

Vaxchora[®] Vaccine - Pediatric Dose Development

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Vaxchora[®] (Cholera Vaccine, Live, Oral)

Vaxchora vaccine is comprised of two packets (sachets) that are reconstituted in 100 mL of water*

- Buffer Component packet:
 - Contents: 4.5 g of white to off-white powder
- Active Component packet:
 - Contents: 2.0 g of white to beige powder
 - *V. cholerae* CVD 103-HgR attenuated vaccine strain



*For children under 6 years of age: following reconstitution of the buffer in 100 mL of water, discard half of the buffer solution prior to addition of the active component. VAXCHORA [package insert]. Redwood City, CA: Emergent BioSolutions; December 2020

Vaxchora Vaccine: Clinical Development Program

Study	Age Range	Dose	# Subjects* (Active)	Objectives	Results
Phase 1 002 ¹	18 to 50	4.4 x 10 ⁸ CFU	66 (55)	Safety Immunogenicity Kinetics (shedding)	Well-tolerated SVA 88.9% (D14) Stool+ 11% (through D7)
Challenge Phase 3 003 ²	18 to 45	5 x 10 ⁸ CFU	197 (95)	Efficacy (challenge) Immunogenicity	SVA 79.8% (D8) SVA 89.4% (D11) Efficacy 90.3% (D11) Efficacy 79.5% (D91)
Lot Consistency Phase 3 004 ³	18 to 45	1 x 10 ⁹ CFU	3146 (2795)	Lot consistency Safety Immunogenicity	Met consistency criteria Well-tolerated SVA: 93.5% (D11)
Older Adult Phase 3 005 ⁴	46 to 64	1 x 10 ⁹ CFU	398 (299)	Safety Immunogenicity Bridging	Well-tolerated SVA 90.4% (D11) Non-inferior to 004
Pediatric Phase 4 006 ^{5,6}	2 to 17	1 x 10 ⁹ CFU	550 (468)	Safety Immunogenicity Bridging	Well-tolerated SVA 98.5% (D11) Non-inferior to 004

*Placebo in the phase 1 trial was lactose powder in water. Placebo was physiological saline in all other trials.

CFU=colony-forming unit; SVA=serum vibriocidal antibody

1. Chen WH, et al. Clin Vaccine Immunol. 2014;21(1):66-73. 2. Chen WH, et al. Clin Infect Dis. 2016;62(11):1329-1335. 3. McCarty JM, et al. Vaccine. 2018;36:833-840. 4. McCarty JM, et al. Vaccine. 2019;37:1389-1397. 5. McCarty JM, et al. Am J Trop Med Hyg. 2020;102(1):48-57. 6. McCarty JM, et al. Am J Trop Med Hyg. 2020;104(5):1758-1760.

Pediatric Study: Dose Development

Vaxchora Vaccine Pediatric Development Goals:

- Use existing, approved Vaxchora vaccine formulation
- Adapt Vaxchora vaccine to children 2 to 6 years of age
 - Reduce volume
 - Flavor/mask taste

Vaxchora Vaccine Pediatric Study: Volume Reduction

Buffer reconstitution volume (mL)	pH*	Buffer capacity (ml, 1M HCl) [†]
100	7.00	25.1
50	7.16	24.3
100 (50 mL discard)	7.02	12.2 [‡]

*pH release specification: 6.7 – 7.1

[†]Buffer Capacity release specification: >21.0 mL 1M HCl neutralized

[‡]Buffer capacity is below specification. Children have smaller stomachs and higher gastric pH²

Reconstitution volume (mL)	T=0	T=15 min
100	11.6 x 10 ⁸	8.99 x 10 ⁸
50	4.68 x 10 ⁸	3.52 x 10 ⁸
100 (Discard 50 mL)	5.49 x 10 ⁸	5.30 x 10 ⁸

Vaccine Potency Specification: 4 x 10⁸ to 2 x 10⁹ CFU/Dose

Conclusions:

- Keep buffer concentration the same as approved formulation
- Vaxchora vaccine is stable when reconstituted in 50 mL of buffered water

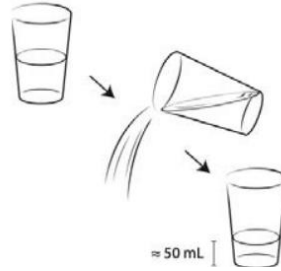
CFU=colony forming units

1. Data on file, Emergent BioSolutions Inc, Duffin P, 2020. 2. Nagita A, et al. *Pediatr Res* 1996;40(4):528-532.

Vaxchora Vaccine: Key Steps for Pediatric Administration



Empty buffer component packet contents into 100 mL of water and stir until completely dissolved



For children less than 6 years of age, discard half (50 mL) of the buffer solution



Empty active component packet contents into the cup and stir for 30 seconds.

If desired, **sugar (sucrose)** (4 grams or 1 teaspoon) or **stevia** (1 gram or ¼ teaspoon) may be stirred into the suspension*

*Proposed added step and language, to be reviewed by FDA



Vaxchora vaccine must be consumed within 15 minutes of reconstitution

Sugar (Sucrose) and Stevia Sweeteners

- Typical sugar (sucrose) packet contains 4g, typical Stevia packet contains 1g
- Stevia is much sweeter than sugar (sucrose), so ‘fillers’ (>95% by weight) are used to bulk stevia extract (<5%)
- Strategy: choose stevia brands that
 - Are available worldwide
 - Market is consolidated and dominated by a few major players including Cargill, Inc. (Truvia®) and Tate & Lyle (Splenda®)
 - Contain the most commonly used ‘fillers’
 - Most common ‘fillers’ by survey of popular brands: inulin, erythritol, maltodextrin, dextrose

Sugar (Sucrose) and Stevia Studies

- Study setup:
 - 1g to 4g sweetener + 50ml reconstituted Vaxchora vaccine
 - Potency tested at 0 and 15 minutes
 - Vaxchora vaccine potency specification: 4×10^8 to 2×10^9 CFU/dose
- Brands were chosen as representative of ‘stevia powder’ or ‘stevia crystals’

Stevia Brand	Filler
Pure Via®	Dextrose
Sweet Additions®	Maltodextrin
Truvia®, Splenda® Naturals	Erythritol
SweetLeaf®	Inulin



Sweetener	CFU/Dose Post Reconstitution (Min)	
	0	15
Sugar (Sucrose)		
1g	7.3×10^8	6.0×10^8
4g	7.0×10^8	6.4×10^8
Stevia Brand (1g)		
Pure Via®	4.9×10^8	4.3×10^8
	12×10^8	11×10^8
	5.6×10^8	5.6×10^8
Truvia®	7.1×10^8	6.3×10^8
Splenda® Naturals	7.1×10^8	6.0×10^8
SweetLeaf®	6.8×10^8	6.2×10^8
Sweet Additions®	7.5×10^8	6.3×10^8

CFU=colony forming units
 Data on file, Emergent BioSolutions Inc, Duffin P, 2020

Conclusion

- Vaxchora is well tolerated and effective in children age 2 to 17 years
- Vaxchora vaccine is compatible with both sugar (sucrose) and stevia powder/crystals
 - Vaxchora vaccine is compatible with
 - ≥ 50 mL reconstitution volume
 - Sugar (Sucrose) (4 g)
 - Stevia (1 g)
 - Tested brands that are available around the globe
 - Tested most common stevia ‘fillers’: inulin, erythritol, maltodextrin, and dextrose
 - Vaxchora vaccine should not be used with:
 - Medicine flavorings (FLAVORx[®], Yummy Meds[®]) due to the presence of propylene glycol

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50ml Pediatric Dose Reconstitution Study: Flavoring

Category	Material	T ₀ (CFU/dose)	Feasible?	Considerations
Flavoring Agents	Stevia (1g)	6.36 x 10 ⁸	Yes	FLAVORx [®] contains propylene glycol, is not compatible with CVD 103-HgR
	OTC medicine flavoring	5.30 x 10 ⁸	No	
Baby Formula	Similac [®]	6.41 x 10 ⁸	Maybe	Pro: High t ₀ potency, stays above potency limit for at least 30 minutes Con: Complicated reconstitution process
	Gerber [®]	7.32 x 10 ⁸	Maybe	
	Enfamil [®]	7.82 x 10 ⁸	Maybe	
Other Foods/ Drinks	Applesauce	6.41 x 10 ⁸	No	Pro: High T ₀ potency, stays above potency limit for 30 minutes Con: Excessive foaming/overflow when buffer added. Not suitable for the clinic.
	Apple Juice	7.47 x 10 ⁸	No	
	Rice Cereal	7.69 x 10 ⁸	No	

- Challenges with specific formulations:
 - Baby formula:** Buffer effervescence caused excessive foaming and sample overflowed unless buffer was added first.
 - Foods and Drinks:** Buffer effervescence caused excessive foaming and sample overflowed. Not suitable for the clinic.



CFU=colony forming units; OTC=over the counter.
 Data on file, Emergent BioSolutions Inc, Duffin P, 2020.

Sugar (Sucrose) and Stevia Studies

- Study setup:
 - 1g to 4g sweetener + 50ml reconstituted Vaxchora vaccine
 - Potency tested at 0 and 15 minutes
 - Vaxchora vaccine potency specification: 4×10^8 to 2×10^9 CFU/dose
- Brands were chosen as representative of ‘stevia powder’ or ‘stevia crystals’

Stevia Brand	Filler
Pure Via®	Dextrose
Sweet Additions®	Maltodextrin
Truvia®, Splenda® Naturals	Erythritol
SweetLeaf®	Inulin

Sugar (sucrose)	CFU/Dose Post Reconstitution (Min)		Stevia Brand (1g)	CFU/Dose Post Reconstitution (Min)	
	0	15		0	15
1g	7.3×10^8	6.0×10^8	Pure Via®	4.9×10^8	4.3×10^8
				12×10^8	11×10^8
				5.6×10^8	5.6×10^8
4g	7.0×10^8	6.4×10^8	Truvia®	7.1×10^8	6.3×10^8
			Splenda® Naturals	7.1×10^8	6.0×10^8
			SweetLeaf®	6.8×10^8	6.2×10^8
			Sweet Additions®	7.5×10^8	6.3×10^8

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