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GLOBAL TASK FORCE ON
CHOLERA CONTROL

December 3rd and 4th, 2019
Domaine de Penthes, Geneva

EBS
LISTED
NYSE

PaxVax is a subsidiary of Emergent BioSolutions Inc.

Cholera Vaccine, Live, Oral in Europe

Reminder

Cholera Vaccine, Live, Oral is an unapproved medicine currently under review with the regulatory authorities

The product is not considered safe or effective until regulatory approval has been received (EMA)

EMA=European Medicines Agency

United States Indication and Limitations of Use – Cholera Vaccine, Live, Oral*

Indication

- VAXCHORA® (Cholera Vaccine, Live, Oral) is a vaccine indicated for active immunization against disease caused by *Vibrio cholerae* serogroup O1. VAXCHORA is approved for use in adults 18 through 64 years of age traveling to cholera-affected areas

Limitations of use

- The effectiveness of VAXCHORA has not been established in persons living in cholera-affected areas
- The effectiveness of VAXCHORA has not been established in persons who have pre-existing immunity due to previous exposure to *V. cholerae* or receipt of a cholera vaccine
- VAXCHORA has not been shown to protect against disease caused by *V. cholera*e serogroup O139 or other non-O1 serogroups

1. Vaxchora [package insert]. Redwood City, CA: PaxVax Bermuda Ltd.; 2019.

Cholera Vaccine, Live, Oral is not approved in the EU
*Subject to change based upon regulatory review in the EU

Important Safety Information from the US Label*

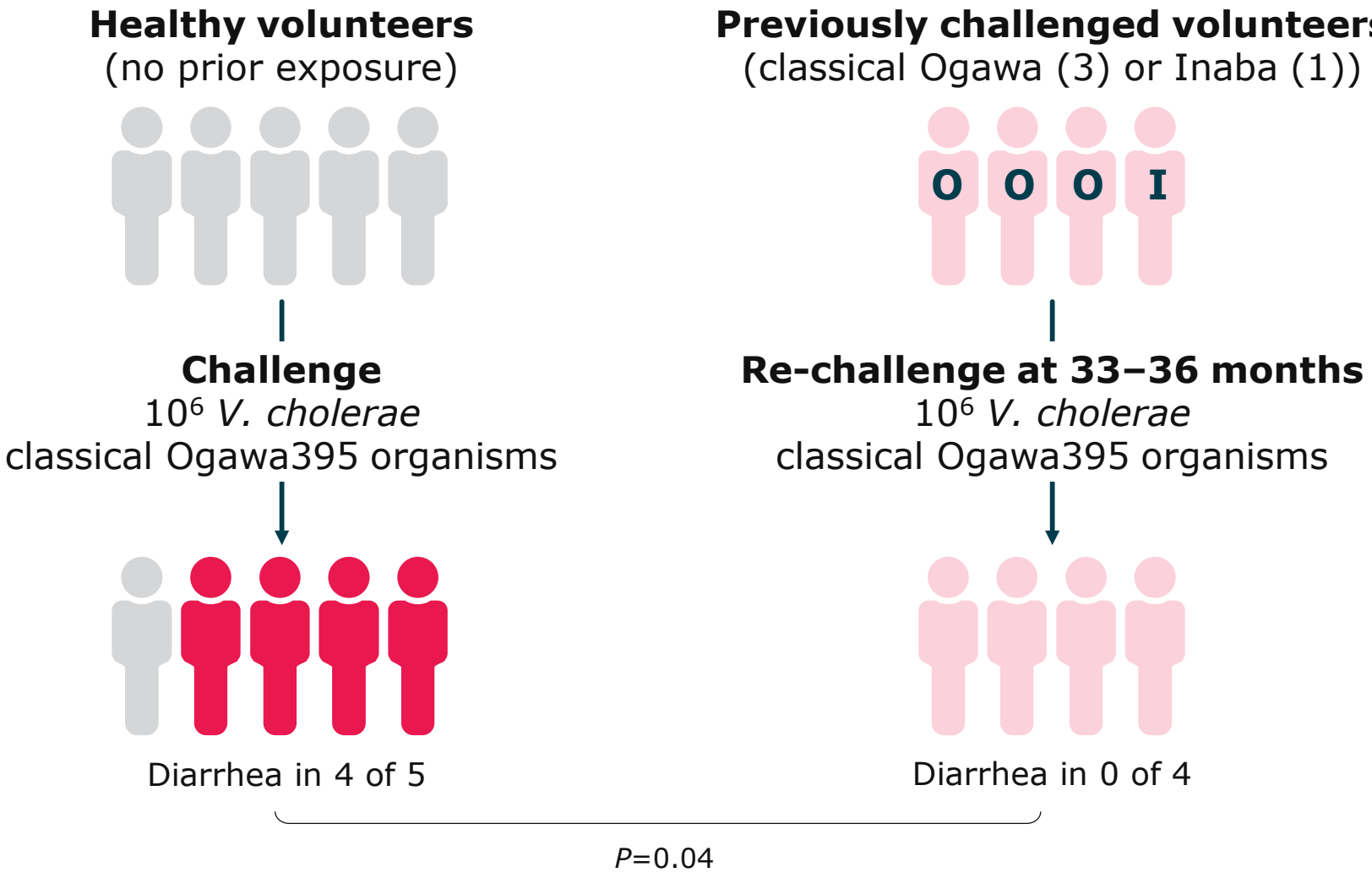
Safety information

- VAXCHORA® (Cholera Vaccine, Live, Oral) is contraindicated in people with a history of severe allergic reaction (e.g., anaphylaxis) to any ingredient of VAXCHORA or to a previous dose of any cholera vaccine
- The safety and effectiveness of VAXCHORA have not been established in immunocompromised persons
- VAXCHORA may be shed in the stool of recipients for at least 7 days. There is a potential for transmission of the vaccine strain to non-vaccinated close contacts (e.g., household contacts). Use caution when considering whether to administer VAXCHORA to individuals with immunocompromised close contacts
- The most common adverse reactions (incidence >3%) were tiredness (31%), headache (29%), abdominal pain (19%), nausea/vomiting (18%), lack of appetite (17%), and diarrhea (4%)

1. Vaxchora [package insert]. Redwood City, CA : PaxVax Bermuda Ltd.; 2019.

Cholera Vaccine, Live, Oral is not approved in the EU,
*Subject to change based upon regulatory review in the EU

Early Study of Natural Infection-Derived Immunity to Cholera



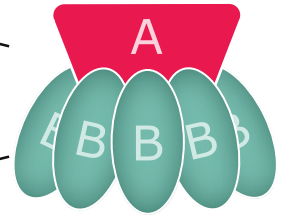
Levine MM, Black RE, Clements ML, Cisneros L, Nalin DR, Young CR. Duration of infection-derived immunity to cholera. *J Infect Dis*. 1981;143(6):818-820.

Vaccine Attenuation

	Wild-type	CVD 103-HgR*
Serogroup	O1	O1
Biotype	Classical	Classical
Serotype	Inaba	Inaba
Cholera toxin subunits	A and B	**B only**

Cholera toxin **subunit A** (toxic component)

Cholera toxin **subunit B** (cell-binding subunit)



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

*Vaccine strain in Cholera Vaccine, Live, Oral

1. Kaper J, et al. *Res Microbiol*. 1990;141(7-8):901-906.
2. Vaxchora [package insert]. Hamilton, Bermuda: PaxVax Bermuda Ltd.; 2019.
3. Clemens JD, et al. *Lancet*. 2017;390(10101):1539-1549.

In challenge studies, CVD 103-HgR has demonstrated efficacy at multiple time points and against heterologous challenge strains

Challenge studies evaluating vaccine efficacy of CVD 103-HgR[1]

Vaccine	Study	Sample size (vaccinees)	Dose (CFU)	Timing of challenge	Challenge strain	VE% MSD
Orochol	Levine et al, 1988[2]	6	5×10^8	1 month	El Tor Inaba	NA
	Tacket et al, 1992[3]	11	$3–5 \times 10^8$	6 months	Classical Inaba	100%
		3	$3–5 \times 10^9$	4 months		100%
		11	$3–5 \times 10^8$	8 days		100%
	Tacket et al, 1999[4]	28	$2–8 \times 10^8$	3 months	El Tor Inaba	91%
CVD 103-HgR	Chen et al, 2016[5]	35	5×10^8	10 days	El Tor Inaba	90.3%
		33		3 months		79.5%

CFU=colony-forming unit; MSD=moderate-to-severe diarrhea; VE=vaccine efficacy.

1. Jackson SS, Chen WH. Future Microbiol. 2015;10:1271-1781. 2. Levine MM, et al. Lancet. 1988;2:467-470.
3. Tacket CO, et al. J Infect Dis. 1992;166:837-841.4. Tacket CO, et al. Infect Immun. 1999;67:6341-6345.
5. Chen WH, et al. Clin Infect Dis. 2016;62:1329-1335. .

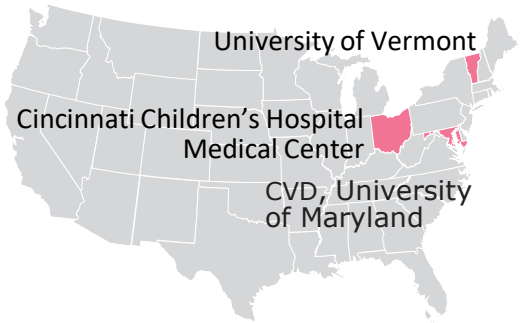
Phase III Clinical Development Program: Randomized, Double Blind, Placebo-Controlled Trials

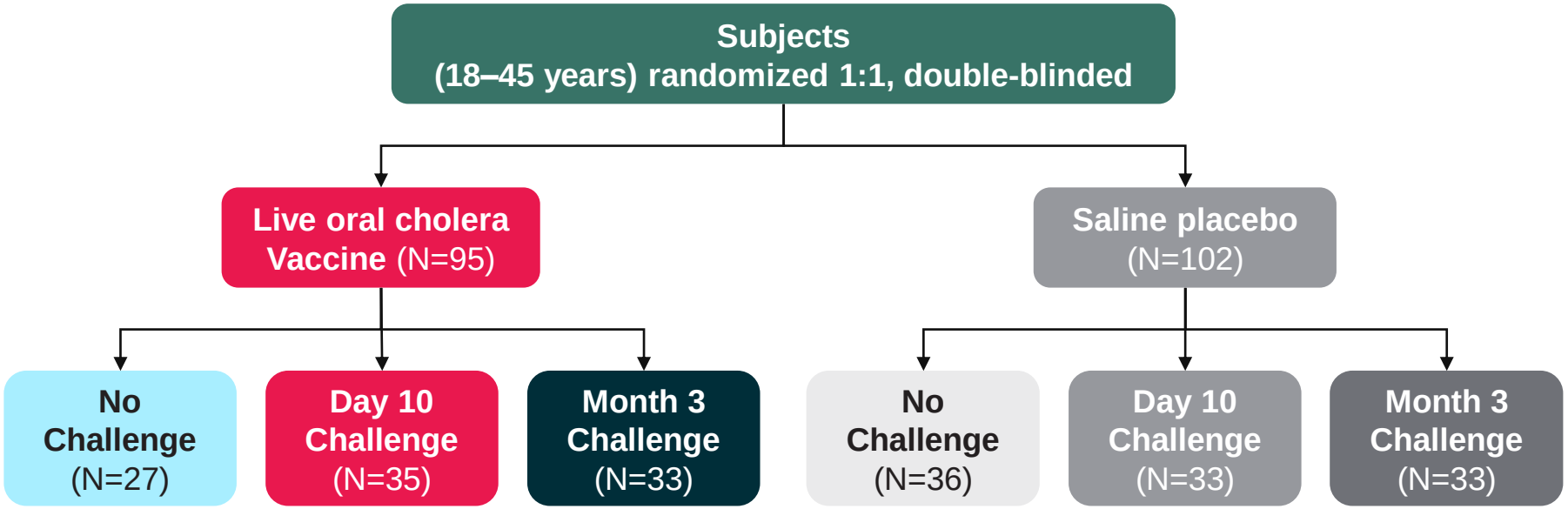
Study	Objectives	Test product(s); route of admin	# subjects*†	Results
003[3] Challenge	Demonstrate protection from live cholera challenge	5 x 10^8 CFU/dose; oral	197 (95 vaccine, 102 placebo)	Efficacy: 90.3% at 10 days, 79.5% at 90 days; SVA: 89.4% at 11 days
004[4] Adults 18–45	Demonstrate clinical lot consistency	1 x 10^9 CFU/dose; oral	3146 (2795 vaccine, 351 placebo)	95% CI within 0.78–1.2 (met criteria 0.67–1.5) SVA: 93.5% at 11 days
005[5] Adults 46–64	Demonstrate equivalence in immune response of older and younger adults (immunological bridging study)	1 x 10^9 CFU/dose; oral	398 (299 vaccine, 99 placebo)	SVA: 90.4% at 11 days

CI=confidence interval; SVA=serum vibriocidal antibody.
*A total of 3235 subjects received PXVX0200 vaccine.
†Placebo in the phase 1 trial was lactose powder in water. Placebo was physiologic saline in all other trials.
1. Summary Basis for Regulatory Action. Silver Spring, MD: US Food and Drug Administration; June 10, 2016.
2. Chen WH, et al. *Clin Vaccine Immunol*. 2014;21:66-73. 3. Chen WH, et al. *Clin Infect Dis.* 2016;62:1329-1335.
4. PaxVax, Inc. Data on file. PXVX-VC-200-004 CSR. 5. PaxVax, Inc. Data on file. PXVX-VC-200-005 CSR.

Efficacy of Cholera Vaccine, Live, Oral Was Assessed in a Placebo-Controlled Challenge Study[1]: Study Design

- **Primary efficacy endpoint:** prevention of moderate (≥3.0 L) to severe (≥5.0 L) cholera diarrhea
  - Diarrhea defined as passage of ≥2 loose stools (grade 3–5) ≥200 mL over a 48-hour period or 1 loose stool ≥300 mL
- **Additional efficacy endpoint:** anti-cholera immunogenicity defined as ≥4 fold increase in serum vibriocidal antibody titers over baseline
- **Safety endpoint:** solicited AEs were recorded for 7 days post-vaccination; serious AEs were recorded through day 180





AE=adverse event.

1. Chen WH, et al. *Clin Infect Dis.* 2016;62(11):1329-1335.

Efficacy of Cholera Vaccine, Live, Oral Was Assessed in a Placebo-Controlled Challenge Study[1]: Results

Number of unvaccinated and vaccinated subjects experiencing moderate or severe diarrhea following a challenge with virulent *Vibrio cholerae*

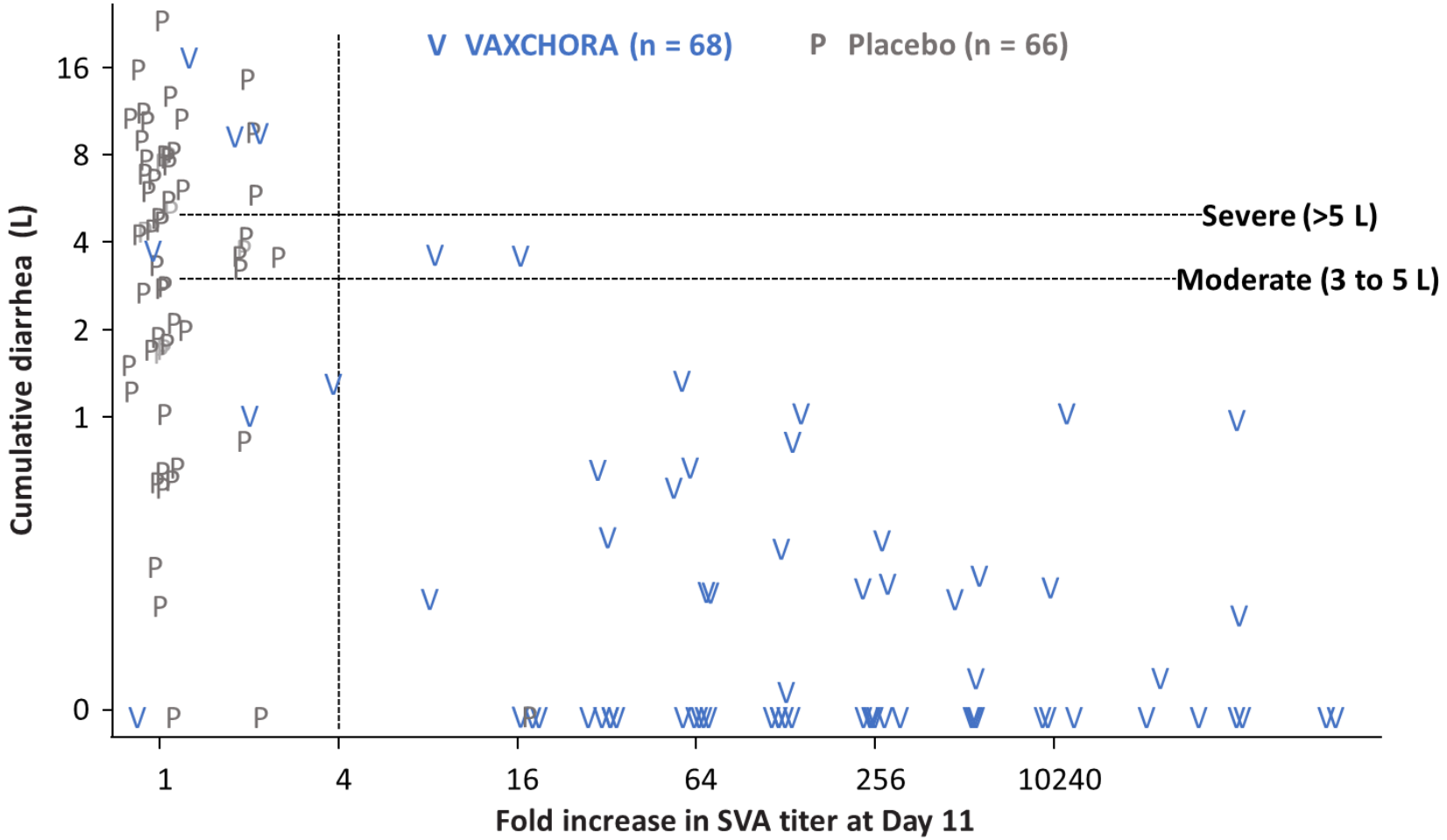
	Moderate or severe cholera	Seroconversion rates	Protection against moderate or severe diarrhea among seroconverters[2]
Placebo	39 out of 66 subjects (59.1%)	2 out of 102 subjects (2.0%)	
Vaccine 10-day group	2 out of 35 subjects (5.7%)	33 out of 35 subjects (94.3%)	32 out of 33 subjects (96.7%)
Vaccine 3-month group	4 out of 33 subjects (12.1%)	29 out of 33 subjects (87.9%)	28 out of 29 subjects (96.6%)

The primary endpoint was met for both the 10-day and 3-month challenge groups with vaccine efficacy of 90.3% and 79.5%, respectively

1. Chen WH, et al. *Clin Infect Dis.* 2016;62(11):1329-1335. 2. Data on file.

Vibriocidal Antibody Seroconversion was Determined to be an Immune Correlate of Protection[1,2]

- Strong correlation between seroconversion and protection from cholera diarrhea
- Approximately 97% of vaccinated subjects who demonstrated a ≥4-fold titer increase were protected against MSC
  - Conversely, 4 of the 6 vaccinated subjects who failed to seroconvert experienced MSC

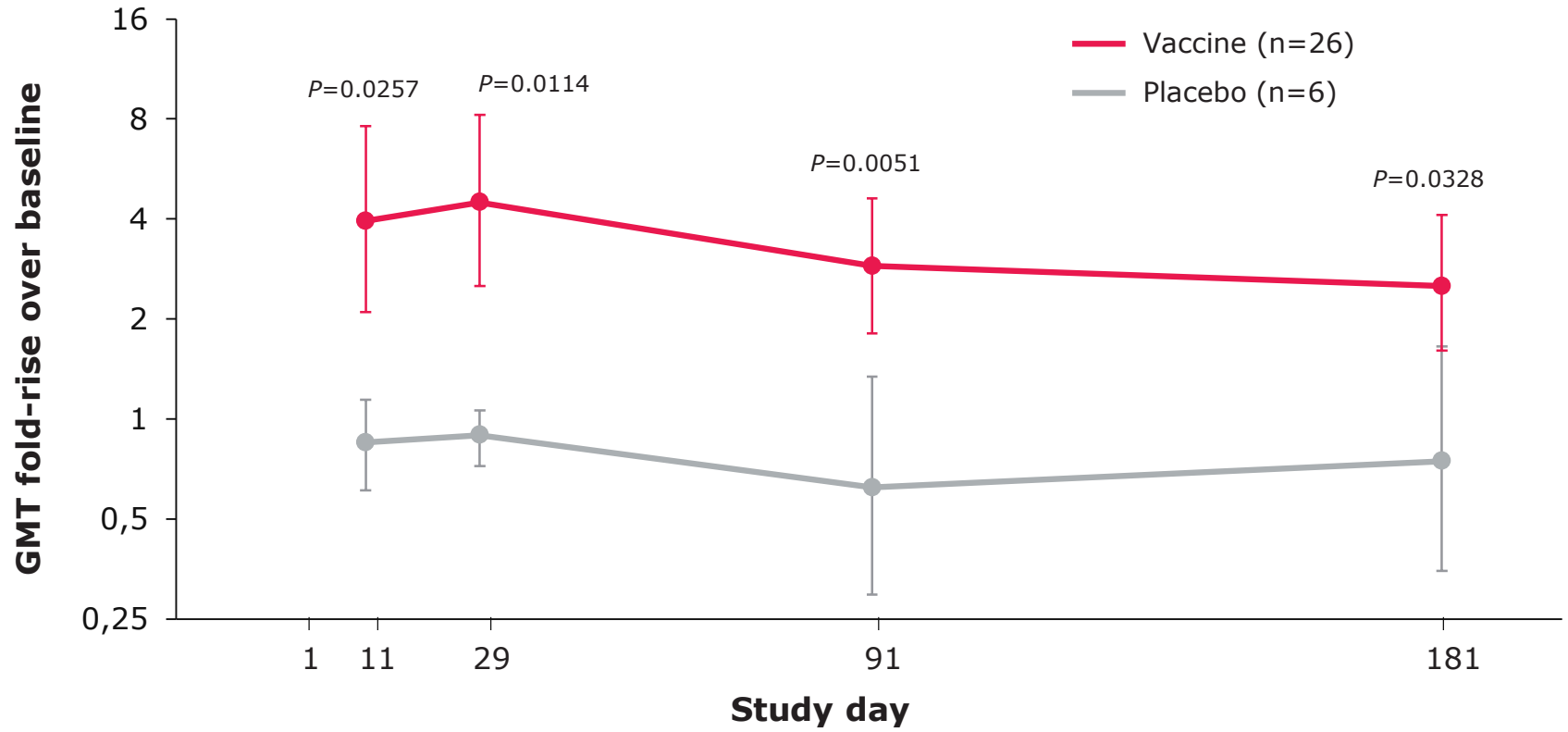


MSC: Moderate to severe cholera diarrhea

1. Chen et al Clinical Infectious Diseases 2016, 2. Haney et al Clin Vaccine Immunol 2017.

Persistence of anti-CT Antibody Response

Geometric mean fold-rise (95% CI) in anti-CT IgG antibody (substudy population*)



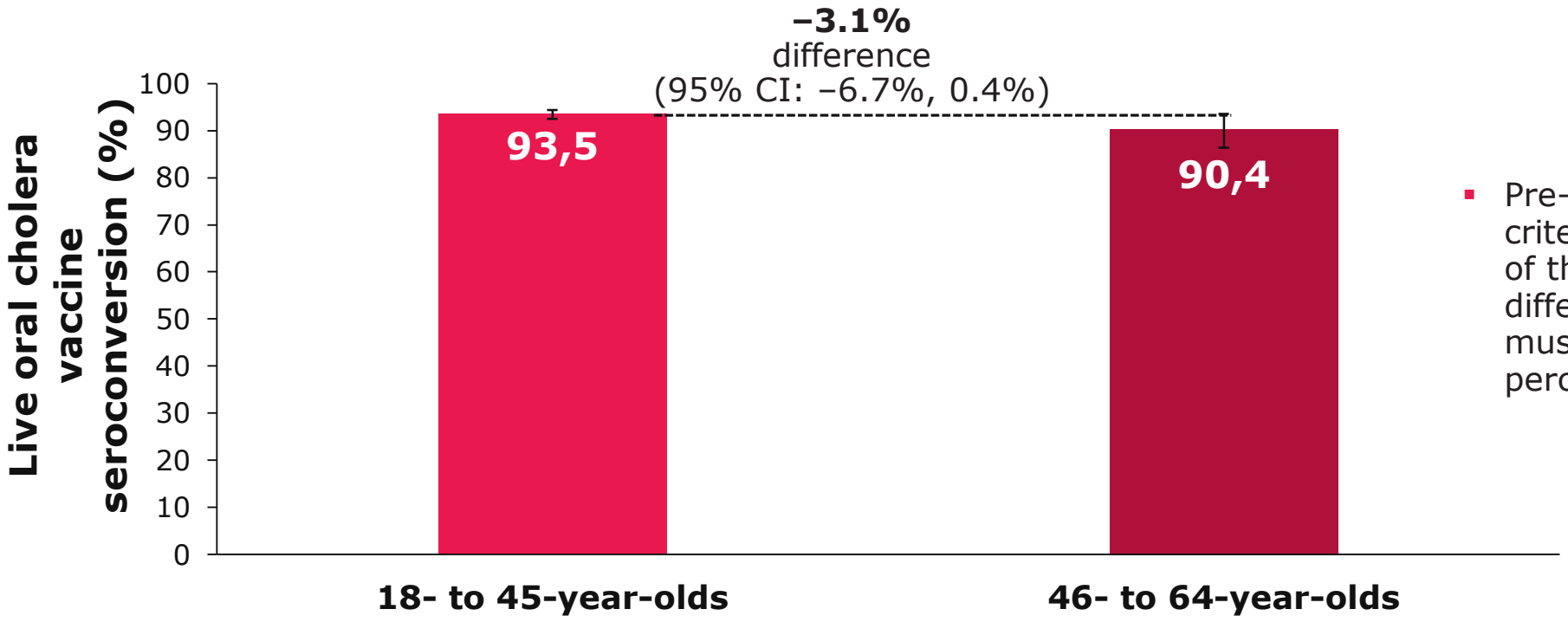
Anti-CT antibody was induced and persisted throughout the study period

P values compare Cholera Vaccine, Live, Oral vs placebo group at each study day.
*The immune substudy population included 26 Cholera Vaccine, Live, Oral and 6 placebo recipients with baseline characteristics comparable to the overall study population.
CI=confidence interval; CT=cholera toxin; GMT=geometric mean titer; IgG=immunoglobulin G

1. McCarty JM, et al. *Vaccine*. 2018;36:833-840.

Cholera Vaccine, Live, Oral Met the Primary Endpoint in an Immunologic Bridging Non-Inferiority Study[1]

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



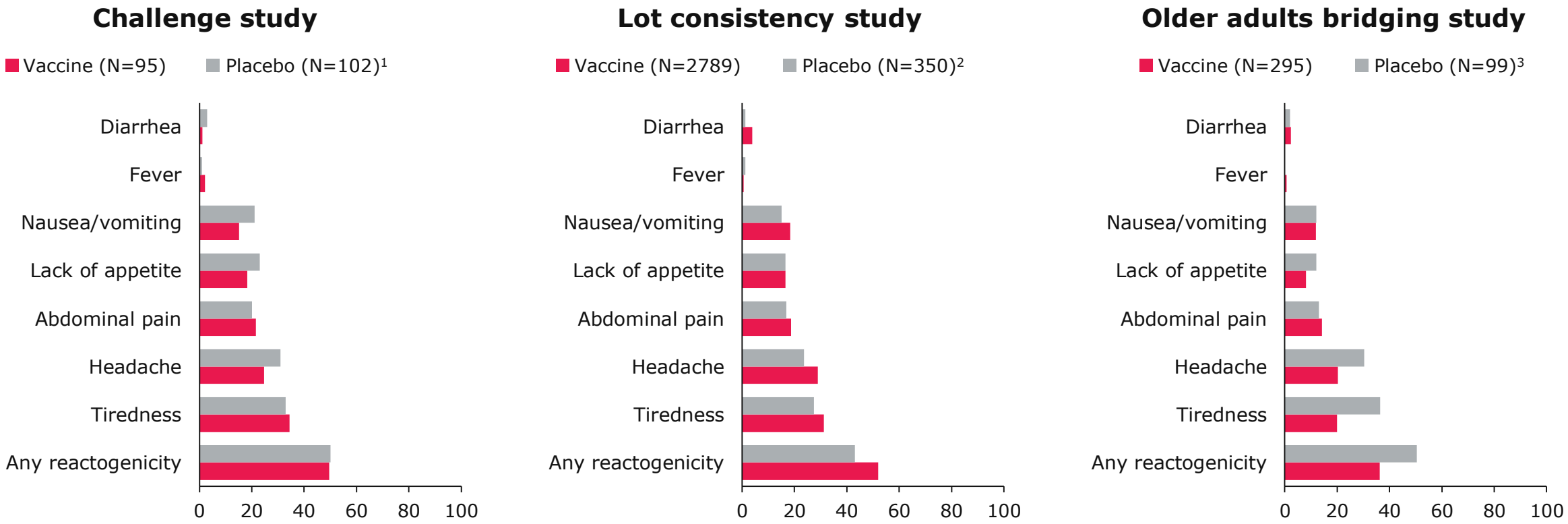
- Pre-specified non-inferiority criterion was that the lower bound of the 2-sided 95% CI on the difference in seroconversion rate must be greater than –10 percentage points

CI=confidence interval.

1. Vaxchora [package insert]. Redwood City, CA: PaxVax Bermuda Ltd.; 2019.

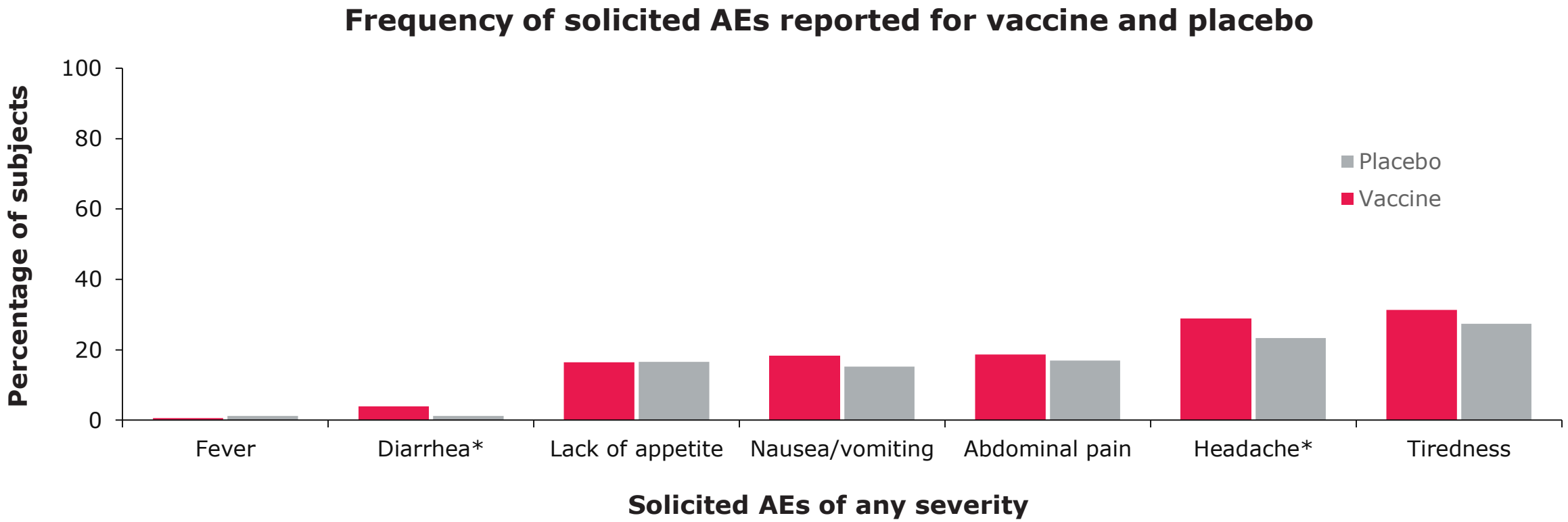
Safety Data: Adults Aged 18–64 Years in Clinical Trials[1–3]

Incidence of reactogenicity signs and symptoms following administration



1. Chen WH, et al. *Clin Infect Dis.* 2016;62(11):1329-1335.
2. McCarty JM, et al. *Vaccine*. 2018;36:833-840.
3. McCarty JM, et al. *Vaccine.* 2019;37:1389-1397.

Reactogenicity Among Vaccine Recipients was Comparable to Placebo Controls



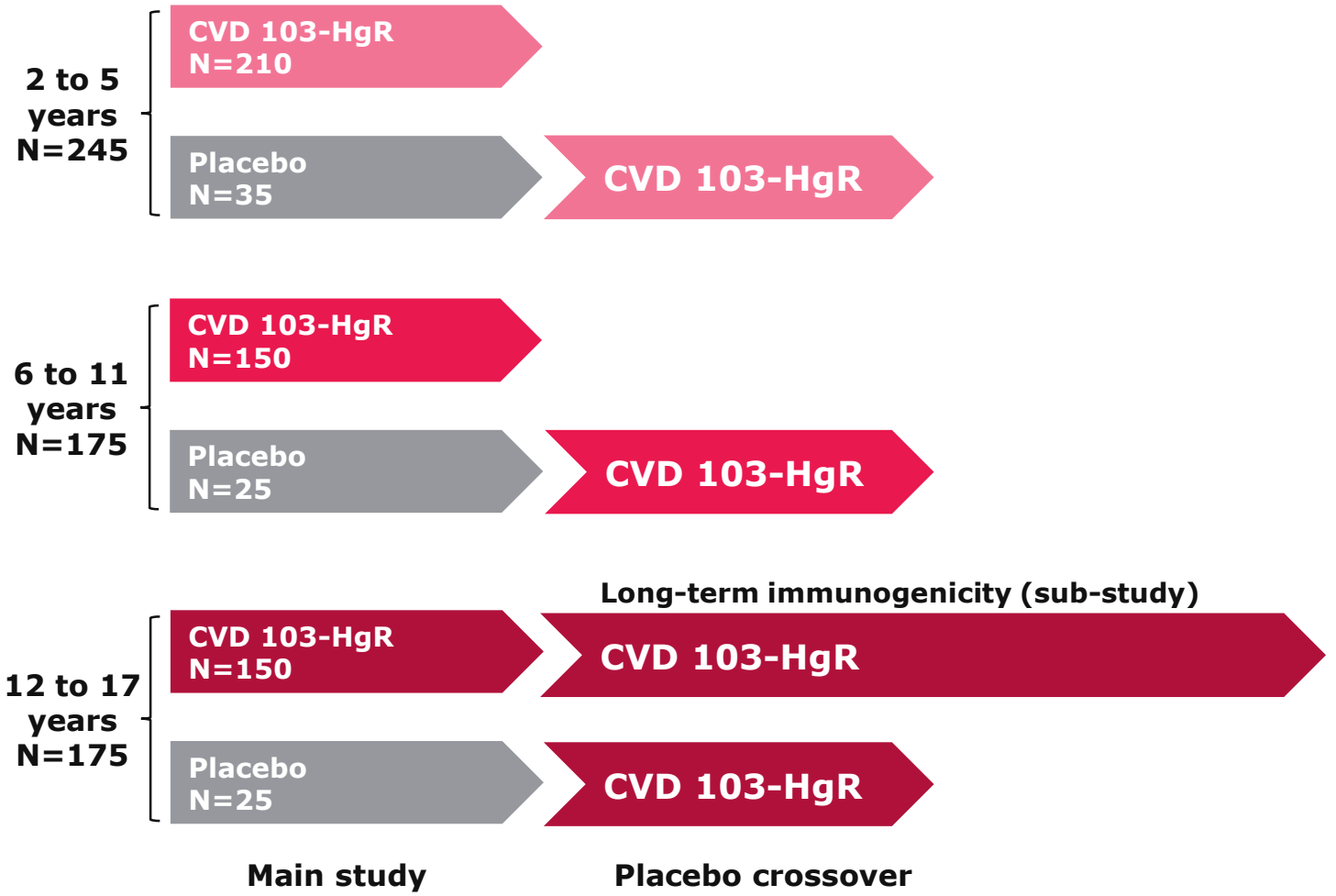
The majority of adverse events were mild and resolved within 1 to 3 days

*Statistically significant difference, AE=adverse event.
McCarty JM, et al. *Vaccine*. 2018;36:833-840.

Cholera Vaccine, Live, Oral Phase IV Pediatric Study Design - Ongoing

Analysis endpoint:

- Safety (adverse events)
  - Solicited adverse events through Day 8
  - Unsolicited adverse events (including serious adverse events)
- **Primary endpoint:**
  SVA seroconversion rate at Day 11
  - 4-fold rise from baseline
  - Non-inferiority versus adults (margin-10%)
  - Minimum seroconversion (lower bound 70%)
- Cumulative SVA seroconversion at Day 29
- SVA geometric mean titer (GMT)
  - 12 to 17 years: through Day 181



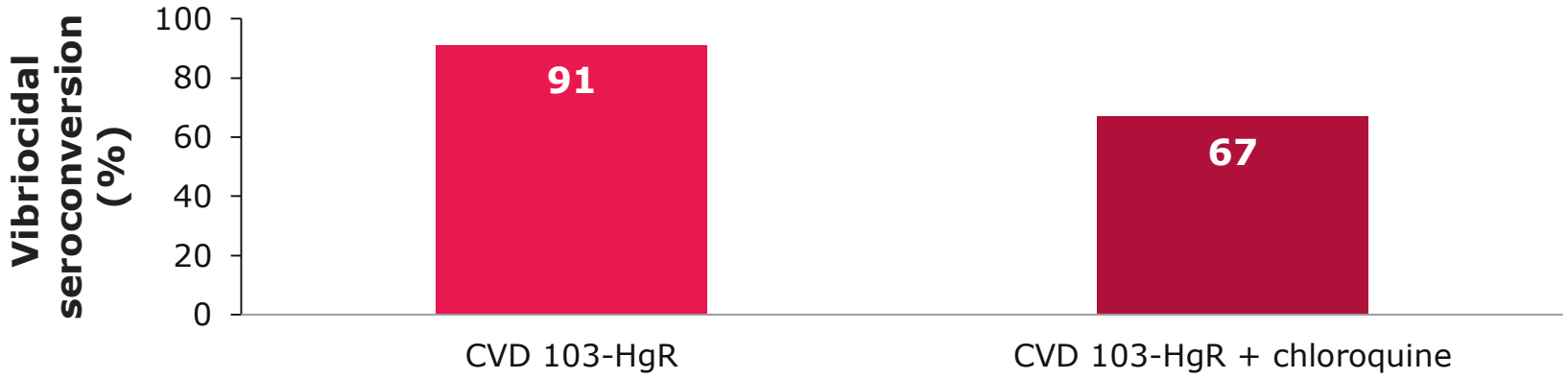
SVA=serum vibriocidal antibody

1. Bennett SR, CISTM, 2019.

Considerations for concomitant use of Cholera Vaccine, Live, Oral with/without other medications and vaccines

- Do not administer Cholera Vaccine, Live, Oral to patients who have received oral or parenteral antibiotics within 14 days prior to vaccination[1]
- Cholera Vaccine, Live, Oral should be separated ≥8 hours from VIVOTIF due to interaction with the buffer solution and enteric coating[2]
- Immune response may be diminished when live Cholera Vaccine, Live, Oral is used concomitantly with other medications[1,3]
  - Data from a study with a similar product indicate that the immune responses to live oral cholera vaccine may be diminished when live oral cholera vaccine is administered concomitantly with chloroquine[1]
  - The coadministration of chloroquine with CVD 103-HgR was previously studied and resulted in a significant (p=0.008) decline in vibriocidal seroconversion rate compared with administration of CVD 103-HgR alone[3]

Effect of concomitant use of CVD 103-HgR with chloroquine on immunogenicity[3]



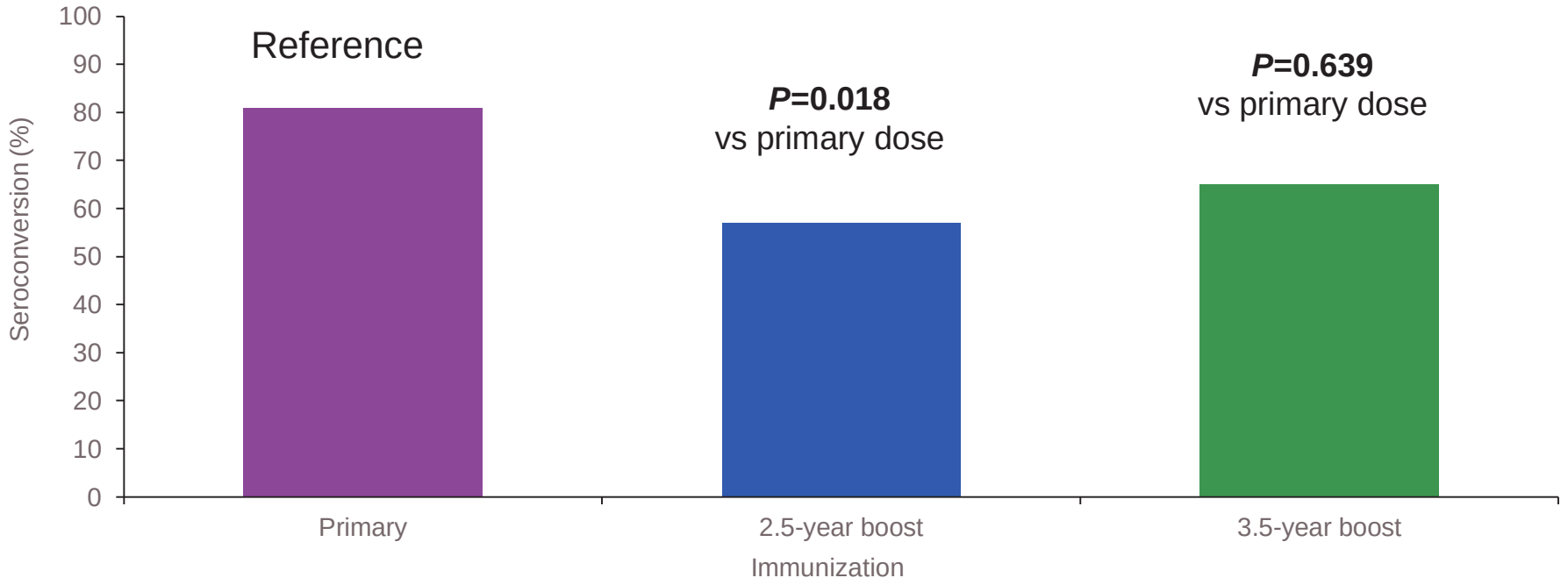
1. Vaxchora [package insert]. Redwood City, CA : PaxVax Bermuda Ltd.; 2019.
2. Wong KK, et al. *MMWR Morb Mortal Wkly Rep.* 2017;66(18):482-485.
3. Kollaritsch H, et al. *J Infect Dis.* 1997;175(4):871-875.

THANK YOU

Back-up Slides

Prior Immunization with CVD 103-HgR Resulted in Reduction of Immune Response to Booster at 2.5 years

Serum vibriocidal response (% seroconversion) following primary immunization and reimmunization with cholera vaccines[1]

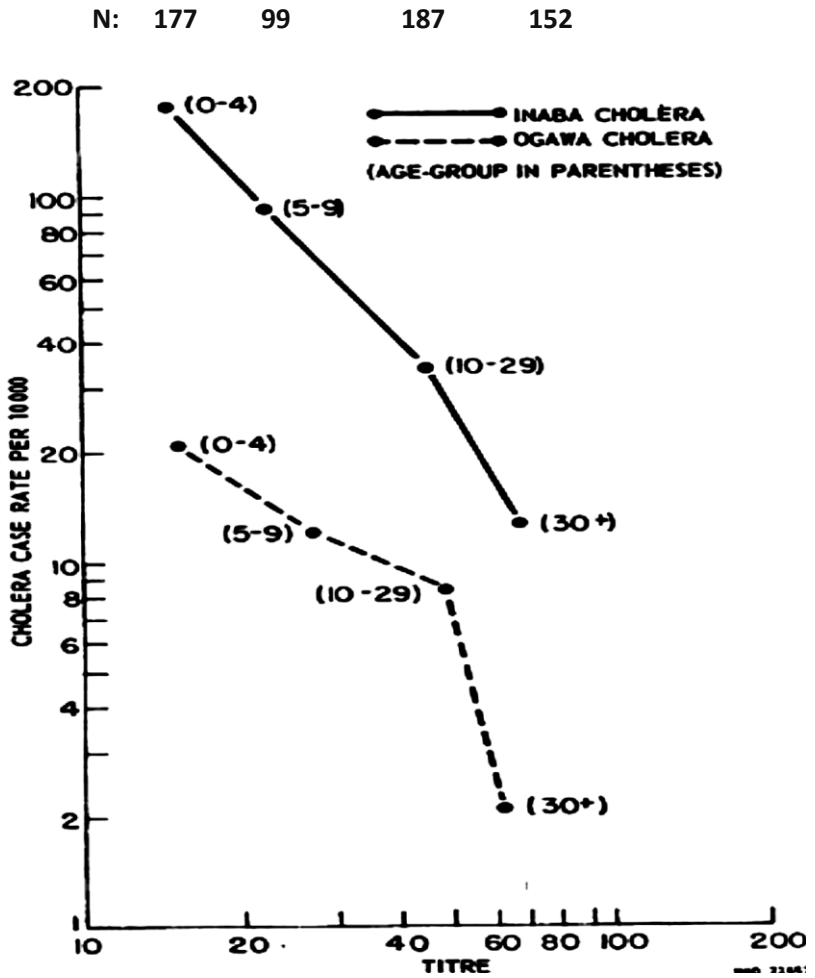


CVD 103-HgR pattern of immune response following re-immunization is similar to immune response data following re-infection with *V. cholerae*

1. Kollaritsch H, et al. *Vaccine.* 2000;18:3031-3039.
2. Levine MM, et al. *J Infect Dis*. 1981;143:818-820.

Correlation Related to Serum Vibriocidal Activity (SVA) and Naturally Acquired Protection Against Cholera

- Observational data from vaccine-naïve Bangladeshi children and adults, Oct 1964 to June 1966
- Children have:
  - Lowest SVA levels
  - Highest disease burden
- SVA titer increases with age
- Cholera case rate declines with age



Mosley WH et al, Bull WHO 1968.

CVD 103-HgR SVA Rates Summary: Biotypes

Against the four major V. cholerae O1 serogroup biotypes and serotypes (10 days post-vaccination)

	Younger adults (18 through 45 year old) CVD 103-HgR		Older adults (46 through 64 year old) CVD 103-HgR	
Cholera Strain	N[a]	%[b] [95% CI[c]]	N[a]	% [95% CI]
Classical Inaba[d]	93	90.3% [82.4%, 95.5%]	291	90.4% [86.4%, 93.5%]
El Tor Inaba	93	91.4% [83.8%, 96.2%]	290	91.0% [87.1%, 94.1%]
Classical Ogawa	93	87.1% [78.5%, 93.2%]	291	73.2% [67.7%, 78.2%]
El Tor Ogawa	93	89.2% [81.1%, 94.7%]	290	71.4% [65.8%, 76.5%]

a N=number of subjects with measurements at baseline and 10 days post-vaccination. One subject in Study 2 did not have a Day 11 measurement and was dropped from the analysis. b Seroconversion is defined as the percentages of subjects who had at least a 4-fold rise in vibriocidal antibody titer at 10 days post-vaccination compared to the titer measured at baseline. c CI=confidence interval. d Vaxchora contains the classical Inaba strain of V. cholerae O1.

CVD 103-HgR SVA Rates Summary: Age

Against classical Inaba V. cholerae vaccine strain (10 days post-vaccination)

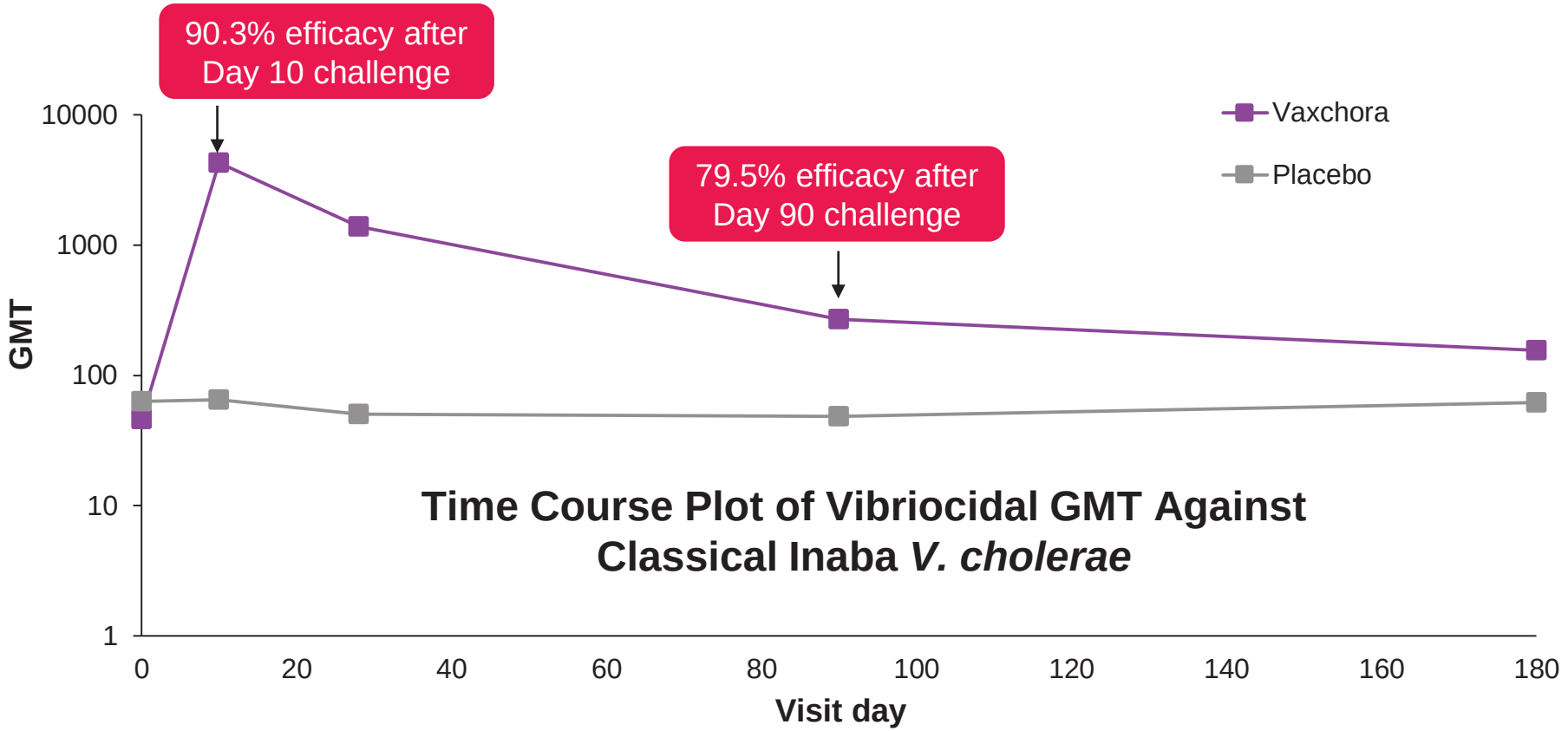
Study	CVD 103-HgR recipients		Placebo recipients		△ Seroconversion rate vs. large trial in 18–45 year olds
(age in years)	N [b]	Seroconversion[a] % [95% CI]	N [b]	Seroconversion[a] % [95% CI[c]]	% [95% CI[c]]
Challenge trial (18–45)	93	90.3% [82.4%, 95.5%]	102	2.0% [0.2%, 6.9%]	-
Large trial (18–45)	2687	93.5% [92.5%, 94.4%]	334	4.2% [2.3%, 6.9%]	-
Older adults (46–64)	291	90.4% [86.4%, 93.5%]	99	0% [0.0%, 3.7%]	−3.1% [−6.7%, 0.4%]
Pediatric trial (6–17)	296	98.6% [96.6%, 99.5%]	47	2.1% [0.4%, 11.1%]	5.1% [2.6%, 6.5%][c]

[a] Seroconversion is defined as the percentages of subjects who had at least a 4-fold rise in vibriocidal antibody titer at 10 days post-vaccination compared to baseline.

[b] N=number of subjects with analyzable samples at Day 1 and Day 11. [c] CI=confidence interval; pediatric trial used 96.7% CI for comparison to adults.

Proposed EU SmPC

Persistence of Vibriocidal GMT



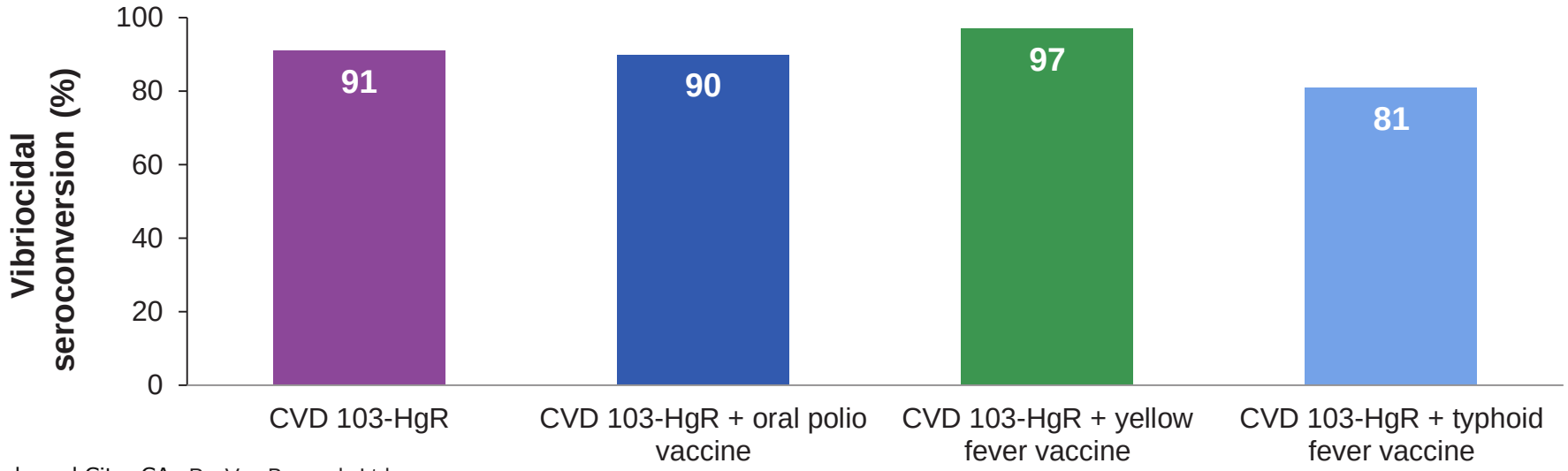
Moderate to severe cholera, vaccinated subjects with ≥4-fold SCR significantly reduced in the 10-day and 3-month challenge groups

GMT=geometric mean titer. Chen WH, et al. *Clin Infect Dis.* 2016;62:1329-1335.

Considerations for Concomitant Use of Cholera Vaccine, Live, Oral with Other Medications and Vaccines

- The concomitant use of Cholera Vaccine, Live, Oral with antibiotics is not recommended[1]
- There are no available data on the concomitant use of Cholera Vaccine, Live, Oral with other vaccines[1]
- Immune response may be diminished when Cholera Vaccine, Live, Oral is used concomitantly with other medications and vaccines[2]
  - Similar studies of the coadministration of oral polio, yellow fever, or typhoid fever vaccine with CVD 103-HgR showed no effect on the immune response relative to administration of CVD 103-HgR alone[2,3]

Effect of concomitant use of CVD 103-HgR with other vaccines on immunogenicity[2,3]



1. Vaxchora® [package insert]. Redwood City, CA : PaxVax Bermuda Ltd.; 2016. 2. Kollaritsch H, et al. *J Infect Dis.* 1997;175(4):871-875 .
3. Kollaritsch H, et al. *Vaccine.* 2000;18(26):3031-3039.