THE DEVELOPMENT OF FUTURE VACCINES AGAINST ENTERIC DISEASES

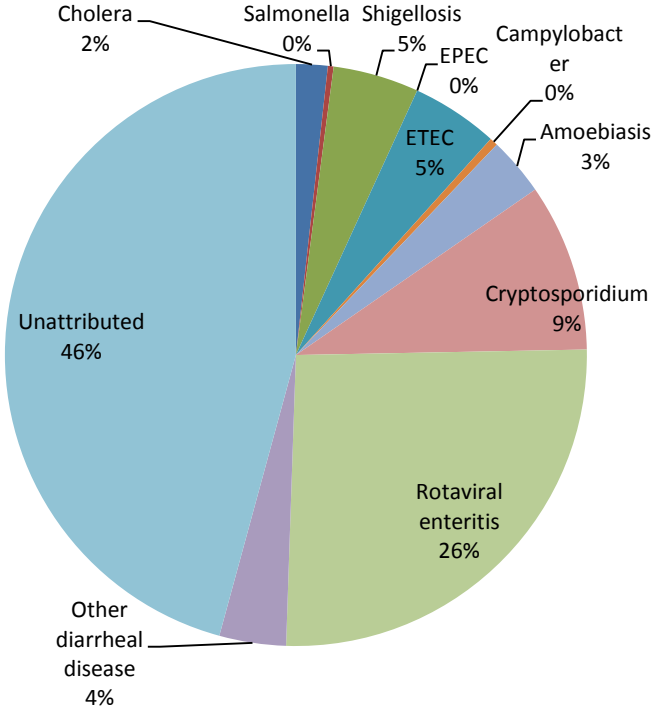
Duncan Steele
Bill & Melinda Gates Foundation

Correlates of enteric-vaccine induced protection
21-23 March, 2016, Fondation Merieux, Annecy

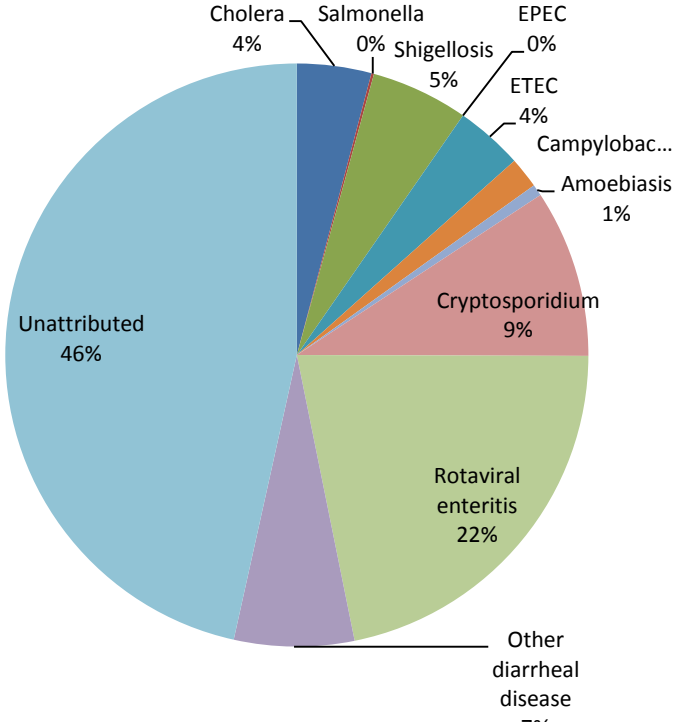
WHAT PATHOGENS ARE CAUSING MODERATE TO SEVERE DIARRHEA IN YOUNG CHILDREN?

- Rotavirus
- Shigella
- ETEC
- Norovirus

- S Typhi



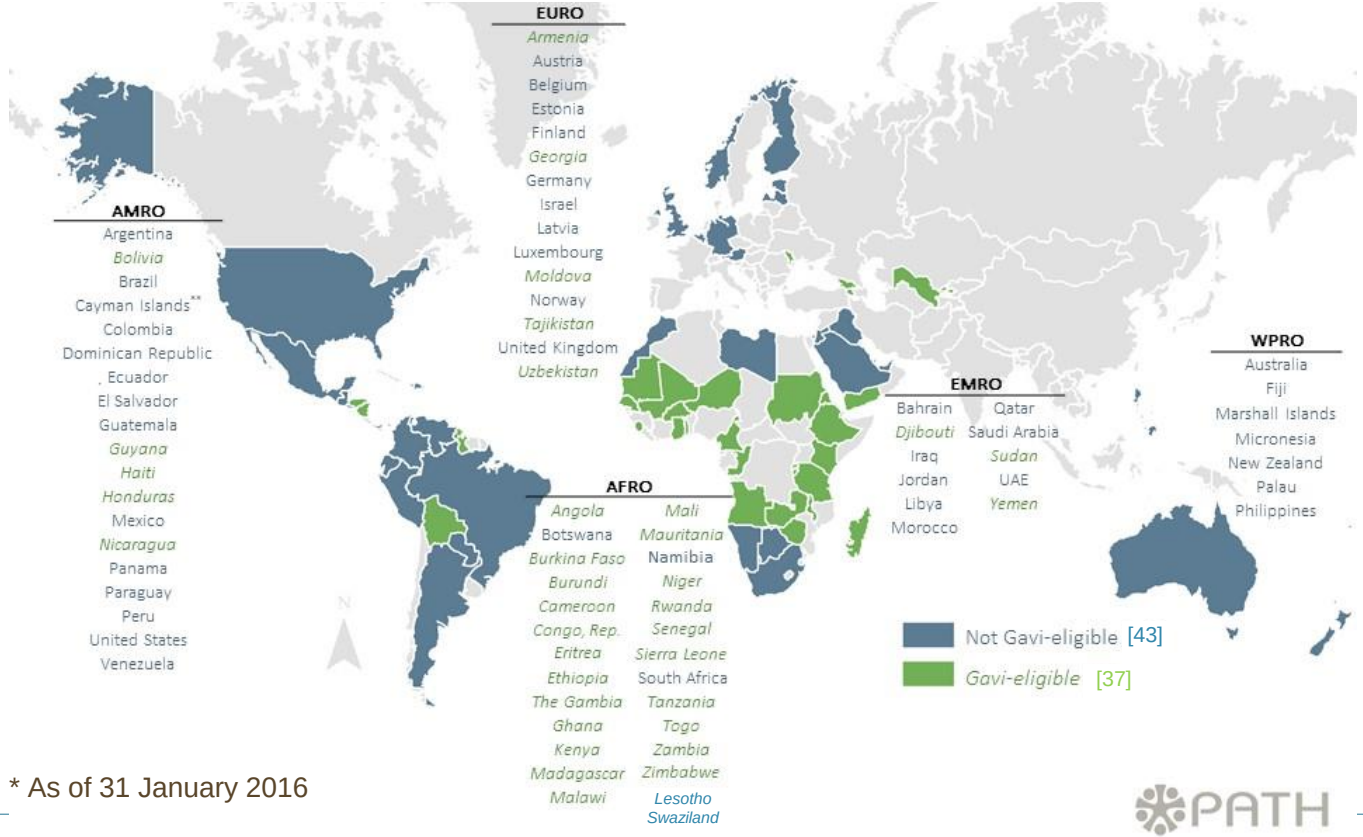
Mozambique



India

Kotloff K et al. Lancet 2013; 382(9888): 209-22

ROTAVIRUS VACCINES – NATIONAL INTRODUCTIONS BY GEOGRAPHIC REGION*

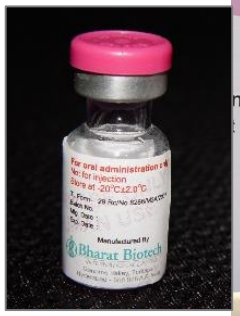


* As of 31 January 2016

ROTAVIRUS VACCINE DEVELOPMENT IN INDIA

ROTAVAC® licensure in India

- Shown to be safe & efficacious in Phase III trial in India
  - 54% efficacy against severe rotavirus gastroenteritis over 2 years of life
  - 56% protection in the first year of life
- ROTAVAC ® products could achieve major impact in India and in Gavi-eligible countries
- First-generation product to be priced at ~$1 per dose



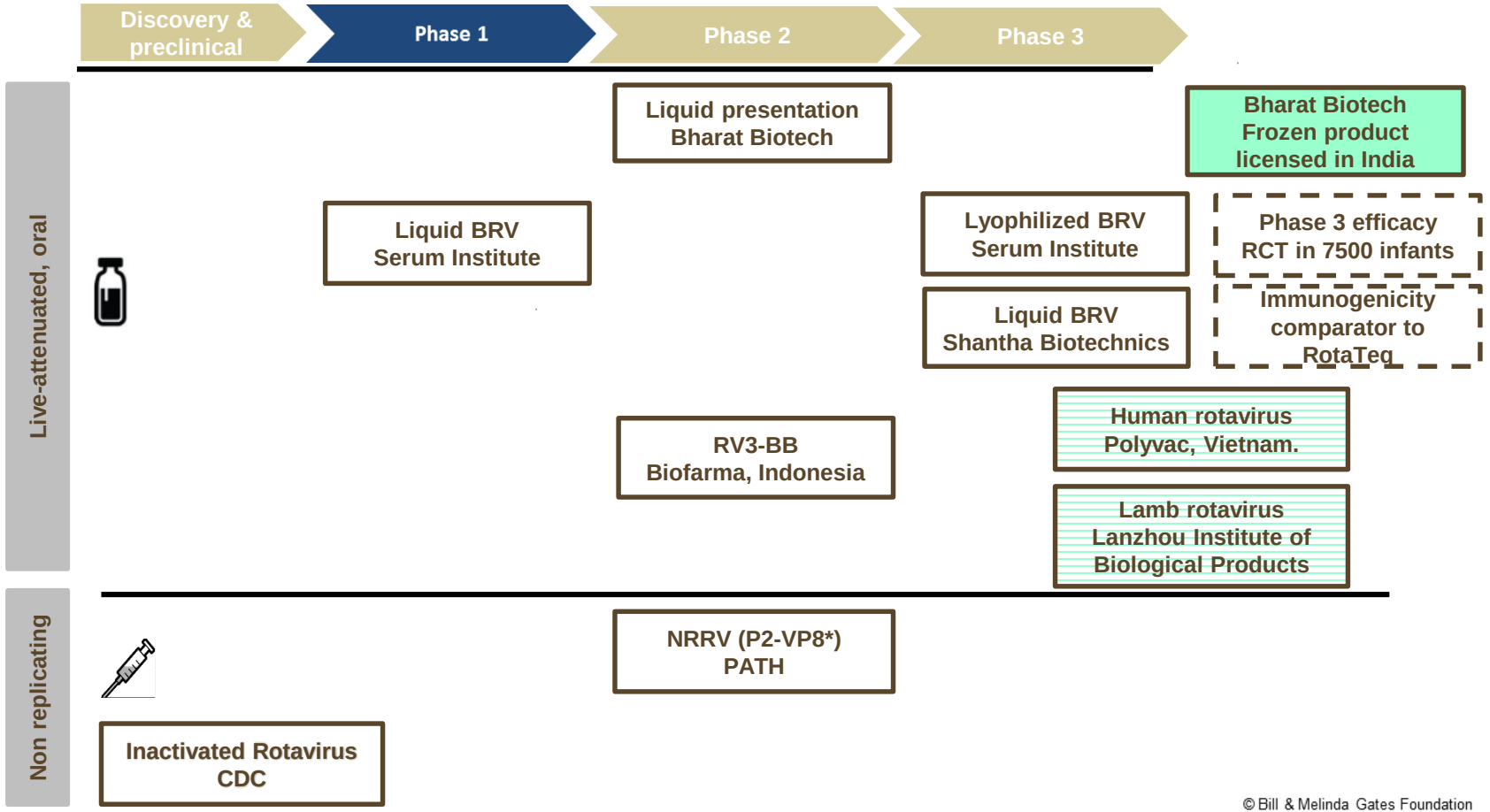
Bharat Biotech
Lead Innovation

Dr MK Bhan, former secretary, Department of Biotechnology, Dr K Vijay Raghavan, Secretary, DBT, Govt of India with Dr Krishna Ella, Chairman & Managing Director, Bharat Biotech, and Dr TS Rao, DBT at the release of Rotavac phase-III trial data in New Delhi

National launch in first 4 States in India on 26th March 2016

Bhandari N, Rongsen-Chondola N, Bavedekar A et al. Lancet 2014; 383:2136-43 & Vaccine 2014; 32S: A110-114

ROTAVIRUS VACCINE CANDIDATE PIPELINE



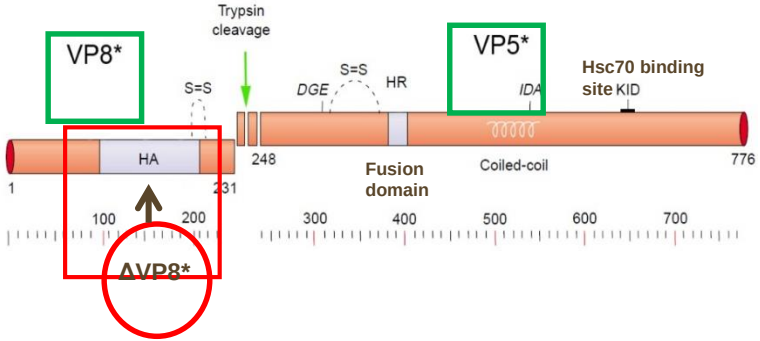
CHARACTERISTICS OF P2-VP8* VACCINE

Developed at US NIH by Yasutaka Hoshino

Truncated VP8* subunit

- human Wa strain (G1 P1a[8])
- fused to the tetanus toxin P2 CD4 epitope
- expressed in *E. coli*

Schematic diagram of rotavirus VP4 protein



No unexpected toxicity in rabbits at doses up to 60 µg

Non-pyrogenic

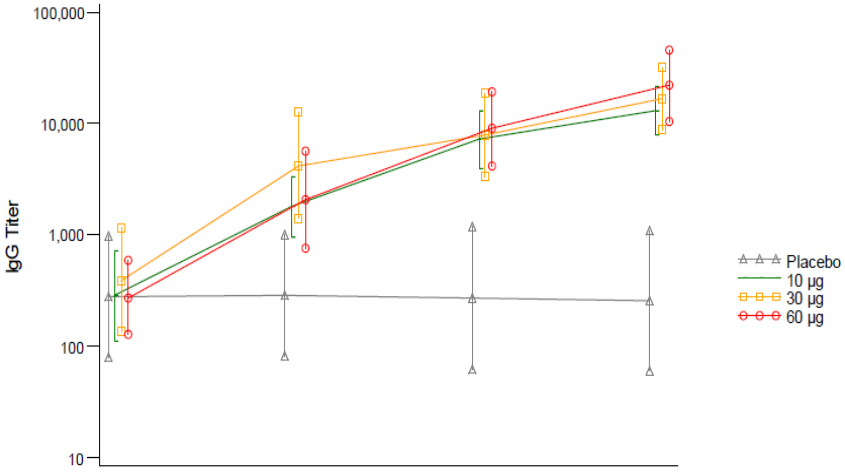
Liquid formulation, adsorbed to aluminum hydroxide

Elicits homotypic and heterotypic anti-[P] antibodies that neutralize P[8] and P[4] rotavirus strains

Wen X, Cao D, Jones RW, et al. Hum Vaccin Immunother. 2015; 11:2483-9

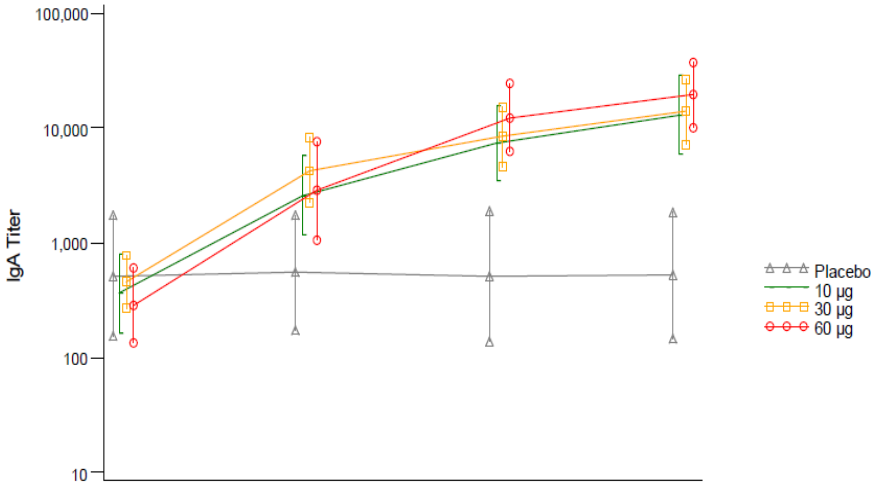
PHASE 1 STUDY OF P2 VP8* NON-REPLICATING ROTAVIRUS VACCINE

ANTI-P2-VP8* IgG EIA TITERS



	0	28	56	84
Placebo	0.0%	0.0%	0.0%	0.0%
10 µg	0.0%	58.3%	90.9%	100.0%
30 µg	0.0%	66.7%	83.3%	91.7%
60 µg	0.0%	58.3%	91.7%	100.0%

ANTI-P2-VP8* IgA EIA TITERS



	0	28	56	84
Placebo	0.0%	0.0%	0.0%	0.0%
10 µg	0.0%	66.7%	90.9%	100.0%
30 µg	0.0%	75.0%	91.7%	100.0%
60 µg	0.0%	66.7%	91.7%	100.0%

Fix A, Harro C, McNeal M et al. Vaccine 2015; 33:3766-3772

 |

NEUTRALIZING ANTIBODY TO OTHER ROTAVIRUS STRAINS (≥4-FOLD INCREASE 28 DAYS AFTER 3RD DOSE)

Strain	10 µg % (CI)	30 µg % (CI)	60 µg % (CI)
Wa (G1P[8])	67 (35, 90)	42 (15, 72)	***58*** (28, 85)
89-12 (G1P[8])	83 (52, 98)	67 (35, 90)	***83*** (52, 98)
P (G3P[8])	58 (28, 85)	67 (35, 90)	***83*** (52, 98)
DS1 (G2P[4])	0 (0, 26)	50 (21, 79)	***58*** (28, 85)
ST3 (G4P[6])	0 (0, 26)	8 (0, 38)	***17*** (2, 48)

Phase 1/2 age-descending, dose-ranging study of P2 VP8* P[8] completed in South Africa
Phase 1/2 age-descending, dose-ranging study of trivalent P2 VP8* P[8]; P[6]; P[4] ongoing currently

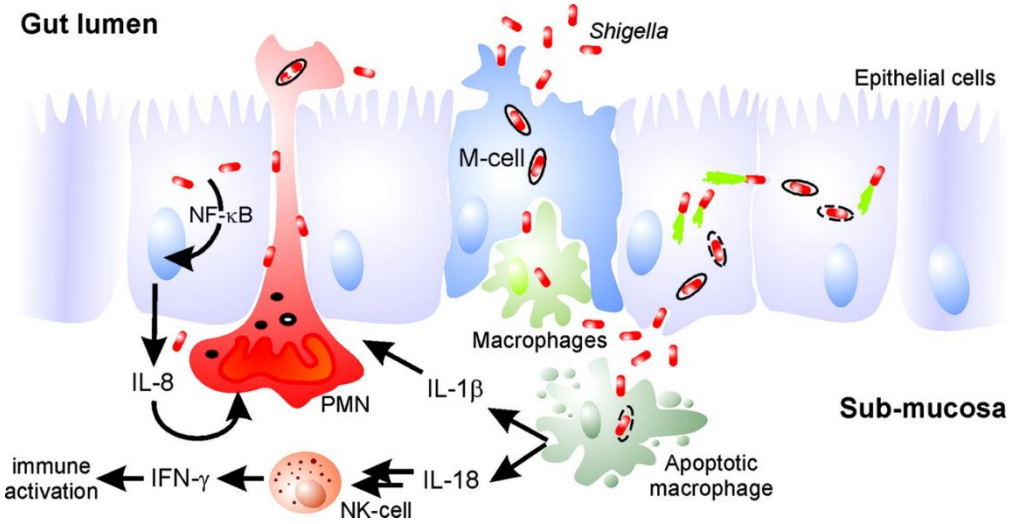
Fix A, Harro C, McNeal M et al. Vaccine 2015; 33:3766-3772

SHIGELLA VACCINES

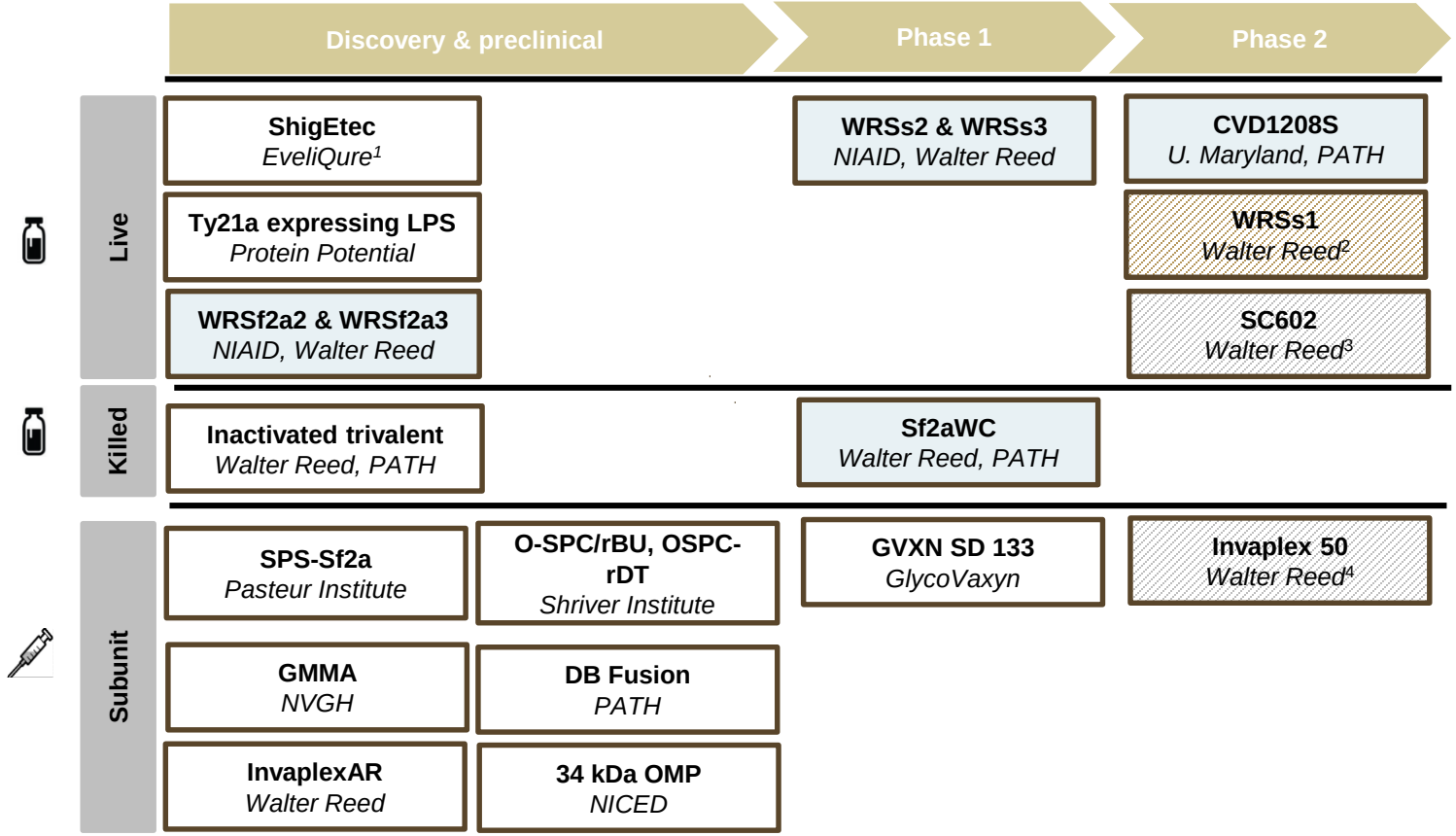
Four serogroups of *Shigella*

- Flexneri (6 serotypes)
- Sonnei (1 serotype)
- Bodyii (19 serotypes)
- Dysenteriae (15 serotypes)

Complex multivalent vaccine construct



SHIGELLA CANDIDATE PIPELINE



1. Shigetec is a combination ETEC-Shigella vaccine currently in development by a private vaccine manufacturer in Austria.
2. 2,3,4. Vaccines currently on hold/no longer in development

CURRENT LANDSCAPE OF *SHIGELLA* VACCINE DEVELOPMENT

Cellular candidates

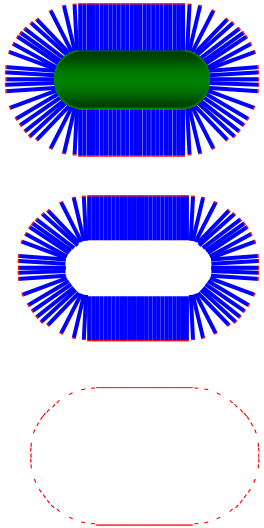
- CVD1208 (live, attenuated)
- WRSS1 (live, attenuated)
- Ty21a + *Shigella* LPS
- *Shigella* whole cell (inactivated)
- Truncated whole cells

Subunit approaches

- Conjugates: chemical, recombinant, synthetic
- Invaplex
- Generalized modules of membrane antigens (GMMA)
- Outer membrane vesicle (OMV)
- DB Fusion
- 34 kDa OMP

Walker RI. *Vaccine.* 2015;33:954-965

ETEC COLONIZATION FACTORS AND TOXINS



Whole cell

Fimbriae

Fimbrial tip adhesins

Fimbriae ***Intestinal adherence***

CFA*/I

CFA/II CS1, CS2, CS3**

CFA/IV CS4, CS5, CS6

Others (CS17, CS14, PCF071)

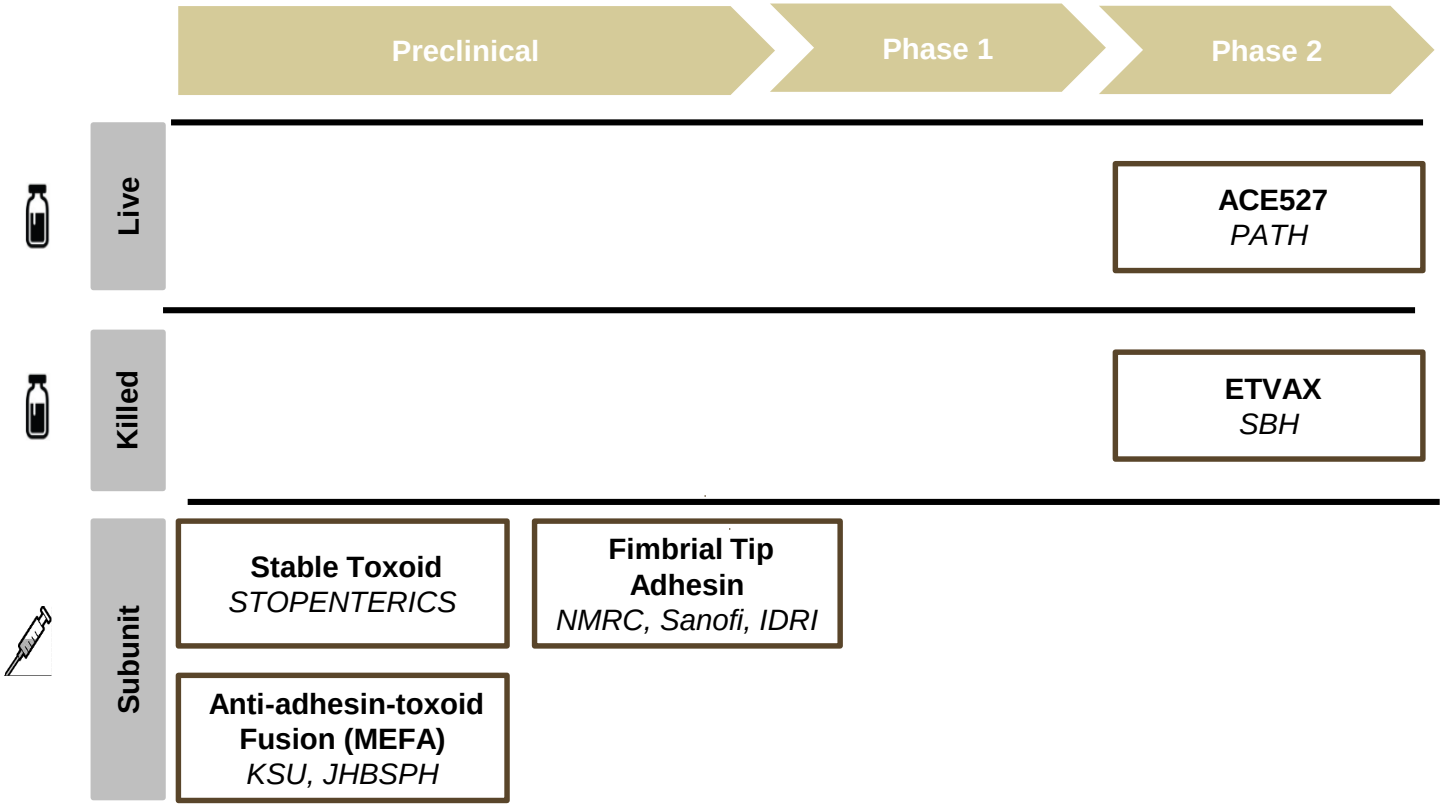
Toxins ***Cause diarrhoea***

LT (Thermal labile)

ST (Thermal stable)

LT/ST

CURRENT PIPELINE OF ETEC VACCINE DEVELOPMENT



CURRENT STATUS OF ETEC VACCINE DEVELOPMENT

Whole cell approaches to ETEC vaccine development

- Killed, whole cell strains (eg. ETVAX, Scandinavian BioPharma)
- Live attenuated strains (eg. ACE 527, TD Vaccines and CNBG)

Subunit/peptide approaches

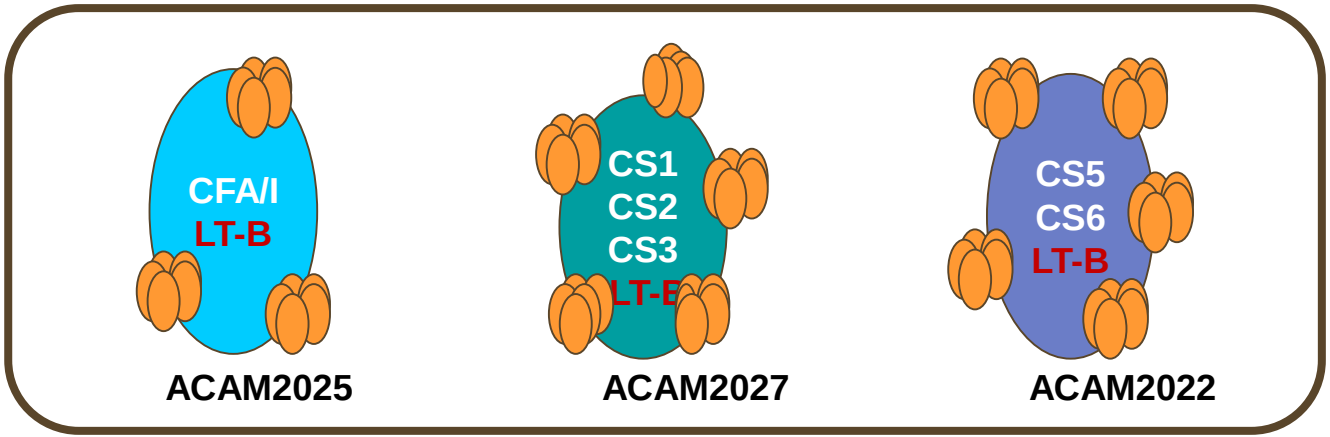
- Fimbrial tip adhesins (FTA) (US NMRC and PATH)
- 7 CFA-based Multi-epitope Fusion Antigen (MEFA)

Other innovative approaches in pipeline

- ST toxoid (CIH, Norway; STOPENTERICS)
- New conserved ETEC antigens
- Vectored combination vaccines (ETEC-Shigella; ETEC-Typhoid)

Walker RI. *Vaccine.* 2015;33:954-965

ACE527 – LIVE, ATTENUATED CANDIDATE IN CLINICAL DEVELOPMENT



- **Vaccine characteristics**
  - All toxin and antibiotic resistance genes deleted
  - *aroC*; *ompC*; *ompF* genes deleted
  - Recombinant CS1 and LTB expressed from chromosome

- **Early Phase 1/2b studies of frozen preparation (10^{11} cfu in two doses):**
  - Majority of subjects (≥50%) mounted mucosal responses to key antigens: LTB; CFA/I; CS3; CS6
    - Did not meet primary endpoint of protection against moderate/severe diarrhoea
    - Significantly impacted secondary measures of incidence and severity of disease; 41% efficacious against severe disease (p = 0.03)
    - Significantly reduced shedding of challenge strain

Darsley M, et al. Clin Vacc Immun 2012

ACE527 ± DMLT: EFFICACY AGAINST SEVERE DIARRHOEA

Study with lyophilized preparation of ACE527 at a dose of 10^{10} cfu in three doses with and without 25 µg dmLT adjuvant

Group	N	Severe Diarrhoea		Protective Efficacy vs. Controls (P-value)
		Yes (%)	No (%)	
Controls	31	21 (68%)	10 (32%)	-
ACE527	13	7 (54%)	6 (46%)	20.5% (0.30)
ACE527 + dmLT	13	3 (23%)	10 (77%)	**65.9%** (0.01)

Primary Endpoint: Prevention of severe diarrhoea defined as cumulative passage of more than 800 grams of grade 3 to 5 diarrhoea stools for episodes beginning during the 120-hour observation period post-challenge

Harro C, et al. 8th Vaccine & International Society for Vaccines Congress. Philadelphia, PA. Oct 2014.

FIMBRIAL TIP ADHESINS (FTA)

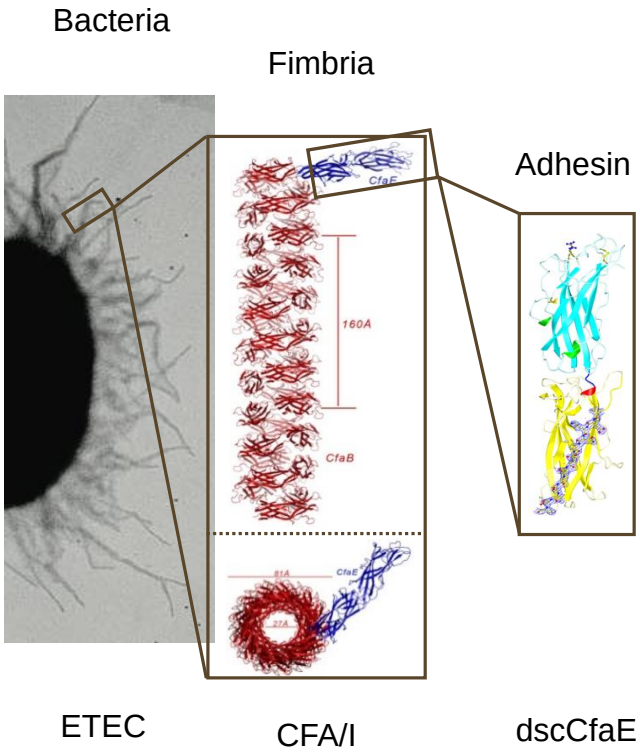
FTA are important antigenic and functional component of the fimbria; the binding site domain

Final vaccine will have 3-5 FTA types.

- May offer broader coverage for strains of ETEC relevant to developing countries

Passive protection in humans; (active protection in non-human primates when given with mLT by ID route)

- Monovalent form (CfaE): 3 doses was safe and immunogenic in adult volunteers
- Challenge study with mLT showed value of protection against severe disease



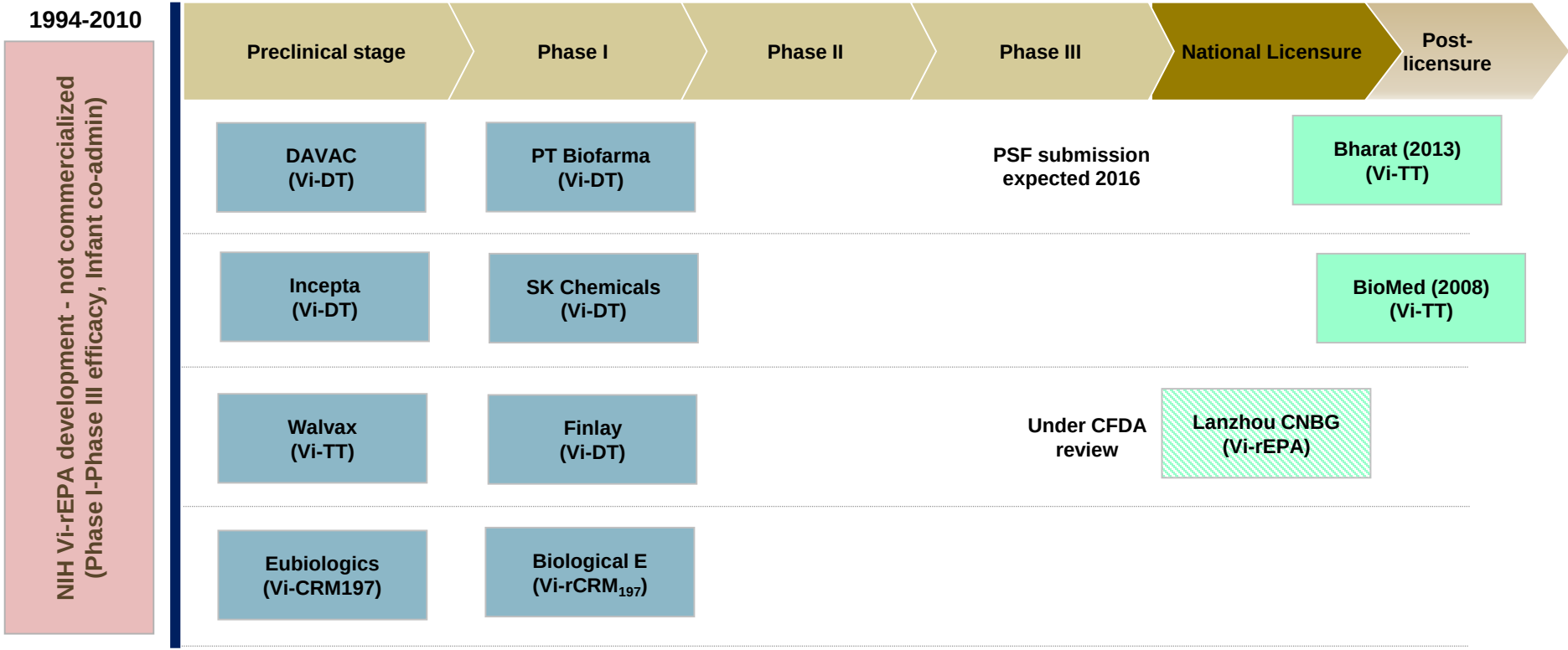
ENTERIC CONTROLLED HUMAN INFECTION MODELS

Pathogen	Strain	Predominant Antigen (s)	Information provided by the Model	Vaccine Applicability (in the near term)	Value Proposition
ETEC	B7A (O148:H28, LT^+, ST^+, $CS6^+$)	LT, ST, CS6	Protection; Establish the role of CS6 in protection	FTA	Predictable model that can be used to evaluate vaccine efficacy Identify correlates of vaccine protection Identify correlates of natural immunity
	E24377A (O139:H:28, LT^+, ST^+, $CS1^+$, $CS3^+$)	LT, ST, CS1, CS3 [Non 078]	Protection; broader applicability to lead candidate (ETVAX) due to use a non-O78 strain;	ETVAX, Combination inactivated oral ETEC-Shigella vaccines	
	ST-ETEC (TBD)	CFA/1, ST	Protection, understanding role of ST;	ST toxoid, parenteral ETEC vaccine that incorporates ST, ST-LT constructs	

ENTERIC CONTROLLED HUMAN INFECTION MODELS

Pathogen	Strain	Predominant Antigen (s)	Information provided by the Model	Vaccine Applicability (in the near term)	Value Proposition
Shigella	*S. sonnei* 53G	*S. sonnei* LPS, Ipa B, C & D	Protection against Shigella species	GMMA	Predictable model that can be used to evaluate vaccine efficacy Identify correlates of vaccine protection Identify correlates of natural immunity
	S. flexneri 2a	*S. flexneri* 2a	Protection against Shigella species	GVXN Recombinant glycoconjugate, TSWC	

PROGRESS IN TYPHOID CONJUGATE VACCINE DEVELOPMENT



VI-rEPA CONJUGATE VACCINE (DEVELOPED BY NIH)

A double-blind, placebo-controlled and randomized efficacy study was conducted in 2 to 5 year-old children in Vietnam

- 11,091 children were injected twice, 6 weeks apart, with the Vi-rEPA vaccine or saline placebo
- Efficacy at 27 months of active surveillance was 91%
- Efficacy at 46 months after additional 19 months of passive surveillance was 89%

A second study was conducted with 301 infants who received Vi-rEPA with routine childhood vaccines at 2,4, 6 months and Hib or Vi-rEPA at 12 months in Vietnam

- Vi-rEPA was safe in infants
- Induced protective anti-Vi levels, with robust GMTs
- Compatible with EPI vaccines and it can be used in infants.

TABLE 3. EFFICACY OF Vi-rEPA CONJUGATE VACCINE.

VARIABLE	VACCINE GROUP	PLACEBO GROUP	VACCINE EFFICACY (95% CI)*	P VALUE†
			%	
Children who received two correctly labeled injections — no.	5525	5566		—
Children with typhoid fever — no.	4	47	91.5 (77.1–96.6)	
Attack rate (cases/1000 children)	0.72	8.44		
All children — no.‡	5991	6017		—
Children with typhoid fever — no.	5	56§	91.1 (78.6–96.5)	
Attack rate (cases/1000 children)	0.83	9.31		

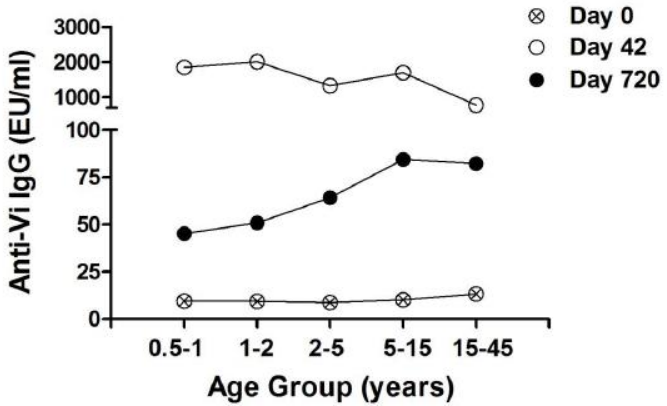
This trial is the source of the only existing efficacy data for any typhoid conjugate vaccine, which has implications for future clinical development and regulatory pathways

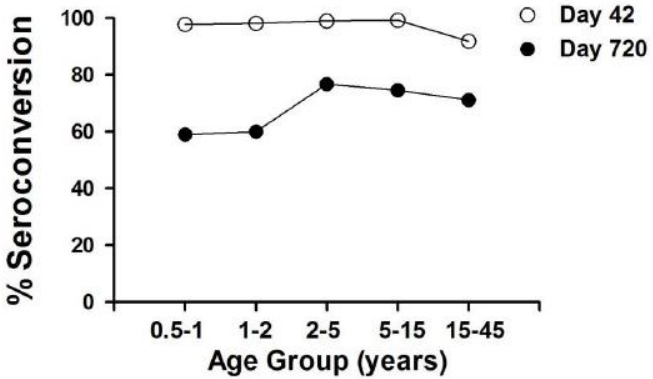
Lin FY et al. NEJM 2001; 344: 1263-69; Thiem VD, et al. Clin Vaccine Immunol 2011;18: 730-5

TYPHOID CONJUGATE VACCINE (VI-TT)

- Bharat Biotech vaccine licensed in India in 2013 on immunogenicity data
- Phase III - RCT in ages 2 - 45 year olds using licensed Typbar (Vi-PS) as an active comparator
- Open Label Trial in 6 months – 2 year olds
- Good immunogenicity responses across all age groups
- Post-licensure studies ongoing, including measles co-administration; evaluation of different dosing schedules; two years follow up for safety and immunogenicity data
- Human challenge study is ongoing at Oxford University to assess a clinical outcome for the vaccine

Immune Response Across Age Groups





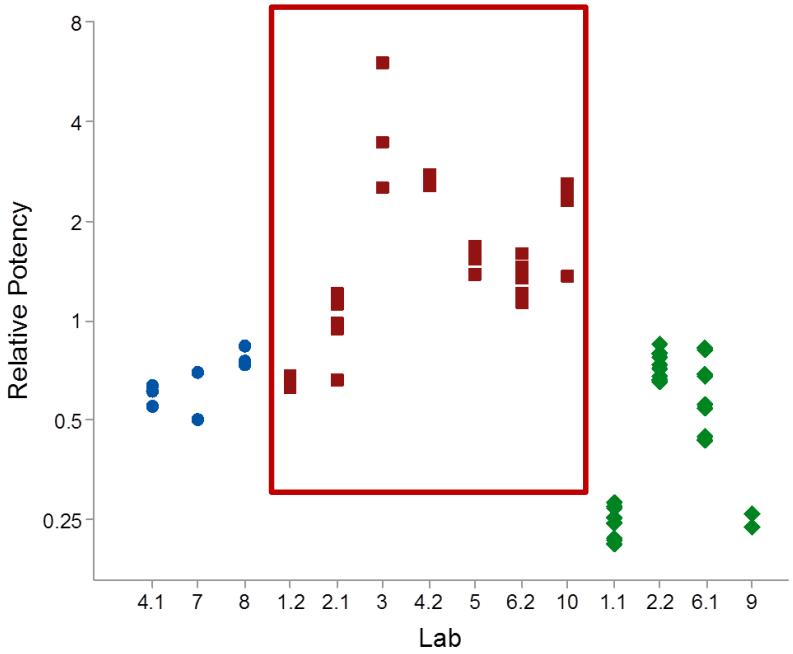
Mohan VK, et al. Clin Infect Dis 2015; doi: 10.1093/cid/civ2015

VI-CONJUGATE VACCINE DEVELOPMENT & LICENSURE

Licensure on the basis of immunogenicity based on the Vi-rPA Vaccine Efficacy Data

1. Need a validated ELISA assay
   - Measures the concentration of anti-Vi IgG in human serum sample

2. Need a valid human reference standard to measure serum anti Vi-IgG
   - Will facilitate comparison of anti-Vi elicited from other manufactures to those of an experimental vaccine manufactured by the NIH (Vi-rPA) that has already undergone a clinical trial with efficacy outcomes
   - Allows for comparisons between laboratories
     - enables the comparison of antibodies elicited from other manufactures to those of Vi-rPA
   - Vi IgG antibody levels are currently being measured by investigators and referenced against arbitrarily-determined EU values assigned by each laboratory against its own in-house standard serum.



TYPHOID CHALLENGE MODELS

Determine the dose of *Salmonella* Typhi required to produce an AR of 60-75%

Clinical and laboratory features
- Time course
- Bacteraemia
- Inflammatory response

Development of immunity
- Innate & humoral
- Cell mediated immunity
- Long-term immunity after treatment

Diagnostics
- PCR-based
- Mass spectrometry

Variation in genomic response

Research mechanisms for related pathogens

Correlates of protection

VACCINE STUDIES

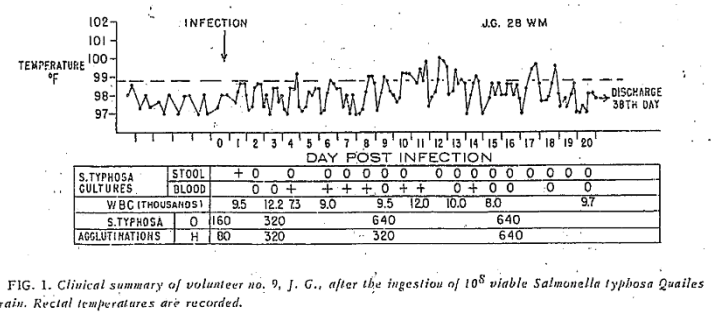
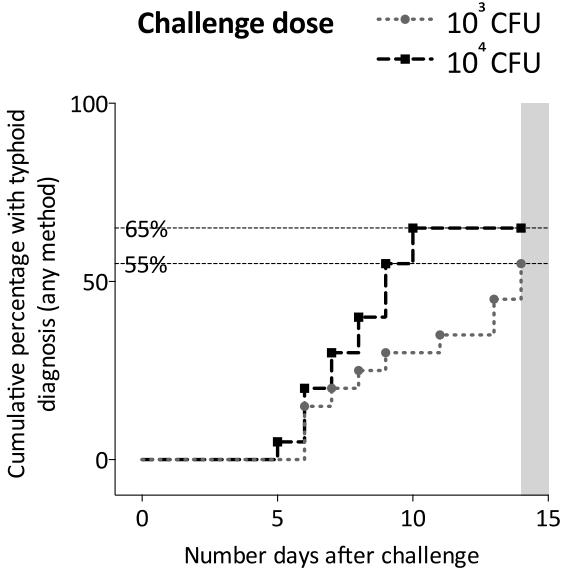
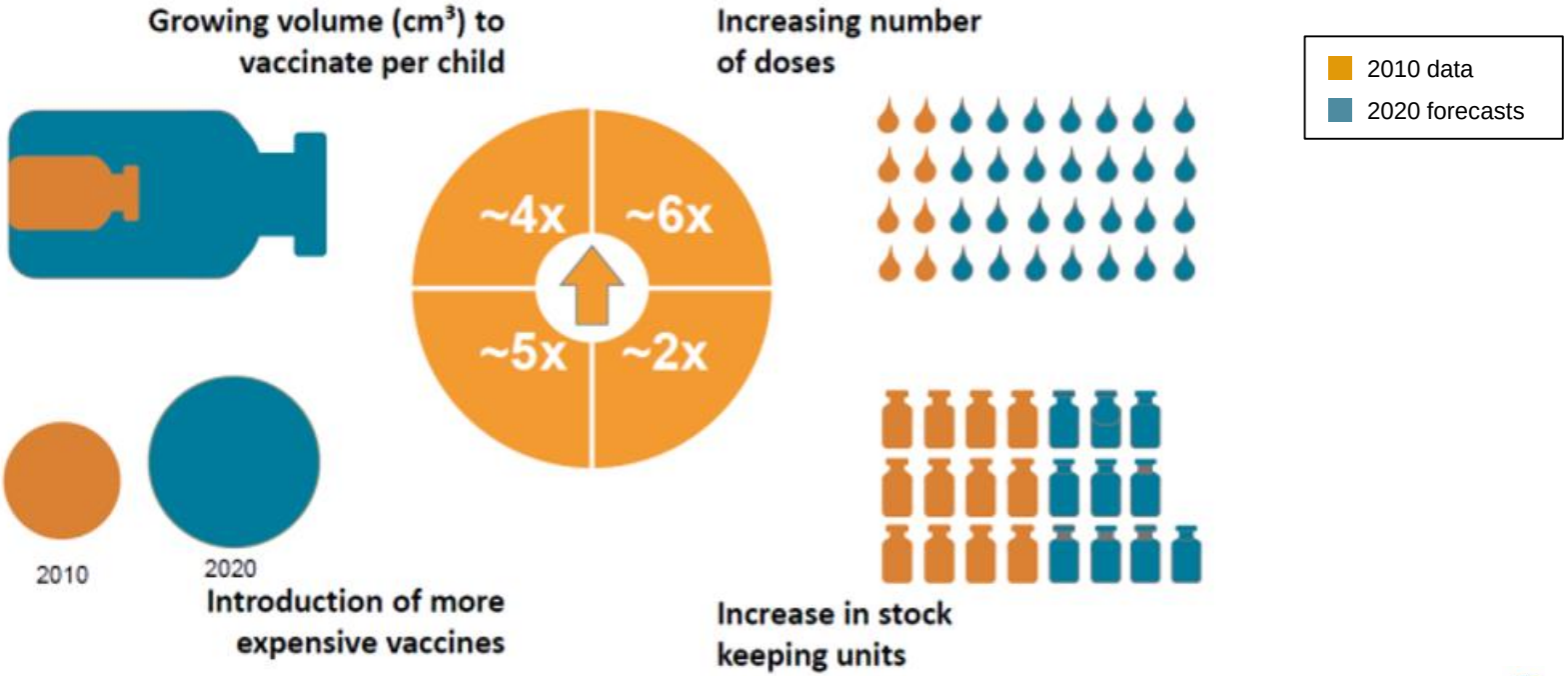


FIG. 1. *Clinical summary of volunteer no. 9, J. G., after the ingestion of 10^8 viable Salmonella typhosa Quailes strain. Rectal temperatures are recorded.*



Waddington CS, et al. *Clin Infect Dis 2014;* 58: 1230-40

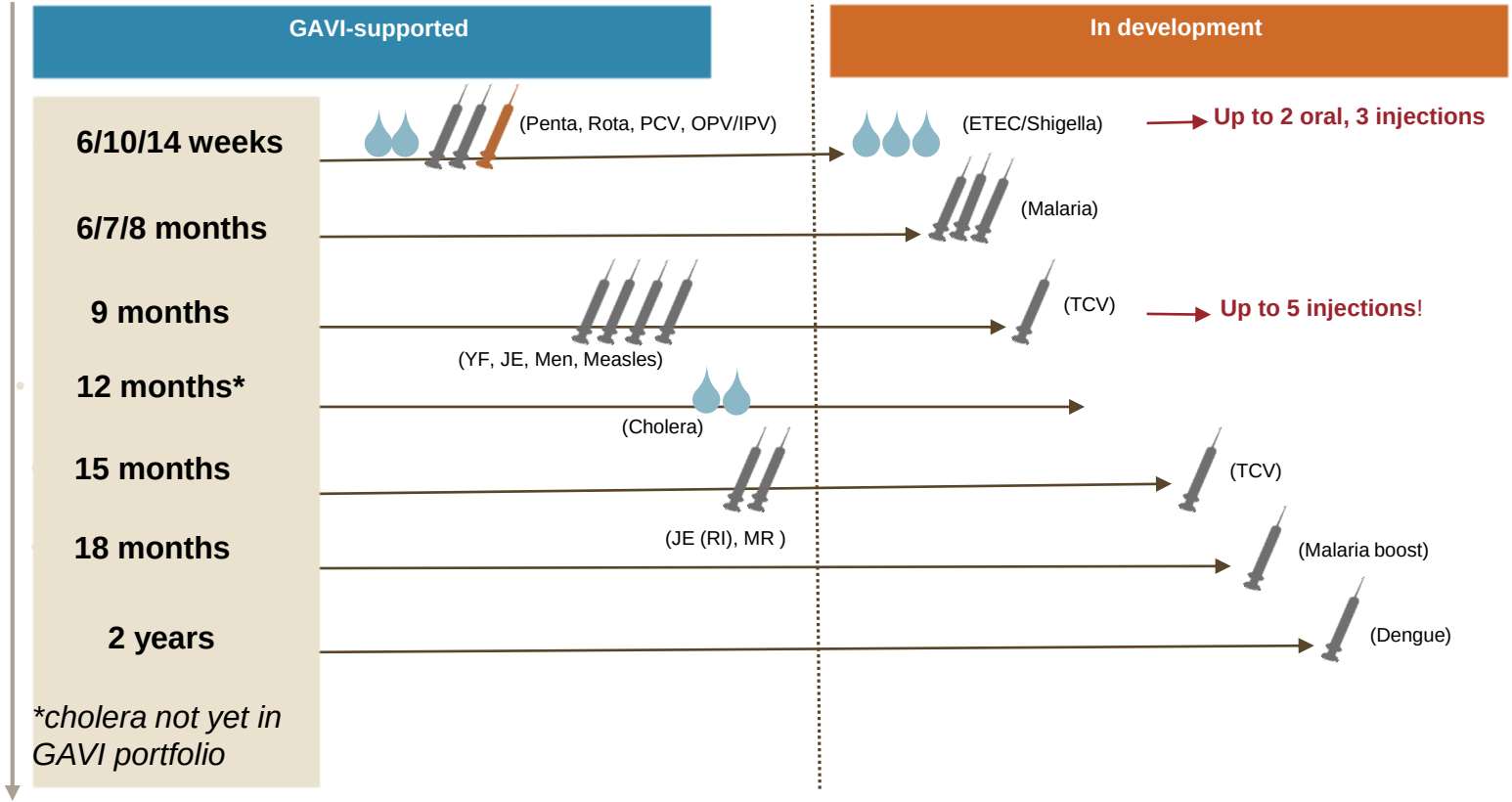
NEW INTRODUCTIONS WILL LEAD TO INCREASED DELIVERY COMPLEXITY AND FINANCIAL CHALLENGES



Note: All figures are based on GAVI-funded vaccines only

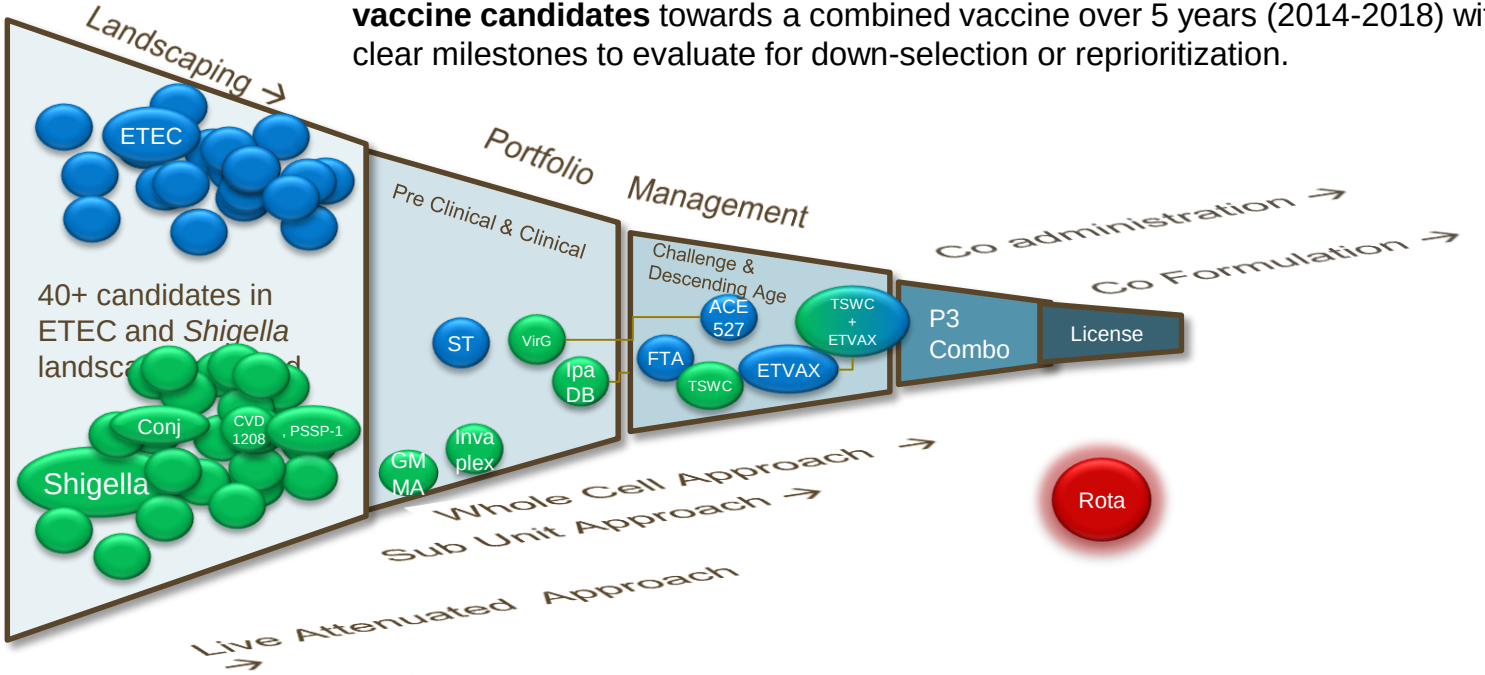
Source: Chart from GAVI Immunization supply chain strategy presentation, 2014: http://www.peoplethatdeliver.org/sites/peoplethatdeliver.org/files/2.%20GAVI%20SCS.pdf; UNICEF Supply 2012 financial report; 2010 GAVI Shipment data; 2012 GAVI SDF Forecast, including volume for future GAVI graduated countries; 2010 vaccines include YF, Measles, Penta, OPV; 2020 vaccines add Rota, Pneumo, HPV; Cost comparison based on 2013 prices; Stock keeping units estimates based on 2009 data for 2010 and 2013 forecast for 2020

VACCINES IN DEVELOPMENT WILL CROWD STANDARD EPI SCHEDULES



ETEC AND *SHIGELLA* COMBINED VACCINE DEVELOPMENT

The goal is **to advance development of a portfolio of ETEC and *Shigella* vaccine candidates** towards a combined vaccine over 5 years (2014-2018) with clear milestones to evaluate for down-selection or reprioritization.



SUMMARY

- Full, robust pipelines for vaccine development for the enteric and diarrhoeal pathogens
  - Multivalent vaccines likely necessary for ETEC and Shigella
  - Various vaccine constructs including live attenuated, killed whole cell, subunit,..
  - Various administration modes (eg. oral, parenteral)
- Controlled human infection models available for many pathogens
- Reliable and validated assays required for comparability of vaccine constructs
- Combination vaccine constructs likely required – adding to complexity of vaccine composition

- Correlates of protection would greatly facilitate vaccine development, however timelines before large phase 3 efficacy studies are required is extremely short

THE WORK IS COMPLICATED.

WHY WE DO IT IS NOT.