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Cholera Human Challenge as Pivotal Efficacy Study

2nd Human Challenge Trials in Vaccine Development
September 28-30

October 10, 2017

Outline

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- Background: cholera/cholera vaccines
- History of CVD 103-HgR
- Challenge study design
- Primary efficacy outcomes
- Bridging to other populations
- Additional benefits
- Potential next steps

What is Cholera?

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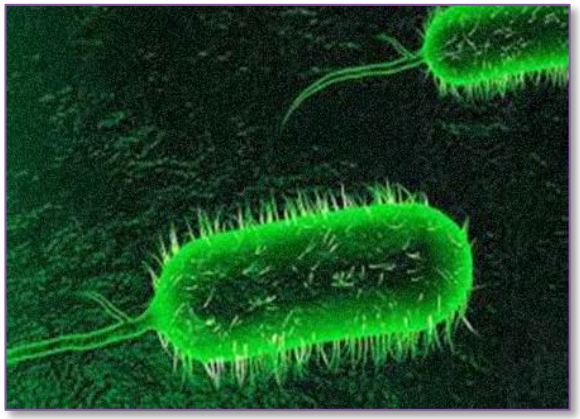
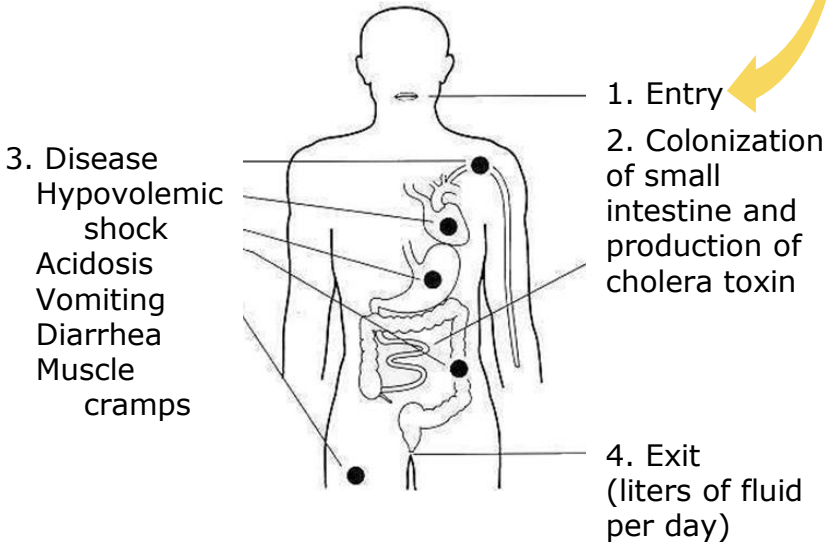
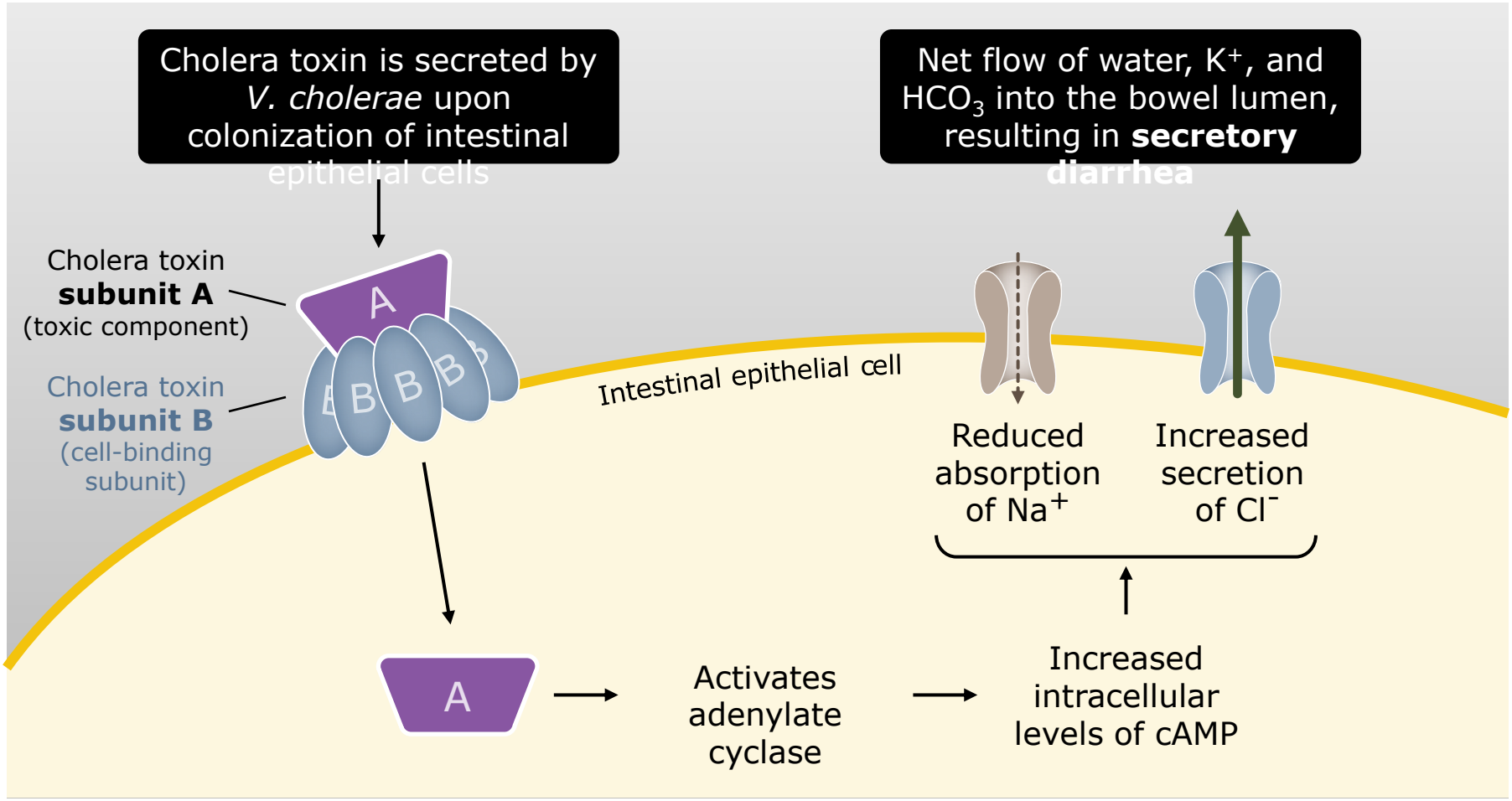
- Infection by the bacteria *Vibrio cholerae*.
- Caused by ingesting water or food contaminated by *V. cholerae*
- Non-invasive diarrheal disease
- Morbidity due to life-threatening secretory diarrhea induced by enterotoxin secreted by *V. cholerae*
- Major epidemic disease





Disease Is Mediated by Cholera Toxin Subunit A[1]



cAMP=cyclic adenosine monophosphate.

1. Reidl J, et al. *FEMS Microbiol Rev*. 2002;26:125-139.

Cholera Vaccines

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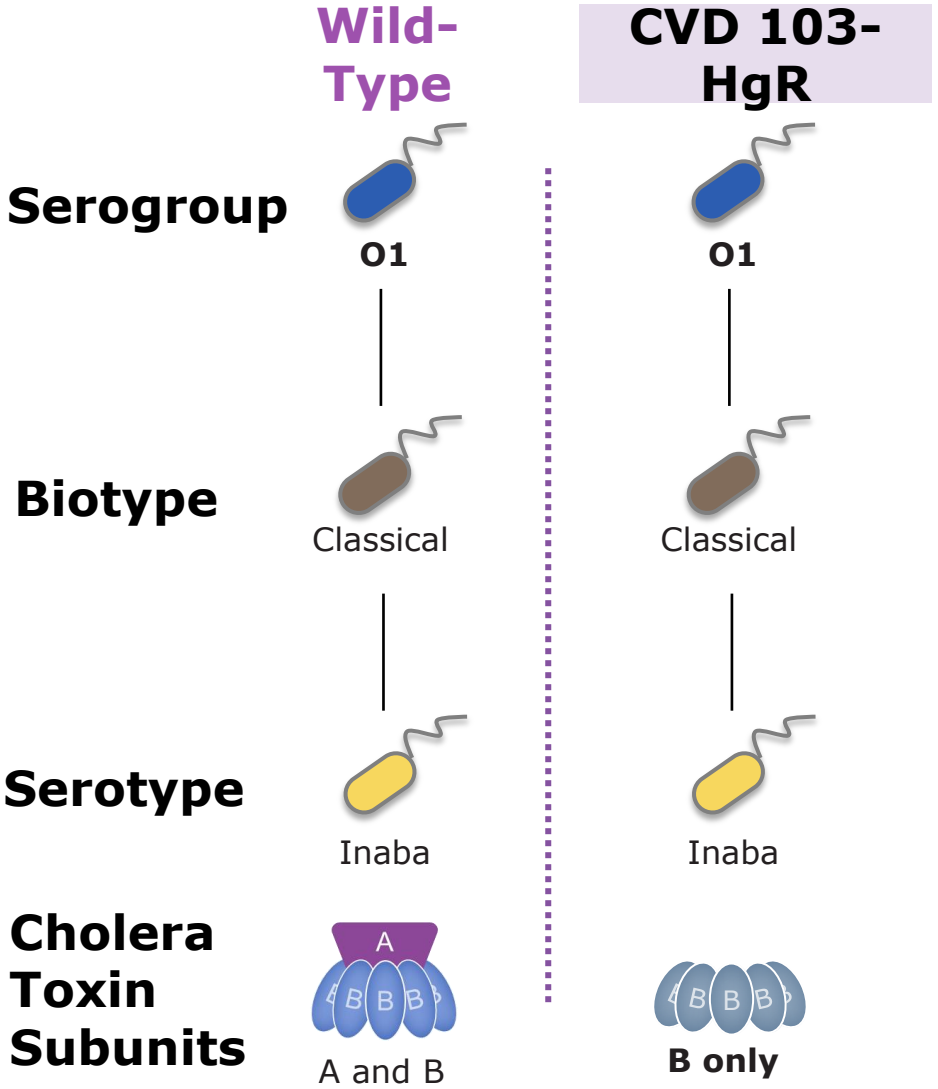
- Parenteral whole inactivated
  - Little or modest efficacy
  - Not available since the 1980s
- Oral inactivated 2-dose vaccines
  - Used in epidemic/endemic areas
    - Inactivated whole cell (O1) + rB subunit of cholera toxin (also travelers)
    - Inactivated whole cell (O1 and O139)
- Oral live attenuated single dose
  - CVD 103-HgR (now "Vaxchora")
    - CVD 103-HgR previously used in endemic areas/travelers
    - Vaxchora recently approved in US for travelers, with efficacy based on challenge studies

CVD 103-HgR Vaccine Attenuation



CVD 103-HgR has both *ctxA* genes disabled, preventing synthesis of subunit A

CVD 103-HgR still synthesizes the immunogenic (but non-toxic) subunit B

1. VaxchoraTM [package insert]. Hamilton, Bermuda: PaxVax Bermuda Ltd.; 2016.

History of CVD 103-HgR

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- Engineered in 1980's at U of Md
- Live attenuated *V. cholerae* Strain
  - O1 Classical Inaba
  - Non-toxigenic (94% gene for A subunit of cholera toxin deleted)
- Developed by Swiss Serum Inst/Berna

- Licensed in 16 countries (including Canada, Australia, Finland, Switzerland, New Zealand, Argentina), but never licensed in US
- Over half million doses distributed
- Crucell purchased Berna in 2006 and did not pursue CVD 103-HgR, as it markets Dukoral

Previous Challenge Studies: Single-Dose CVD 103-HgR - All

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Severity	Vacc	Ctrls	Efficacy	p
> 5.0 liters	1/103	10/86	92%	<.002
> 3.0 liters	1/103	16/86	95%	<.001
> 1.0 liter	7/103	41/86	96%	<.001
Any	19/103	54/86	76%	<.001

Composite of 8 separate challenges with El Tor Inaba, El Tor Ogawa, classical Inaba and classical Ogawa

Significant protection is already present 8 days after ingesting the single dose

Previous Challenge Studies: Single-Dose CVD 103-HgR – El Tor

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Severity	Vacc	Ctrls	Efficacy	p
> 5.0 liters	1/64	10/47	92%	<.002
> 3.0 liters	1/64	16/47	95%	<.001
> 1.0 liter	8/64	34/47	96%	<.001
Any	19/64	31/47	76%	<.001

Composite of challenges with El Tor Inaba and El Tor Ogawa

Significant protection is already present 10 days after ingesting the single dose

Redevelopment of CVD 103-HgR

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- CVD 103-HgR was approved and marketed in certain countries as "Orochol" a single dose, live-attenuated vaccine against cholera
- PaxVax is redeveloping this vaccine for US and EU
  - Initially targeted towards developed world: travelers, aid workers, military
- Pre-IND discussions
  - Re-confirm of safety and immunogenicity of PaxVax formulation of CVD 103-HgR (PXVX0200 [ultimately Vaxchora®])
    - Small phase 1 study and Phase 3 safety and immunogenicity
  - ***Efficacy to be demonstrated in cholera challenge study***
    - Field trial for targeted population not feasible due to low rate of cholera infections
    - Populations in endemic areas will require different formulation
      - Higher dose, improved stability and presentation

Rationale for Challenge Studies – Safety

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- Since mortality or significant morbidity is entirely due to fluid loss, fluid and electrolyte replacement, orally or IV, protects the volunteers
- Antibiotic rescue therapy if needed, is also available
- Many previous cholera challenge studies have confirmed that ongoing fluid replacement protects both placebo and vaccine recipients

Rationale for Challenge Studies - Efficacy

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- Field efficacy in US/European population not feasible
- Cholera challenge mirrors natural cholera, at least in immunologically naïve subjects
- Cholera morbidity/mortality is mainly, if not entirely, due to copious diarrhea, leading to life threatening fluid/electrolyte depletion
- Prevention of significant diarrhea in challenge study should mirror natural cholera
- Vaccine efficacy can be inferred from prevention of significant diarrhea and fluid loss
  - Although human challenge studies have shown efficacy in various diseases – influenza, malaria – no vaccine previously approved on the basis of efficacy in challenge studies

Overview of CVD 103-HgR Redevelopment Program (1)

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- Small Phase 1 placebo-controlled study (66 participants) to confirm safety – not final formulation
- Phase 3 program – following pre-Ph 3 meeting with FDA
  - Efficacy based on cholera (El Tor Inaba) placebo-controlled challenge at 10 or 90 days post-vaccination
    - Vaccine Efficacy: LB 95% CI ≥ 30%
    - Pooled placebo group from 10 and 90 day challenges

Overview of CVD 103-HgR Redevelopment Program (2)

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- Safety and immunogenicity from placebo-controlled lot consistency (≥3000 subjects) and "older" adults, 45-64 yrs (400 subjects) studies
  - Protective immunogenicity inferred from challenge study, allowing bridging to lot consistency study and other populations
- BLA approved by US FDA in June, 2016
- Phase 4 Study in Children – Ongoing
- Formulation improvement - Ongoing

Efficacy – Human Cholera Challenge Study

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Goal: Pivotal vaccine efficacy (VE) study for regulatory approval

Objectives:

- 95% CI for VE ≥ 30% at 10 days post-vaccination challenge
- 95% CI for VE ≥ 30% at 90 days post-vaccination challenge

Design: Double blind placebo controlled V:P = 1:1 (5x10^8 CFU)

  - 50% blood group O *(to target mod/sev diarrhea rate of 45% in placebo group)*

- Single dose with challenge at 10 or 90 days
- 1x10^5 CFU El Tor Inaba challenge

Subjects: Healthy adults 18-45 years

Primary Endpoint: Moderate/severe diarrhea (total liquid stools ≥ 3L)

Secondary Endpoints: Vibriocidal antibody seroconversion, GMT, peak titer, memory B cells, anti-CT antibody, duration of V. vholerae shedding, tolerability of vaccine pre-challenge

Sites: Experienced in-patient units

  - U of MD, U of VT, Cincinnati U

Challenge Immunogenicity
Vibriocidal Antibody Response

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	Day 0	Day 7	Day 10	Day 28
GMT (95% CI)				
Placebo	49 (36 – 68)	51 (36 – 73)	50 (36 – 71)	37 (25 – 55)
Vaccine	36 (27 – 48)	806 (532 – 1,223)	4,250 (2,801 – 6,437)	1,377 (849 – 2,233)
Type O	39 (26-59)	872 (503-1,512)	4,290 (2,505-7,347)	1,599 (821-3,115)
Non-O	33 (22-48)	744 (388-1,425)	4,209 (2,183-8,117)	1,191 (570-2,489)
% Seroconversion (95% CI)				
Placebo	-	2 (0-5)	2 (0-5)	2 (0-5)
Vaccine	-	82 (74-90)	90 (84-96)	90 (84-96)

Primary Efficacy Endpoint – Prevention of Moderate/Severe Diarrhea

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Parameter	Vaccine 10-Day N=35	Vaccine 3-Month N=33	Placebo N=66
Attack Rate – Total liquid stool volume ≥ 3L	6%	12%	59%
Vaccine Efficacy	90%	79%	
LB 95% CI	63%	50%	

Met primary endpoints of 95% CI low ≥30%
10-Day and 3-Month challenge

Percent of Subjects with Diarrhea
(≥2 loose stools over 48 hrs ≥ 200 mL or a single loose stool ≥ 300 ml)

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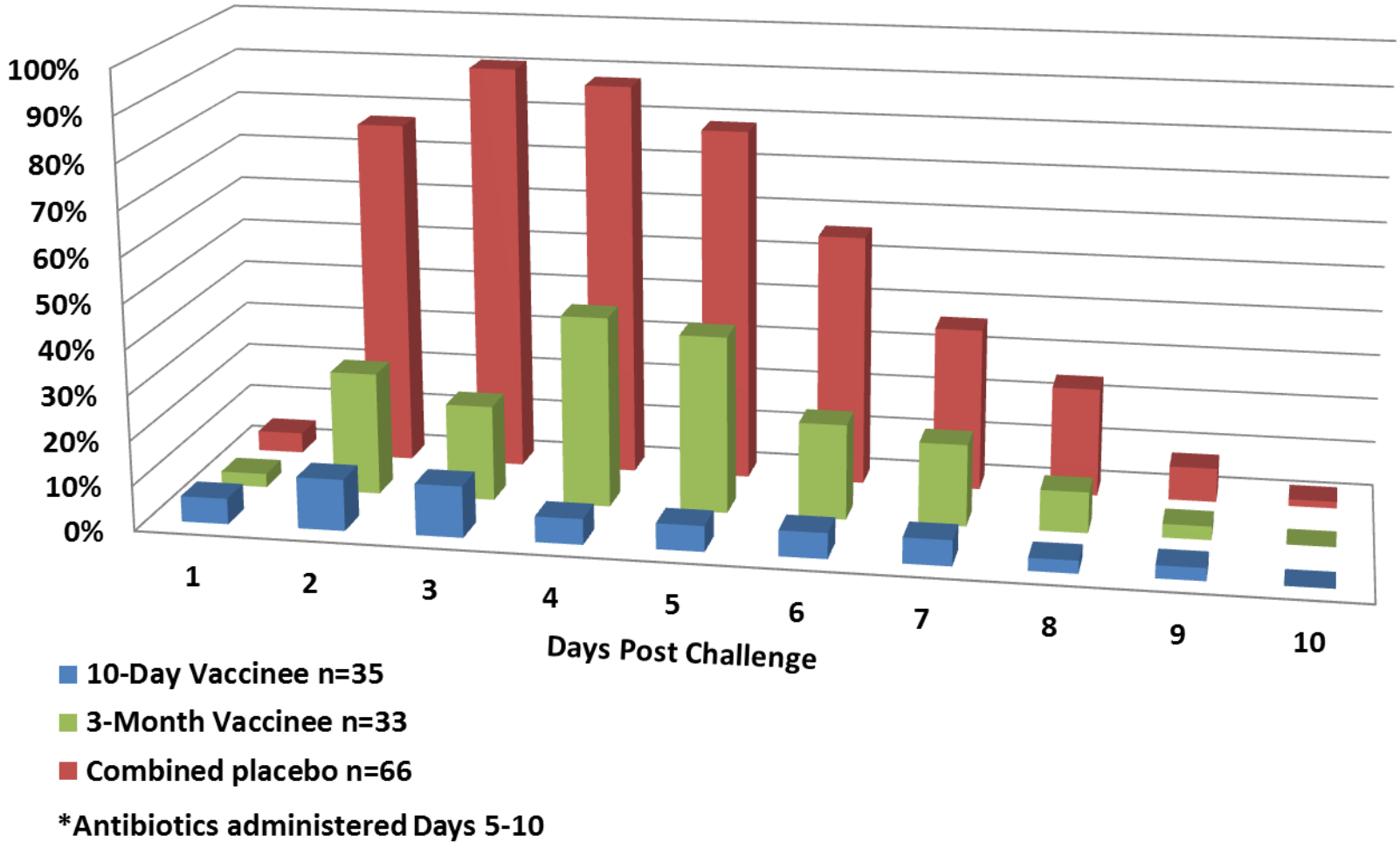

Average Volume of Diarrhea (L) by Day

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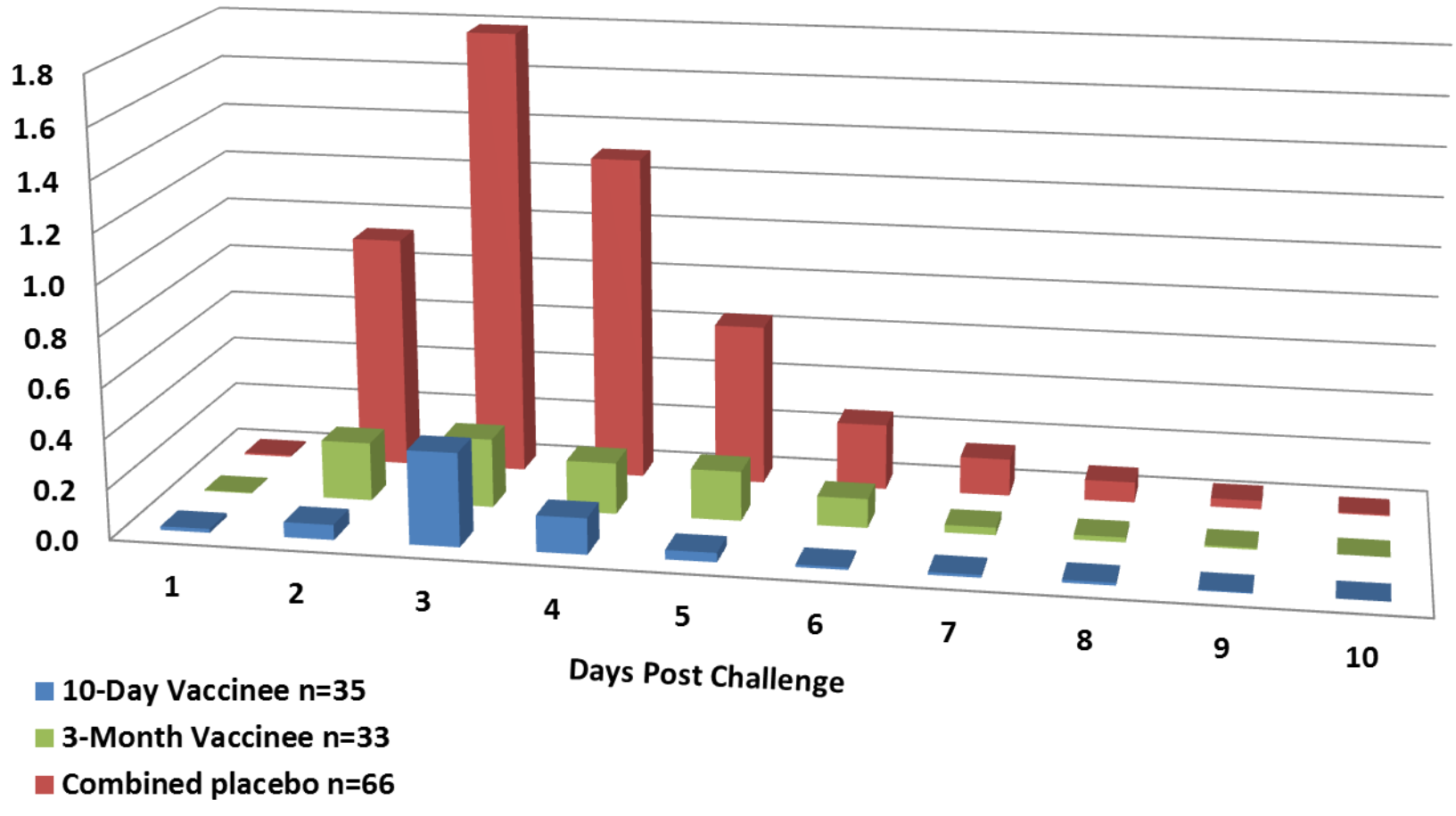

*Cumulative total per group divided by n; antibiotics administered Days 5-10

Average Number of Diarrheal Stools by Day

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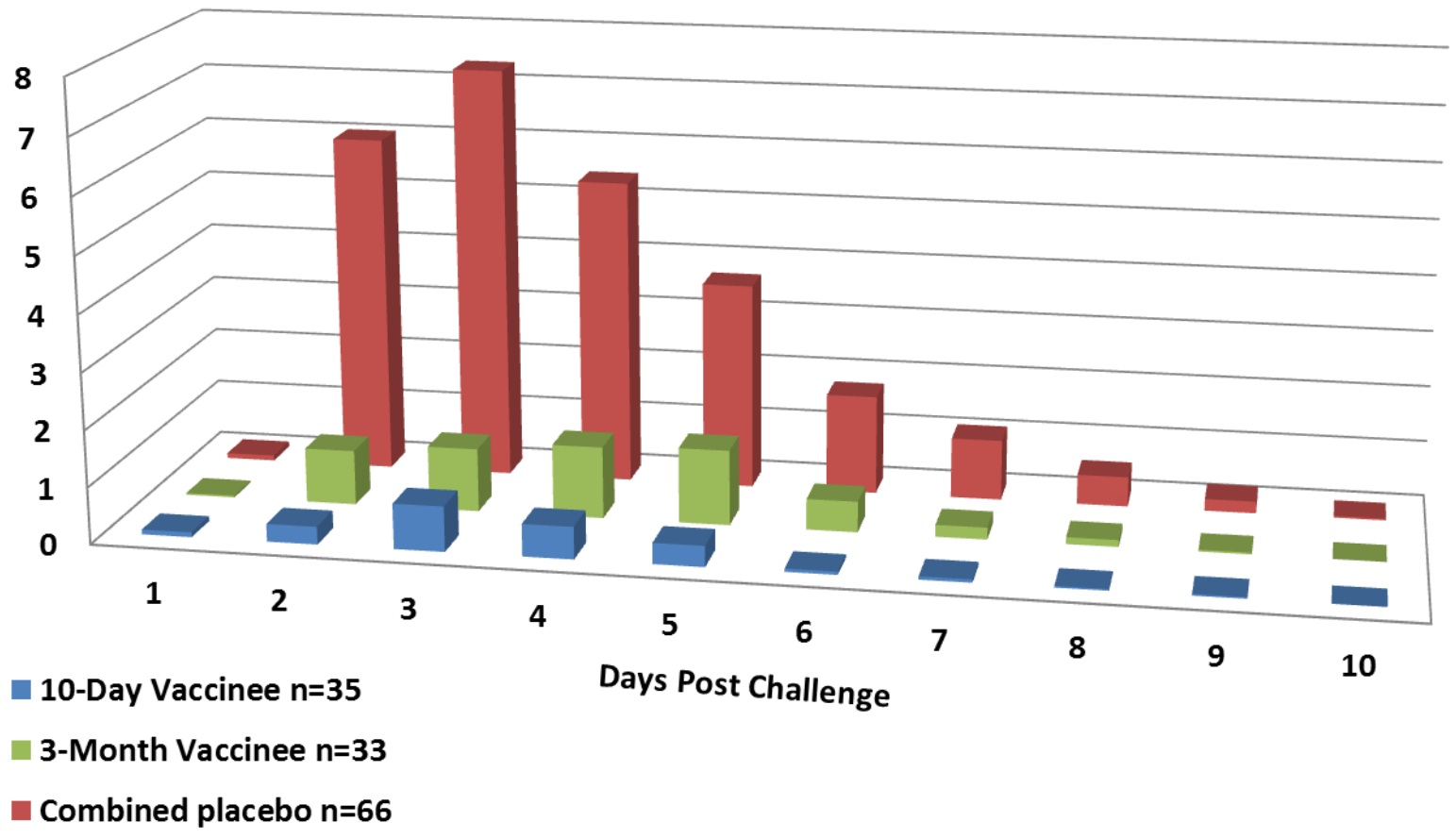

*Cumulative total per group divided by n; antibiotics administered Days 5-10

Median Peak *V. cholerae* CFU/g

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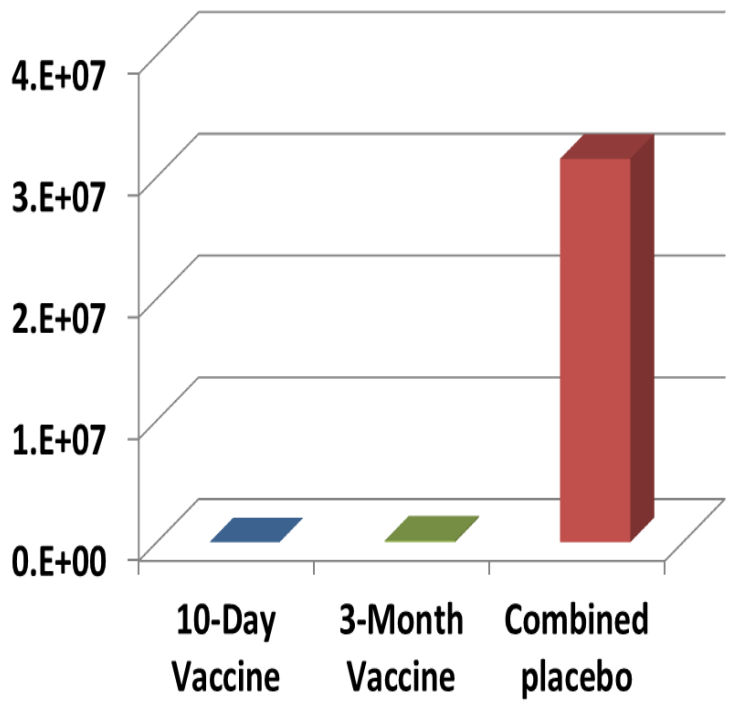
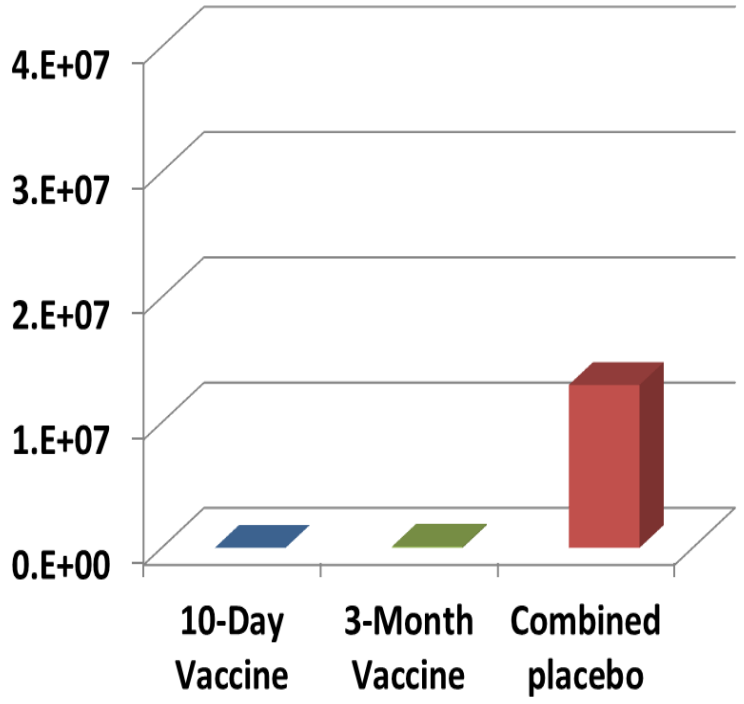
All Subjects



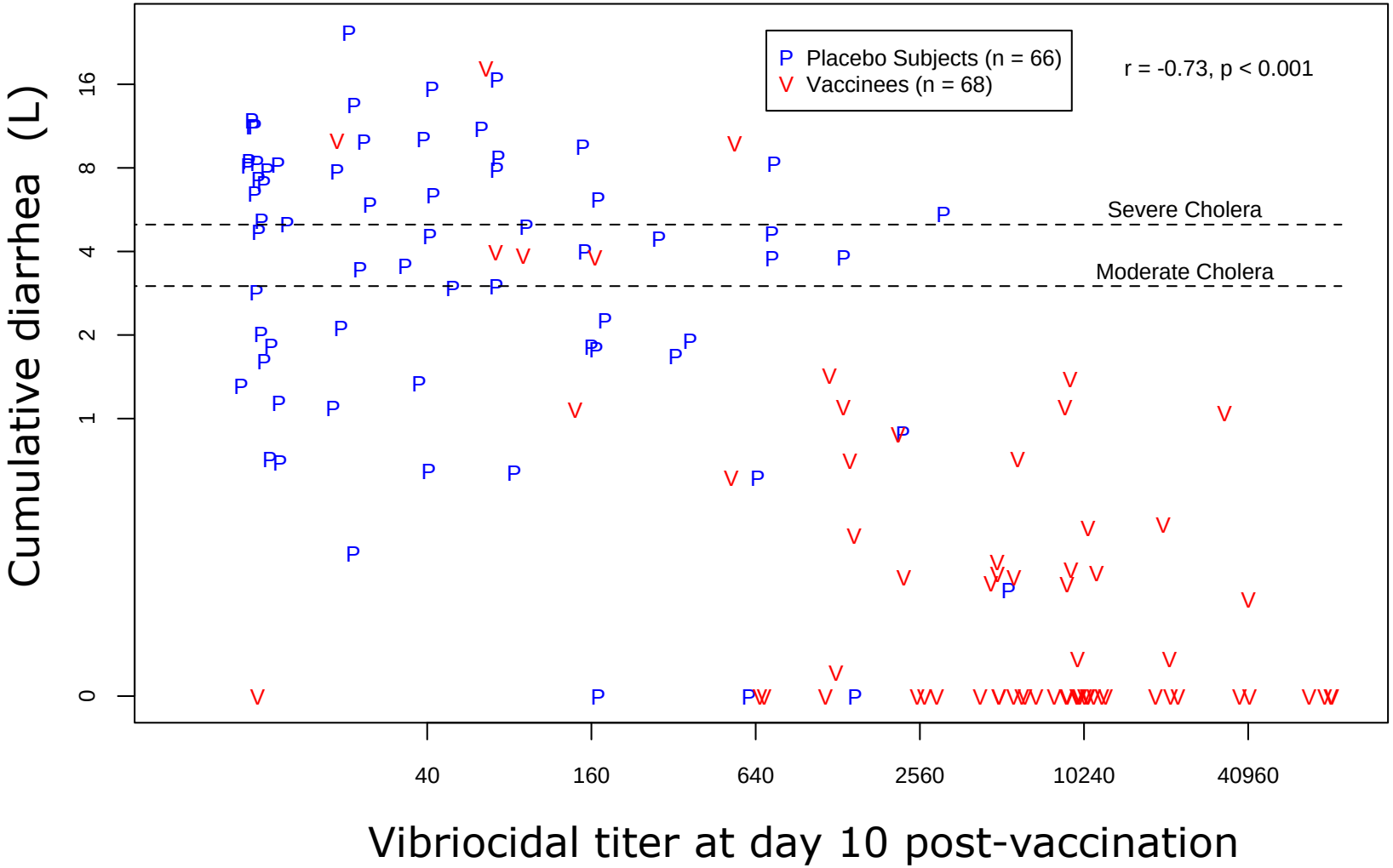
No.	35	33	66
CFU/g	0	1E+05	3E+07
% red	100	99.6	NA

Subjects without diarrhea



No.	30	18	5
CFU/g	0	8E+04	1E+07
% red	100	99.3	NA

Vibriocidal Antibody Titer as Immune Correlate of Protection



Vibriocidal Antibody Seroconversion as Immune Correlate of Protection

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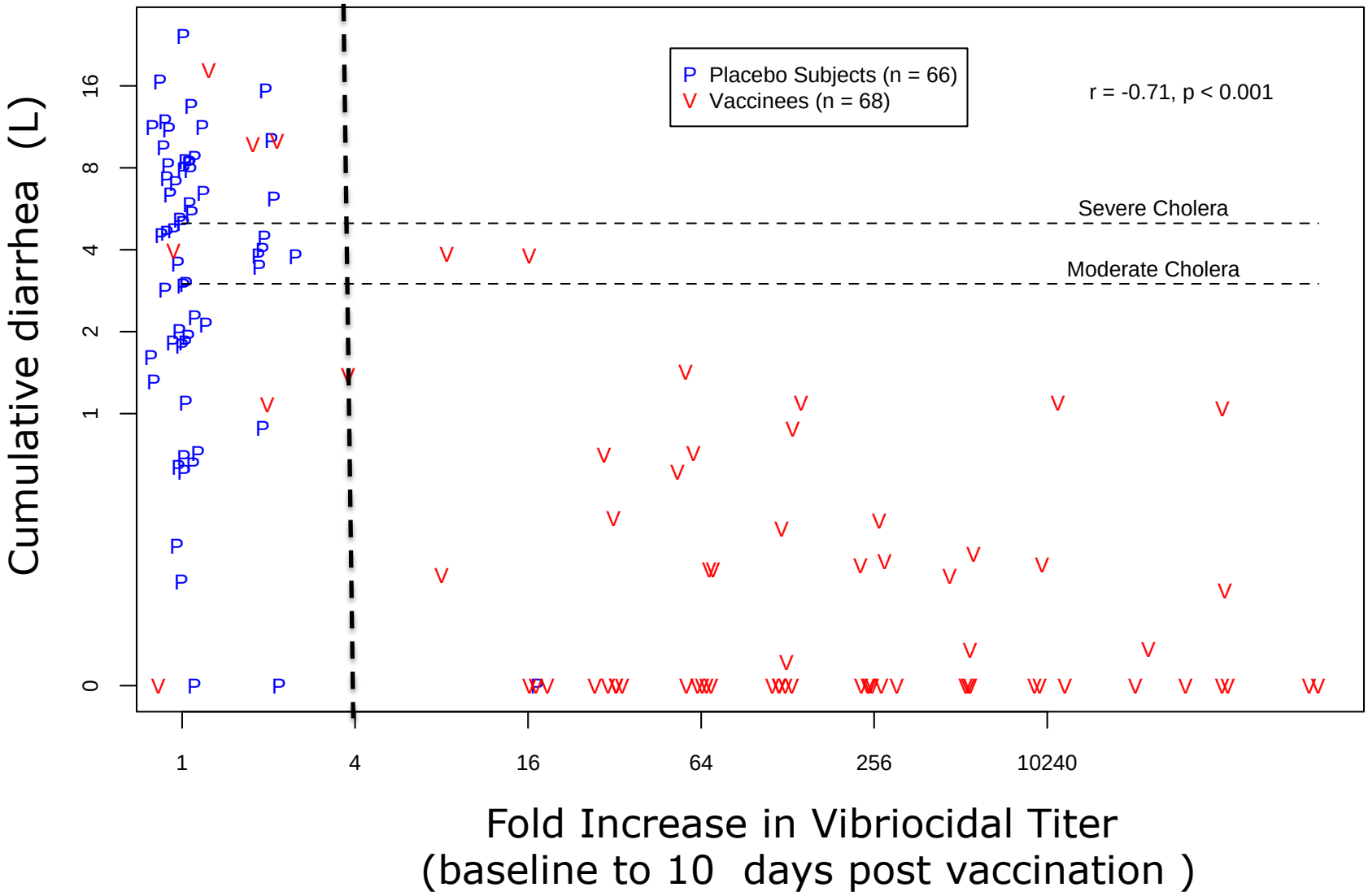

Antigen specific Memory B Cell following PXVX0200 or *V. cholerae* Challenge

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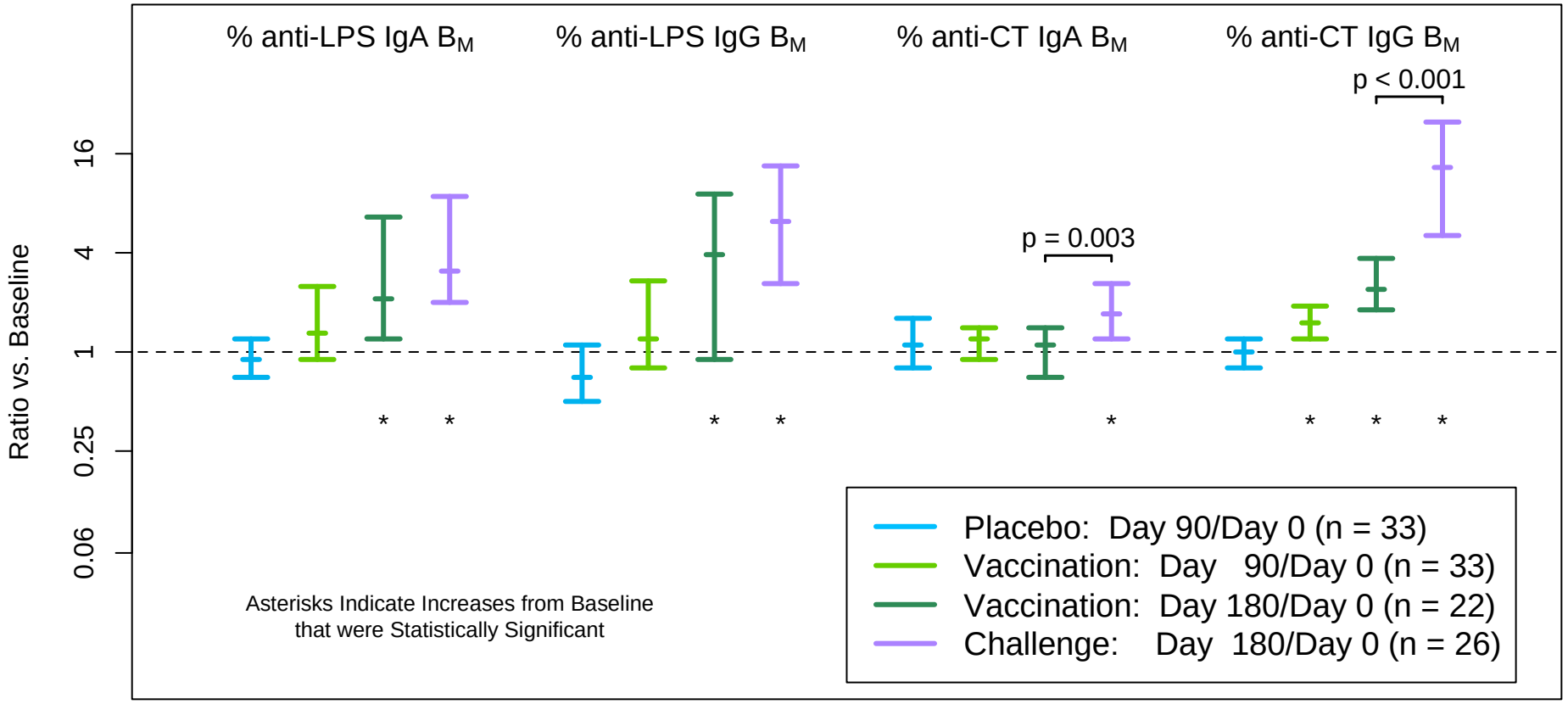

LPS IgA Responders Have Lower Post-Challenge Stool Volumes than non-Responders

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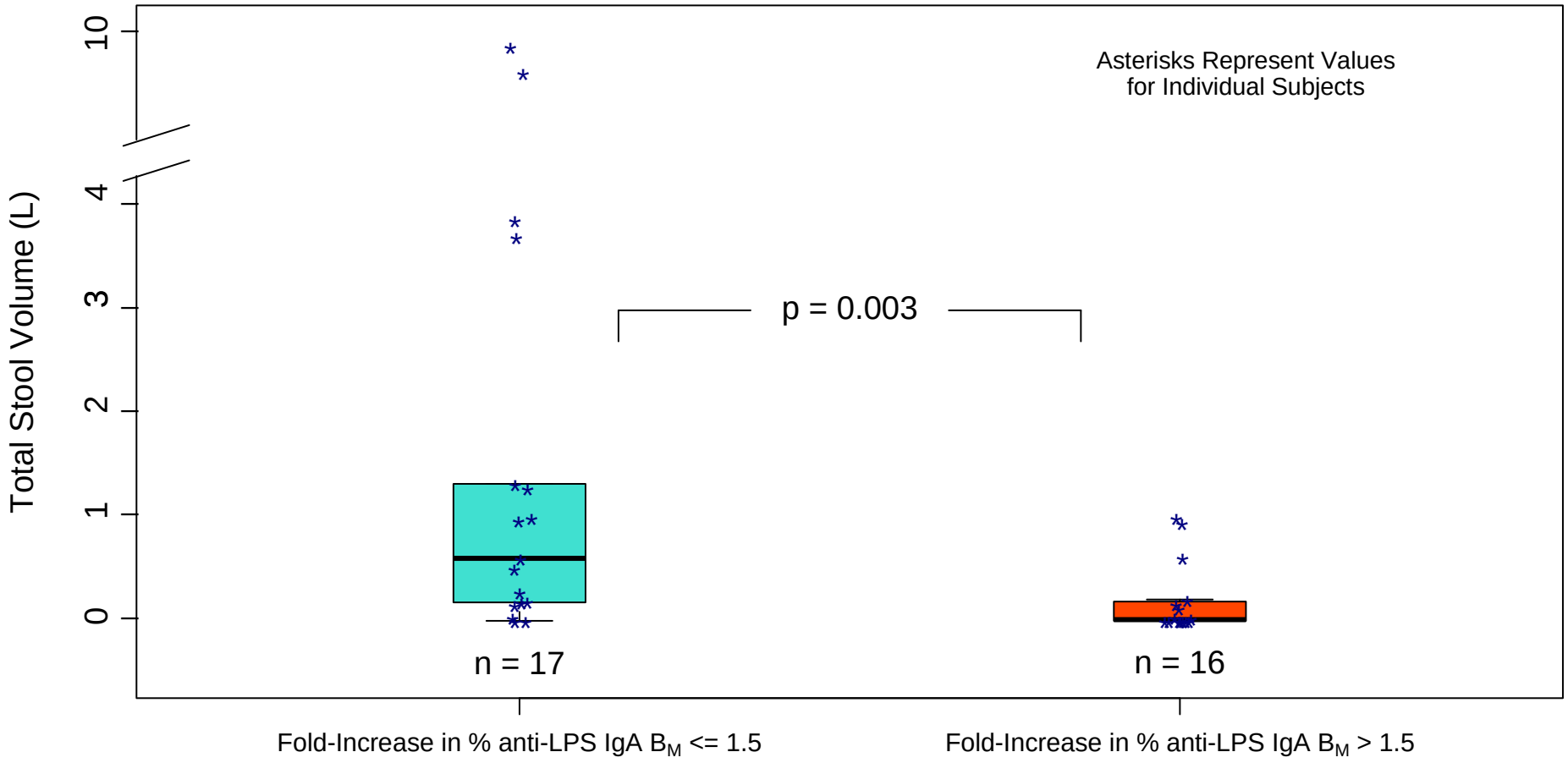

Safety and Immunogenicity Studies in Other Populations

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Goal: Demonstrate immunogenicity and safety in larger populations & consistency of manufacture

Objectives:

- Safety (at least 3000 subjects exposed to CVD 103-HgR), ages 18-65
- Bridge efficacy from challenge study in larger population
  - Immunological equivalence of 3 different production lots
  - Vibriocidal GMT of each lot must be within ±50% of each other lot with 95% confidence
  - Safety and immunogenicity in children in Phase 4

Design: Double blind placebo controlled

- Healthy adults 18-45 years and 46-65 years in Phase 3 (completed)
- Phase 4 pediatric safety and immunogenicity studies ongoing

Immunological Endpoints: Vibriocidal GMT at 10 days, seroconversion, memory B cells

Sites: US and Australia

Vaccine Induced Vibriocidal Anybody Levels in Other Populations Correlates with Levels in Human Challenge Studies

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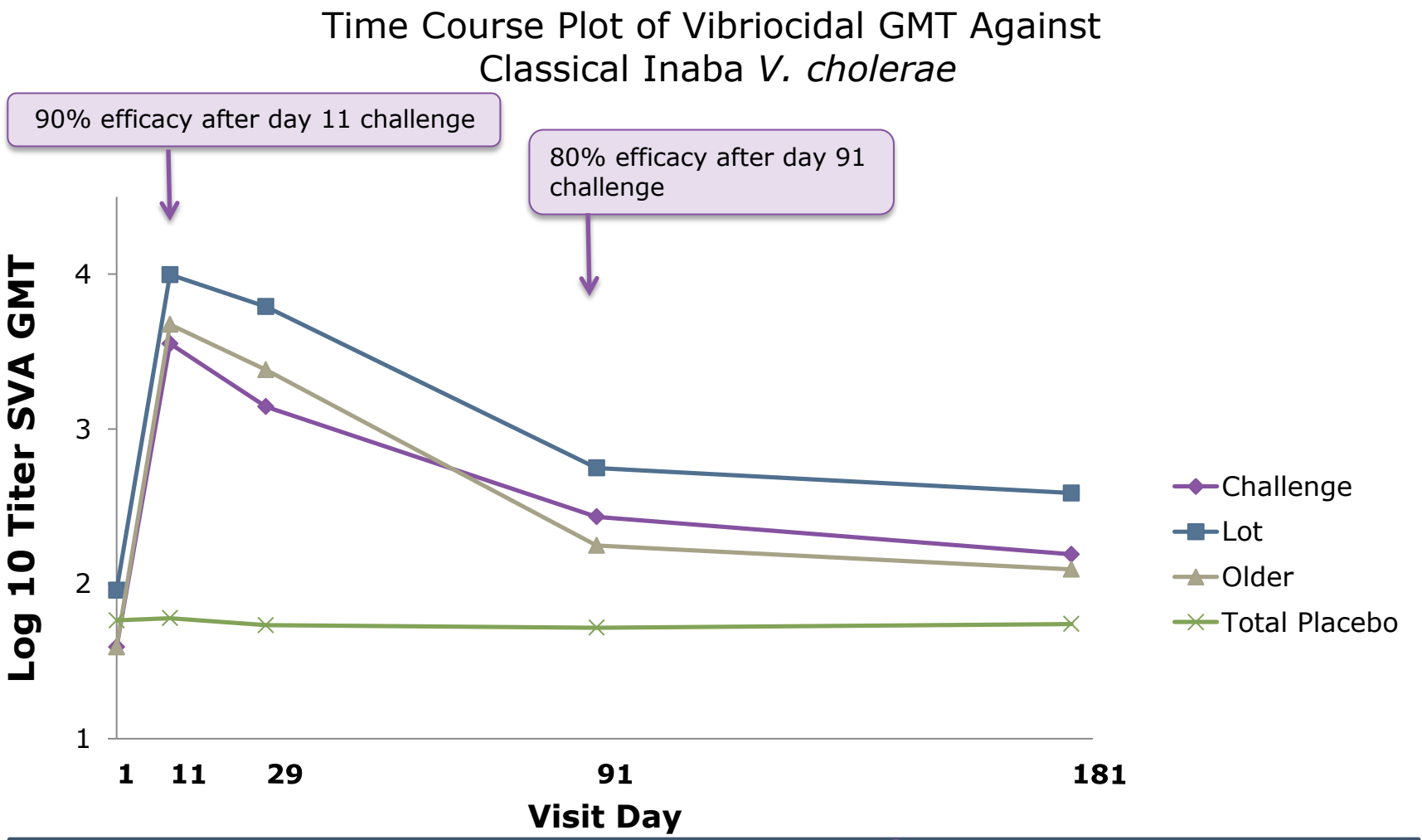

CFU/dose for vaccines: Challenge: $5x10^8$ Lot-Lot: $1X10^9$ Older Adults: $1x10^9$

Levine MM, et al. *Exp Rev Vaccines*. 2017;16(3):197-213.

Immunological Bridging to Infer Efficacy in Older Adults: High Rates of Seroconversion in Both Age Groups

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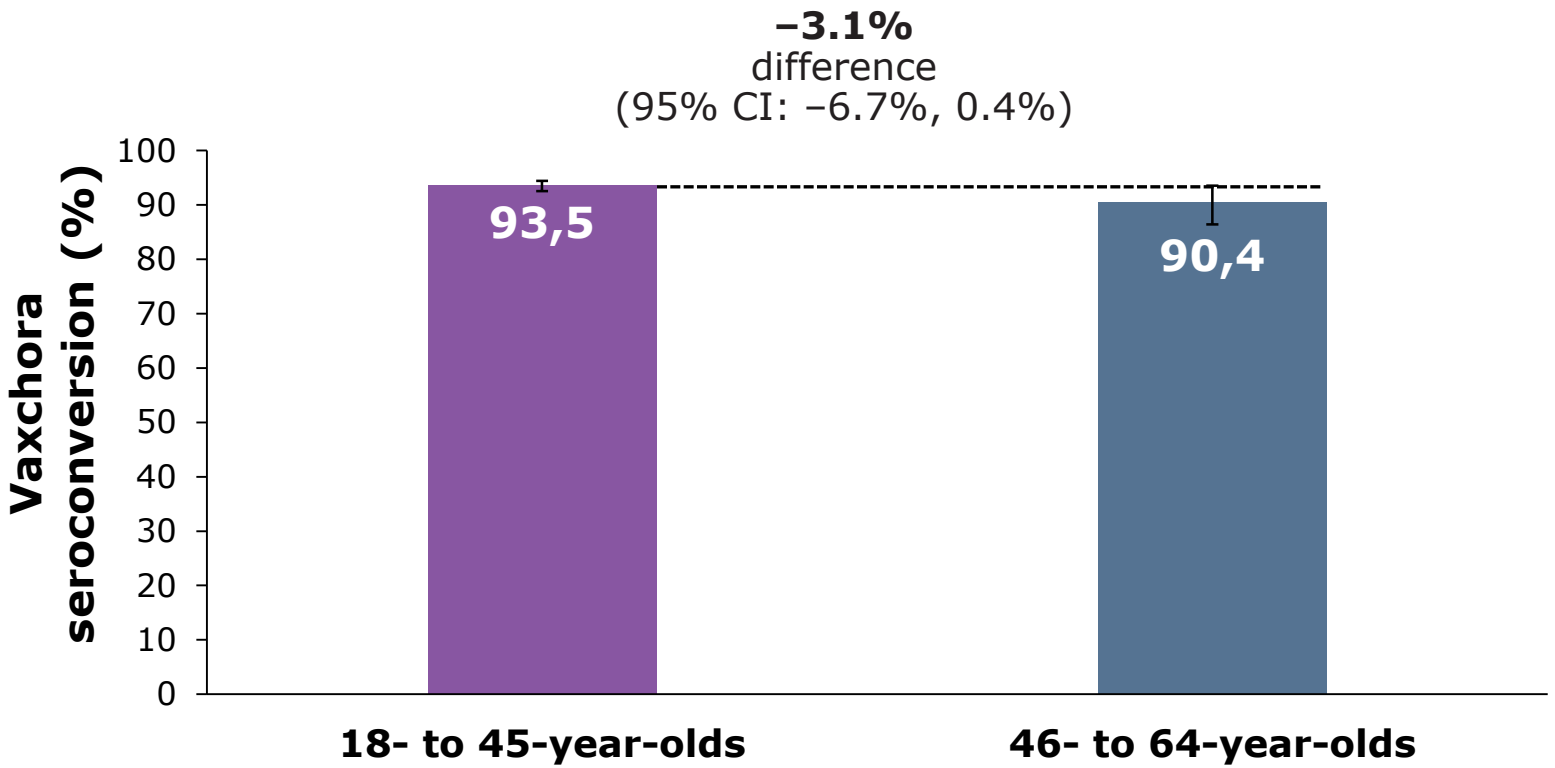
Vibriocidal Antibody Seroconversion Against Classical Inaba *V. cholerae* Vaccine Strain at 10 Days Post-Vaccination in Adults 46–64 Years of Age Compared With Adults 18–45 Years of Age



- Pre-specified non-inferiority criterion was that the lower bound of the 2-sided 95% CI on the difference in seroconversion rate must be greater than –10 percentage points

Summary – Challenge Study

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- Redeveloped CVD 103-HgR (PXVX0200, Vaxchora):
  - Protects against experimental cholera induced diarrhea
    - VE against moderate to severe diarrhea (3-5L total purge): 90% at 10 days; 79% at 3 months
  - Best correlate of protective efficacy for early or late (90 day) challenge is vibriocidal response at 10 days post vaccination
- Provided efficacy data for BLA in healthy young adults in developed country where field efficacy study is not feasible
  - Vibriocideal correlates allow bridging to other populations such as older adults and children
- Cholera challenge study was "safe"
  - Oral and IV fluid replacement as needed
  - Only challenge related SAE: severe hypokalemia in placebo recipient (treated with IV potassium)

Summary – Challenge Study Correlates

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- Serum vibriocidal response
  - Best non-mechanistic correlate that signifies vaccine take and protection against cholera
- Anti-cholera toxin response
  - Weakly correlates with protection
  - Adds little to virbriocidal response
- Memory B cell response
  - Oral cholera vaccine induces anti-LPS and anti-CT memory B cell responses
  - Anamnestic LPS-specific IgA response may contribute to long-term protection.

Plan for 2nd Generation Vaccine: Developing Country/Epidemic Response Formulation

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- CMC
  - Improve yield
  - Improve presentation
  - Improve thermostability
- Clinical
  - Re-confirm that higher (5 X 10^9 CFU) dosage required in developing countries, particularly in non-endemic areas
    - Phase 1 study in Mali completed
    - Additional Phase 1/2 studies
  - Phase 3 safety and immunogenicity studies
  - Phase 3 efficacy
    - Large field efficacy studies?
    - Any role for challenge studies either in non-endemic or endemic populations?

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