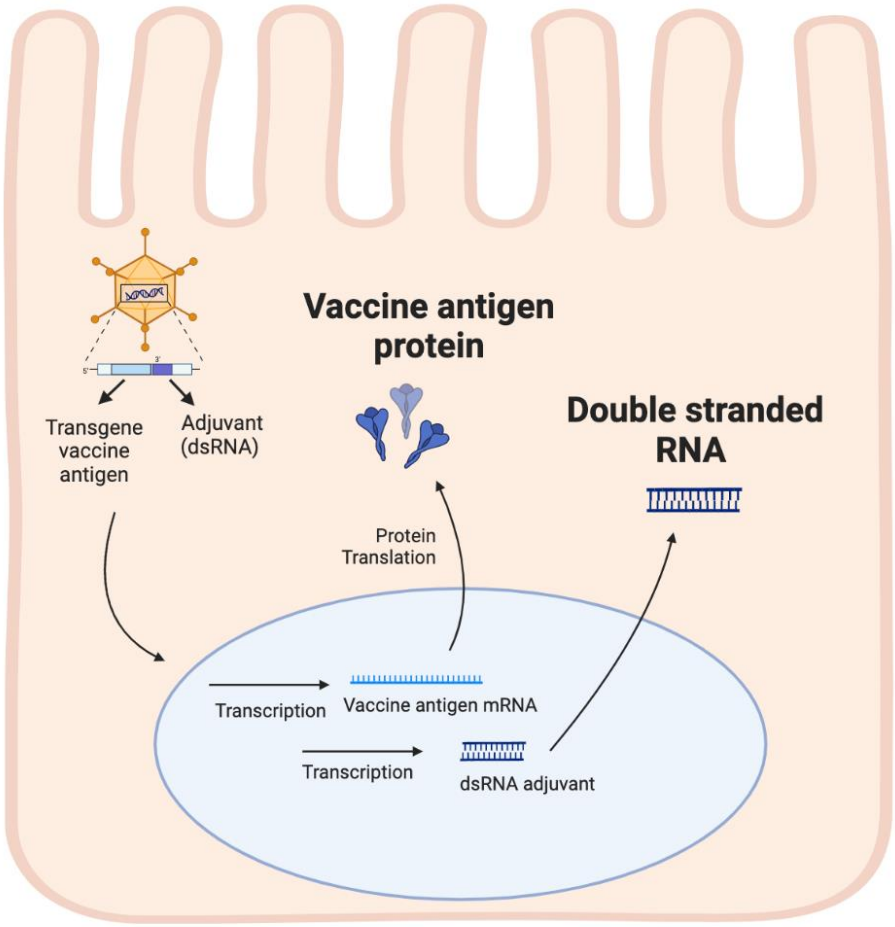
- Well tolerated and safe

Immunogenicity

- Vaccine antigens delivered to the mucosal surface
- Enhances immune responses at the site of infection
  - Mucosal homing plasmablasts
  - IgA production in the mucosa

Expression of protein antigen in the same cell as the dsRNA (immune activator) creates a highly specific immune response

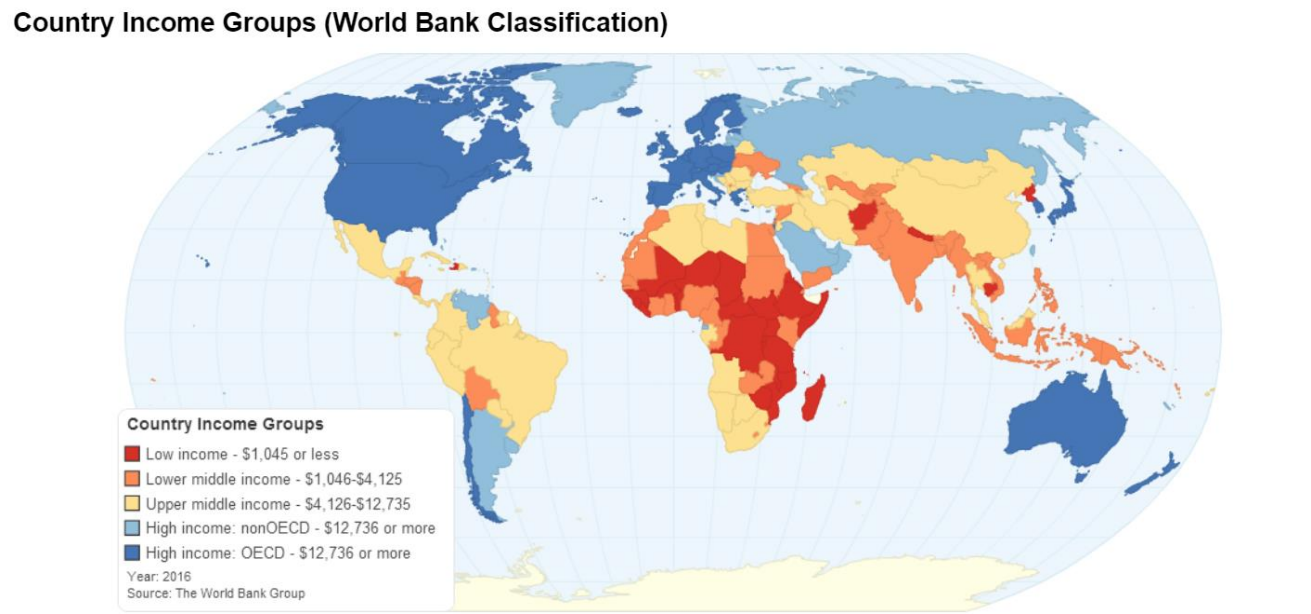
Epithelial cell expressing antigen and dsRNA



Room-temperature stable enteric-coated tablets

Global Norovirus Impact $60 Billion[1] (2016)

Burden of Disease in High Income Countries $34+ Billion



High Income Countries

- U.S., Europe, Japan, others
- 1.2 Billion population

Target Population for Vaccination

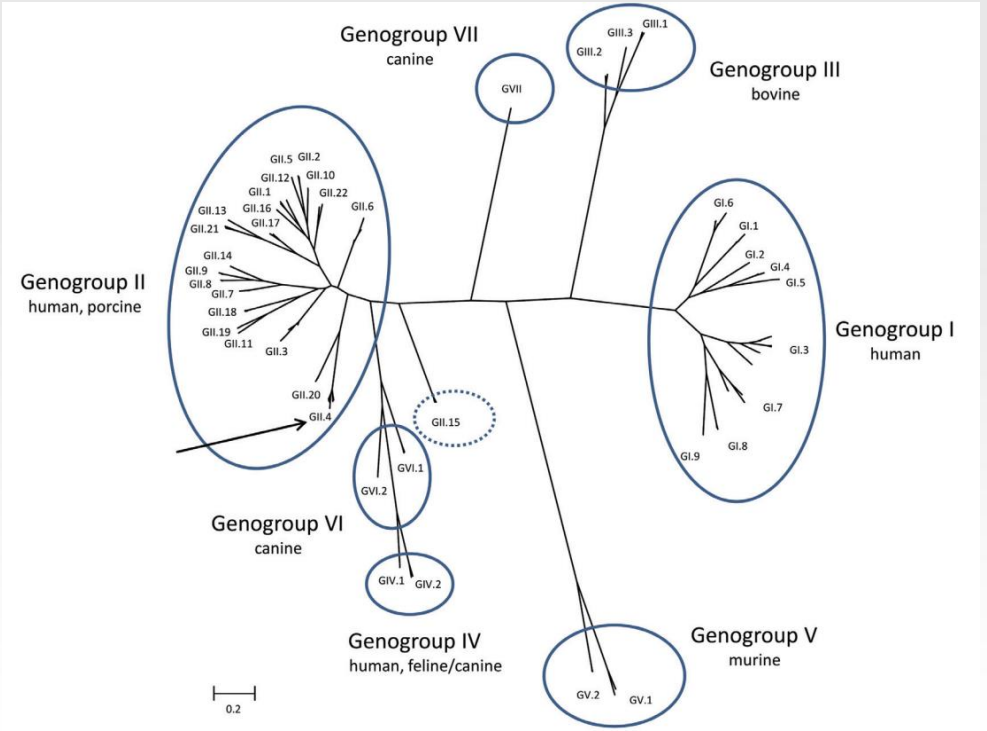
- Older Adults (65+)
- Very Young (6m-4)

Burden of Disease in the US $10.6 Billion, JID July 2020

1) Global Economic Burden of Norovirus, Bartsch S et al., PLOS ONE 2016;

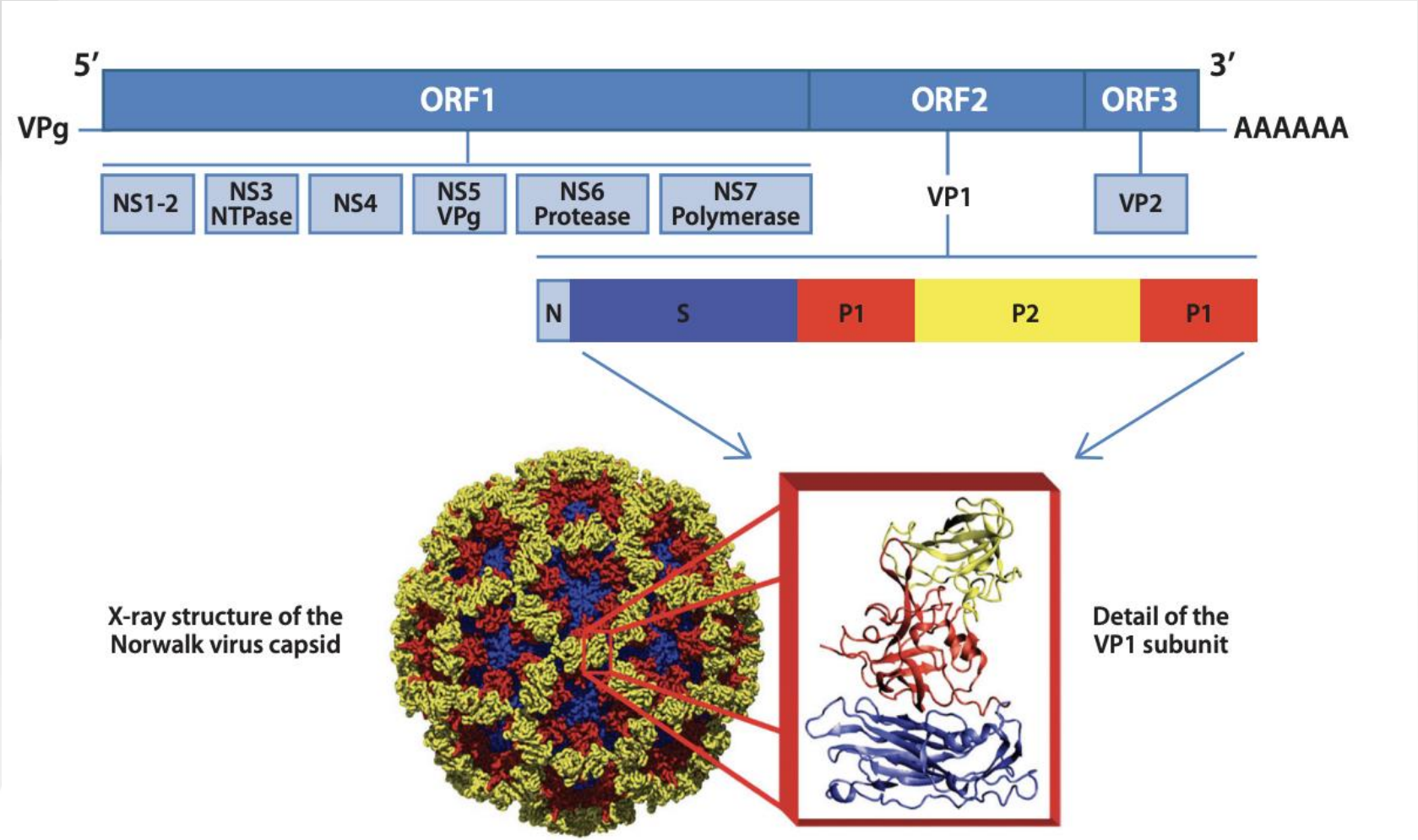
Norovirus biology

- Noroviruses are non-enveloped, single-stranded RNA viruses ~7.5kb
- Highly contagious through fecal-oral transmission
  - 18 - 1000 particles infectious dose
  - 10^{12} viral copies are shed/gram feces
- 7 genogroups (GI to GVII)
  - classified based on amino acid sequence diversity of VP1 capsid
- Difficult to work with the virus
  - Hard to propagate *in-vitro*
  - No good small animal models



VP1 capsid protein is the antigen in oral rAd5 vaccine

VP1 mediates attachment to epithelial cells through interactions with carbohydrates



VXA NVV-104 Study Design and Objectives

Protocol VXA-NVV-104 Objectives:

Primary: The primary objective was to evaluate the safety and tolerability of VXA-GI.1-NN with a 2-dose vaccination schedule in older adults ages 55-80 years old, at 3 dose levels

Secondary: The secondary objective was to assess the immunogenicity of VXA-GI.1-NN with a 2-dose vaccination schedule in older adults ages 55-80 years old, at 3 dose levels

Study Design:

This was a phase 1b, multicenter, randomized, double-blind, placebo-controlled study in health stable older adults 55 to 80 years old.

Study Design and Vaccine Groups

Group	Study Drug	Dose (IU±0.5 log)	No. of Doses	Dosing Schedule	No. of Subjects (Day1/Day29)
Cohort 1 (low dose)	VXA-GI.1-NN	$1x10^{10}$	2	Day 1 & Day 29	16/16
	Placebo	N/A	2	Day 1 & Day 29	8/7
Cohort 2 (medium dose)	VXA-GI.1-NN	$3 x10^{10}$	2	Day 1 & Day 29	16/16
	Placebo	N/A	2	Day 1 & Day 29	8/8
Cohort 3 (high dose)	VXA-GI.1-NN	$1x10^{11}$	2	Day 1 & Day 29	11/11
	Placebo	N/A	2	Day 1 & Day 29	6/5
				Total	**65/63**

VXA NVV-104 Safety – Solicited Adverse Events Dose 1

Topline Results

Summary of Solicited Adverse Events Occurring For 7 Days Following Vaccine Dose 1 (Safety Population)

Dose 1, ages 55-80	Cohort 1 (low dose) N=16	Cohort 2 (medium dose) N=16	Cohort 3 (high dose) N=11	All Cohorts N=43	All Placebo N=22
	n (%)	n (%)	n (%)	n (%)	n (%)
# subjects with any solicited symptoms	4 (25.0)	5 (31.3)	0 (0.0)	9 (20.9)	5 (22.7)
Malaise/Fatigue	3 (18.8)	2 (12.5)	0 (0.0)	5 (11.6)	2 (9.1)
Myalgia (Muscle Pain)	1 (6.3)	1 (6.3)	0 (0.0)	2 (4.7)	2 (9.1)
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Headache	2 (12.5)	3 (18.8)	0 (0.0)	5 (11.6)	3 (13.6)
Fever	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	2 (12.5)	2 (12.5)	0 (0.0)	4 (9.3)	2 (9.1)
Nausea	1 (6.3)	1 (6.3)	0 (0.0)	2 (4.7)	2 (9.1)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal Pain	1 (6.3)	2 (12.5)	0 (0.0)	3 (7.0)	2 (9.1)

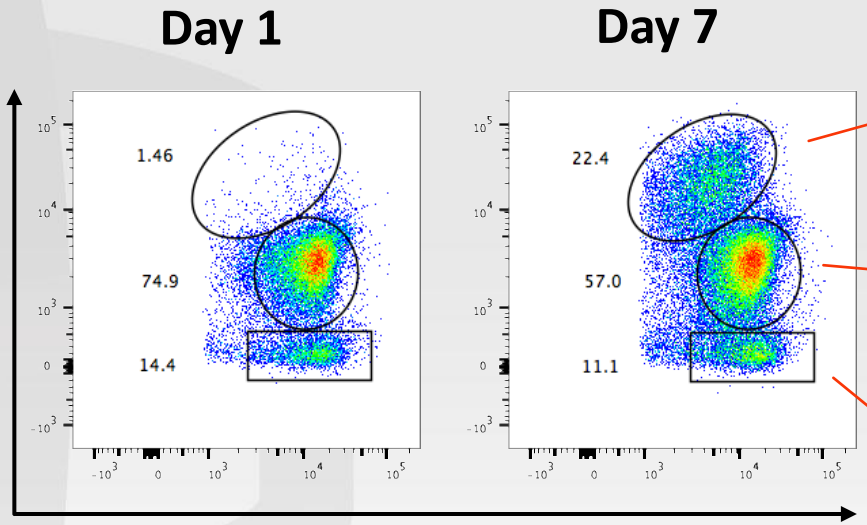
VXA NVV-104 Safety – Solicited Adverse Events Dose 2

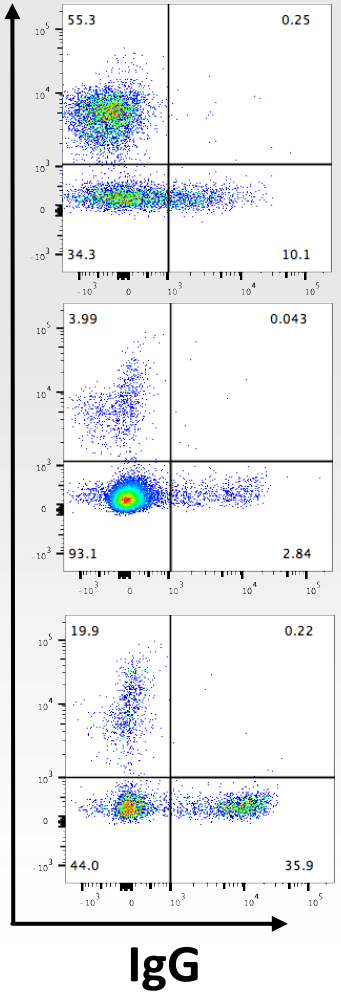
Topline Results

Summary of Solicited Adverse Events Occurring For 7 Days Following Vaccine Dose 2 (Safety Population)

Dose 2, ages 55-80	Cohort 1 (low dose) N=16	Cohort 2 (medium dose) N=16	Cohort 3 (high dose) N=11	All Cohorts N=43	All Placebo N=20
	n (%)	n (%)	n (%)	n (%)	n (%)
# subjects with any solicited symptoms	2 (12.5)	4 (25.0)	0 (0.0)	6 (14.0)	4 (20.0)
Malaise/Fatigue	1 (6.3)	2 (12.5)	0 (0.0)	3 (7.0)	1 (5.0)
Myalgia (Muscle Pain)	1 (6.3)	1 (6.3)	0 (0.0)	2 (4.7)	1 (5.0)
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)
Headache	0 (0.0)	2 (12.5)	0 (0.0)	2 (4.7)	2 (10.0)
Fever	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)
Nausea	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.3)	0 (0.0)
Vomiting	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.3)	0 (0.0)
Abdominal Pain	1 (6.3)	1 (6.3)	0 (0.0)	2 (4.7)	0 (0.0)

Vaxart Oral Norovirus G1.1 Vaccine Elicits Mucosal Homing B cells that are Enriched for IgA Production



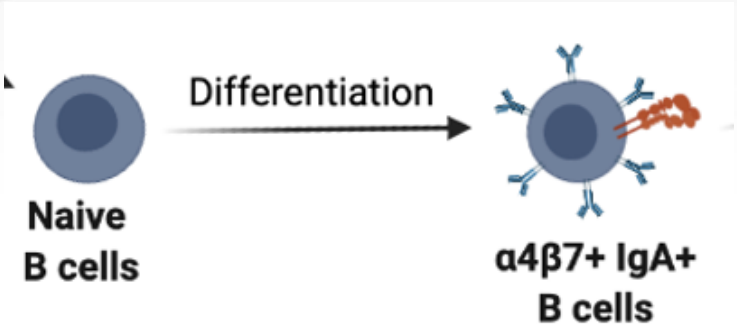


% of IgA+

55.3%

3.99%

19.9%



Kim et al. *JCI,* 2018

Clinical trial # NCT02868073

IgA responses and protection against norovirus

IgA is cross-reactive and can neutralize

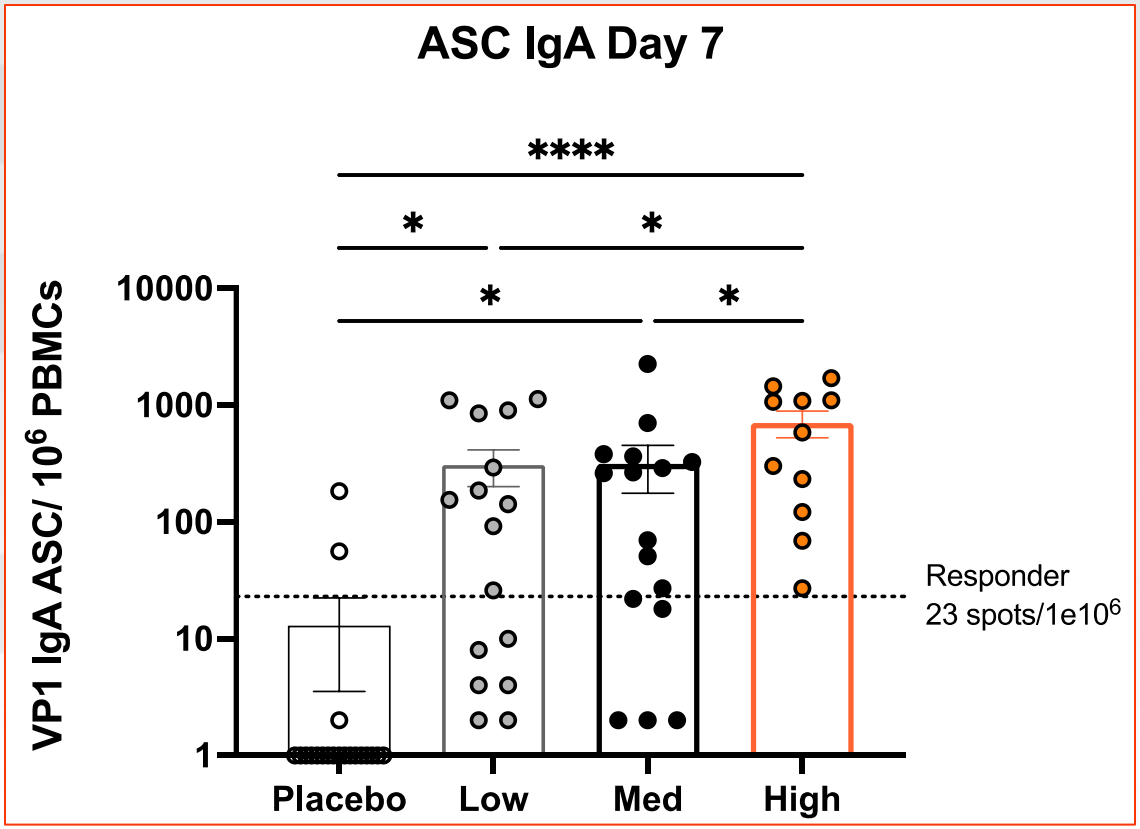
- IgA is more effective at blocking GI.1 VLPs from binding HBGAs than IgG (Sapparuapu et al 2016)
- Serum IgA is cross-reactive against norovirus serotypes and once purified, lower IgA concentrations are needed to to block VLP binding (BT50) than unpurified fraction (Lindesmith, et al, 2015)

IgA responses are a possible correlate for protection

- Norovirus specific IgA is protective against natural infection in a human G1.1 clinical challenge (Ramani et al, 2015)
  - Higher titers of pre-challenge NV-specific salivary IgA, correlated with reduced severity of gastroenteritis
- VLP intranasal immunization elicits elevated serum IgA that correlates with a reduction in illness following challenge (Atmar et al, 2011)
  - Serum BT50 did not correlate with protection

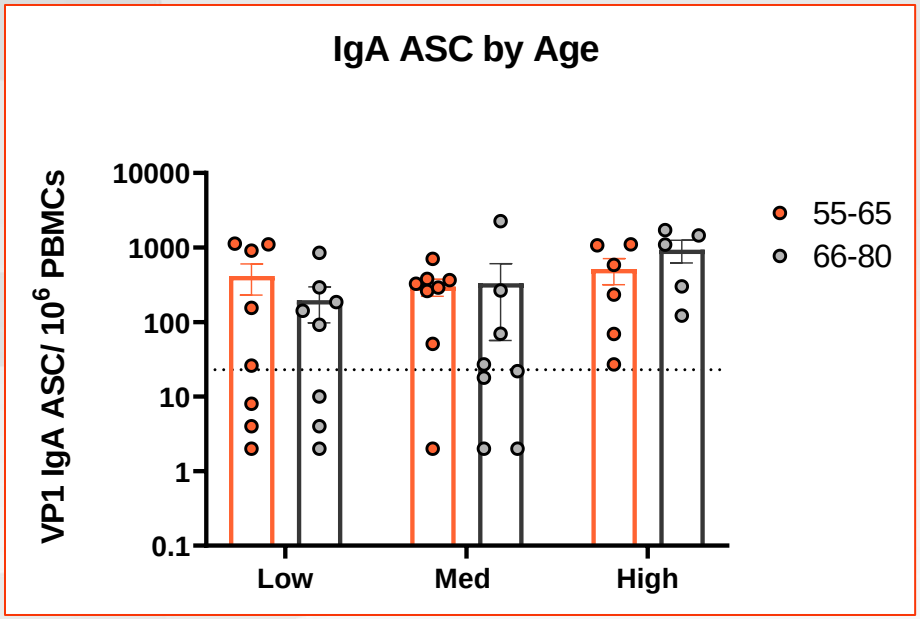
Ramani, et al, Mucosal and Cellular Immune Responses to Norwalk Virus JID 2015
Atmar, et al, Norovirus Vaccine against Experimental Humand Norwalk Virus Illness NEJM 2011
Sapparapu et al, *Frequent use of the IgA Isotype in Human B cells Encoding Potent Norovirus-specific Monoclonal Antibodies that Block HBGA Binding*, Plos Path 2016
Lindesmith et *al Serum Immunoglobulin A Cross-Strain Blockade of Human Noroviruses*, ORID 2015

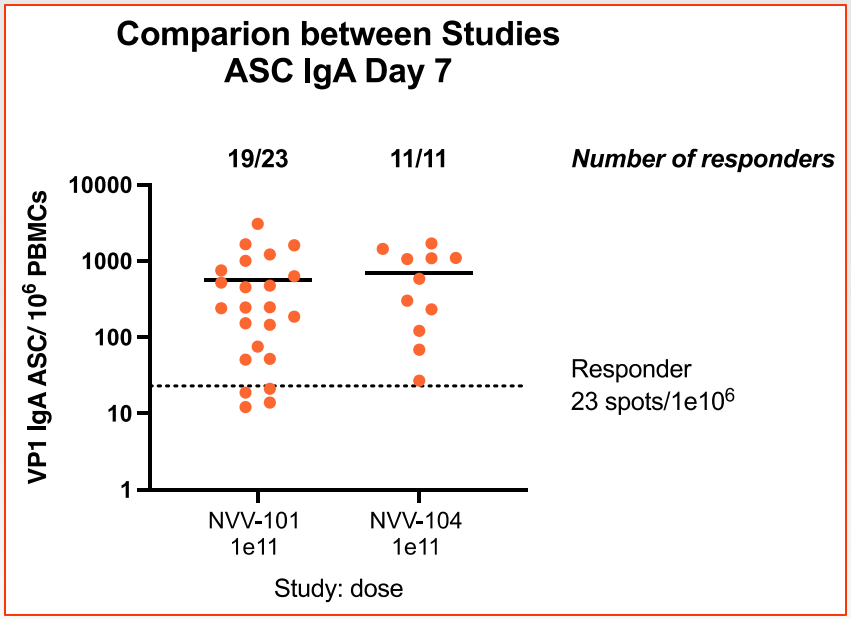
Anti-VP1 (G1.1) IgA ASC Responses Significantly Increase 7 days Post Immunization



ASC = antibody secreting cells

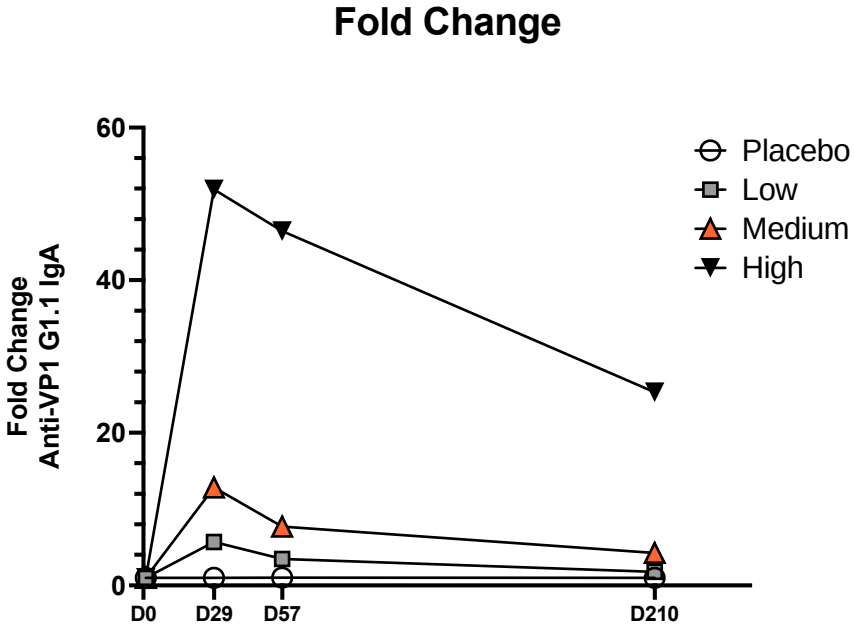
No difference in ASC IgA response is detected when stratifying by age or when comparing to previous G1.1 monovalent clinical trials

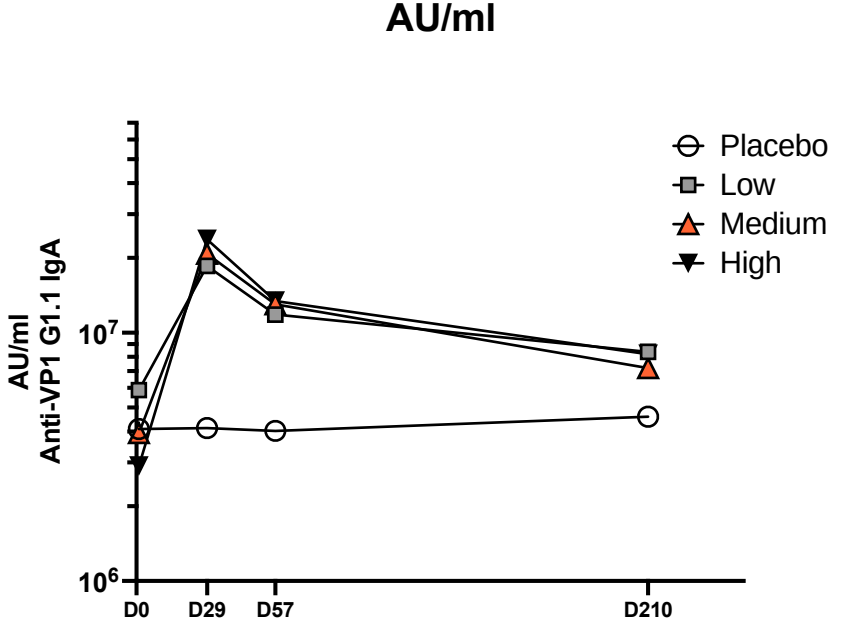




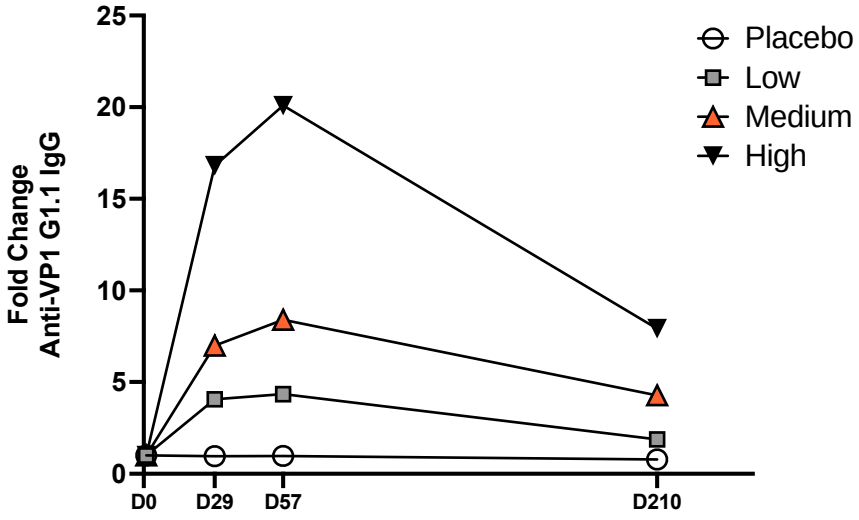
Cut-off for responder (dotted line) is 23 spots

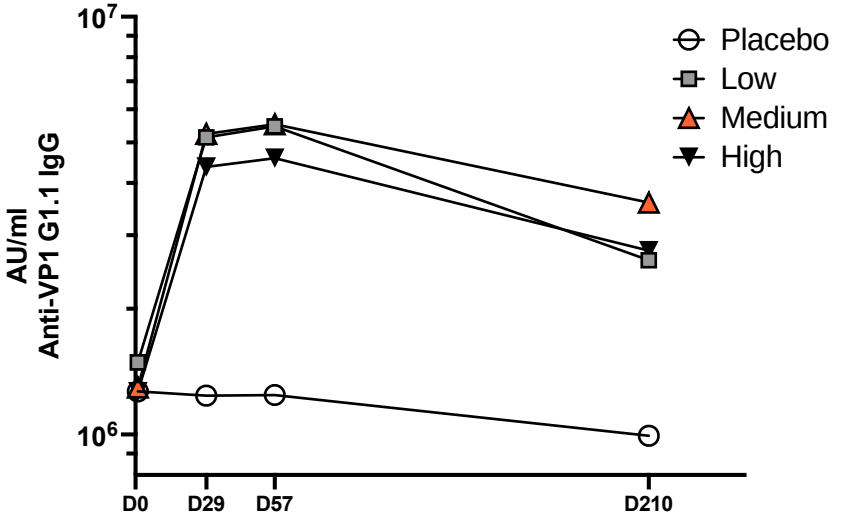
Sustained Serum IgA Antibody Responses after 200 days





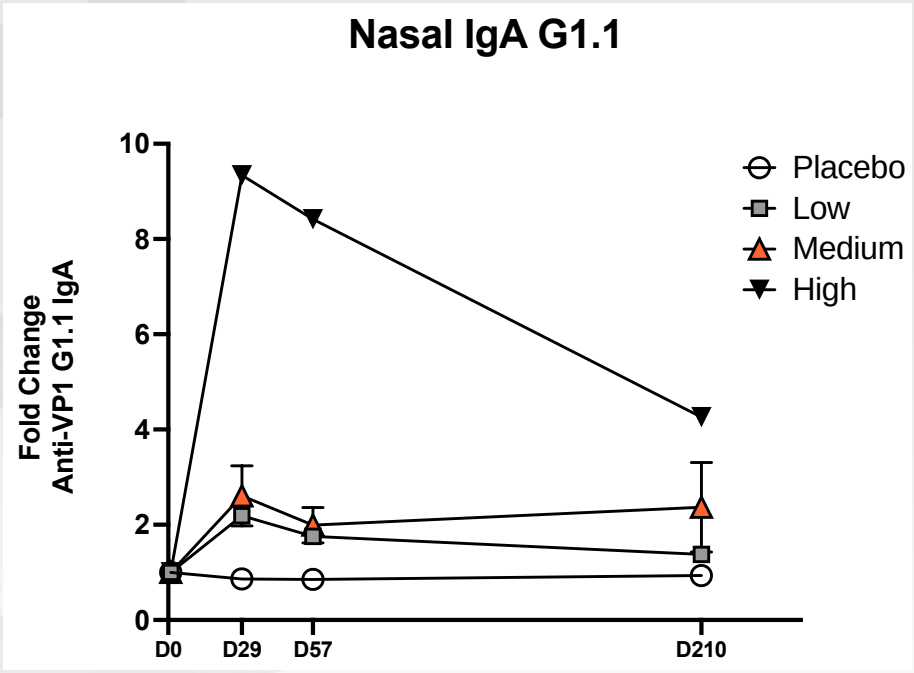
Sustained Serum IgG Antibody Responses after 200 days



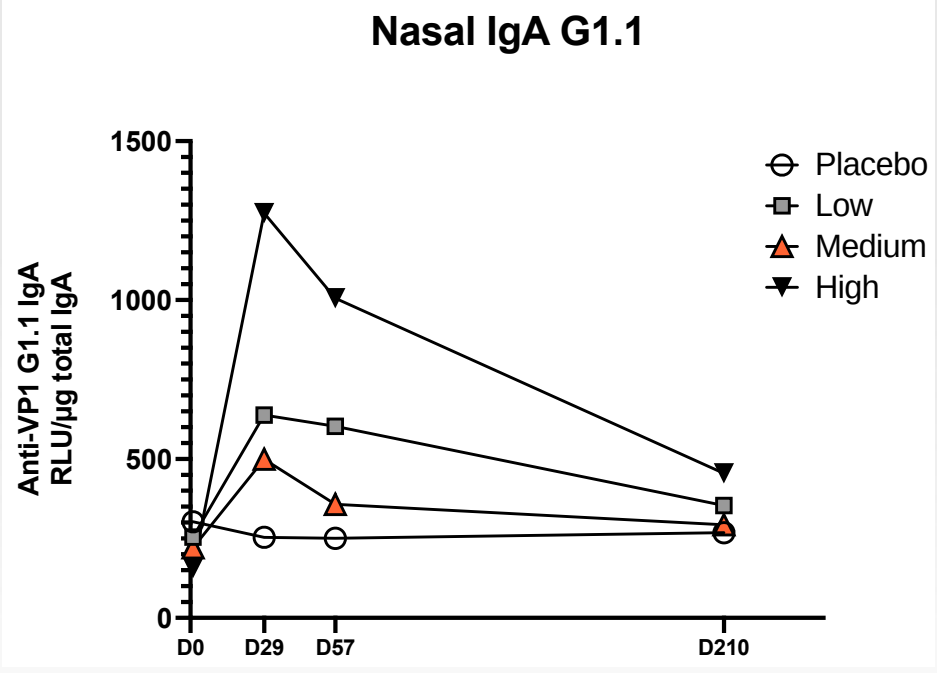


Distal mucosal IgA is detected in subjects given norovirus vaccine

Fold Change



MSD RLU per µg of Total IgA



Summary

- Vaccine was safe and well tolerated
- Vaccine provided dose dependent immune response in the elderly (55-80yo) that paralleled findings in 18-55yo
- Immune responses were both:
  - Mucosal: IgA
  - Systemic IgA and IgG (MSD) & IgA (ASC)
  - Durable immune responses of 200+ Days

Next Steps

VXA-NVV-201 – Challenge Study (begun in 2022)

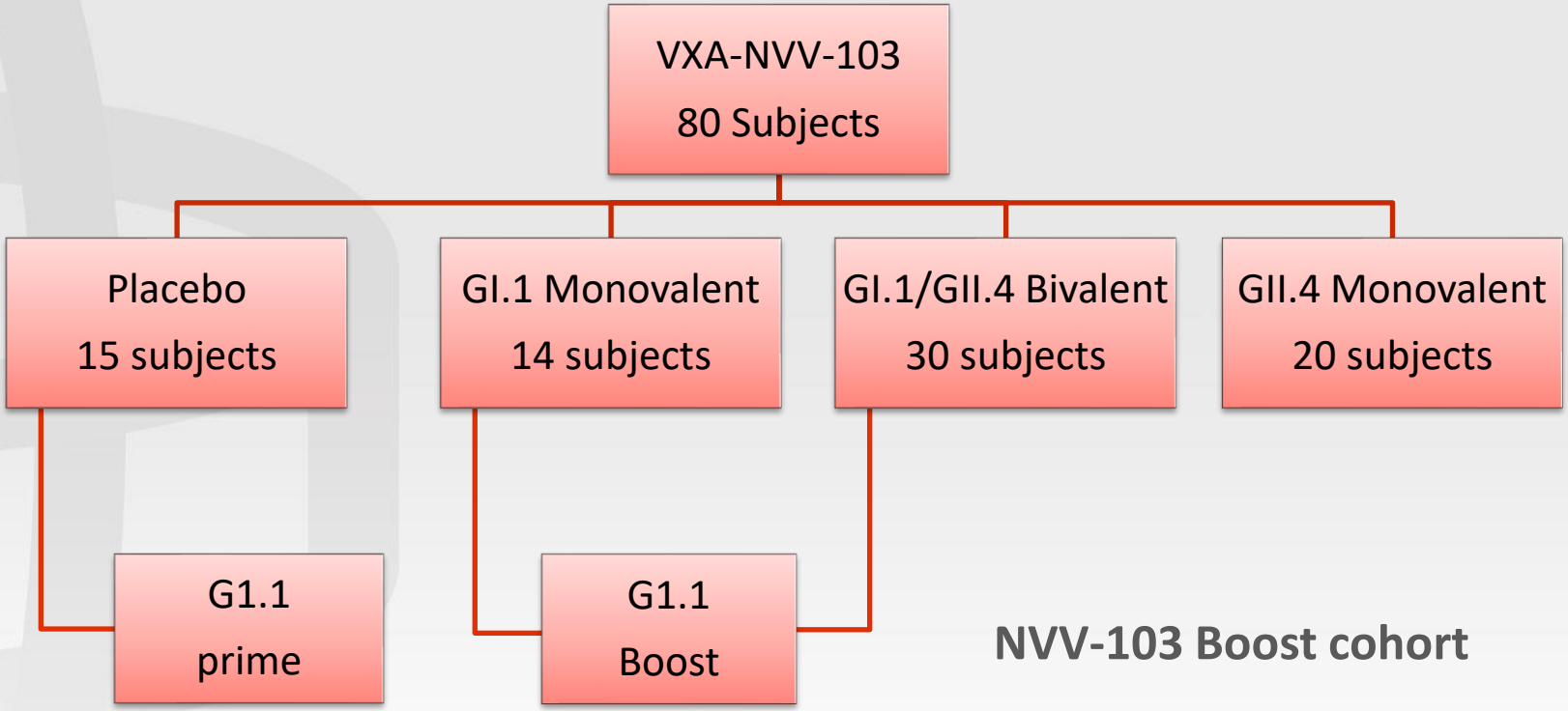
A Phase 2 Randomized, Placebo-Controlled, Norovirus G1.1 Challenge Study Following Administration of an Oral Adenoviral-vector GI.1-NN Vaccine

- Active Vaccine: GI.1 Norwalk VPI Vaccine (VXA-G1.1-NN)
  - Single dose administration @ $1x10^{11}$ I.U.
- Placebo Control: Matching oral tablets
- Challenge Virus: Norovirus GI.1
  - Norwalk Virus Inoculum Lot 001-09NV, IND 14697 (UNC)
  - Dose: $1x10^{6}$ GC: A dose which allows 60% - 70% infectivity in the healthy adult population (per NV infection rate observed in the ongoing viral titration study under protocol VXA-G1.1-201.1)
- The data collected from this study will help to inform what is the best correlate for our norovirus vaccine

- Questions?

Appendix

Can we boost 18 months after prime?

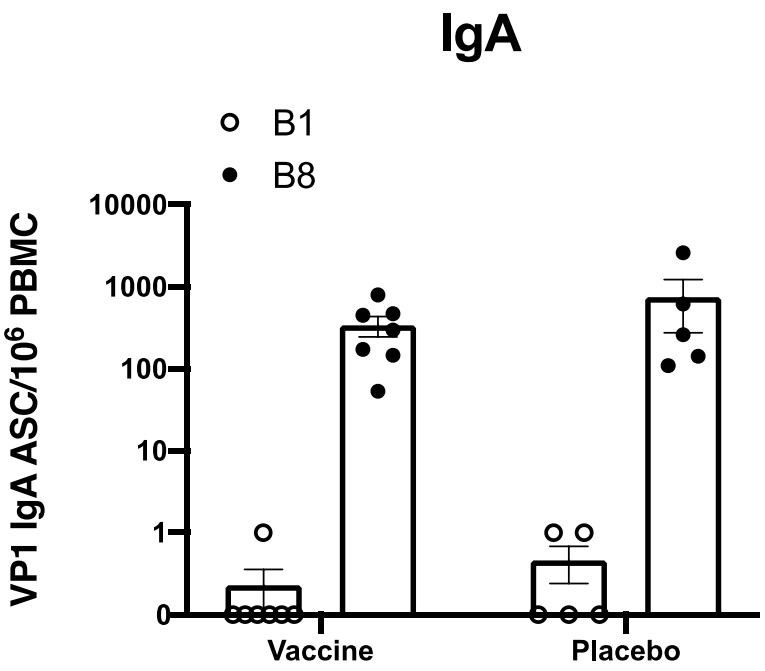


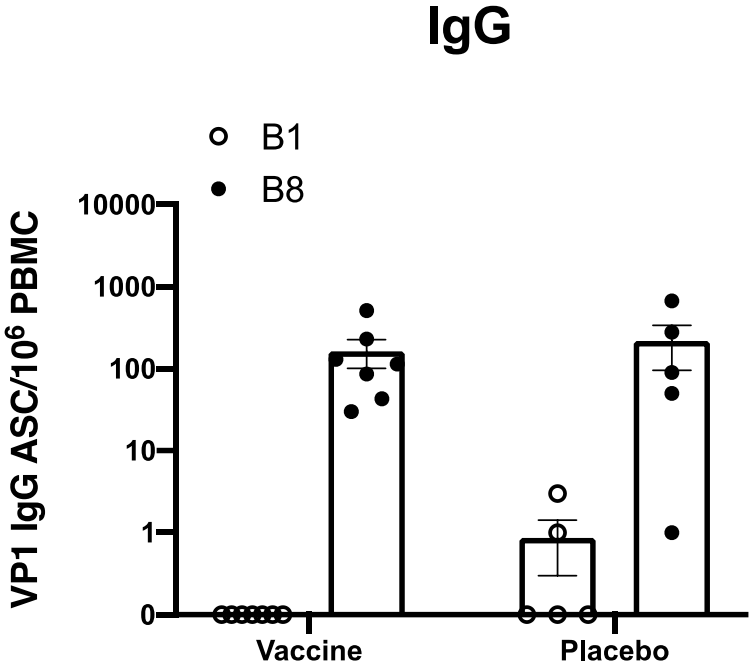
NVV-103 Boost cohort

n = 5
prior placebo

n = 7
prior vaccinated

Anti-VP1 (G1.1) IgA and IgG ASC Responses Increased 7 days Post Boost Immunization

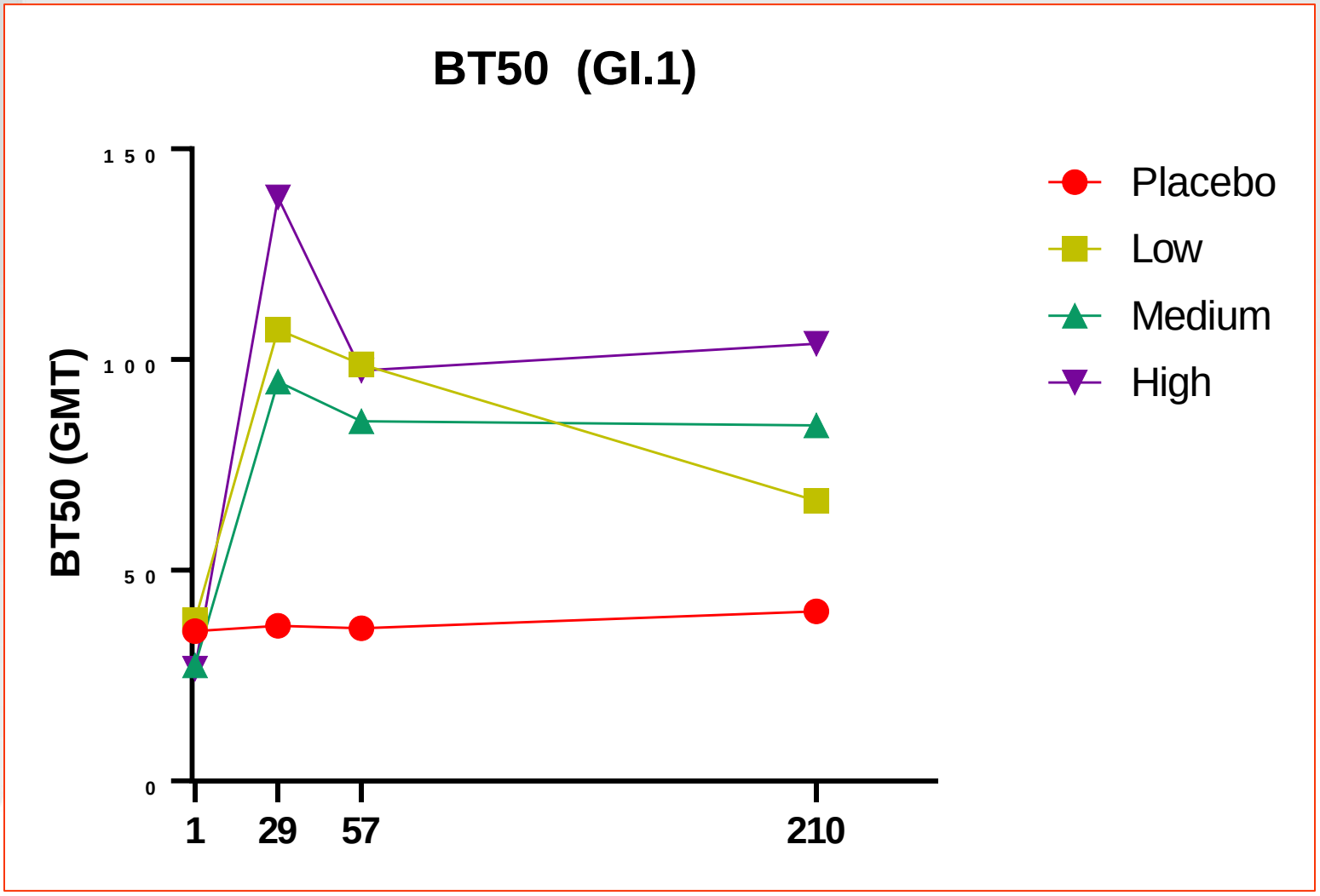




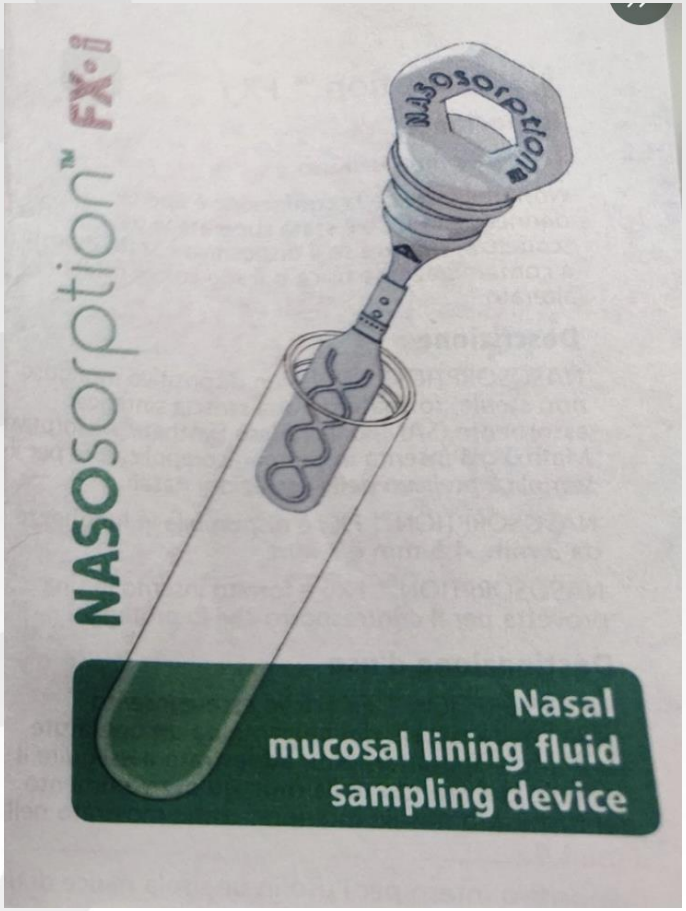
No significant difference between subjects that received a prior oral norovirus vaccine and those who were not previously vaccinated

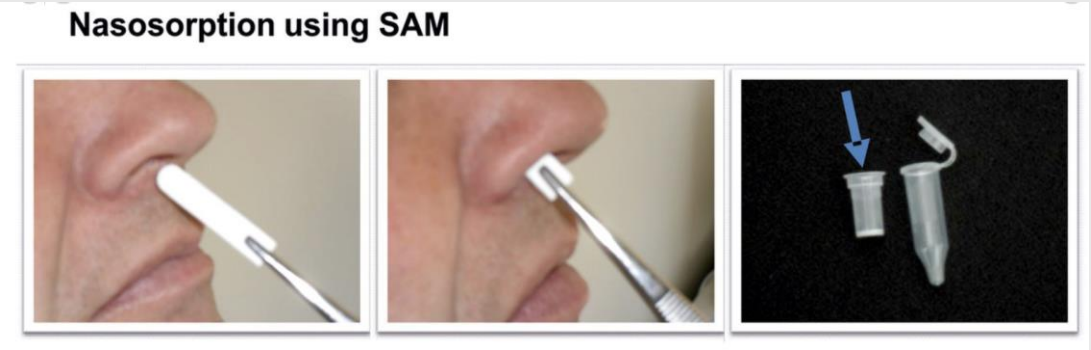
BT50 is maintained for >210 days

VXA-NVV-104 – BT50



Nasosorption (SAM) devices





- Currently exploring this as another option
  - NVV-106 - optimization
  - NVV-105 – first real test
- Can an orally deliver vaccine that targets the ileum induce mucosal crosstalk??