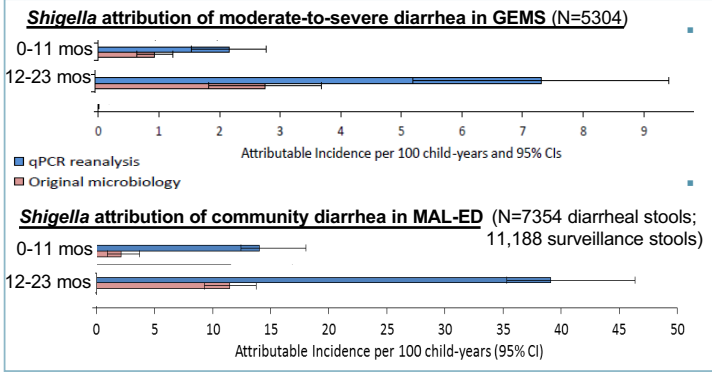
Novel Shigella Vaccine Candidates

Cal MacLennan
Bill & Melinda Gates Foundation
DCVMN Annual Meeting
23 October 2019 Rio de Janeiro

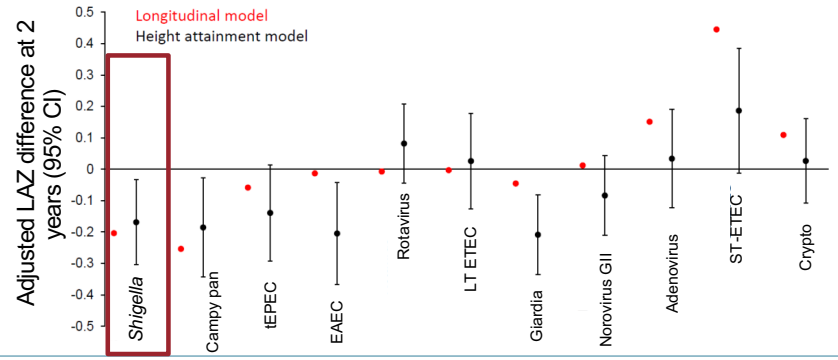
THE CASE FOR A *SHIGELLA* VACCINE

1 *Shigella* burden is greater than we thought…

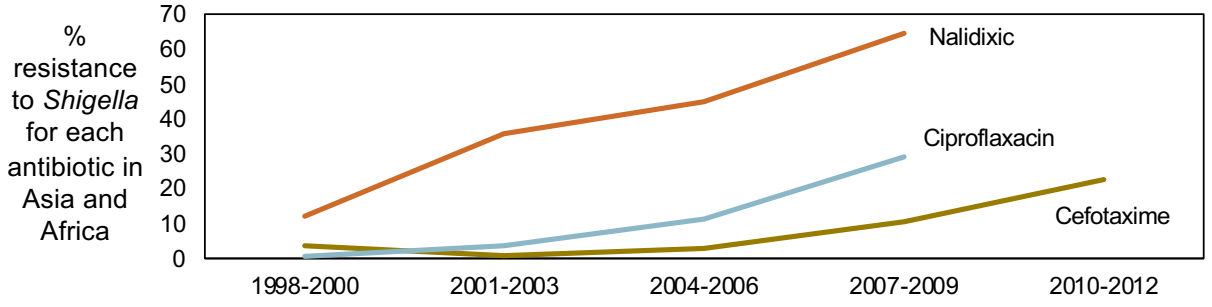


- Quantitative PCR re-analysis of GEMS increased *Shigella* attribution of moderate-to-severe diarrhea by ~2-3X per 100 child-years
- Quantitative PCR re-analysis of MAL-ED increased *Shigella* attribution of community diarrhea by ~7X and ~3X per 100 child-years among infants 0-11m and 12-23m, respectively

2 …its impact on growth faltering is significant…



3 …and the threat of AMR is growing



Adapted from Gu B et al. Int J Antimicrob Agents 2012 and Gu B et al, Epidemiol Infect 2015

From GEMS:

- Only 35% of Indian *Shigella* isolates were sensitive to ciprofloxacin (WHO-recommended antibiotic for *Shigella* dysentery)
- > 80% of African *Shigella* isolates were resistant to cotrimoxazole (most commonly prescribed antibiotic in African sites)

Source: GEMS; MAL-ED; AMR data adapted from Gu et al. *2012 and 2015*

Killed-whole cell parenteral approaches

Live-attenuated approaches

Sub-unit era

Slide Courtesy of Mark Riddle

Shigella Vaccine History: *in 59 seconds or less*

S. dysenteriae discovered (1897)
Kiyoshi Shiga

Ether-killed S. dysenteria discovered (1921)
H. Vincent

Heat-killed Parenteral Egypt Pediatric RCT (1953)
Higgins, Floyd & Kader

Streptomycin-dependent oral mutant (attenuated) Mel et al (1956-74)

Proteosome, T3SS, intranasal, killed whole-cell vaccines (Fries, Lowell Oaks, Walker, early 2000s)

1890s 1900s 1910s 1920s 1930s 1940s 1950 1960 1970 1980 1990 2000

S. flexneri discovered (1900)
Simon Flexner

Sanitation revolution and wandering years of vaccine development

Interinstitutional Conference on Problems of Enteric Infections in Moscow, Russia (1961)

Better-animal models developed

CHIM developed / applied

Genomics / recombinant enginr'ing

USU
Uniformed Services University

PHASE 3 EFFICACY WITH SHIGELLA SONNEI CONJUGATE VACCINE IN YOUNG ADULTS

(Cohen D et al. Lancet 1997)

Young Israeli military recruits

S. Sonnei LPS O-antigen – rEPA conjugate 25 ug/75 ug – **single dose**

Overall Vaccine Efficacy **74% (95%CI 28-100)**

Protection GMT IgG to S. sonnei O-antigen 12761 units (day 17)

Vaccine failure GMT IgG to S. sonnei O-antigen 4904 units (day 17)

Clinical Proof of Concept for O-antigen-based approach

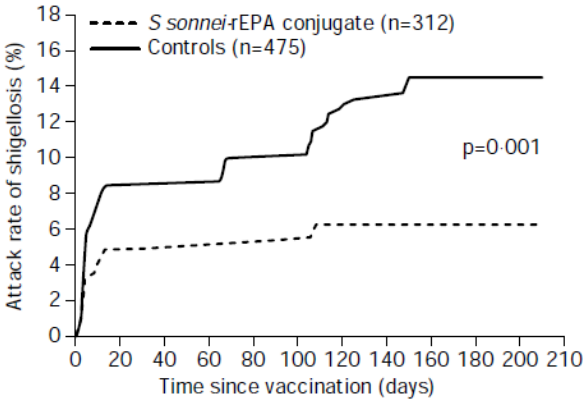


Figure 2: **Attack rates of culture-proven *S sonnei* shigellosis in recipients of *S sonnei* conjugate vaccine and controls in groups A–D**

Note – this was the **1st generation** Shigella conjugate vaccine.

'**lattice-type**' conjugate with random conjugation chemistry.

→ large complex vaccine structure with limited batch-to-batch consistency

PHASE 3 EFFICACY WITH SHIGELLA SONNEI CONJUGATE VACCINE IN ISRAELI CHILDREN DOWN TO 3 YEARS AGE

(Passwell JH et al. Vaccine 2010)

Bivalent vaccine S. sonnei/S. flex 2a

2 doses 6 weeks apart. 2 year follow up

71.1% vaccine efficacy against S. sonnei diarrhea at 3-4 yrs age, but not < 3yrs

(Insufficient S. flex 2a diarrhea cases for efficacy)

Age	Efficacy	(95% CI)	P
a. *Shigella sonnei*			
1–2 years	3.8%	(101.1, 46.5)	0.91
>2–3 years	35.5%	(−56.4, 73.4)	0.33
>3–4 years	71.1%	(−4.43, 92.0)	0.04
All ages	27.5%	(−16.9, 54.0)	0.18

G.M. IgG anti-LPS (EU)*			
Vaccine	Age (years)	N	*S. sonnei*
S. sonnei	1–2	38	1.40
	>2–3	44	3.71
	>3–4	29	6.38

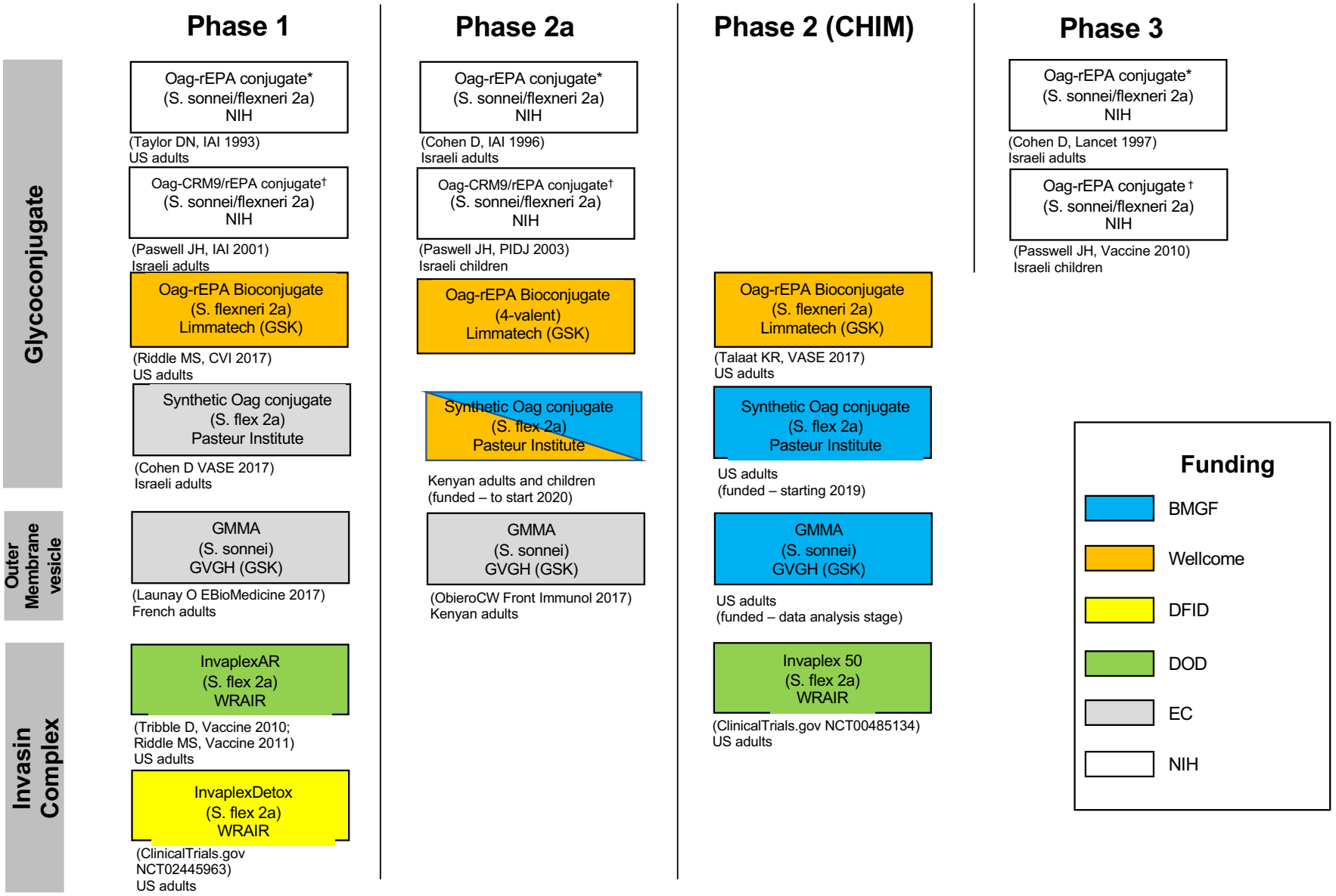
Loss of efficacy with reduced IgG LPS O-antigen titer*

→ **Important for new O-antigen-based vaccines to induce high titers of IgG to O-antigen**

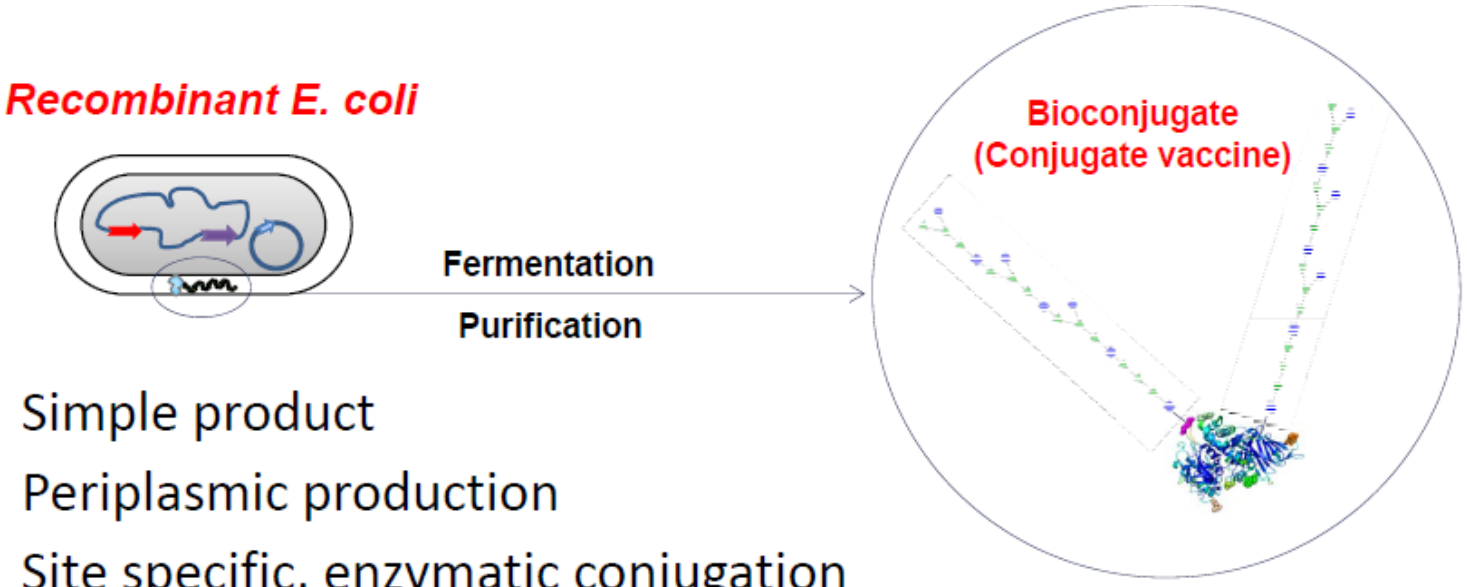
(**different assay to one used in Cohen et al 1997 – indicates urgent need for international assay and standards*)

Target Product Profile for Shigella Vaccines

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point.*	Optimistic *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact.*
Indication*	Prevention of moderate to severe diarrhea due to *Shigella* in children six months to two years of age	Prevention of moderate to severe diarrhea due to *Shigella* in children six months to five years of age.
Target Population*	Children six months to two years of age.	Children six months to five years of age.
Dosing Schedule and Route of Administration*	EPI schedule - 2 doses + booster IM route.	EPI schedule - 1 dose IM route.
Safety	Safety and reactogenicity profile should be clinically acceptable Contraindications should be restricted to know hypersensitivity to any of the vaccine components	Safety and reactogenicity profile should be clinically acceptable. Contraindications should be restricted to know hypersensitivity to any of the vaccine components
Efficacy*	50% efficacy against moderate to severe diarrhea caused by *Shigell*a strains in the vaccine	70% efficacy against moderate to severe diarrhea caused by all *Shigella* strains
Duration of Protection	To 2 years, with boosting possible to extend protection	To 5 years.
Cost	$1 - $3	< $1
Co-administration	With EPI vaccines without interference	With EPI vaccines without interference
Vaccine volume	0.5 ml/dose	0.5 ml/dose
Target Countries	GAVI-eligible and lower-middle income countries	GAVI-eligible and lower-middle income countries
Onset of immunity	2 weeks after 2 doses	2 weeks after 1 dose
Indirect (herd) protection	No	Yes


Phase 1
Phase 2a
Phase 2 (CHIM)
Phase 3
Glycoconjugate
Outer Membrane vesicle
Invasin Complex
Oag-rEPA conjugate* (S. sonnei/flexneri 2a) NIH
(Taylor DN, IAI 1993) US adults
Oag-CRM9/rEPA conjugate† (S. sonnei/flexneri 2a) NIH
(Paswell JH, IAI 2001) Israeli adults
Oag-rEPA Bioconjugate (S. flexneri 2a) Limmatech (GSK)
(Riddle MS, CVI 2017) US adults
Synthetic Oag conjugate (S. flex 2a) Pasteur Institute
(Cohen D VASE 2017) Israeli adults
GMMA (S. sonnei) GVGH (GSK)
(Launay O EBioMedicine 2017) French adults
InvaplexAR (S. flex 2a) WRAIR
(Tribble D, Vaccine 2010; Riddle MS, Vaccine 2011) US adults
InvaplexDetox (S. flex 2a) WRAIR
(ClinicalTrials.gov NCT02445963) US adults
Oag-rEPA conjugate* (S. sonnei/flexneri 2a) NIH
(Cohen D, IAI 1996) Israeli adults
Oag-CRM9/rEPA conjugate† (S. sonnei/flexneri 2a) NIH
(Paswell JH, PIDJ 2003) Israeli children
Oag-rEPA Bioconjugate (4-valent) Limmatech (GSK)
Synthetic Oag conjugate (S. flex 2a) Pasteur Institute
Kenyan adults and children (funded – to start 2020)
GMMA (S. sonnei) GVGH (GSK)
(ObieroCW Front Immunol 2017) Kenyan adults
Oag-rEPA Bioconjugate (S. flexneri 2a) Limmatech (GSK)
(Talaat KR, VASE 2017) US adults
Synthetic Oag conjugate (S. flex 2a) Pasteur Institute
US adults (funded – starting 2019)
GMMA (S. sonnei) GVGH (GSK)
US adults (funded – data analysis stage)
Invaplex 50 (S. flex 2a) WRAIR
(ClinicalTrials.gov NCT00485134) US adults
Oag-rEPA conjugate* (S. sonnei/flexneri 2a) NIH
(Cohen D, Lancet 1997) Israeli adults
Oag-rEPA conjugate † (S. sonnei/flexneri 2a) NIH
(Passwell JH, Vaccine 2010) Israeli children
Funding
BMGF
Wellcome
DFID
DOD
EC
NIH

LIMMATECH (GSK) – SHIGELLA BIOCONJUGATE



- Simple product
- Periplasmic production
- Site specific, enzymatic conjugation

LIMMATECH (GSK) – BIOCONJUGATE PHASE 1 & CHIM

Phase 1 – US adults (Riddle MS et al CVI 2017)

S flex 2a O-antigen/EPA 10 ug/50 ug

2 doses 4 weeks apart

19-fold increase in O-antigen IgG titers

Immune response and sample day	Vaccination group		
	Flexyn2a (n = 12)		
	GMT	Responders[c]	P value[d]
Anti-Sfl2a LPS Serum IgG			
Day 0	2,397		NS
Day 28	45,614	11/12	<0.0001
Day 56	40,637	11/12	<0.0001

CHIM – US adults (Talaat KR et al VED Conference 2017)

2 doses 4 weeks apart

- 30% (non-significant) efficacy at preventing shigellosis (primary endpoint)
- **52% efficacy** at preventing moderate and severe shigellosis
- 72% efficacy at presenting more severe diarrhea
- Correlation between serum IgG and IgA to O-antigen and protection

'Flexyn2a, a candidate bioconjugate vaccine against *Shigella flexneri* 2a induces protective immune response in a controlled human infection model'

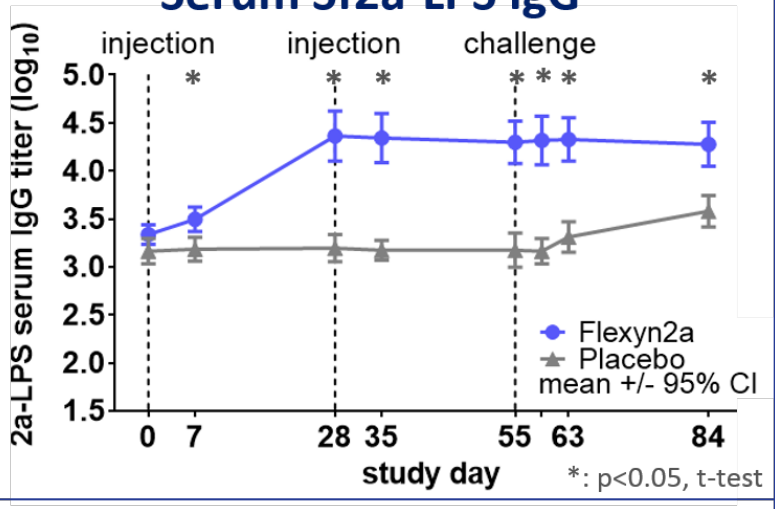
Kawsar R. Talaat[1], Cristina Alaimo[2], A. Lou Bourgeois[1], Robert W. Kaminski[3], Anita Dreyer[2], Chad K. Porter[4], Subhra Chakraborty[1], Kristen A. Clarkson[3], Jessica Brubaker[1], Daniel Elwood[1], Rahel Frolich[2], Barbara DeNearing[1], Hailey Weerts[3], Brittany Feijoo[1], Jane Halpern[1], David Sack[1], Mark S. Riddle[4], Patricia Martin[2] and Veronica Gambillara Fonck[2]

([1] Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [2] LimmaTech Biologics AG, Schlieren, Switzerland; [3] Walter Reed Army Institute of Research, Silver Spring, Maryland, USA; [4] Naval Medical Research Center, Silver Spring, Maryland, USA)

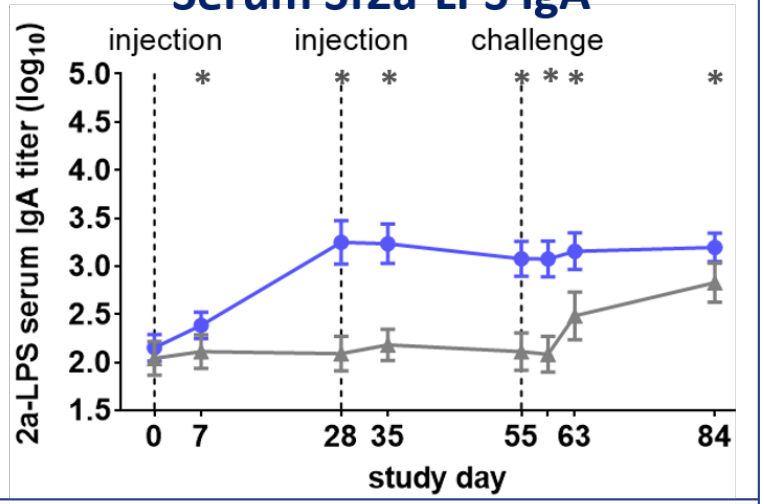
Flexyn2a Immunogenicity

Talaat VED 2017

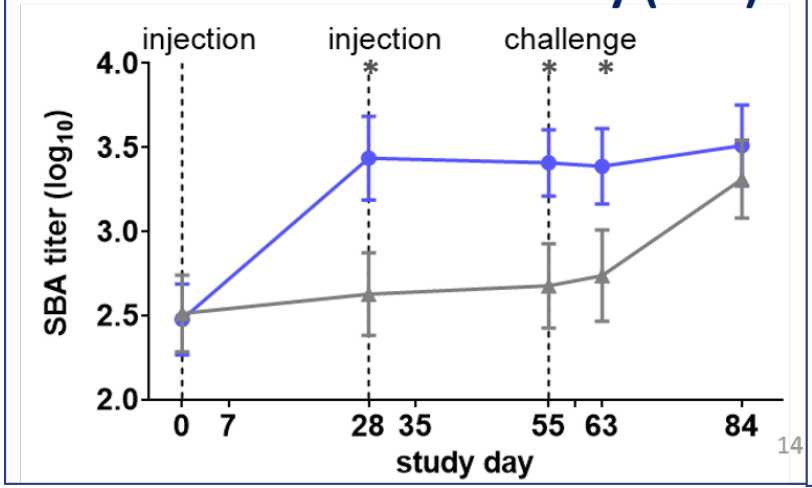
Serum Sf2a-LPS IgG



Serum Sf2a-LPS IgA



Serum Bactericidal Activity (SBA)



≥4-fold rise from baseline

	Serum Sf2a-LPS IgG		Serum Sf2a-LPS IgA	
	Flexyn2a	Placebo	Flexyn2a	Placebo
Day 0 to Day 28	26/34 **(76.5%)**	0/30 **(0%)**	26/34 **(76.5%)**	1/30 **(3.3%)**
Day 0 to Day 55	27/33 **(81.1%)**	1/30 **(3.3%)**	26/33 **(78.8%)**	1/30 **(3.3%)**

Uniformed Services University

LIMMATECH BIOCONJUGATE SUMMARY

Strengths

- Most advanced candidate
- Bioconjugate technology - conjugation occurs within bacteria
- Purification as for recombinant protein

GENERALIZED MODULES FOR MEMBRANE ANTIGENS (GMMA) PLATFORM

Pure outer membrane buds by genetic engineering (*tolR*$^{-}$) → efficacy & affordability of whole cell vaccine without the side effects

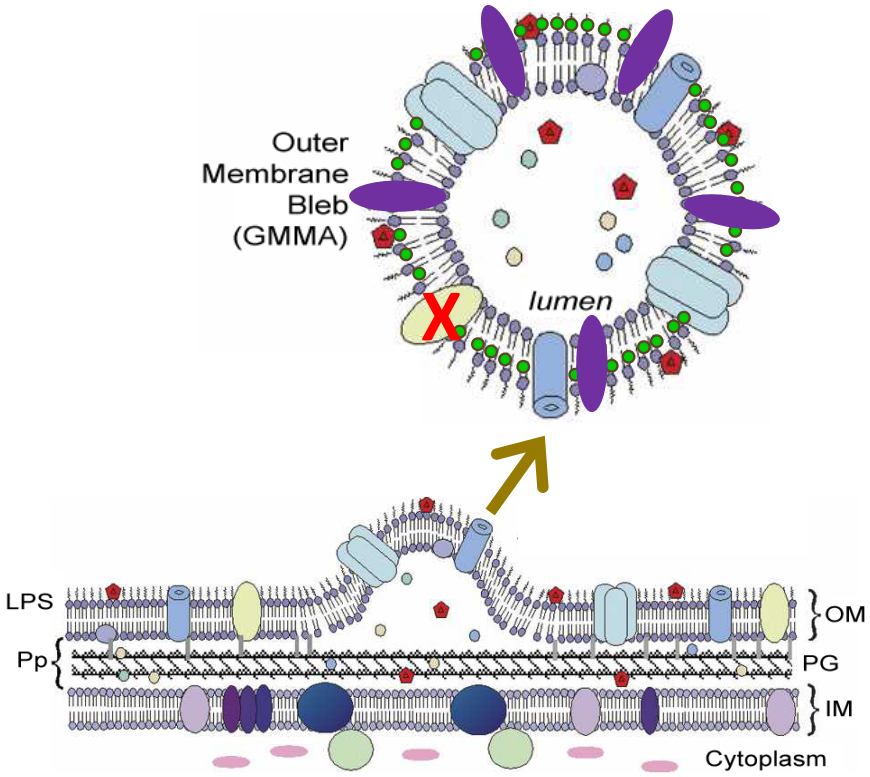
Modify toxic component (*msbB*$^{-}$)

- Lipid A of LPS

Stabilize Sonnei plasmid

4-valent GMMA formulation (*S. sonnei, S. flexneri* 2a, 3a and 6) immunogenic in mice

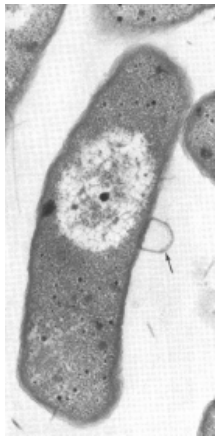
S. sonnei prototype safe and immunogenic in phase 1; descending age and challenge trial start 2017



Gerke C et al. PLoS One 2015

GMMA manufacturing – Generic, simple and robust

Building on Shigella GMMA and a technology suited to sub-Saharan Africa



Genetic modifications

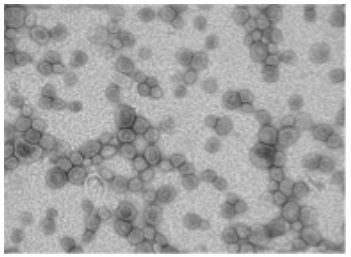
1. Increase GMMA production
   ΔtolR
2. Decrease LPS innate immune stimulation
   ΔhtrB or
   ΔmsbB
3. Other mutations
   virG nadA/B knock-in

Fermentation

Purification

Micro-filtration
Collect 0.22 µm permeate

Ultra-filtration
Collect 300 kD retentate



Berlanda Scorza et al PLoS One 2012
Gerke et al. PLoS One 2015

Sterile filtration 0.22 µm

DS and DP characterization

- Generic panel of release tests
- CQA

Formulation

Adsorption on Alhydrogel

GVGH (GSK) GMMA – PHASE 1 & 2

Phase 1 - French adults (Launay O et al EBioMedicine 2017)

Dose-escalating Phase 1 study with monovalent *S.* sonnei GMMA

O-antigen/protein 0.059/1, 0.29/5, 1.5/25, 2.9/50 & 5.9/100 µg

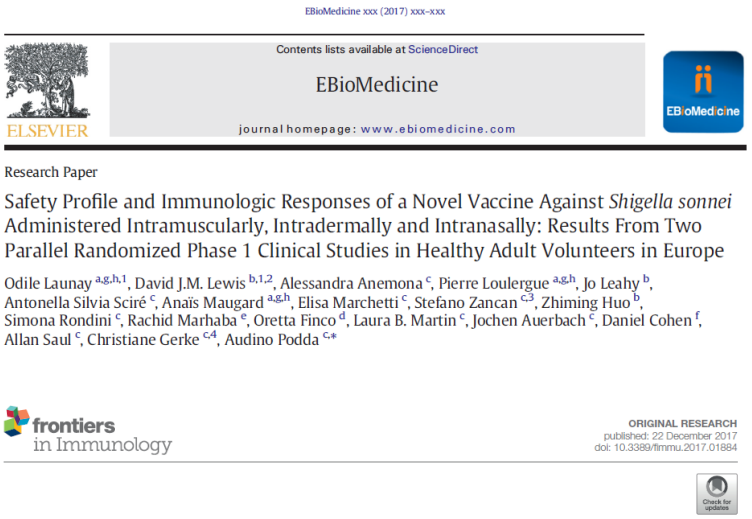
3 vaccinations, 4 weeks apart

Median GMT post 3rd dose for 3 highest dose groups = **305 ELISA U**

Phase 2 - Kenyan adults – high pre-existing antibody titers - levels boosted

CHIM study with current monovalent *S.* sonnei GMMA

Interim efficacy data expected November 2019



EBioMedicine xxx (2017) xxx–xxx

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Research Paper

Safety Profile and Immunologic Responses of a Novel Vaccine Against *Shigella sonnei* Administered Intramuscularly, Intradermally and Intranasally: Results From Two Parallel Randomized Phase 1 Clinical Studies in Healthy Adult Volunteers in Europe

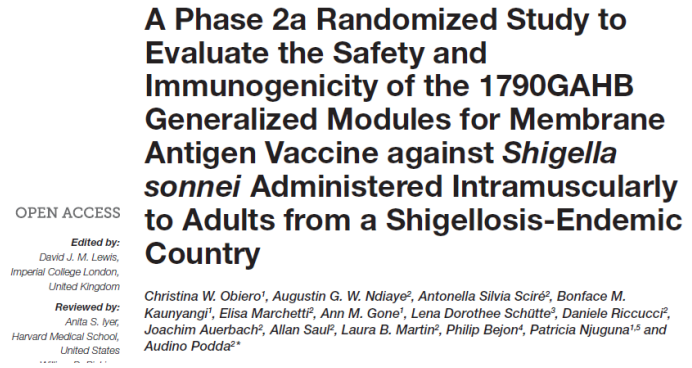
Odile Launay [a,g,h,1], David J.M. Lewis [b,1,2], Alessandra Anemona [c], Pierre Loulergue [a,g,h], Jo Leahy [b], Antonella Silvia Sciré [c], Anaïs Maugard [a,g,h], Elisa Marchetti [c], Stefano Zancan [c,3], Zhiming Huo [b], Simona Rondini [c], Rachid Marhaba [e], Oretta Finco [d], Laura B. Martin [c], Jochen Auerbach [c], Daniel Cohen [f], Allan Saul [c], Christiane Gerke [c,4], Audino Podda [c,*]

frontiers in Immunology

ORIGINAL RESEARCH

published: 22 December 2017

doi: 10.3389/fimmu.2017.01884



OPEN ACCESS

Edited by:
David J. M. Lewis, Imperial College London, United Kingdom

Reviewed by:
Anita S. Iyer, Harvard Medical School, United States

A Phase 2a Randomized Study to Evaluate the Safety and Immunogenicity of the 1790GAHB Generalized Modules for Membrane Antigen Vaccine against *Shigella sonnei* Administered Intramuscularly to Adults from a Shigellosis-Endemic Country

*Christina W. Obiero[1], Augustin G. W. Ndiaye[2], Antonella Silvia Sciré[2], Bonface M. Kaunyangi[1], Elisa Marchetti[2], Ann M. Gone[1], Lena Dorothee Schütte[3], Daniele Riccucci[2], Joachim Auerbach[2], Allan Saul[2], Laura B. Martin[2], Philip Bejon[4], Patricia Njuguna[1,5] and Audino Podda[2]**

GSK GMMA VACCINE - SUMMARY

Strengths

- Simplicity of manufacture and low COGs
- Multiplicity of Shigella antigens delivered to immune system
- Potentially highly immunogenic due to self-adjuvanting effect

NEW CONJUGATES

PNAS

Synthesis, characterization, and immunogenicity in mice of *Shigella sonnei* O-specific oligosaccharide-core-protein conjugates

John B. Robbins[a,1], Joanna Kubler-Kielb[a], Evguenii Vinogradov[b], Christopher Mocca[a], Vince Pozsgay[a], Joseph Shiloach[c], and Rachel Schneerson[a]

[a]National Institute of Child Health and Human Development, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892; [b]Institute for Biological Sciences, National Research Council, 100 Sussex Drive, Ottawa, ON, Canada K1A 0R6; and [c]National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD 20892

Robbins JB et al PNAS 2009

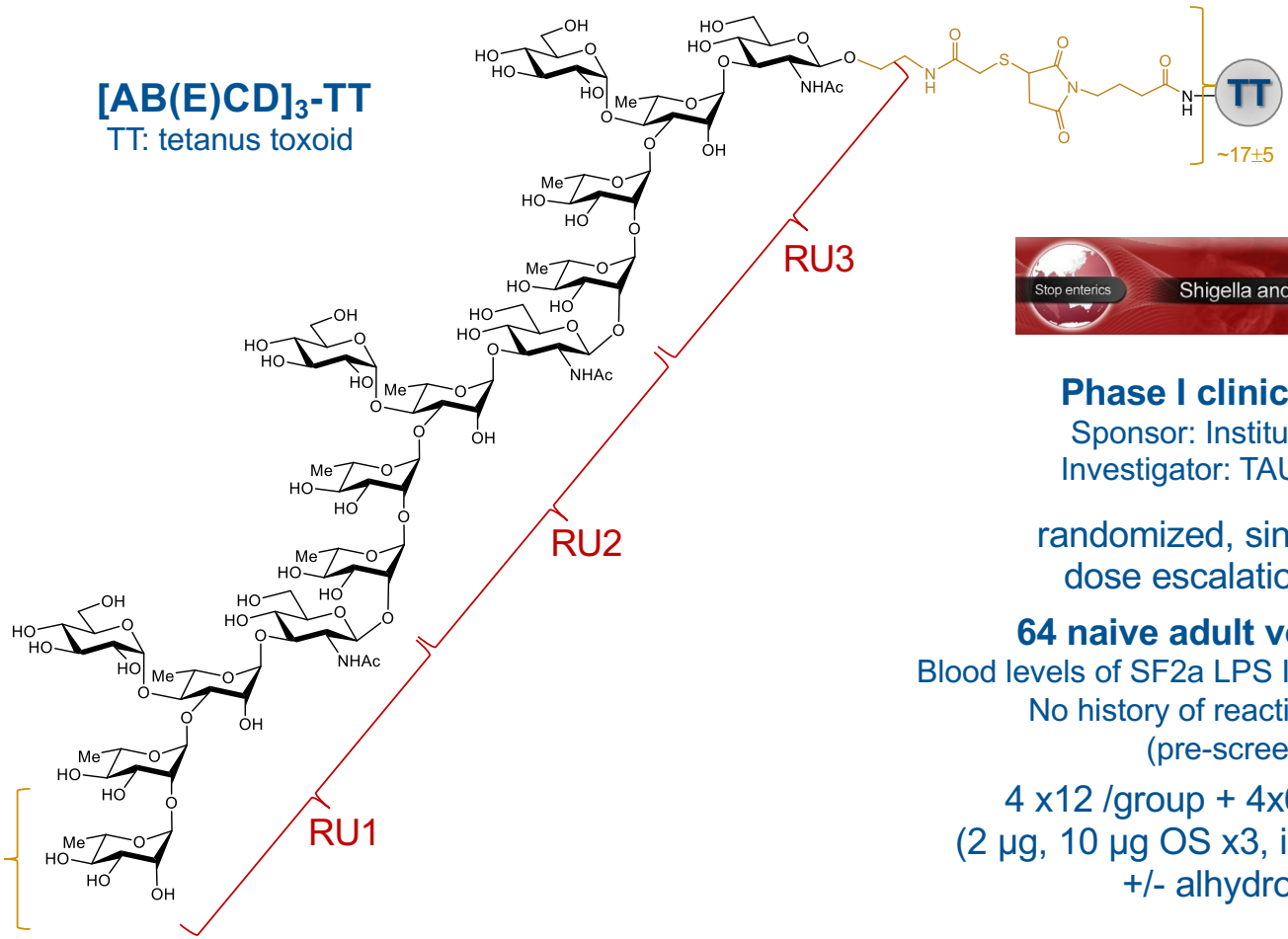
Sun-type v Lattice-type configuration

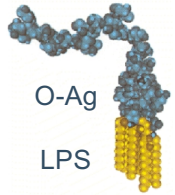
Conjugates with shorter O-antigens induce higher IgG O-antigen titers in mice

No.	Conjugate	Molecular mass of conjugate, kDa	Molecular mass of sugar part, kDa	No. O-SPC chains per protein molecule	IgG, EU			
					Anti-LPS		Anti-rDT	
					Second injection	Third injection	Second injection	Third injection
1	BSA/O-SPC-F2*	93.1	22.2	7	79	366	ND	ND
2	rDT/O-SPC-F2	80.6	18.5	6	5	392	2	91
3	rDT/O-SPC-F2	99.5	37.4	12	11	150	0.1	2
4	BSA/O-SPC-F3†	95.2	24.3	11	ND	ND	ND	ND
5	rEPA/O-SP‡	ND	ND	ND	11	67	ND	ND

A synthetic carbohydrate-based vaccine candidate against *S. flexneri* 2a produced for a phase I clinical trial

[AB(E)CD]$_3$-TT
TT: tetanus toxoid





Phase I clinical study
Sponsor: Institut Pasteur
Investigator: TAU, TASMC

randomized, single-blind
dose escalation study

64 naive adult volunteers
Blood levels of SF2a LPS IgG ≤ percentile 80
No history of reactive arthritis
(pre-screen)

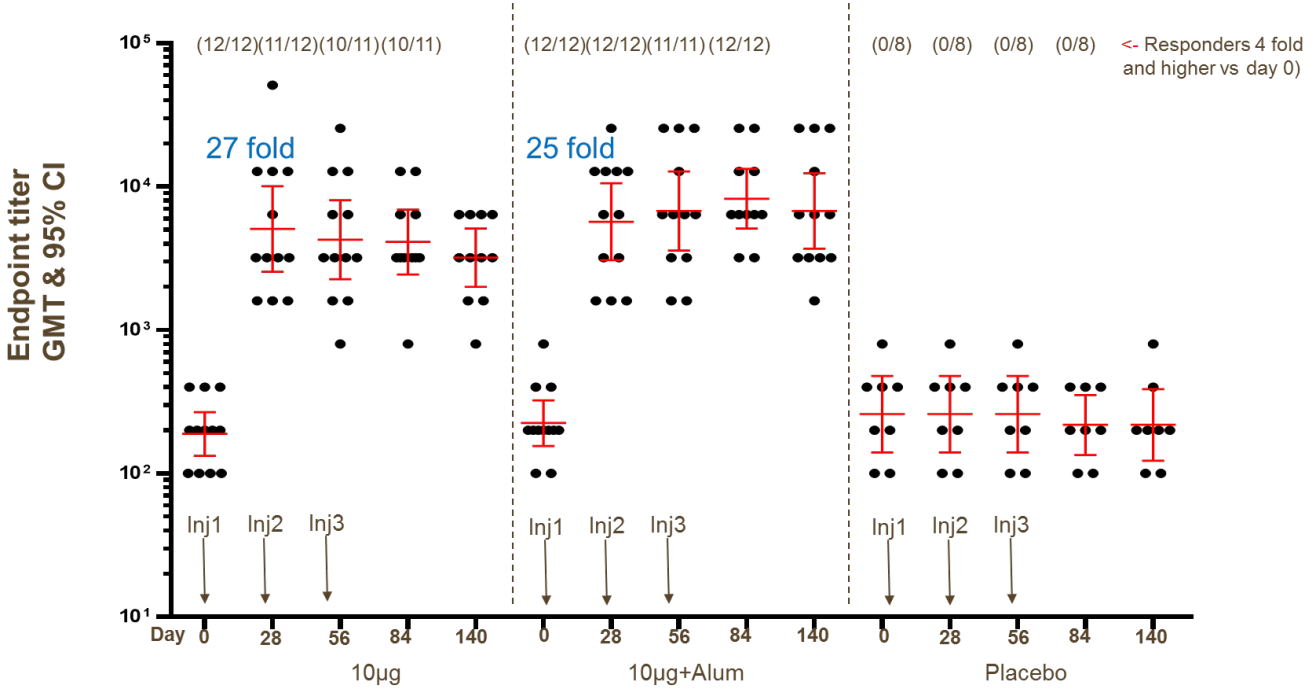
4 x12 /group + 4x6 placebos
(2 µg, 10 µg OS x3, i.m., 4w apart)
+/- alhydrogel

https://clinicaltrials.gov/ct2/show/NCT02797236

Bioconjugate Chem 27 883 (2016)

Institut Pasteur

INSTITUTE PASTEUR SYNTHETIC CONJUGATE: ~27-FOLD RESPONSE POST 10 µg SINGLE DOSE



Synthetic conjugate:

Synthetic production of *S.* flex 2a O-antigen – 3 repeating units

Optimised design for immunogenicity

Conjugated to tetanus toxoid.

'**Sun-type**' configuration

- High immunogenicity post a single dose with 10 ug O-antigen
- **27-fold increase** in IgG titer to O-antigen without alum (higher than 1st generation conjugates)
- High avidity and functional activity of antibodies
- *S.* flex 3a conjugate already produced. *S.* sonnei and *S.* flex 6 and 1b in progress.

INSTITUTE PASTEUR SYNTHETIC CONJUGATE CURRENT ASSESSMENT

Strengths

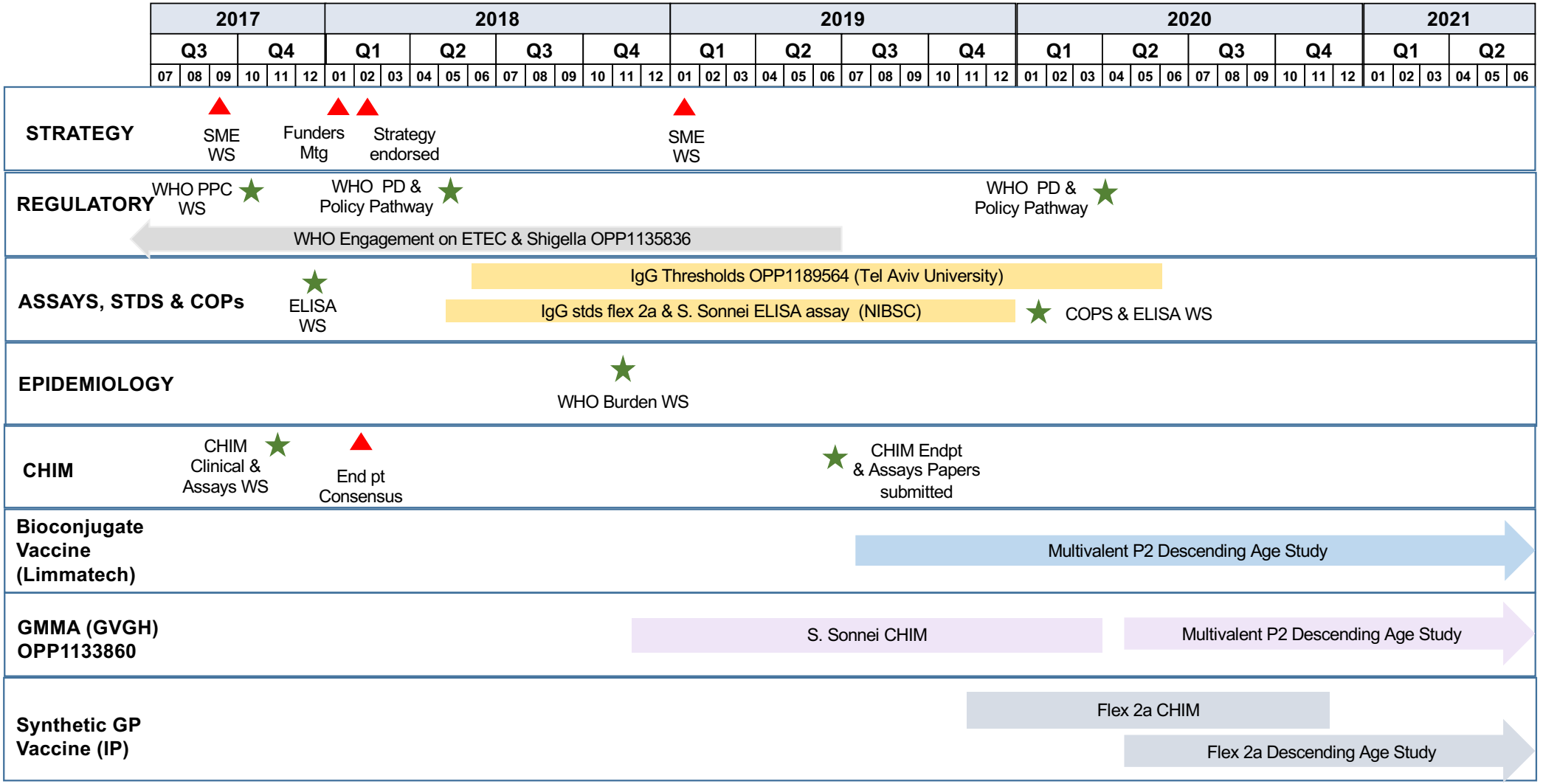
- Defined short O-antigen
- Promising strategy with likely improved immunogenicity compared with first generation NIH conjugates vaccines
- Does not require bacterial fermentation – small footprint for production

IMMUNOGENICITY STUDIES IN TARGET POPULATION

Are candidates sufficiently immunogenic to confer protection in LMIC children?

- No parenteral *Shigella* vaccine has been tested to date in the target population: children 6 to 12 months in LMICs.
- Must evaluate immunogenicity in this target population, as soon as safety has been established in naive adults
- This requires a safety and immunogenicity study in descending age groups (to <12 months) in LMICs.

- **Age-descending studies of the three leading O-antigen-based *Shigella* vaccines (Limmatech, GVGH and Institut Pasteur) are being co-funded by BMGF and Wellcome**


2017
2018
2019
2020
2021
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Q4
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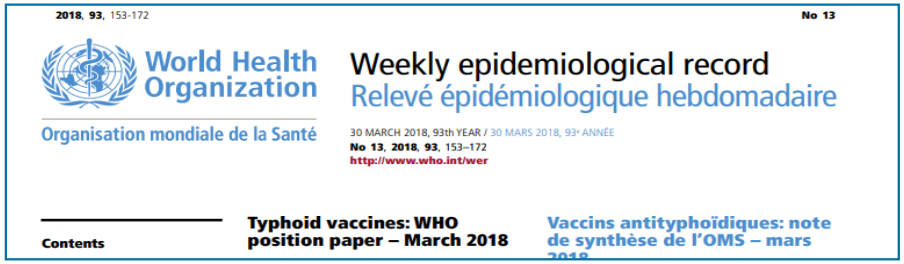
STRATEGY
SME WS
Funders Mtg
Strategy endorsed
SME WS
REGULATORY
WHO PPC WS
WHO PD & Policy Pathway
WHO PD & Policy Pathway
WHO Engagement on ETEC & Shigella OPP1135836
ASSAYS, STDS & COPs
ELISA WS
IgG Thresholds OPP1189564 (Tel Aviv University)
IgG stds flex 2a & S. Sonnei ELISA assay (NIBSC)
COPS & ELISA WS
EPIDEMIOLOGY
WHO Burden WS
CHIM
CHIM Clinical & Assays WS
End pt Consensus
CHIM Endpt & Assays Papers submitted
Bioconjugate Vaccine (Limmatech)
Multivalent P2 Descending Age Study
GMMA (GVGH) OPP1133860
S. Sonnei CHIM
Multivalent P2 Descending Age Study
Synthetic GP Vaccine (IP)
Flex 2a CHIM
Flex 2a Descending Age Study

DOES THE *SHIGELLA* CHIM HAVE A ROLE IN LATE PRODUCT DEVELOPMENT AND LICENSURE/POLICY RECOMMENDATION?

Precedent:

- Role of CHIM in cholera and typhoid conjugate vaccine licensure/recommendation
- No established regulatory pathway for using CHIM to facilitate licensure/policy recommendation
- Advice from regulators: all vaccines and diseases needed to be treated separately
- For a first Shigella vaccine: need for field data for safety and efficacy

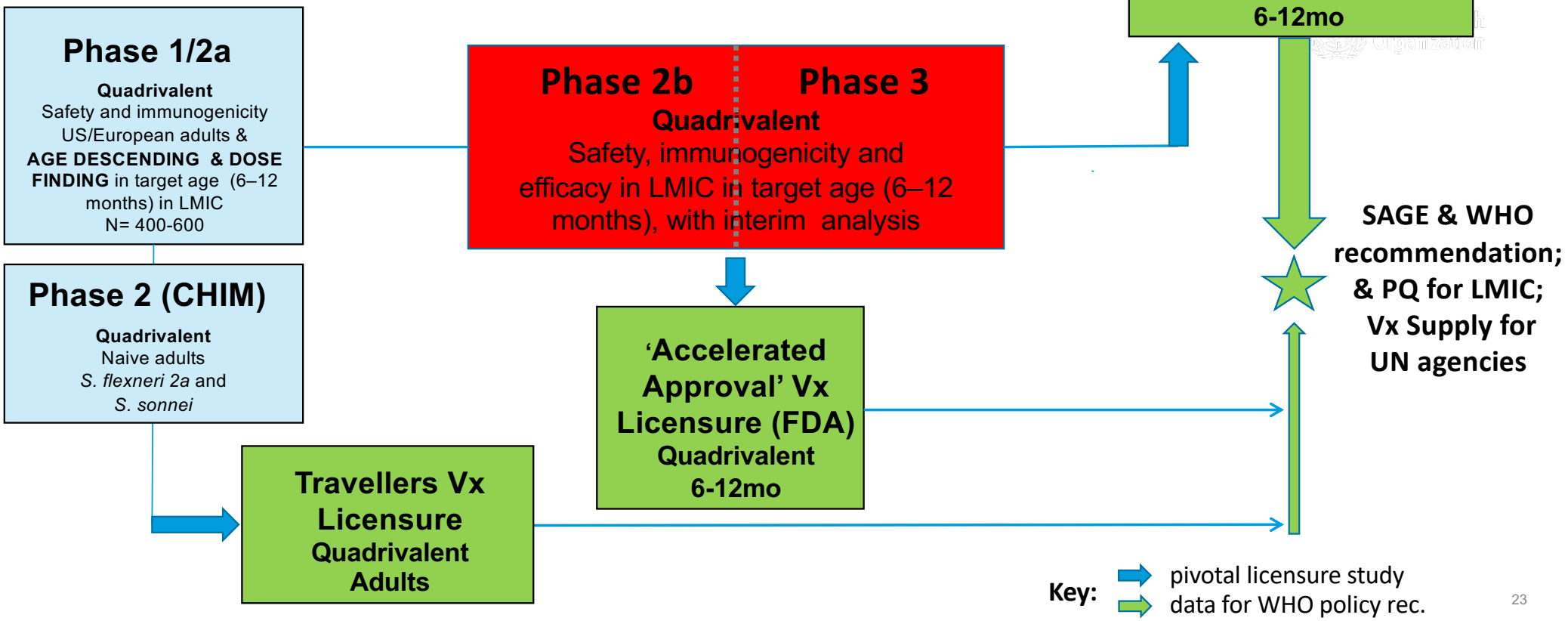


http://apps.who.int/iris/bitstream/handle/10665/272272/WER9313.pdf?ua=1

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm506305.htm

Stakeholder consultation identified three potential licensure routes

- Travellers vaccine dependant on efficacy from CHIM
- Accelerated approval supported by efficacy data from CHIM
- **What role does CHIM play in licensure and a policy recommendation for LMICs?**



SUMMARY

- Multiple O-antigen-based subunit vaccines in clinical trials
- 3 lead candidates, each employing a different novel technological approach
- Evaluated for efficacy in monovalent formulation in CHIM studies
- All funded for descending-age studies into target population (LMIC children 9 months – 2 years)
- Two in quadrivalent format
- Regulatory clinical pathway under discussion – WHO-led
- Work on parallel enabling activities – international ELISA and serum standard
- Each candidate likely in need of a manufacturing partner for late-stage clinical development

BACK-UP SLIDES

SHIGELLA: STRATEGIC SHIFTS IN OUR APPROACH

2007-2014: Broad portfolio approach

- PATH EVI (1-2) re-ignites the field and evaluates ~50 ETEC & *Shigella* vaccine constructs.

2014-2016: Toward a combination ETEC & *Shigella* vaccine

- 2014: EVI 3 funded; portfolio down-selected to 9 candidates. Lead oral ETEC and *Shigella* candidates with combination potential.
- 2015: GSK GMMA platform funded outside of EVI.

2017-2018: Shifting focus towards *Shigella*

- No go decision for lead EVI ETEC candidate (ETVAX), based on Phase 2a data. → **Q1/Q2 2018 decision** on future investment in **ETEC** vaccines, pending additional burden data.
- No go decision for lead EVI *Shigella* candidate (TSWC), given manufacturing delays and ETVAX no go. → **New *Shigella* vaccine approach**:
  - Focus on 2nd generation O-antigen vaccine candidates
  - New regulatory approach to accelerate vaccine licensure (~2023)
  - New partner: Gates MRI.

New 3-5 year goals:

1. Advance lead O-antigen-based *Shigella* vaccine candidates to efficacy in CHIM and immunogenicity in target population by 2021
2. Advance enabling technologies (e.g. validated international ELISA, human challenge models) and accelerate regulatory pathway to achieve licensure by 2023
3. Identify new target antigens to support 3rd generation *Shigella* vaccine development by 2020
4. Prepare the evidence and policy in support of a future delivery strategy of *Shigella* vaccines

SHIGELLA: 2ND GENERATION O-ANTIGEN-BASED VACCINES

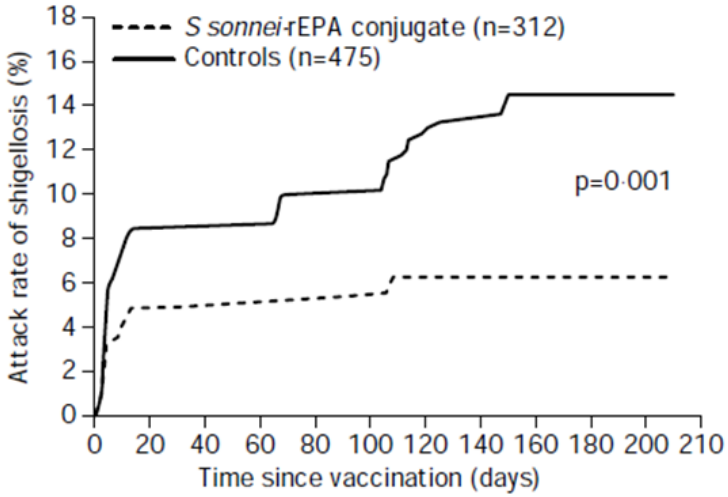


Figure 2: **Attack rates of culture-proven *S sonnei* shigellosis in recipients of *S sonnei* conjugate vaccine and controls in groups A–D**

20 years ago, a 1st generation NIH 'lattice-type' *S.* sonnei conjugate vaccine gave 74% efficacy among Israeli military. Protection was strongly associated with the IgG antibody response to LPS O-antigen…

…but many years later, the same vaccine failed to protect children <3 years. Loss of protection closely associated with decreased induction of LPS O-antigen IgG *(Passwell JH et al Vaccine 2010)*

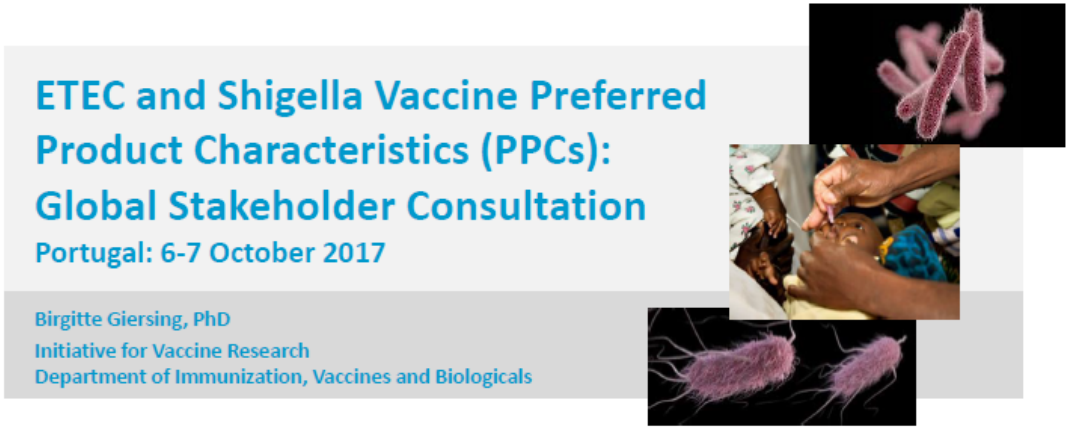
Hypothesis: a 2nd generation vaccine that induces higher levels of IgG to O-antigen will protect young children…

Lead candidates:

1. Limmatech/GSK Bioconjugate vaccine
2. GVGH/GSK GMMA vesicle vaccine
3. Pasteur Institute Synthetic O-antigen conjugate vaccine

Key messages: 1. O-antigen-based conjugate vaccines can protect against Shigella 2. serum IgG titer to Shigella O-antigen is a strong associate of protection

PREFERRED PRODUCT CHARACTERISTIC



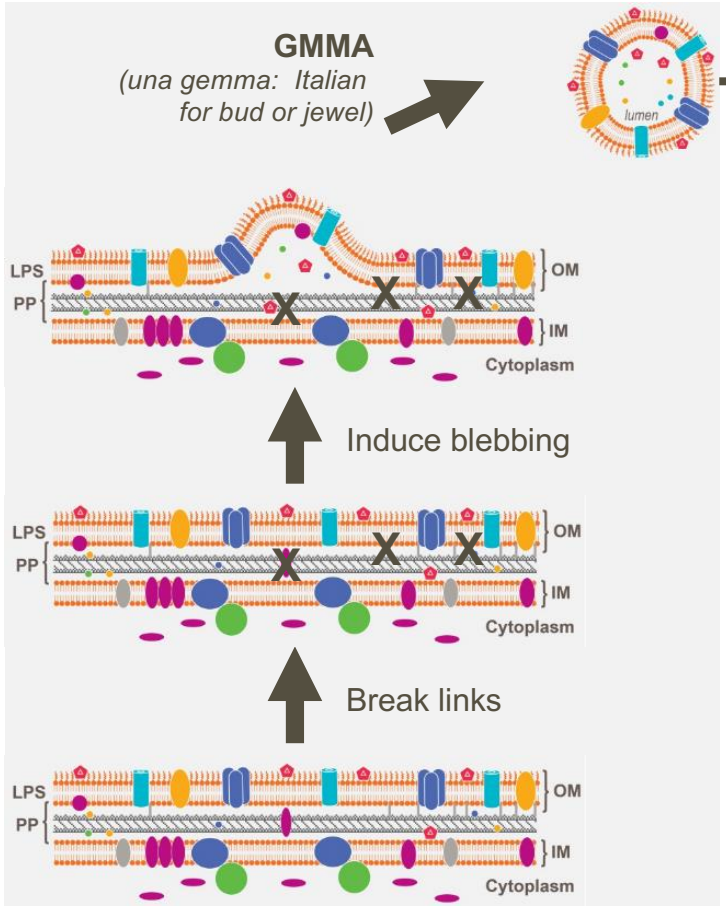
To develop a safe, effective, affordable vaccine to reduce diarrhea, dysentery and morbidity caused by Shigella in children under 5 years of age, in LMICs

Shigella bioconjugate vaccine

- *S. dysenteriae* O1 phase 1 in 2010 *(Hatz et al., Vaccine 2015*)
- *S. flexneri 2a* phase 1 and 2b (Wellcome Trust program) 2014-2016
  - Phase 1 results obtained:
    - Safety and immunogenicity (*Riddle et al., Clin Vaccine Immunol 2016*)
  - Phase 2b results obtained:
    - Proof of concept for early indication of efficacy (results will be presented at VED 2017 and Human Challenge Workshop 2017)
    - Supportive data of serological correlation with protection against clinical shigellosis
- Multivalent Shigella conjugate including the four most-dominant serotypes; projected coverage - Sf2a, Sf3a, Sf6 and *S. sonnei* in descending-age study to chidlren 9 months to two years in Kenya

From GMMA theory to GVGH examples

Simple to prepare but capable of sophisticated manipulation



Remove, modify toxic components

– LPS

Delete antigens / genes

– *Shigella virG*

Modify composition

– Multivalent vaccine

GVGH (GSK) GMMA

OPEN ACCESS Freely available online

PLoS one

High Yield Production Process for *Shigella* Outer Membrane Particles

Francesco Berlanda Scorza[1¤], Anna Maria Colucci[1], Luana Maggiore[1], Silvia Sanzone[1], Omar Rossi[1], Ilaria Ferlenghi[2], Isabella Pesce[1], Mariaelena Caboni[1], Nathalie Norais[2], Vito Di Cioccio[1], Allan Saul[1], Christiane Gerke[1]*

Production of a *Shigella sonnei* Vaccine Based on Generalized Modules for Membrane Antigens (GMMA), 1790GAHB

Christiane Gerke[1]*, Anna Maria Colucci[1], Carlo Giannelli[1], Silvia Sanzone[1], Claudia Giorgina Vitali[2], Luigi Sollai[1], Omar Rossi[1], Laura B. Martin[1], Jochen Auerbach[1], Vito Di Cioccio[1], Allan Saul[1]

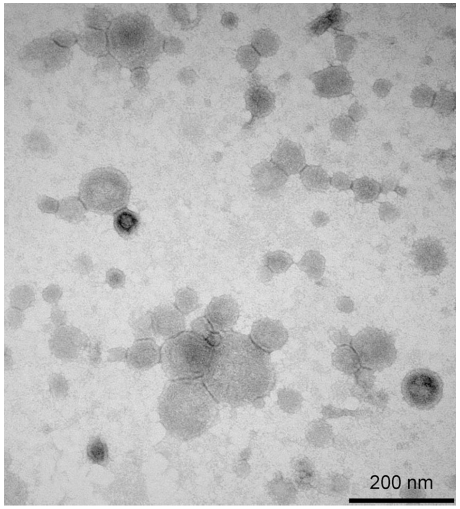
1 Sclavo Behring Vaccines Institute for Global Health S.r.l., Siena, Italy, 2 Novartis Vaccines and Diagnostics, S.r.l., Siena, Italy

Gerke C et al PLoS One 2016

Up to 5 O-antigen repeat units per LPS molecule

Low O-antigen content - Protein:O-antigen ratio 16:1

<10% of LPS molecules have O-antigen



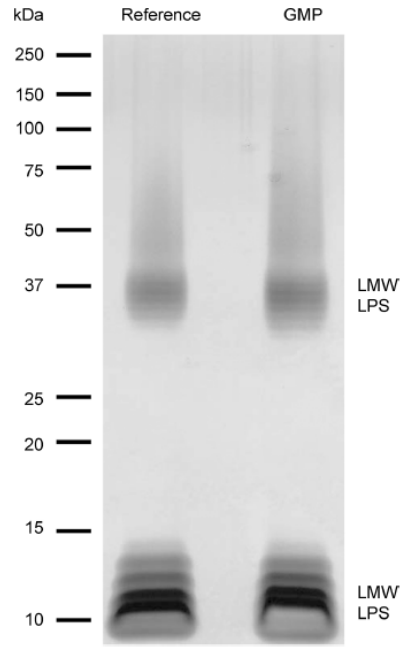
Berlanda Scorza F et al PLoS One 2012

Novel O-antigen vaccine strategy

Enriched for outer membrane proteins

Simplified production process

Potential very low cost of good



Synthetic carbohydrates vaccine for *Shigella*

- Homogeneous, well defined oligosaccharides (OS) as alternative to conjugates of detoxified LPS
- SF2a-TT15
- Optimum OS selected on basis of immunogenicity testing and protection in mice.
- Phase 1 initiated 2Q2016 (10 and 2 mg/dose ± alum 3 doses at 3 week intervals
- Financial support: EC-FP7 STOPENTERICS

Data Courtesy of Armelle Phalipon, Institut Pasteur