Novel Shigella Vaccine Candidates

Cal MacLennan
Bill & Melinda Gates Foundation
DCVMN Annual Meeting
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THE CASE FOR A SHIGELLA VACCINE

1. **Shigella burden is greater than we thought...**
   - Shigella attribution of moderate-to-severe diarrhea in GEMS (N=5304)
   - Shigella attribution of community diarrhea in MAL-ED (N=7354 diarrheal stools; 11,188 surveillance stools)

2. **...its impact on growth faltering is significant...**
   - 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

3. **...and the threat of AMR is growing**
   - % resistance to Shigella for each antibiotic in Asia and Africa
   - 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

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Shigella Vaccine History: *in 59 seconds or less*

- S. dysenteriae discovered (1897)
  - Kiyoshi Shiga
- S. flexneri discovered (1900)
  - Simon Flexner
- S. dysenteriae discovered (1921)
  - Ether-killed
  - K. Vincent
- Heat-killed Parenteral
  - Egypt Pediatric
  - RCT (1953)
  - Higgins, Floyd &
  - Kader
- Streptomycin-dependent oral mutant (attenuated)
  - Mel et al (1956-74)
- Killed-whole cell parenteral approaches
- Live-attenuated approaches
- Sub-unit era
- Proteosome, T3SS, intranasal, killed whole-cell vaccines
  - (Fries, Lowell
  - Oaks, Walker, early 2000s)
- 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 engin’r’ing
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

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)

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minimum</th>
<th>Optimistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong>*</td>
<td>Prevention of moderate to severe diarrhea due to <em>Shigella</em> in children six months to two years of age.</td>
<td>Prevention of moderate to severe diarrhea due to <em>Shigella</em> in children six months to five years of age.</td>
</tr>
<tr>
<td><strong>Target Population</strong>*</td>
<td>Children six months to two years of age.</td>
<td>Children six months to five years of age.</td>
</tr>
<tr>
<td><strong>Dosing Schedule and Route of Administration</strong>*</td>
<td>EPI schedule - 2 doses + booster IM route.</td>
<td>EPI schedule - 1 dose IM route.</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Safety and reactogenicity profile should be clinically acceptable. Contraindications should be restricted to known hypersensitivity to any of the vaccine components.</td>
<td>Safety and reactogenicity profile should be clinically acceptable. Contraindications should be restricted to known hypersensitivity to any of the vaccine components.</td>
</tr>
<tr>
<td><strong>Efficacy</strong>*</td>
<td>50% efficacy against moderate to severe diarrhea caused by <em>Shigella</em> strains in the vaccine.</td>
<td>70% efficacy against moderate to severe diarrhea caused by all <em>Shigella</em> strains.</td>
</tr>
<tr>
<td><strong>Duration of Protection</strong></td>
<td>To 2 years, with boosting possible to extend protection.</td>
<td>To 5 years.</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$1 - $3</td>
<td>&lt; $1</td>
</tr>
<tr>
<td><strong>Co-administration</strong></td>
<td>With EPI vaccines without interference.</td>
<td>With EPI vaccines without interference.</td>
</tr>
<tr>
<td><strong>Vaccine volume</strong></td>
<td>0.5 ml/dose</td>
<td>0.5 ml/dose</td>
</tr>
<tr>
<td><strong>Target Countries</strong></td>
<td>GAVI-eligible and lower-middle income countries.</td>
<td>GAVI-eligible and lower-middle income countries.</td>
</tr>
<tr>
<td><strong>Onset of immunity</strong></td>
<td>2 weeks after 2 doses</td>
<td>2 weeks after 1 dose</td>
</tr>
<tr>
<td><strong>Indirect (herd) protection</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*18 January 2018*
**Phase 1**

- Oag-rEPA conjugate* (S. sonnei/flexneri 2a) NIH
  - Taylor DN, IAI 1993
  - US adults
- Oag-CRM197/EPA conjugate† (S. sonnei/flexneri 2a) NIH
  - Paswell JH, IAI 2001
  - Israeli adults
- Oag-rEPA Bioconjugate (S. flexneri 2a) Limmatech (GSK)
  - Cohen D, IAI 1996
  - Israeli 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

**Phase 2**

- Oag-rEPA conjugate* (S. sonnei/flexneri 2a) NIH
  - Cohen D, IAI 1996
  - Israeli adults
- Oag-CRM197/EPA conjugate† (S. sonnei/flexneri 2a) NIH
  - Paswell JH, PIDJ 2003
  - Israeli children
- Oag-rEPA Bioconjugate (4-variant) Limmatech (GSK)
  - Cohen D, IAI 1996
  - Israeli adults
- Synthetic Oag conjugate (S. flex 2a) Pasteur Institute
  - Cohen D, VASE 2017
  - Israeli adults
- GMMA (S. sonnei) GVGH (GSK)
  - Obiero CW Front Immunol 2017
  - Kenyan adults

**Phase 2 (CHIM)**

- Oag-rEPA Bioconjugate (S. flexneri 2a) Limmatech (GSK)
  - Cohen D, IAI 1997
  - Israel adults
- Synthetic Oag conjugate (S. flex 2a) Pasteur Institute
  - Cohen D, VASE 2017
  - Israeli adults
- GMMA (S. sonnei) GVGH (GSK)
  - Obiero CW Front Immunol 2017
  - Kenya adults

**Phase 3**

- Oag-rEPA conjugate* (S. sonnei/flexneri 2a) NIH
  - Cohen D, IAI 1997
  - Israel adults
- Oag-rEPA conjugate† (S. sonnei/flexneri 2a) NIH
  - Paswell JH, Vaccine 2010
  - Israeli children
- Oag-rEPA Bioconjugate (S. flexneri 2a) Limmatech (GSK)
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  - Obiero CW Front Immunol 2017
  - Kenya adults

**Funding**

- BMGF
- Wellcome
- DFID
- DOD
- EC
- NIH

**Notes**

- **InvaplexAR** (S. flex 2a) WRAIR
- **InvaplexDetox** (S. flex 2a) WRAIR
- **Invaplex 50** (S. flex 2a) WRAIR
- ClinicalTrials.gov NCT00485134
- US adults
- (funded – data analysis stage)
- (funded – to start 2020)
- (funded – starting 2019)
- (funded – starting 2019)
- (funded – to start 2020)
LIMMATECH (GSK) – SHIGELLA BIOCONJUGATE

Recombinant E. coli

- 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

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

<table>
<thead>
<tr>
<th>Immune response and sample day</th>
<th>Vaccination group</th>
<th>P value$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flexyn2a (n = 12)</td>
<td></td>
</tr>
<tr>
<td>Anti-Sfl2a LPS Serum IgG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>2,397</td>
<td>NS</td>
</tr>
<tr>
<td>Day 28</td>
<td>45,614</td>
<td>11/12</td>
</tr>
<tr>
<td>Day 56</td>
<td>40,637</td>
<td>11/12</td>
</tr>
</tbody>
</table>
Flexyn2a Immunogenicity

**Serum Sf2a-LPS IgG**

- Injection: 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5 (log₁₀)
- Challenge: 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5 (log₁₀)

**Serum Sf2a-LPS IgA**

- Injection: 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5 (log₁₀)
- Challenge: 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5 (log₁₀)

* * *: p<0.05, t-test

**Serum Bactericidal Activity (SBA)**

- Injection: 2, 2.5, 3, 3.5, 4 (log₁₀)
- Challenge: 2, 2.5, 3, 3.5, 4 (log₁₀)

≥4-fold rise from baseline

<table>
<thead>
<tr>
<th></th>
<th>Serum Sf2a-LPS IgG</th>
<th>Serum Sf2a-LPS IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexyn2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0 to</td>
<td>26/34</td>
<td>26/34</td>
</tr>
<tr>
<td>Day 28</td>
<td>(76.5%)</td>
<td>(76.5%)</td>
</tr>
<tr>
<td>Day 0 to</td>
<td>27/33</td>
<td>26/33</td>
</tr>
<tr>
<td>Day 55</td>
<td>(81.1%)</td>
<td>(78.8%)</td>
</tr>
</tbody>
</table>
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

GMMA manufacturing – Generic, simple and robust

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

Genetic modifications

1. Increase GMMA production
   $\Delta tolR$
2. Decrease LPS innate immune stimulation
   $\Delta htrB$ or $\Delta msbB$
3. Other mutations
   virG nadA/B knock-in

Fermentation

Purification

- **Micro-filtration**
  Collect 0.22 µm permeate
- **Ultra-filtration**
  Collect 300 kD retentate

Formulation

- Adsorption on Alhydrogel

DS and DP characterization

- Generic panel of release tests
- CQA

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
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

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

- High immunogenicity post a single dose with 10 μg 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

**Synthetic conjugate:**
- Synthetic production of *S*. flex 2a O-antigen
  - 3 repeating units
- Optimised design for immunogenicity
- Conjugated to tetanus toxoid.
- ‘Sun-type’ configuration
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
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.
### 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**

### Who Engagement on ETEC & Shigella OPP1135836

- **IgG Thresholds OPP1189564 (Tel Aviv University)**

### Who Engagement on ETEC & Shigella OPP1135836

- **IgG stds flex 2a & S. Sonnei ELISA assay (NIBSC)**
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

[Links to relevant sources]

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

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

**Phase 1/2a**

- Quadrivalent
- Safety and immunogenicity
- US/European adults & age descending & dose finding in target age (6-12 months) in LMIC
- N= 400-600

**Phase 2 (CHIM)**

- Quadrivalent
- Naive adults
- S. flexneri 2a and S. sonnei

**Phase 2b**

- Quadrivalent
- Safety, immunogenicity and efficacy in LMIC in target age (6-12 months), with interim analysis

**Phase 3**

- ‘Accelerated Approval’ Vx Licensure (FDA)
- Quadrivalent 6-12mo

**Traditional licensure**

- Includes LMICs (EMA/Article 58)
- Quadrivalent 6-12mo

SAGE & WHO recommendation; & PQ for LMIC; Vx Supply for UN agencies

Key:
- pivotal licensure study data for WHO policy rec.

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**Key Points**

- Phase 1/2a:
  - Quadrivalent
  - Safety and immunogenicity
  - US/European adults & age descending & dose finding in target age (6-12 months) in LMIC
  - N= 400-600

- Phase 2 (CHIM):
  - Quadrivalent
  - Naive adults
  - S. flexneri 2a and S. sonnei

- Phase 2b:
  - Quadrivalent
  - Safety, immunogenicity and efficacy in LMIC in target age (6-12 months), with interim analysis

- Phase 3:
  - ‘Accelerated Approval’ Vx Licensure (FDA)
  - Quadrivalent 6-12mo

- Traditional licensure:
  - Includes LMICs (EMA/Article 58)
  - Quadrivalent 6-12mo

- SAGE & WHO recommendation; & PQ for LMIC; Vx Supply for UN agencies

---

**Questions for Consideration**

- 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.
- No go decision for lead EVI *Shigella* candidate (TSWC), given manufacturing delays and ETVAX no go.  

**Q1/Q2 2018 decision** on future investment in ETEC vaccines, pending additional burden data.

**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: 2\textsuperscript{ND} GENERATION O-ANTIGEN-BASED VACCINES**

20 years ago, a 1\textsuperscript{st} 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 2\textsuperscript{nd} 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
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 children 9 months to two years in Kenya
From GMMA theory to GVGH examples

Simple to prepare but capable of sophisticated manipulation

GMMA
(una gemma: Italian for bud or jewel)

Induce blebbing

LPS
PP
OM
Cytoplasm

Break links

LPS
PP
OM
Cytoplasm

Remove, modify toxic components
- LPS

Delete antigens / genes
- Shigella virG

Modify composition
- Multivalent vaccine

GSK Vaccines Institute for Global Health
GVGH (GSK) GMMA

High Yield Production Process for *Shigella* Outer Membrane Particles

Francesco Berlanda Scorza¹, Anna Maria Colucci¹, Luana Maggiore¹, Silvia Sanzone¹, Omar Rossi¹, Ilaria Ferlenghi², Isabella Pesce¹, Mariaelena Caboni¹, Nathalie Norais², Vito Di Cioccio¹, Allan Saul¹, Christiane Gerke¹,

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

Christiane Gerke¹*, Anna Maria Colucci¹, Carlo Giannelli¹, Silvia Sanzone¹, Claudia Giorgina Vitali², Luigi Sollai¹, Omar Rossi¹, Laura B. Martin¹, Jochen Auerbach³, Vito Di Cioccio¹, Allan Saul¹

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


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


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