

The potential role of the Controlled Human Infection Model (CHIM) in advancing licensure and introduction of next-generation O-antigen-based vaccines against *Shigella*

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Background

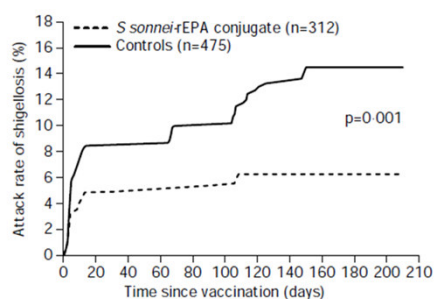


Figure 2: Attack rates of culture-proven *S. sonnei* shigellosis in recipients of *S. sonnei* conjugate vaccine and controls in groups A-D

20 years ago, a 1st generation NIH 'lattice-type' *S. sonnei* conjugate vaccine (*S. sonnei*-rEPA) 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...

...meanwhile: the NIH team demonstrated that conjugates with shorter O-antigens and 'sun-type' configuration induce higher levels of O-antigen IgG in mice. (Robbins JB *et al* PNAS 2009)

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Rationale for new O-antigen-based candidates

- WHO 2017: the strategic goal for Shigella vaccines for use in LMICs is to develop a safe, effective, affordable vaccine to reduce diarrhea, dysentery and morbidity caused by Shigella in children under 5 years of age
- New vaccines build on historical proof-of-concept efficacy studies with *S. sonnei*-rEPA
- Must protect the target population of young children in LMICs
- Need for multivalent vaccine for sufficient global health coverage: *Shigella sonnei*, and *Shigella flexneri* 2a, 3a and 6

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Serum O-antigen IgG correlate of protection and threshold titer

- Evidence from historic vaccine efficacy studies and natural infection studies in the field support serum O-antigen IgG as a correlate of protection.
- Immunologic data from vaccine failures can help indicate the O-antigen IgG level where protection to infection is lost, helping establish the O-antigen IgG protective threshold.

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New candidate *Shigella* O-antigen-based vaccines are currently in clinical development

- Limmatech (GSK) bioconjugate - *Shigella* O-antigen of wild-type length covalently coupled in sun-type format to rEPA within genetically-engineered *E. coli*
 - Monovalent *S. flexneri* 2a bioconjugate immunogenic in phase 1 US adults & protected in CHIM study
- GSK Vaccines Institute for Global Health (GVGH) outer membrane vesicle vaccine 'GMMA' (Generalized Modules for Membrane Antigens)
 - Monovalent *S. sonnei* GMMA induced less serum O-antigen IgG in phase 1 in French/UK adults compared with *S. sonnei*-rEPA in Israeli adults
- Institut Pasteur synthetic O-antigen tetanus toxoid conjugate – truncated O-antigen (15 monosaccharides). Sun-type format
 - *S. flexneri* 2a synthetic O-antigen conjugate induced high levels of serum O-antigen IgG in phase 1 Israeli adults

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Shigella CHIM studies

- Established in three centres in US – currently limited to *S. sonnei* and *S. flexneri* 2a
- Performed in naive adults
- Considered a Go/No Go stage-gate in clinical development
- May enable identification of immunological correlates, surrogates and threshold levels of protection, to be validated through field efficacy studies
- Further support serum O-antigen IgG as a correlate of protection.
- Provide opportunity to link vaccine efficacy to immunological thresholds (comparators) in clinical studies.
- Potential role in vaccine regulatory approval, particularly for a travellers indication

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Immunogenicity studies in target population

- Are candidates sufficiently immunogenic to confer protection in LMIC children?

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.

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Serum O-antigen IgG threshold

- Establishing protective threshold O-antigen serum IgG titers in the CHIM that is associated with protection in the target population would inform vaccine candidate prioritization and help accelerate clinical development pathways.
- Depends on the ability to 'bridge' immunologic responses in LMIC children to those in protected individuals from the historical efficacy studies
- Informed by CHIM, historic efficacy and field infection studies to be directly comparable
- Requires a standardized O-antigen ELISA and global reference reagents

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Efficacy and/or immunologic data to guide serum O-antigen IgG notional surrogate threshold titers

Strain	Historical efficacy	CHIM data	Convalescent sera in LMIC U3's
Sonnei	✓	✓ (planned)	Under evaluation
Flexneri 2a		✓	Under evaluation
Flexneri 3			Under evaluation
Flexneri 6			Under evaluation

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Strategy for progression

- O-antigen IgG notional surrogate needs to be established for *S. sonnei* and *S. flexneri* 2a components of a quadrivalent vaccine
- Aligning data from CHIM, historical efficacy studies, and convalescent serum samples from naturally-acquired shigellosis could help determine threshold titers for protection
- Use above information to leverage a large phase 2 safety and immunogenicity study in the target population as the basis of accelerated licensure
- Evidence of efficacy in LMIC children will likely be needed for policy decision to introduce into most LMIC countries
- Engagement with regulatory bodies and global health policy makers is needed to assess the acceptability of utilizing *Shigella* CHIM to accelerate vaccine licensure and introduction.

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Policy implications for consideration

- Is there a benefit for LMICs in encouraging accelerated licensure of travellers vaccines for *Shigella*, based on CHIM?
- What role do CHIM studies play in policy- decision making for and access to *Shigella* vaccines in LMICs?
- What are key enabling activities that should be prioritized to advance *Shigella* vaccine development to licensure and introduction?