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Vaxchora™ Clinical Data Summary

Advisory Committee on Immunization Practices, Atlanta
24 February 2016

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VP Clinical Development and Medical Affairs

Agenda

- PaxVax Introduction
- Cholera
- CVD 103-HgR History
- Vaxchora Clinical Data
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- Summary

A Fully Integrated Specialty Vaccine Company

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- PaxVax is a privately held global specialty vaccines company with a mission to develop, manufacture and commercialize innovative vaccines against infectious diseases in a socially responsible manner

- Approximately 180 employees at locations in the US and Europe
  - Redwood City, CA - company headquarters
  - San Diego, CA - GMP facility and operations base for the R&D program
  - Thörishaus, Switzerland - site includes multiple manufacturing, office and lab spaces for Vivotif® production, quality testing, product release and supply chain

- PaxVax is initially focused on delivering vaccines for the travelers' markets
  - Vivotif – typhoid vaccine live oral Ty21a (commercial)
  - Vaxchora – oral cholera vaccine (BLA)
  - Ad4 vector program (HIV, Flu, Anthrax, Ad4/7) – R&D
  - New R&D (travel and specialty focus including Zika)

Cholera

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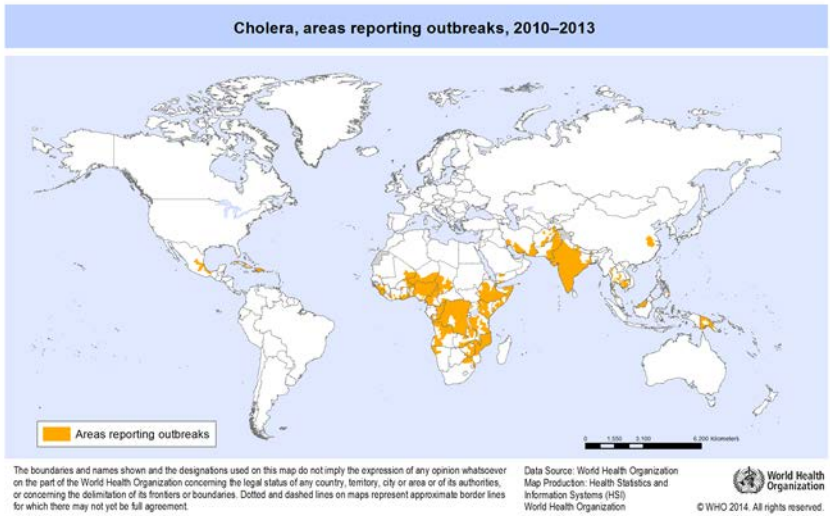
- *Vibrio cholerae* O1 and O139
  - O1 biotypes: Classical and El Tor
  - Each biotype has 2 distinct serotypes
- Transmission route via contaminated water and food
- Toxin-mediated secretory diarrhea, which if severe can be rapidly fatal if untreated (cholera gravis)
- Endemic in >50 countries; primarily in Asia, Africa and recently in the Caribbean
- 3-5 Million cases/year; >100,000 deaths
- Estimated that majority (80%) of mild-moderate diarrhea cases do not come to medical attention, and therefore go unreported
- All are susceptible, even greater risk with Blood group O, hypochlorhydria

Biotype	Classical		El Tor	
Serotype	Inaba	Ogawa	Inaba	Ogawa



There is no licensed cholera vaccine in the U.S.

Ali M, Nelson AR, Lopez AL, Sack DA. Updated global burden of cholera in endemic countries. PLoS Negl Trop Dis 2015;9(6):e0003832.

CVD 103-HgR: Brief History

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- *V. cholerae* O1 classical Inaba 569B
- *ctxA* gene deleted
- Mercury resistance gene inserted in *hlyA*

Previous Commercial Timeline:

1988	First lots tested in volunteers
1994	Available from Berna commercially as Orochol, Mutacol & Orochol E
1990s	Licensed in Switzerland, Canada, Argentina, Australia, NZ
1997	Berna files BLA with FDA (VRBPAC 1998)
2004	Production ceases (business reasons)
2006	Crucell buys SBL (maker of Dukoral)
2010	PaxVax acquires license and re-develops CVD 103-HgR (Vaxchora)

- BLA for adult indication submitted 16 October 2015, filed on 15 December 2015
- Review classification: Priority
- Review goal date 15 June 2016
- Proposed labeling feedback anticipated 16 May 2016, No Advisory Committee planned

CVD 103-HgR History as Orochol, Mutacol, Orochol E 500,000 Doses Administered

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- Commercial experience: 500,000 doses distributed over 10 years
  - Well tolerated with an excellent safety profile
- More than 35 scientific publications between 1988 and 2010
  - Efficacy in non-endemic populations demonstrated in healthy volunteer cholera challenge studies from 8 days to 6 months following vaccination[1]
  - Field efficacy studies in endemic populations[2]
  - Safety, immunogenicity, and dose-finding studies in developed and developing countries[3] (Orochol E, higher dose)
  - Special populations including Pediatric and HIV[4]
  - Concomitant YF, malaria prophylaxis, and OPV[5]
  - Safety and immunogenicity of re-immunization at 2.5 and 3.5 years[6]
    - SVA seroconversion following primary immunization 81%
    - SVA following re-immunization
      - at 2.5 years was 57% (significantly lower than 1^{o} response)
      - at 3.5 years was 65%

[1] Orochol Historical Studies: Table 1. North America Challenge Studies – (El Tor Inaba, El Tor Ogawa, Classical Inaba strains tested)
[2] Orochol Historical Studies: Table 5. Studies in Cholera Endemic Areas
[3] Orochol Historical Studies: Table 2. RCT N. America or European Adults, Table 6: Non-pivotal Safety/Immunogenicity Studies
[4] Orochol Historical Studies: Table 3: Pediatric Studies, Table 4: Special Populations
[5] Orochol Historical Studies: Table 6: Non-Pivotal Safety/Immunogenicity Studies and Other Studies of Relevance
[6] Kollaritsch et. al. Vaccine 18 (2000) 3031-3039 Levine *BMC Biology* 2010, **8**:129

PXVX0200 (Vaxchora)-Cholera Vaccine Single Dose Oral-Clinical Program

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Study	Objective(s)	Design & Type of Control	Test Product; Route of Administration
Phase 1 Safety 002	Safety and immunogenicity	Randomized, double-blind, placebo-controlled	4×10^8 CFU/dose; oral
Phase 3 Challenge 003	Demonstrate protection from live cholera challenge	Randomized, double-blind, placebo-controlled	5×10^8 CFU/dose; oral
Phase 3 Lot Consistency 004	Demonstrate clinical lot consistency	Randomized, double-blind, placebo-controlled	1×10^9 CFU/dose; oral
Phase 3 Older Adult 005	Demonstrate equivalence in immune response of older and younger adults	Randomized, double-blind, placebo-controlled	1×10^9 CFU/dose; oral

PXVX-VC-200-002: Safety, Immunogenicity, Shedding, and Potential Transmission to HHC

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Safety and immunogenicity confirmed with early formulation
Limited shedding without transmission to household contacts

Safety and Immunogenicity of Single-Dose Live Oral Cholera Vaccine Strain CVD 103-HgR, Prepared from New Master and Working Cell Banks

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Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland, USA[a]; Division of Infectious Diseases, University of Kentucky, Lexington, Kentucky, USA[b]; PaxVax, Inc., Menlo Park, California, USA[c]

Currently, no cholera vaccine is available for persons traveling from the United States to areas of high cholera transmission and who for reasons of occupation or host factors are at increased risk for development of the disease. A single-dose oral cholera vaccine with a rapid onset of protection would be particularly useful for such travelers and might also be an adjunct control mea- sure for cholera outbreaks. The attenuated *Vibrio cholerae* O1 vaccine strain CVD 103-HgR harbors a 94% deletion of the cholera toxin A subunit gene (*ctxA*) and has a mercury resistance gene inserted in the gene encoding hemolysin A. We undertook a phase I randomized placebo-controlled two-site trial to assess the safety and immunogenicity of a preliminary formulation of CVD 103-HgR prepared from new master and working cell banks. Healthy young adults were randomized (5:1 vaccinees to placebo recipients) to receive a single oral dose of ~4.4×108 CFU of vaccine or a placebo. Blood serum vibriocidal and cholera toxin-specific IgG antibodies were measured before and 10, 14, and 28 days following vaccination or placebo. Excretion of the vaccine strain in the stool was assessed during the first week postvaccination. A total of 66 subjects were enrolled, comprising 55 vaccinees and 11 placebo recipients. The vaccine was well tolerated. The overall vibriocidal and anti-cholera toxin seroconversion rates were 89% and 57%, respectively. CVD 103-HgR is undergoing renewed manufacture for licensure in the United States under the auspices of PaxVax. Our data mimic those from previous commercial formulations that elicited vibriocidal antibody seroconversion (a correlate of protection) in ~90% of vaccinees. (This study has been registered at ClinicalTrials.gov under registration no. NCT01585181.)

Clinical and Vaccine Immunology p. 66 –73 January 2014 Volume 21 Number 1

PXVX-VC-200-003 Challenge Study to Demonstrate Efficacy at Two Time Points

Primary Objective(s)

Determine whether a single dose of PXVX0200 provides significant protection against a challenge with virulent

V. cholerae O1 El Tor Inaba N16961 strain at 1 x10^5 CFU

- at 10 days after vaccination
- at 3 months after vaccination

Primary Endpoint

The occurrence of moderate or severe diarrhea (equal to or greater than 3.0 L purge)*

Success Criteria

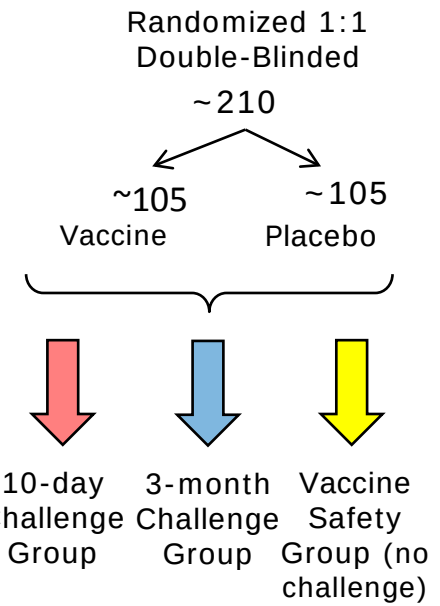
The lower, two-sided 95% confidence bound on protective efficacy must be ≥30%

Secondary Objectives

Evaluate the impact of vaccination on disease severity

Total weight (1gm~1mL) of diarrheal stools; incidence of diarrhea of any severity, incidence of fever, incidence of fecal shedding of wild type *V. cholerae*, peak concentration *V. cholerae* detected in stool

Evaluate the tolerability of vaccine



*Moderate diarrhea defined as ≥3.0 L and severe diarrhea defined as ≥5.0 L purge during course of illness

VE 90% after Challenge 10 Days after Vaccine
VE 80% after Challenge 3 Months after Vaccine

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Primary Objective(s)

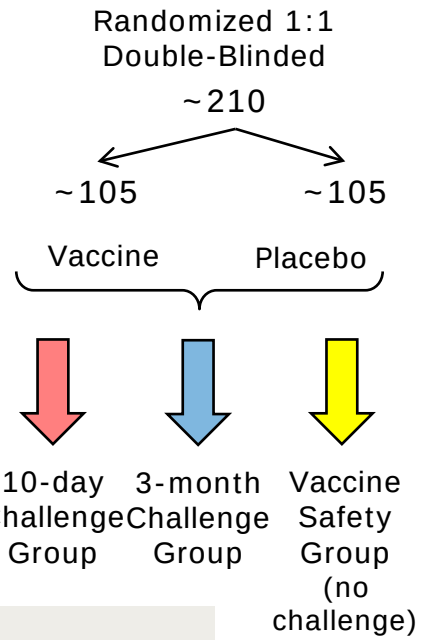
Determine whether a single dose of PXVX0200 provides significant protection against a challenge with virulent *V. cholerae* O1 El Tor Inaba N16961 strain at 1 x10^5 CFU

- at 10 days after vaccination
- at 3 months after vaccination

Primary Endpoint

- The occurrence of moderate or severe diarrhea (equal to or greater than 3.0 L purge)

Parameter measured after challenge	Vaccine 10-Day post N=35	Vaccine 3-Month post N=33	Placebo N=66
Attack Rate ≥ 3L liquid stool	6%	12%	59%
Vaccine Efficacy	90%	80%	
Lower Bound of 95% CI	63%	50%	



- Met primary endpoints of 95% CI lower bound ≥30%
- Subgroup analyses on the 1° endpoint – no differences (±O, m/f, b/w)

003 Secondary Endpoints – Post Challenge Diarrhea, Shedding of Challenge Strain

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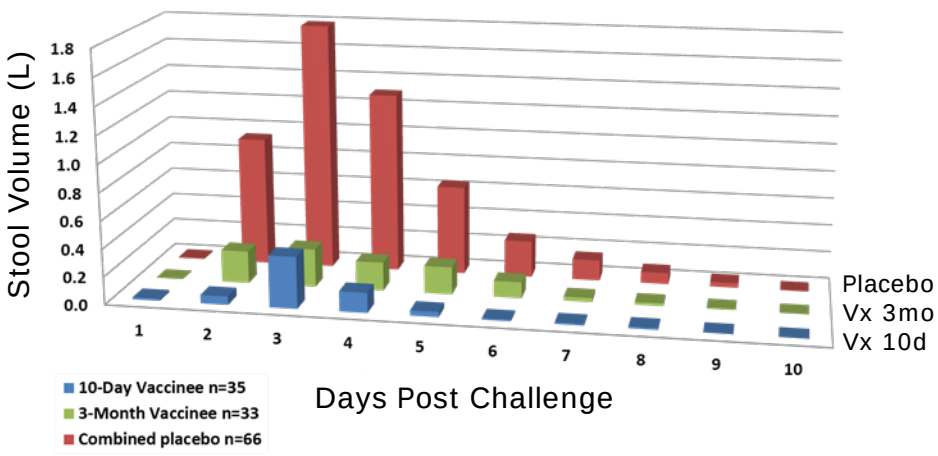
Average Volume of Diarrhea by Day Post Challenge

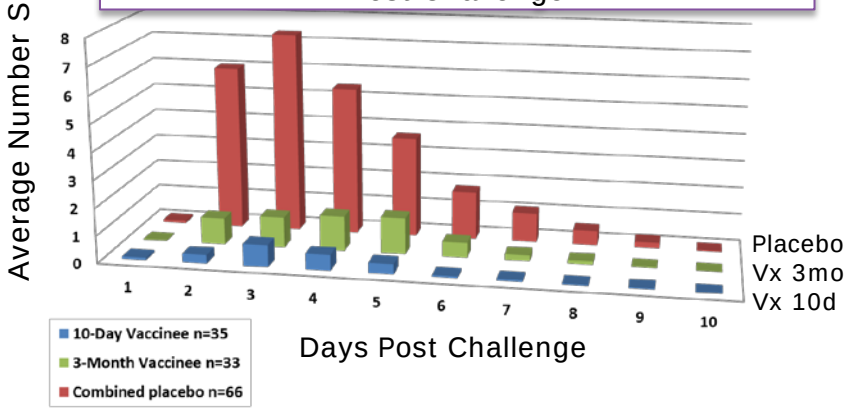


*Cumulative total per group divided by n; antibiotics administered Days 5-10

Protection was demonstrated for secondary endpoints including

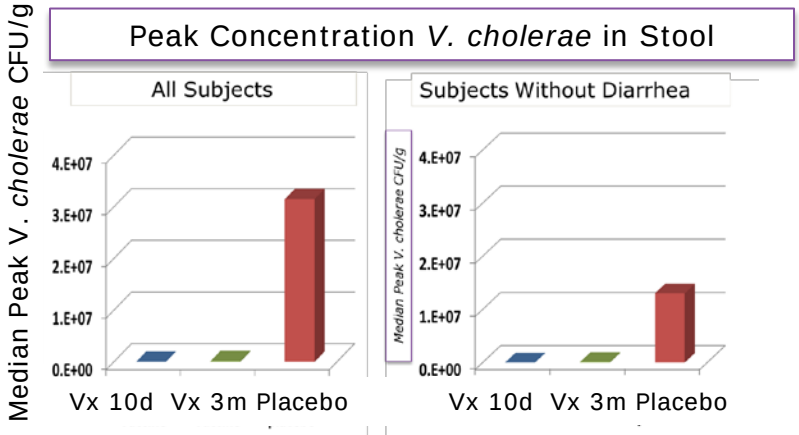
- diarrhea of any severity (defined as >4 loose stools within a 24 hour period)
- volume of diarrhea
- number of loose stools
- number of days passing loose stools
- 99% reduction shedding of the challenge strain in vaccine vs placebo during 11 days following challenge

Average Number of Diarrheal Stools by Day Post Challenge



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

Peak Concentration *V. cholerae* in Stool



N	35	33	66
CFU/g	0	1E+05	3E+07
% Reduction	100	99.6	NA

N	30	18	5
CFU/g	0	8E+04	1E+07
% Reduction	100	99.3	NA

Challenge Study Vaccine-induced Vibriocidal Titers Prior to Challenge - PXVX-VC-200-003

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Vibriocidal antibodies are a measure of immunity and have been inversely correlated with infection with cholera[1]

Serum Vibriocidal Antibody Classical Inaba GMT (95% CI) Prior to Challenge						
		Day 1	Day 8	Day 11	Day 29	Day 91
	N(n)	P (102) V (94)	P (100) V (93)	P (99) V (93)	P (68) V (57)	P (33) V (33)
Placebo	102	63 (48 – 84)	65 (48 – 89)	65 (48 – 88)	50 (36 – 71)	48.3 (30-79)
Vaccine	94	46 (37 - 58)	831 (554 – 1,245)	4,313 (2,873 – 6,476)	1,394 (866 – 2,242)	271 (158-462)

Peak vibriocidal response (100 x baseline) occurs on Day 11

[1]M. Pasetti and M. Levine, Clinical and Vaccine Immunology, 19(2012) N11 p.1707–1711

Vibriocidal Antibody Seroconversion as Immune Correlate of Protection

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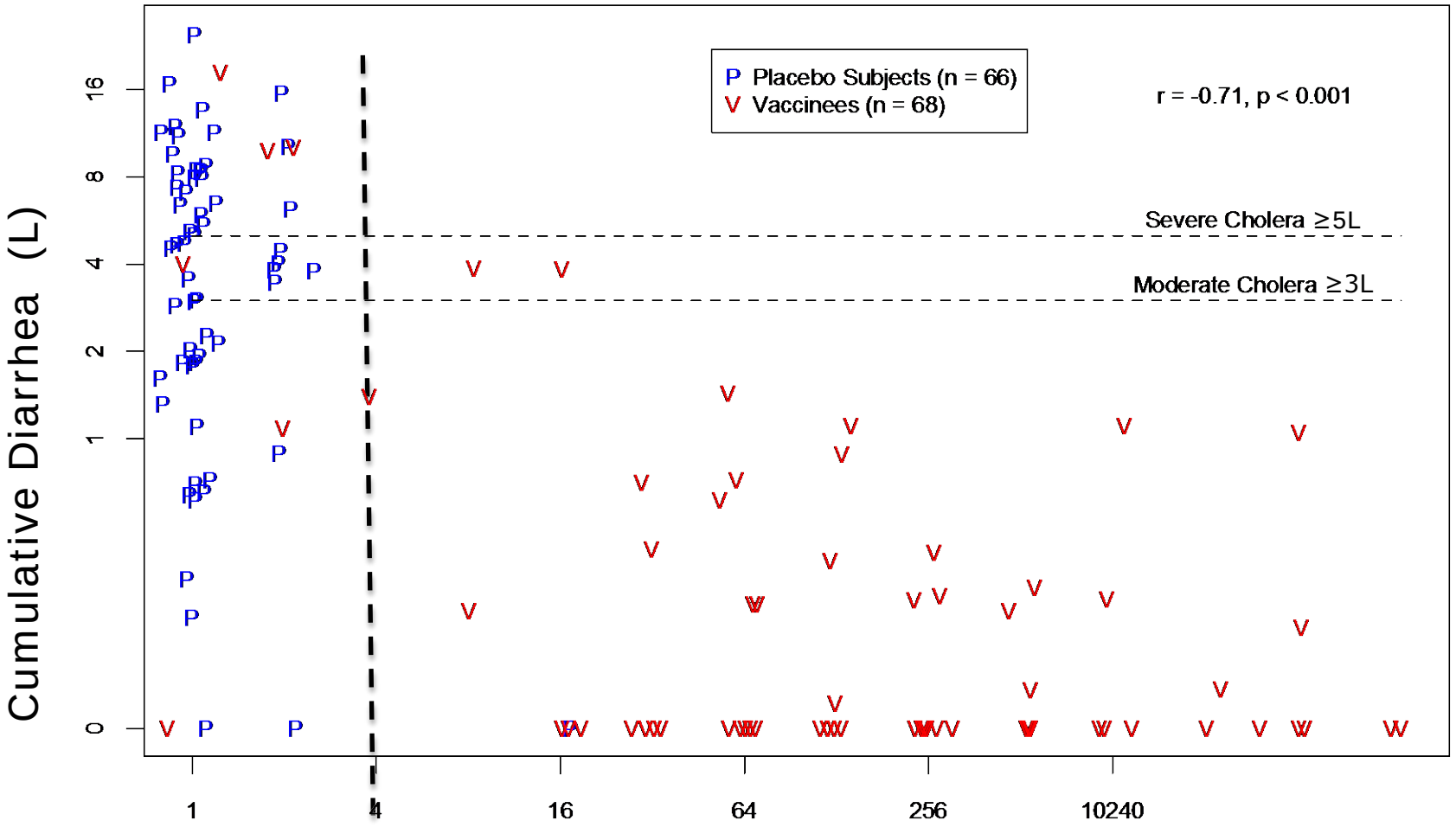

Vibriocidal Seroconversion Demonstrated as Immune Correlate of Protection

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Serum Vibriocidal Fold-increase Measured on Day 11 as a Predictor of Protection Against Development of Moderate/Severe Cholera Following Challenge in Study 003

Fold-increase on Day 11		Mod/Sev Cholera 11d		p	OR	Chi^2	Mod/Sev Cholera 3m		p	OR	Chi^2
		Yes	No				Yes	No			
≥ 2	Yes	7	34	0.001	6	9	5	30	< 0.001	8	12
	No	15	12				18	13			
≥ 4	Yes	1	33	< 0.001	50	24	1	28	< 0.001	39	20
	No	21	13				22	15			
≥ 8	Yes	1	33	< 0.001	50	24	1	27	< 0.001	35	19
	No	21	13				22	16			
≥ 16	Yes	0	32	< 0.001	und*	26	1	27	< 0.001	35	19
	No	22	14				22	16			

*und = undefined

003 – Serum Vibriocidal Responses Assessed Across Biotypes and Serotypes

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Challenge Study 003 Post-immunization Vibriocidal GMT and Percent 4-Fold Rise				
	Vibriocidal GMT Day 11 (95% CI)		Percent With 4-fold Vibriocidal Rise at Day 11	
Cholera Strain used in Serum Vibriocidal Assay	PXVX0200 N = 94	Placebo N=102	PXVX0200 N = 94	Placebo N=102
Classical Inaba	4313*	65	89%*	2%
El Tor Inaba	6898*	63	90%*	4%
Classical Ogawa	2324*	94	86%*	3%
El Tor Ogawa	2239*	72	88%*	5%

* $p < 0.0001$

Source: PaxVax Data - PXVX-VC-200-003 Clinical Study Report Table 23
Note: Statistics describe the cumulative number and percentage of subjects who had at least a 4-fold rise in titer over the titer measured by Day 1

Equivalence Demonstrated in Lot Consistency CI for three lot GMRs within (0.78-1.20)

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Primary Equivalence Analysis	
Lot A:B	
Geometric Mean Ratio	0.92
95% CI[b]	(0.78, 1.08)
Lot B:C	
Geometric Mean Ratio	1.02
95% CI[b]	(0.87, 1.20)
Lot A:C	
Geometric Mean Ratio	0.94
95% CI[b]	(0.80, 1.10)

	Lot A N=892	Lot B N=887	Lot C N=909
N	892	887	909
GMT	9220	10034	9827
95% CI[a]	(8219, 10343)	(8942, 11260)	(8770, 11012)

Assay results assessed vibriocidal activity against the classical Inaba biotype of *V. cholerae*

The primary objective of the study was met since the CI of the geometric mean ratio for each pair of lots was within the pre-specified interval (0.67, 1.5)

[a] Confidence interval estimated directly from ANOVA model with log-transformed vibriocidal titer at Day 11 as the outcome and lot as the single explanatory factor.
[b] Confidence intervals for geometric mean ratios were estimated using a common standard error derived from an ANOVA model with log-transformed vibriocidal titer at Day 11 as the outcome and lot as the single explanatory factor.
Source: PXVX-VC-200-004 Clinical Study Report Table 18

004 Safety Profile – Well Tolerated Slight Increase in Headache, Diarrhea

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Reactogenicity signs and symptoms after vaccine administration reported by 51.90% of vaccine and 43.15% of placebo recipients (p=0.0024)

No meaningful differences in reactogenicity across lots

No significant differences between vaccine and placebo recipients with exception of

- Headache reported in 28.93% (791 of 2734) vaccine recipients and 23.62% of (81 of 343) placebo recipients (p=0.0419), Most were mild (516 vaccine, 50 placebo) or moderate (261 vaccine, 30 placebo)
- Diarrhea although rare in both vaccine and placebo groups was reported 3x more frequently in vaccine (3.88%) vs placebo (1.17%) (p=0.0079) Most diarrhea was mild or moderate (defined as ≥4 or ≥5 loose stools/24h respectively) Severe diarrhea was defined as ≥ 6 loose stools/24h and was reported in 0.8% (22 of 2789) vaccine recipients and 0.0% (0 of 350) placebo recipients

  The median duration 1 d (range 1-2 d) and resolved in all subjects within 2 d of onset

  Median day of onset was 2 d after vaccination (range 1-7 d) and all severe diarrhea occurred within one week of vaccination

There was one death (suicide, unrelated) and 20 subjects reported at least one SAE (17 Vaccine, 3 Placebo) which were all considered unrelated to study

Source: PXVX0200-004 Clinical Study Report

Immunogenicity Bridge to Older Adult Population PXVX-VC-200-005

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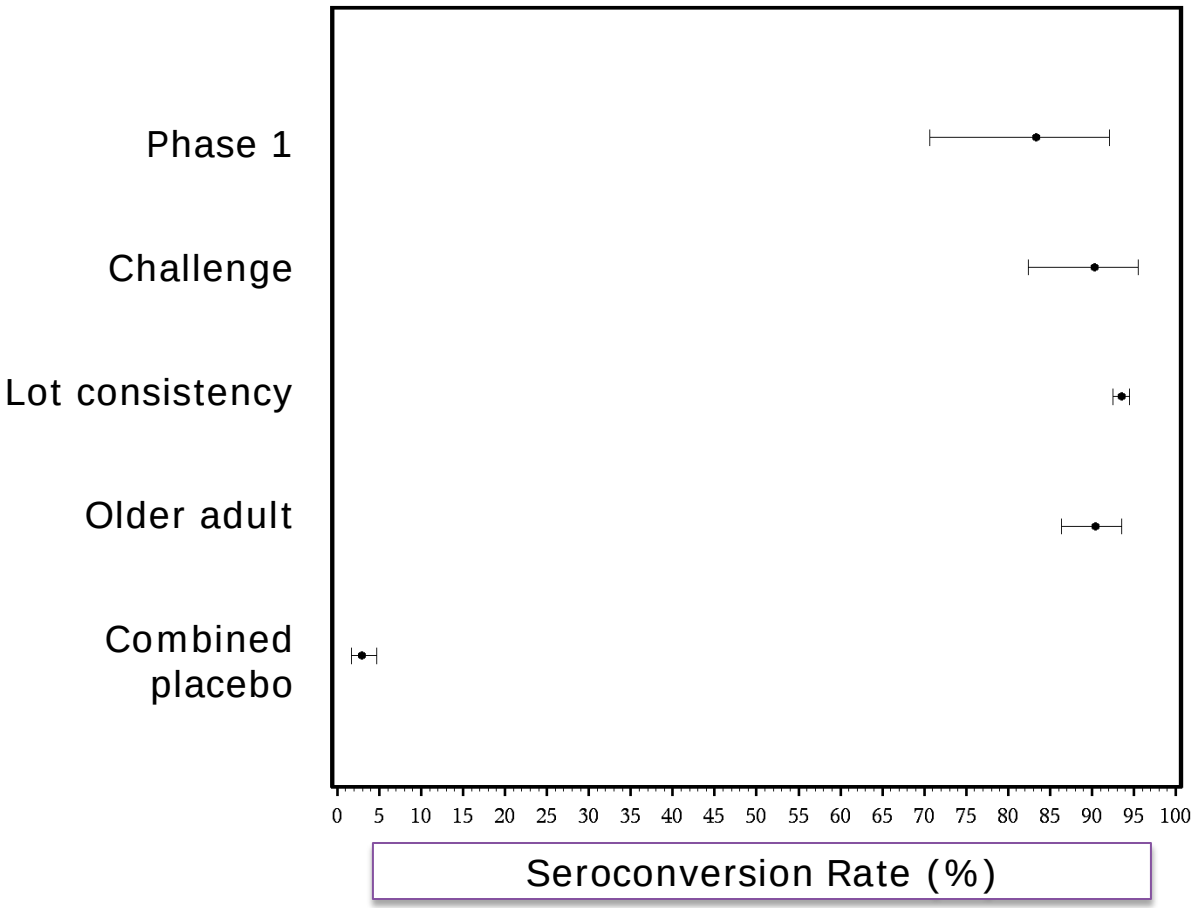
Study	004 Lot-lot	005 Older adult
Age Group (N)	18-45y (2688)	46-64y (291)
Seroconversion[a]	93.5%	90.4%
95% CI LB	92.5%	86.4%
% diff between older-younger adults	-3.1%	
95% CI LB	-6.7%	

[a] Vibriocidal activity against classical Inaba biotype of *V. cholerae*

Study met primary endpoints by demonstrating with 95% confidence

- The seroconversion rate in older adults is within 10% of the rate in younger adults
- The seroconversion rate in older adults is at least 70%

PXVX0200 (Vaxchora) is Immunogenic ~90% Seroconversion in Phase 3 Studies



Forest Plot of Vibriocidal Antibody Seroconversion (95% CI) against Classical Inaba *V. cholerae* Through Day 11 Immunogenicity Evaluable Population

Note: N analyzable: Phase 1=54; Challenge=93; Lot=2687; Older=291; Combined placebo=544.

Source: Figure 11.4.1; Table 11.3.1.1; Phase 1 (CSR PXVX-VC-200-002); challenge (CSR PXVX-VC-200-003); lot consistency (CSR PXVX-VC-200-004); older adult (CSR PXVX-VC-200-005).

Safety Summary – Most Reactogenicity Described as Mild or Moderate Severity

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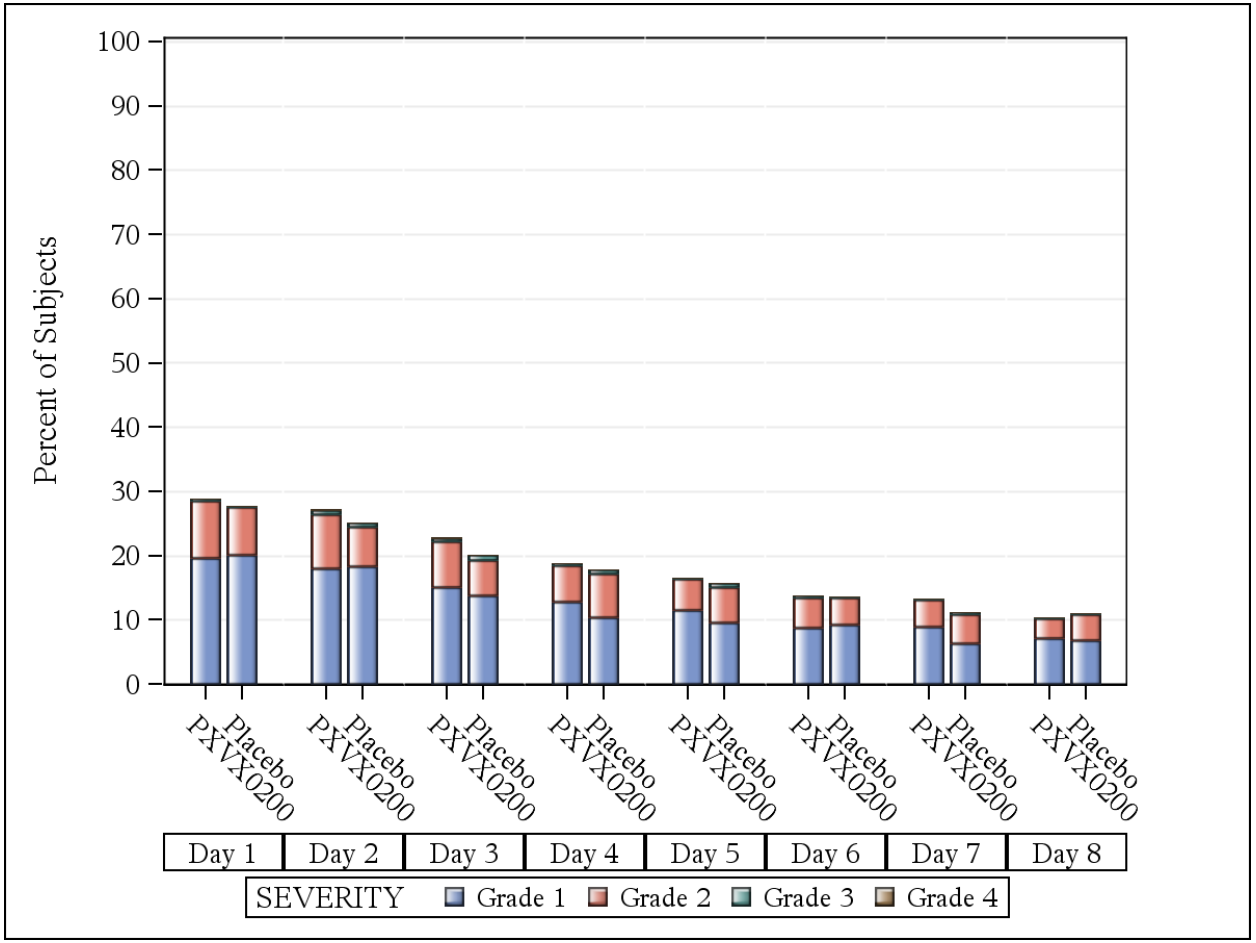
Subjects with Any Reactogenicity by Day and Severity



"Any" reactogenicity was reported in 50% of Vaccinees and 46% of Placebo (p=0.06) PaxVax Integrated Summary of Safety

Summary Reactogenicity Overall No Differences Except Slight Increase in Diarrhea

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Solicited Post-immunization Reactions within 7 days Combined Analysis for Studies 003, 004, 005

Symptom	Vaxchora n=3325	Placebo n=562	*p-value*
Malaise	30.0%	29.4%	0.8
Headache	27.8%	26.0%	0.4
Abdominal Pain	18.3%	17.0%	0.5
Nausea	17.4%	15.6%	0.3
Anorexia	15.6%	16.8%	0.4
Diarrhea (≥4 loose stools/24h)	3.8%	1.6%	0.008
Fever	0.7%	1.1%	0.3

Well tolerated, no significant differences between groups with exception of diarrhea (~2% more frequent in vaccine group, mostly mild)

Source: PaxVax Data on file, PXVX0200 Integrated Summary of Safety (ISS)

Adverse Events Uncommon
Most Frequently Reported Events <3%

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Adverse Events (Unsolicited) Reported Through Day 29

Symptom	Vaxchora n=3235	Placebo n=562
Headache	2.5%	2.7%
Fatigue	2.2%	3.2%
URI	2.1%	2.1%
Back pain	1.4%	1.1%
Flatulence	1.1%	1.8%
Abdominal pain	1.1%	0.9%
Diarrhea (≥4 loose stools/24h hr)	0.5%	1.1%

No meaningful differences between rates of vaccine and placebo recipients reporting adverse events (unsolicited) during study

No SAEs considered related to vaccine

Note: Challenge Study 003 (N=210) and a subset from 004,005 included follow-up to 181 days also included in this dataset. Source: PXVX0200 Integrated Summary of Safety (ISS)

Vaxchora: Efficacy Demonstrated in Human Challenge Correlates with Immune Response

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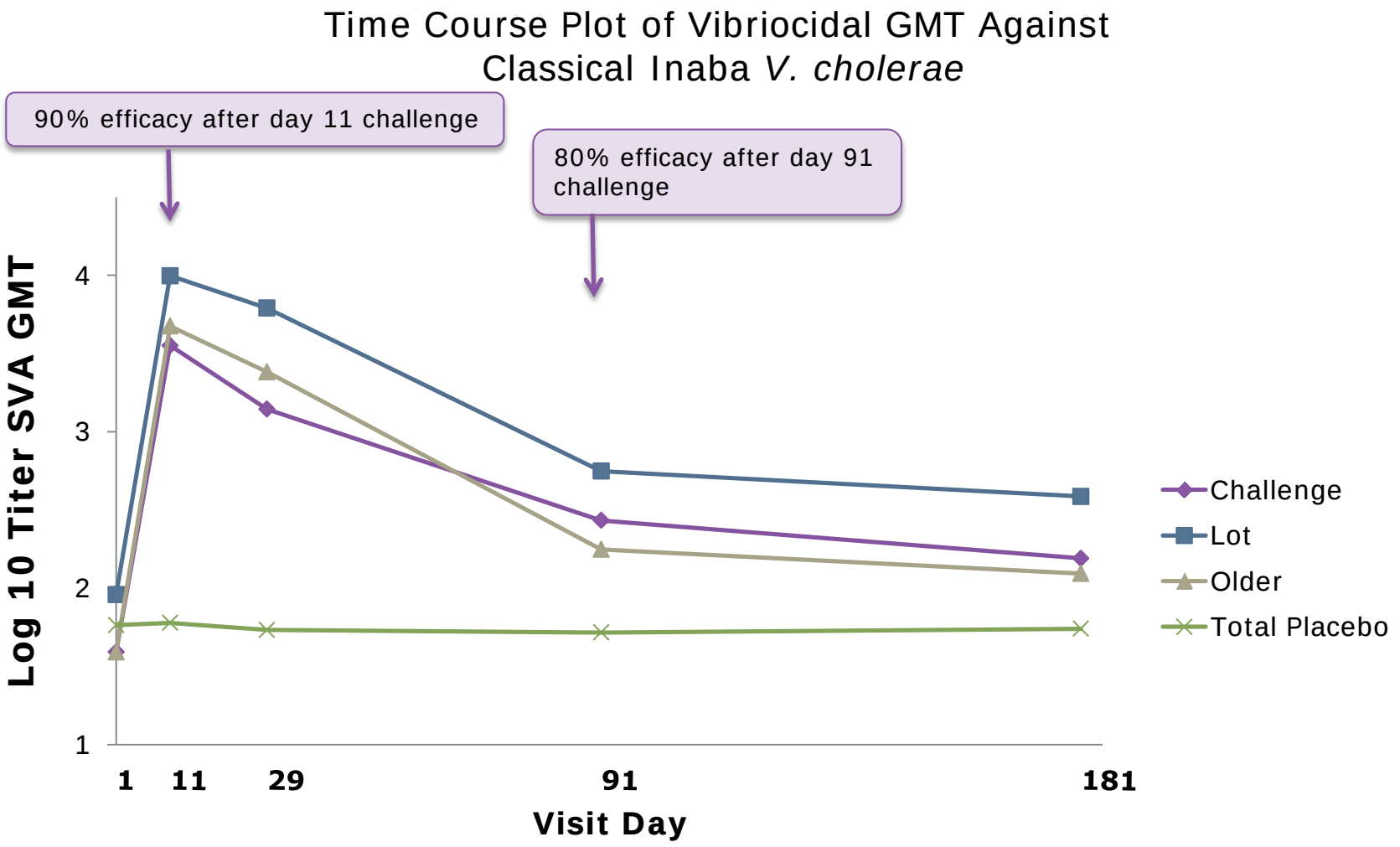

Anti-LPS IgA Memory B Cell after Vaccination or Challenge in Study 003 Healthy Adults

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Mean Percent anti-LPS Memory B Cell/total Memory B Cell

	Unchallenged Vaccinees	Vaccine group pre-challenge	Placebo group 170 days post-cholera challenge
N	22	33	26
Day of sample			
Day 1	0.089	0.086	0.077
Day 91	n/a	0.153*	n/a
Day 181	0.135*	n/a	0.191*

n/a = not assessed
*p<0.05 Wilcoxon signed rank test when compared to Day 1

Anti-LPS memory B cells increase and remain elevated at Day 181

The memory B cell immunogenicity endpoints were assessed using a qualified Enzyme-Linked ImmunoSpot (ELISPOT) method performed by PaxVax using assays developed in collaboration with the Cellular Immunology Section of CVD UMB (PTR-RD-CVD-001)

Vaxchora Summary

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- Redeveloped CVD 103-HgR (PXVX0200, Vaxchora)
  - Well tolerated
    - No related SAEs
    - Slight (~2%) increase in diarrhea
    - Similar profile to Orochol
  - Protective efficacy against challenge
    - 90% at 10 days following vaccination
    - 80% at 3 months following vaccination
  - Immunogenic in healthy adults 18-45 and 46-65 years
    - 90-94% seroconversion by SVA to Classical Inaba
    - Seroconversion was also demonstrated by SVA with other biotype/serotypes (Classical Ogawa, El Tor Inaba, El Tor Ogawa)
    - Vibriocidal serocoversion correlates with efficacy
  - Vibriocidal Ab levels remain well above baseline at Day 181
  - Anti-LPS memory B cells increase and remain elevated at Day 181

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Clinical Investigation Sites for Challenge Study 003

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Challenge Strain

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InClin

Clinical Investigator Sites for Studies 004 and 005

Richard Greenberg	University of Kentucky, Lexington, KY
Caroline Lyon	University of Vermont, Burlington, VT
Evan Anderson	Emory University, Atlanta, GA
James Borders	Central Kentucky Research Associates, Inc
John Ervin	Center for Pharmaceutical Research, Kansas City, MO
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Isaac Marcadis	Palm Beach Research, West Palm Beach, FL
Fred DeLooze	AUS Trials Pty Ltd, QLD, Australia
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Jason Lickliter	Nucleus Network, VIC, Australia
Jana Krishnarajah	Linear Clinical Research, WA, Australia
Sepehr Shakib	Cmax, SA, Australia
Paul Griffin	Q-Pharm Pty Ltd, QLD, Australia

Orochol History References 1/3

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