



## Commentary

## Shigella conjugate vaccine efficacy trial in controlled human model and potential immune correlates of protection

Rubhana Raqib<sup>a,\*</sup>, Malabi Venkatesan<sup>b</sup>

<sup>a</sup> Infectious Diseases Division, icddr,b, Dhaka, Bangladesh

<sup>b</sup> Department of Enteric Infections, Bacterial Diseases Branch, Walter Reed Army Institute of Research, Maryland, USA (recently retired)



## ARTICLE INFO

## Article History:

Received 30 March 2021

Accepted 30 March 2021

Available online xxx

Currently there are no licensed *Shigella* vaccines even though *Shigella* was the second leading cause of diarrheal mortality in 2016 among all ages, accounting for 212,438 deaths (13.2% of all diarrheal deaths). Based on the report from the Global Burden of Disease study, *Shigella* was responsible for 63,713 deaths in <5 years old children mostly in low- and middle-income countries (LMIC) in South Asia and Sub-Saharan Africa [1]. Agencies such as the World Health Organization, the Gates Foundation, and the Wellcome Trust have placed a priority for development of multivalent *Shigella* vaccines containing the prevalent serotypes to target infants/toddlers in LMICs. Such a vaccine, it is hoped, will reduce the burden of global diarrhoea, contributing to enhanced safety and reduction of post-infectious sequelae like chronic inflammatory bowel diseases in travellers to *Shigella*-endemic regions. Moreover, it will improve linear growth, reduce stunting and other forms of malnutrition, increase immune function, and enhance cognitive development of children affected by successive bouts of diarrhoea. Several O-antigen-based parenteral vaccines are being evaluated since it is known that the O-antigen of the bacterial lipopolysaccharide is a prominent surface antigen responsible for the serotype-specific protection. Against this background, are two back-to-back papers recently published in *The Lancet's EBioMedicine*, describing a proof-of-concept efficacy [2] and immunogenicity [3] study of a novel, bioglycoconjugate *S. flexneri* 2a monovalent vaccine candidate, Flexyn2a. These papers score high points for providing an impressive array of clinical and immunogenicity data that is one of its kind in the field and will be used as a comparator for several *Shigella* vaccine studies to come.

DOI of original article: <http://dx.doi.org/10.1016/j.ebiom.2021.103308>, <http://dx.doi.org/10.1016/j.ebiom.2021.103310>.

\* Corresponding author.

E-mail address:

<sup>1</sup> The views expressed are those of the authors and do not represent the views of the US Department of the Army.

Flexyn2a vaccine or placebo was intramuscularly administered to healthy North American adults twice, one month apart. Following vaccination, volunteers were challenged orally with a standardized strain of *S. flexneri* 2a which had been previously characterized in CHIM studies for a 70% attack rate dosage along with definition of the primary end points of shigellosis [4,5]. In this study, while the desired attack rate in unvaccinated subjects was reached (60–64%), validating both the challenge strain and the dose, the efficacy for this monovalent vaccine was disappointingly low (30.2%) against the primary definition of shigellosis as well as a “consensus definition” of shigellosis (32%). A tetravalent bioglycoconjugate vaccine may lower the efficacy even further. Thus, there is room for improvement, in dosing regimen and in dosage. When individual symptoms were graded into moderate, severe and most severe, the vaccine efficacy increased, reaching 57% and 72% respectively for severe shigellosis and severe diarrhoea. Although the protected vaccinees showed amelioration of several clinical parameters such as requiring less IV fluid and antibiotics, the definitions of shigellosis are clearly population-specific and will require adjustments when this vaccine goes into different populations and/or into children. Whether Flexyn2a elicits an immune response and provides protection in the endemic settings of Kenya in adults, children and toddlers remains to be seen. Previously, a well-characterized O-antigen-based parenteral vaccine developed by John Robbins and team showed 70% efficacy in adults in field studies [6] but less than 30% efficacy in children <3 years of age who are the target population [7].

The accompanying manuscript describing immunogenicity responses among vaccinated-protected and -unprotected subjects provides detailed comparison of several key immune responses that will help to guide the immunological assays for other/future vaccine candidates. These include association of protection with high LPS-specific serum IgG titres on day of challenge, a feature that validates field studies observation by John Robbins but which is much better understood here in a stringent CHIM study. Protected vaccinees had higher serum bactericidal antibody levels compared to unprotected vaccinees or placebos emphasizing that Flexyn2a induces functional antibodies which contribute to protection. Another key observation is the correlation of protection with serum IgG1, rather than serum IgG2, which is not seen when placebos are challenged orally indicating that oral challenge and oral vaccination may induce protective responses that are

different from parenteral vaccines. A new and intriguing observation in this study was that parenteral immunization with Flexyn2a induced robust LPS-specific homing mucosal responses ( $\alpha 4\beta 7^+ \text{IgG/IgA}$ ). What remains to be unravelled now is why some vaccinees are protected and what are the drivers for the protective immunity- is it cytokine- or growth factor-mediated, are there other yet-to-be-identified factors, is there a genetic predisposition?

The lack of increased immune responses after a second Flexyn2a dose or after challenge in protected volunteers indicates that for protection to occur, a threshold level of serum IgG/IgA antibodies and/or mucosal response is needed. In this case, the vaccinees that attained threshold levels of immune responses pre-challenge, were subsequently protected. This can explain why adults and older children in endemic countries gain immunity after repeated exposures to *Shigella*, leaving the very young and unexposed population susceptible to the disease. It is these < 5 years old children, the future generation, that need to be vaccinated and protected by a *Shigella* vaccine.

### Contributors

RR and MV co-wrote this commissioned Commentary.

### Declaration of Competing Interest

The authors declare no conflicts of interest.

### References

- [1] Khalil IA, Troeger C, Blacker BF, Rao PC, Brown A, Atherly DE, Brewer TG, Engmann CM, Houpt ER, Kang G, Kotloff KL, Levine MM, Luby SP, MacLennan CA, Pan WK, Pavlinac PB, Platts-Mills JA, Qadri F, Riddle MS, Ryan ET, Shoultz DA, Steele AD, Walson JL, Sanders JW, Mokdad AH, Murray CJL, Hay SI, Reiner Jr. RC. Morbidity and mortality due to shigella and enterotoxigenic *Escherichia coli* diarrhoea: the Global Burden of Disease Study 1990-2016. *Lancet Infect Dis* 2018 Nov;18(11):1229–40.
- [2] Talaat KR, Alaimo C, Martin P, Bourgeois AL, Dreyer AM, Kaminski RW, Porter CK, Chakraborty S, Clarkson KA, Brubaker J, Elwood D, Frölich R, DeNearing B, Weerts HP, Feijoo B, Halpern J, Sack D, Riddle MS, and Fonck VG. Human challenge study with a *Shigella* bioconjugate vaccine: Analyses of clinical efficacy and correlate of protection. *E Bio Med.* (in press)
- [3] Clarkson KA, Talaat KR, Alaimo C, Martin P, Bourgeois AL, Dreyer A, Porter CK, Chakraborty S, Brubaker J, Elwood D, Frölich R, DeNearing B, Weerts HP, Feijoo B, Halpern J, Sack D, Riddle MS, Fonck VG and Kaminski RW. Immune response characterization in a human challenge study with a *Shigella flexneri* 2a Bioconjugate Vaccine. *E Bio Med.* (in press)
- [4] MacLennan CA, Riddle MS, Chen WH, Talaat KR, Jain V, Bourgeois AL, Frenck R, Kotloff K, Porter CK. Consensus report on shigella controlled human infection model: clinical endpoints. *Clin Infect Dis* 2019 Dec 9;69(Suppl 8):S591–5.
- [5] Porter CK, Lynen A, Riddle MS, Talaat K, Sack D, Gutiérrez RL, McKenzie R, DeNearing B, Feijoo B, Kaminski RW, Taylor DN, Kirkpatrick BD, Bourgeois AL. Clinical endpoints in the controlled human challenge model for *Shigella*: a call for standardization and the development of a disease severity score. *PLoS One* 2018 Mar 28;13(3):e0194325.
- [6] Cohen D, Ashkenazi S, Green MS, Gdalevich M, Robin G, Slepion R, Yavzori M, Orr N, Block C, Ashkenazi I, Shemer J, Taylor DN, Hale TL, Sadoff JC, Pavliakova D, Schneerson R, Robbins JB. Double-blind vaccine-controlled randomised efficacy trial of an investigational *Shigella sonnei* conjugate vaccine in young adults. *Lancet* 1997 Jan 18;349(9046):155–9.
- [7] Passwell JH, Ashkenazi S, Banet-Levi Y, Ramon-Saraf R, Farzam N, Lerner-Geva L, Even-Nir H, Yerushalmi B, Chu C, Shiloach J, Robbins JB, Schneerson R, Group Israeli *Shigella* Study. Age-related efficacy of *Shigella* O-specific polysaccharide conjugates in 1–4-year-old Israeli children. *Vaccine* 2010 Mar 2;28(10):2231–5.