| **GVIRF 2018 Workshop 2**: **Research and Development Updates - Enteric Vaccines** | |
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| **Rapporteur**: Shahida Baqar (NIAID) | |
| **Session Outline** | **Chairs:**<br>Gagandeep Kang (Professor, Christian Medical College, Vellore)<br>Jean-Pierre Amorij (Consultant, AH BV)<br>**Presentations:**<br>*An update on rotavirus vaccines*, Gagandeep Kang (Professor, Christian Medical College, Vellore)<br>*Subunit vaccine technologies for bacterial enteric diseases: Shigella, ETEC and nontyphoidal Salmonella vaccines*, Calman MacLennan (Senior Program Officer, Bill & Melinda Gates Foundation)<br>*Controlled Human Infection Models and Enteric Vaccine Development*, Beth Kirkpatrick (Director, University of Vermont College of Medicine)<br>**Panelists:**<br>Firdausi Qadri (Senior Director, International Centre for Diarrhoeal Disease Research, Bangladesh)<br>Norman Baylor (President and CEO, Biologics Consulting Group, Inc)<br>Dilara Islam (Scientist, Armed Forces Research Institute of Medical Sciences) |
| **Objectives of the session** | *To discuss:*<br>• Updates on rotavirus vaccine Introduction and impact and new vaccine candidates<br>• Advances in bacterial enteric vaccine development<br>• The role of human challenge models |
| **Main outcome** | • Because the efficacies of enteric vaccines have been observed to differ between high income and low-income countries and between age groups, it is crucial to test new vaccines in the specific target populations that need them most. |
| **Summary** | Significant progress has been made in rotavirus vaccination. There are 7 licensed rotavirus vaccines, of which 3 are prequalified. They are in use in about 50% of countries and show excellent efficacy in high income countries and moderate efficacy in low income countries. They have had a measurable impact on gastroenteritis hospitalizations and mortality.[a] Significant reductions in hospitalizations have been observed for non-vaccinated children in some settings, providing evidence for herd protection.<br>However, much remains to be done. Current efforts focus on understanding current vaccines and developing better vaccines. Based on immunogenicity, Rotateq and Rotarix are interchangeable, and this is likely to translate to equivalent efficacy in mixed regimens. The gut environment influences how well these oral vaccines work and differences have been observed in the microbiota of children who respond or do not respond to the vaccine in some studies, but |

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| | not others.[b] Additional products are in development, including non-replicating vaccines for systemic delivery. A correlate of protection that would facilitate new produce licensure is not defined, but these new vaccine studies offer opportunities for exploration. Should efficacy trials be required, ethical concerns would need to be addressed by multiple approaches, depending on study design and location.<br><br>The *Shigella* vaccine pipeline is robust, with 5 candidates currently in trials. All build on proof-of-concept established by a NIH *Shigella sonnei* conjugate vaccine. The new candidates use novel conjugation technologies (Flexyn2a, LimmaTech Biologics), synthetic carbohydrates (SF2a-TT15, Institut Pasteur), or membrane vesicles displaying multiple antigens (*S*. *sonnei* GMMA, GSK). Because the NIH vaccine was not effective in infants, these development programs prioritize age-de-escalation.<br><br>The enterotoxogenic *E*. coli (ETEC) vaccine pipeline is weaker. Two candidates have not advanced beyond Phase 2 due to poor immunogenicity in infants. A fimbrial tip adhesin vaccine (NMRC, Sanofi, IDRI) recently entered Phase 1 and additional subunit vaccines are undergoing preclinical evaluation.<br><br>Two candidates are in preclinical development for nontyphoidal *Salmonella*: a glycoconjugate vaccine by University of Maryland and Bharat Biotech and a membrane vesicle vaccine by GSK.<br><br>Issues for these programs include i) induction of protective immunity in infants in low-resource settings, ii) difficulties in assessing immunogenicity in the target population, iii) lack of confirmed correlates of protection, iv) developing standardized and qualified assays and v) poor clarity on pathways to licensure and implementation.<br><br>Controlled Human Infection Models (CHIMs) can accelerate and de-risk vaccine development. They have been used to study pathogenesis and determine correlates of protection, and have provided efficacy data for cholera and typhoid vaccine licensure. These successes were possible because the biology of the pathogens was well understood and the CHIMs were safe, with clear endpoints and consistently high attack rates. CHIMs for other diseases have been challenging due to complex biology, variable attack rates, and complex disease profiles. Future directions for CHIMs include evolving pathways to support licensure, greater standardization, application of advanced immunology for immune correlates, and a focus on end-target populations and consideration of endemic site CHIMs. |
| **Key references or quotes** | a. Jonesteller CL, Burnett E, Yen C, et al. *Effectiveness of Rotavirus Vaccination: A Systematic Review of the First Decade of Global Postlicensure Data, 2006–2016.* Clinical Infectious Diseases. 2017;65(5):840-850.<br>b. Parker EPK, Praharaj I, Zekavati A, et al. *Influence of the intestinal microbiota on the immunogenicity of oral rotavirus vaccine given to infants in south India*. Vaccine. 2018;36(2):264-272. |