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W7 New vaccines on the horizon

Enteric Disease: *Shigella* and ETEC Vaccine Development

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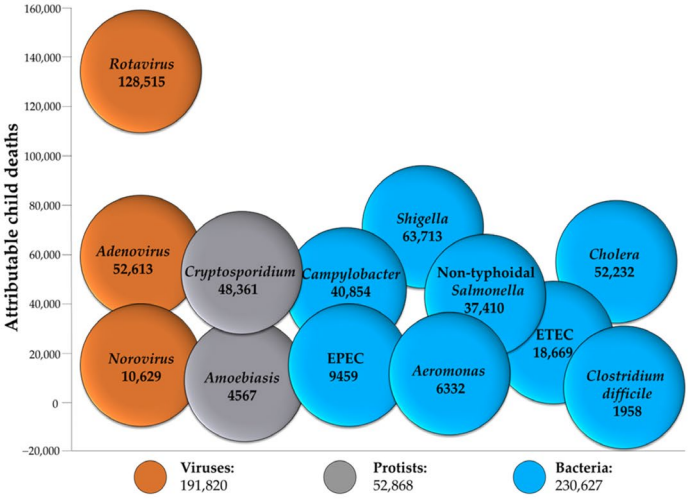
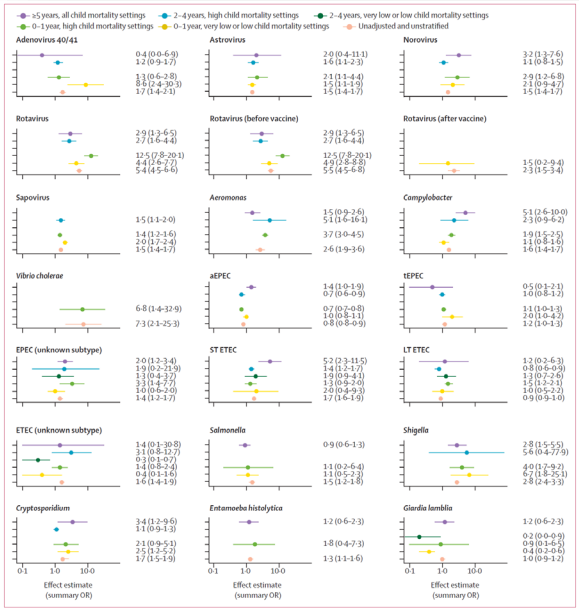


Raso MM, Arato V, Gasperini G, Micoli F. Toward a Shigella Vaccine: Opportunities and Challenges to Fight an Antimicrobial-Resistant Pathogen. Int J Mol Sci. 2023 Feb 28;24(5):4649. doi: 10.3390/ijms24054649. PMID: 36902092; PMCID: PMC10003550.



Pathogen	0-1 High mortality setting	0-1 Low mortality setting	2-4 High mortality setting	2-4 Low mortality setting	All child mortality settings
Shigella	4.0	6.7	5.6		**2.8**
LT ETEC	1.5	1.0	0.8	1.3	**1.2**
ST-ETEC	1.3	2.0	1.4	1.9	**5.2**
Unk ETEC	1.4	0.4	3.1	0.3	**1.4**

Baker JM, Hasso-Agopsowicz M, Pitzer VE, Platts-Mills JA, Peralta-Santos A, Troja C, Archer H, Guo B, Sheahan W, Lingappa J, Jit M, Lopman BA. Association of enteropathogen detection with diarrhoea by age and high versus low child mortality settings: a systematic review and meta-analysis. Lancet Glob Health. 2021 Oct;9(10):e1402-e1410. doi: 10.1016/S2214-109X(21)00316-8. PMID: 34534487; PMCID: PMC8456779.

Characteristics of licensed vaccines available for enteric infections

Disease	Vaccine name	Manufacturer	Type	Coverage	Availability	Indication
Typhoid	Typbar-TCV	Bharat Biotech	Vi-TT	*S.* Typhi	India, Nepal (global following WHO prequalification)	Children >6 months adults
Typhoid	PedaTyph	BioMed	Vi-TT	*S.* Typhi	India	Children >3 months adults
Typhoid	Typherix®	GSK	Vi PS	*S.* Typhi	Global	1 Dose children >2 yrs & adults
Typhoid	Ty21a (Vivotif)	PaxVax	Live-attenuated	*S.* Typhi	Global	3 Doses children >2 yrs & adults
Rotavirus	Rotarix	GSK	Live oral	Human rotaviruses	Global	2 Doses, infants over 6 weeks age
Rotavirus	RotaTeq	Merck	Live oral	Human rotaviruses	Global	3 Doses, infants >6 weeks of age
Rotavirus	Rotavac	Bharat Biotech	Live oral	Human rotaviruses	WHO PQ, India	3 Doses, infants >6 weeks of age
Rotavirus	RotaSiil	Serum Institute of India	Live oral	Human rotaviruses	India	3 Doses, infants >6 weeks of age
Cholera	Dukoral	Valneva	Inactivated	*V. cholerae* serogroup O1 (both Inaba and Ogawa serotypes of classical biotypes and an El Tor Inaba) plus recombinant cholera toxin B subunit (rCTB)	Europe, Australia, Canada, New Zealand, and many other countries; not in US	Primary immunization of adults and children age ≥6 years: oral two doses, 1 week apart and primary immunization of child 2–6 years old: oral three doses, 1 week apart
Cholera	mORC-Vax	Vabiotech	Inactivated	*V. cholerae* serogroup O1 (both Inaba and Ogawa serotypes of classical biotypes and an El Tor Inaba) and an O139 strain	Vietnam	Primary immunization of adults and children age ≥1 year: oral two-dose, two weeks apart
Cholera	Shanchol	Shantha Biotechnics Ltd	Inactivated	*V. cholerae* serogroup O1 (both Inaba and Ogawa serotypes of classical biotypes and an El Tor Inaba) and an O139 strain	WHO stockpile	Primary immunization of adults and children age ≥1 year: oral two doses, 2 weeks apart
Cholera	Euvichol	EuBiologics Co Ltd	Inactivated	*V. cholerae* serogroup O1 (both Inaba and Ogawa serotypes of classical biotypes and an El Tor Inaba) and an O139 strain	WHO stockpile	Primary immunization of adults and children age ≥1 year: oral two doses, 2 weeks apart
Cholera	Vaxchora	PaxVax Inc	Live	*V. cholerae* serogroup O1 classical biotype Inaba serotype, engineered with a deletion mutation in ctxA	US only	Primary immunization of adults, age 18–64 years: oral single dose

Riddle MS, Chen WH, Kirkwood CD, MacLennan CA. Update on vaccines for enteric pathogens. Clin Microbiol Infect. 2018 Oct;24(10):1039-1045. doi: 10.1016/j.cmi.2018.06.023. Epub 2018 Jun 28. PMID: 29964231

Characteristics of lead novel enteric vaccines in advanced (phase II and beyond) clinical development

Pathogen	Developer	Construct	Status	Current trials
Shigella	LimmaTech/GSK	Tetravalent O-PS—rEPA bioconjugate	Phase I trial and controlled human challenge model demonstrating efficacy with monovalent *Shigella flexneri* 2b construct completed	ClinicalTrials.gov Identifier: NCT02646371
	GVGH/GSK	GMMA (Generalized Modules for Membrane Antigens)	phase I trial in European adults and phase IIa trial in Kenyan adults	Information not yet available (no current trials – CHIM due to start in next few months)
ETEC	Scandanavian Biopharma	Pentavalent killed whole cell	Phase I trial and controlled human challenge model demonstrating efficacy completed. Preliminary field efficacy being evaluated in an expanded phase II trial among Finnish adult travellers to Benin at risk of travellers' diarrhoea	EudraCT number: 2016-002690-35
	US Department of Defense/Sanofi Pasteur	Multivalent subunit tip adhesion protein	Phase I and IIb human challenge model of monovalent construct demonstrating evidence of effectiveness with second monovalent construct in phase I	Clintrials.gov Identifier: NCT01922856, NCT03404674
Rotavirus	PATH/SK Chemicals	Trivalent vaccine based on truncated VP8 subunits of rotavirus P[4], P[6] and P[8] genotypes	Phase I and IIa immunogenicity and safety studies in adults, toddlers and infants, demonstrated excellent immune responses of the monovalent P2-VP[8] component. Phase IIb age de-escalation and dose escalation of the trivalent vaccine has been completed, with immunogenicity results pending	Clintrials.gov Identifier: NCT01764256, NCT02109484, NCT02646891
Norovirus	Takeda Vaccines	GI.1/GII.4 virus-like particle, parenteral, one to two doses	Phase I trials and phase II controlled human challenge model demonstrating efficacy completed. Phase II studies in young adults (including preliminary field efficacy), elderly, paediatric populations under way	EudraCT Number: 2016-004288-37; Clintrials.gov Identifier: NCT03039790, NCT02661490, NCT02153112, NCT02669121

Riddle MS, Chen WH, Kirkwood CD, MacLennan CA. Update on vaccines for enteric pathogens. Clin Microbiol Infect. 2018 Oct;24(10):1039-1045. doi: 10.1016/j.cmi.2018.06.023. Epub 2018 Jun 28. PMID: 29964231

Current landscape of ETEC vaccine development.

vaccine candidate	vaccine type/description	target antigens	clinical phase				
			pre	1	2	3	reference(s)
whole cell-bacteria							
ETVAX±dmLT	whole-cell inactivated, recombinant LTCBA	CFA/I, CS3,5,6; LT			*a*		(73)
ACE527±dmLT	live-attenuated, recombinant LT-B	CFA/I, CS1–3,5,6, LT			*b*		(75)
Shigella-ETEC multivalent	live-attenuated *Shigella*-ETEC *heterologous expression*	CFA/I, CS1–6, 14; LThA2B					(94)
recombinant subunits							
dmLT LT(R192G/L211A)	recombinant antigen/adjuvant	LT		*d,f*			(73, 75, 100, 101)
LT-ST fusion (ENTVAC)	recombinant toxoid fusion STa(N12S)^3-LT(R192G/L211A)	LT/ST					(109, 122)
fimbrial tip adhesins	recombinant dscCfaE + LT(R192G)	CFA/I, LT		*g*	*h*		(112)
	recombinant cssBA ± dmLT	CS6, LT		*i*			(115)
	chimeric recombinant dsc14CfaE-sCTA2/LTB5	CFA/I, LT		*j*			(114)
MEFA	multi-epitope fusion antigen + dmLT	CFA/I, CS1–6, LT					(123)
EtpA	recombinant adhesin	EtpA					(36, 37)
EatA	recombinant mucin-degrading protease	EatA					(29)
YghJ(SslE)	recombinant metalloprotease	YghJ(SslE)					(45)

Fleckenstein JM. Confronting challenges to enterotoxigenic Escherichia coli vaccine development. Front Trop Dis. 2021;2:709907. doi: 10.3389/fitd.2021.709907. Epub 2021 Sep 24. PMID: 35937717; PMCID: PMC9355458.

Table 1. Status of vaccine candidates in development against *Shigella*.

Technology	Name	Composition	Developer	Stage	References
Whole-cell Killed Vaccines	SsWc	Formalin-inactivated *S. sonnei*	WRAIR	Discontinued after Ph1	[149]
	Sf2aWC	Formalin-inactivated *S. flexneri* 2a	WRAIR	Discontinued after Ph1	[150]
Live Attenuated Vaccines	FS	*S. flexneri* 2a and *S. sonnei*	Lanzhou Institute of Biological Products	Licensed (limited China)	
	SmD	Streptomycin-dependent *Shigella* strains	Yugoslav Army	Discontinued after Ph3	[154]
Live Attenuated Vaccines	CVD 1208S	*guaBA*-based live attenuated candidates from *S. flexneri* 2a 2457T strain	University of Maryland	Discontinued after Ph2	[155]
	SC602	*virG* and *tuc* deletions from *S. flexneri* 2a 494 wild type strain	Pasteur Institute	Discontinued after Ph2	[157]
	WRSS2	*S. sonnei* Moseley Δ*virG*, *senA* and *senB*	WRAIR	Phase 1	[162]
	WRSS3	*S. sonnei* Moseley Δ*virG*, *senA*, *senB*, and *msBb*			
	Truncated *Shigella*	Attenuated Δ*uxuy Shigella flexneri* 2a strain	IVI	Preclinical	[163]
	ShigETEC	*S. flexneri* 2a 2457T Δ*rfbF*, *ipaBC*, and *setBA* expressing fusion protein B subunit of ETEC	EveliQure	Phase 1	[164]
	Ty21a typhoid vaccine expressing *Shigella*	Ty21a typhoid vaccine displaying *Shigella* LPS	Protein Potential	Discontinued after Ph2	[165]
Subunit Vaccines	Shigellvak	*S. sonnei* LPS		Licensed (limited to Russia)	
	S. sonnei O-antigen/rEPA	*S. sonnei* monovalent O-antigen glycoconjugate	NIH	Discontinued after Ph3	[125]
	S4V-EPA	Quadrivalent *S. flexneri* 2a, 3a, 6 and *S. sonnei* OAg bioconjugate	LimmaTech	Phase 2	[166]
	Sf2a-TT15	*S. flexneri* 2a synthetic OAg conjugate	Institute Pasteur	Phase 2	[167]
	ZF0901	*S. flexneri* 2a and *S. sonnei* OAg conjugate	Beijing Zhifei Lvzhu Biopharmaceuticals	Phase 3	[168]
	$Invaplex_{AR-DETOX}$	LPS from *S. flexneri* 2a 2457T Δ*msBb* and recombinant IpaB and IpaC	WRAIR	Phase 1	[169]
	altSolflex1–2-3	Quadrivalent *S. flexneri* 1b, 2a, 3a, and *S. sonnei* outer membrane vesicles (GMMA)	GVGH (GSK)	Phase 2	[170]
	OMV Sf2a	*S. flexneri* 2a outer membrane vesicles	Navarra University	Preclinical	[171]
	Ipa DB Fusion	Recombinant protein	PATH	Preclinical	[172]
	34kDa OmpA Sf2a	Recombinant protein	NICED	Preclinical	[173]
	PS5P-1	Recombinant protein	IVI	Preclinical	[174]

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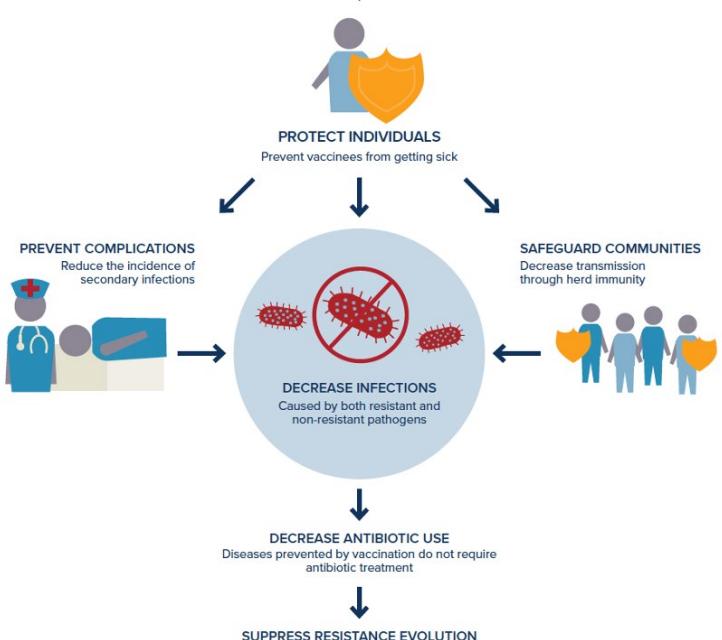
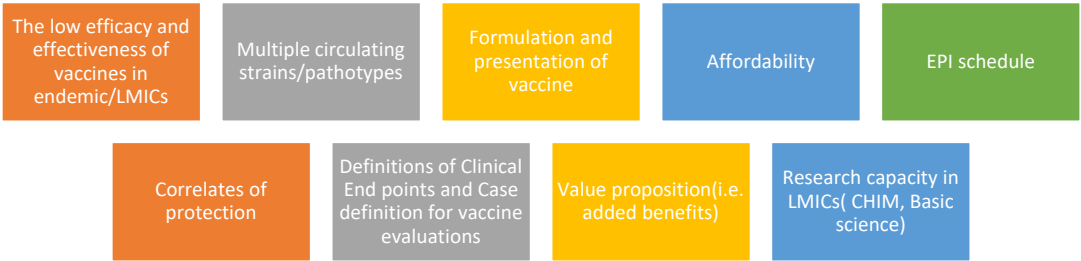

PROTECT INDIVIDUALS
Prevent vaccinees from getting sick
PREVENT COMPLICATIONS
Reduce the incidence of secondary infections
SAFEGUARD COMMUNITIES
Decrease transmission through herd immunity
DECREASE INFECTIONS
Caused by both resistant and non-resistant pathogens
DECREASE ANTIBIOTIC USE
Diseases prevented by vaccination do not require antibiotic treatment
SUPPRESS RESISTANCE EVOLUTION


The low efficacy and effectiveness of vaccines in endemic/LMICs
Multiple circulating strains/pathotypes
Formulation and presentation of vaccine
Affordability
EPI schedule
Correlates of protection
Definitions of Clinical End points and Case definition for vaccine evaluations
Value proposition(i.e. added benefits)
Research capacity in LMICs(CHIM, Basic science)

Thank you for listening