**IVI-WHO Consultation on *Salmonella* Combination Vaccines**
**3:30 PM – 6:30 PM, December 4, 2023**
**Simba Ballroom, Four Points by Sheraton Kigali, KN 3 Ave Kigali, Rwanda**

**Chair: Debbie King, Wellcome Trust, co-Chair: Adwoa Bentsi-Enchill, World Health Organization**


**Summary**

- Support for the geographical approach to combinations based on epidemiology.
- Expression of caution about the iNTS-TCV trivalent approach considering different peak age burden of disease profiles for iNTS disease and typhoid, and that these fundamentals must drive any combination vaccine approaches. This is more pronounced given recent data to suggest substantial waning of immune response 3-4 years after TCV vaccination at infancy. This data suggests that TCV may require a subsequent booster dose/second dose in pre-school years as short intervals between doses do not generate substantial booster responses.
- iNTS clinical efficacy studies will be required.
- The concept of an iNTS consortium to test multiple vaccine candidates within a single multi-centre efficacy trial was raised as a potential way to accelerate the identification of efficacious candidates and reduce cost.
- Research gaps for *Salmonella* vaccines include burden data, diagnostics, and duration of immunogenicity and protection following TCV and iNTS vaccination in different age groups.
- Combination vaccines should not be pursued for the sake of doing so, and consideration should be given to combining *Salmonella* vaccines with other antigens if it makes sense to do so, e.g., by age group.
- Countries face considerable pressures with multiple new vaccine introductions, so any new introductions need to be carefully considered.
- Manufacturers need/want guidance on combination products; this should be driven by the burden of disease and the age profile for each disease.
- A better understanding of the data that regulators require would benefit many stakeholders.
- The pricing and cost-effectiveness of any combined vaccine are critical.
- Countries need support as they graduate from Gavi eligibility.


**Key discussion points**

1. **Public health needs**

   **Should we consider regional combos: trivalent vaccine for Africa targeting typhoid + iNTS vs. bivalent vaccine for Asia targeting typhoid + paratyphoid A or bivalent iNTS standalone or universal quadrivalent (iNTS + typhoid + paratyphoid A)?**

   - The group was nearly unanimous in favour of region-specific vaccines based on disease burden, and they presented compelling arguments to support their case.
   - A quadrivalent including Paratyphoid A (ParaA) would not fit because ParaA is almost non-existent in younger age groups.
   - While higher valency vaccines may enhance protection, the main challenge in introducing them in low- and middle-income countries (LMICs) and low-income countries (LICs), where the disease burden is high, lies in their increased COGs and GMP manufacturing complexity.

- Combination vaccines mitigate the challenges of the introduction of multiple vaccines (the more vaccines, the more introductions).
- Programmatic challenges and immunization strategies are what health policymakers will consider as priorities to address.
- The adoption of the iNTS-TCV combination has been influenced, in part, by the licensing of TCV for infants from 6 months of age. However, both disease burden and immune response data suggest that this timing might be too late for iNTS prevention, especially considering that the highest disease burden occurs in infancy, and immunity should ideally be established by the age of six months, suggesting starting immunization at 4 months. However, the immune response at that age may also be poor and non-functional. Recent data from TyVAC Bangladesh in infants and young children have revealed a decline in immunity over 4 years following TCV administration from 9 months of age, a concerning finding given the high disease burden among pre-school children. While the longevity of immunogenicity for TCV appeared promising in earlier Phase 1 studies, discussions at the TyVAC meeting suggested that, especially for the youngest children, TCV may require a pre-school booster and potentially another booster around one year of age due to substantial waning immunity. This requirement of a booster represents a challenge, as many countries lack a pre-school vaccine touchpoint. Furthermore, additional TCV doses during infancy may not be effective if waning immunity is pronounced and boosting becomes necessary. Additional data on iNTS is needed for informed decision making. It was reminded that a single dose of Hib was less immunogenic in US and Europe but elicited good responses in children in LATAM.
- To consider the combination vaccine and dosing strategy, in-depth immune response data analysis is needed, especially when contemplating two or three doses of a combined vaccine. In the case of iNTS disease, there is the theoretical potential for natural boosting through exposure after early infancy vaccination. This is consistent with the rapid acquisition of natural immunity during early childhood and the declining disease burden with age.
- The main topic was a combined *Salmonella* vaccine, but there was a question about whether we should focus on creating effective vaccines to reduce *Salmonella* disease in general. For example, the combined iNTS vaccine may or may not include components from the traditional TCV. It could potentially be integrated into existing vaccines, but this requires further investigation. The main aim is to develop an effective and affordable vaccine that can be used alone or in combination with other vaccines as necessary.
- Priority Considerations for combination vaccines: introduction of multiple new vaccines recommended for young children, reduction in the number of injections, risk of immunologic interference, epidemiology, route of administration, CMC complexity, regulatory pathways, partners needed for collaboration, commercial attractiveness.
- Vaccine schedules are already crowded, and introducing a multiple-dose vaccine poses a significant challenge.
- We need to be very cautious about what countries can bear; they are being asked to introduce multiple vaccines and vaccine schedules and not necessarily just new ones (e.g., new data to show 2 doses of MR are needed). The optimal schedule for Salmonella vaccines has not been definitively established, and it's important to acknowledge that combination vaccines may not be the solution.

**What would be prioritization of research gaps to ensure the maximum impact of *Salmonella* vaccines?**

- **Burden data**: Burden data as well as the ongoing collection of such data to monitor changes in epidemiology over time, are crucial. These data align with the requirements set by SAGE for data-driven policy at a global level. Additionally, there is a growing demand among country-level policymakers, particularly concerning bloodstream infections (BSI), for more detailed burden data, including subnational heterogeneity.
- **Diagnostics**: Diagnostic data pose significant challenges for countries to make informed decisions due to the unclear burden of diseases. Similar issues are observed with other pathogens, such as HPV. In West Africa, there is an ongoing discussion about the 'typhoid-malaria' diagnosis, emphasizing the need for diagnostic tests that can differentiate between these diseases accurately. The lack of data primarily arises from challenges and diagnostic capabilities in high-endemic countries. Addressing these issues is essential before generating accurate burden data.
- **Longevity of immunogenicity and vaccine efficacy for TCV and iNTS:** Additional data on the duration of protection for both TCV and iNTS vaccines is imperative. As an example, early phase I studies for TCV demonstrated immunogenicity longevity. However, there remains uncertainty about the number of doses required and the optimal ages for administration.

## 2. Regulatory pathway to licensure

- We do not know what the regulators want, particularly in the countries of introduction.
- There is a clear need to bring together regulatory authorities, including FDA, EMA, as well as NRAs from countries of vaccine manufacture, and the WHO PQ team. This consultation would review and discuss the current knowledge of the vaccine field, the gaps and potential options to seek guidance. It is crucial to gain a better understanding of their specific expectations and requirements to guide the development process to licensure.
- It was suggested to organize a global consortium looking at different vaccines in a similar manner as that done for typhoid vaccines in 1950s and acellular pertussis vaccines in the 1990s.
- A WHO consultation could be organized by the WHO Regulatory Team.

**What would be the potential needs and requirements (or challenges) for immunogenicity versus clinical efficacy data?**

- Clear standards for standalone vaccines streamline the regulatory process, facilitating the possibility of combinations when these standards are met. This approach has proven successful in securing regulatory approvals for complex vaccines like hexavalent vaccines. However, there exists uncertainty concerning the precise regulatory requirements for *Salmonella* combination vaccines, encompassing both high-income country regulatory authorities and country-specific regulators involved in vaccine production.

- While post-vaccination efficacy studies were suitable for TCV prequalification, it is apparent that this approach will not directly apply to iNTS vaccines. Efficacy studies become mandatory for iNTS vaccines.
- Resource constraints pose a challenge for conducting phase 3 studies, as they are notably expensive. This necessitates careful consideration when selecting candidates for such substantial funding. Innovative approaches may be essential, given that efficacy trials can incur costs in the tens of millions of USD.
- However, recent estimates suggest that conducting such trials is feasible, particularly when a well-defined high-risk population is properly chosen. It is estimated that with a sample size of < 10,000 participants, an iNTS vaccine efficacy study for 6 months to 5 years is possible.
- It was also noted that additional NI efficacy trials in <6 months and in 3-5 years could be addressed post-licensure. However, it was recommended to include upfront a broader age range (6m-5 years), a strategy usually preferred by regulators and manufacturers as well as policymakers.
- One large efficacy trial with one single vaccine should suffice for licensure. This would allow non-inferiority trials. The issue is that we would have to wait for the results of this efficacy trial before testing other candidates, hence the proposal of a consortium. However, resources may not be there for such a strategy.
- However, achieving a robust immune response in phase 2 and then proceeding to phase 3 with the most promising dosing and timing options for iNTS vaccines can serve as a proactive step to address some of these challenges.

**What role would Controlled Human Infection Model (CHIM) studies play?**

- Concerning PTA, PDVAC has mentioned the importance of supporting data from Controlled Human Infection Model (CHIM) studies given the difficulty in performing efficacy trials due to the large sample sizes that would be required. However, it is crucial to note that for PTA, regulators have not yet reviewed a portfolio and granted approval based on CHIM data alone. The immunogenicity of PTA vaccines remains largely unknown, and the availability of an animal model for PTA could potentially aid in this aspect.
- The Imperial NTS CHIM model, which is currently underway for may produce a colonisation or a diarrheal model, which contrasts with the expected presentation of a disease characterized by bacteraemia. Regulatory authorities are unlikely to accept a diarrheal model for a disease primarily associated with bloodstream infection.
- With respect to iNTS CHIM, CVD considered a CHIM model using a highly invasive iNTS strain that had been attenuated and using this at high doses to achieve a bacteraemia (based on studies of under-attenuated typhoid vaccine strains that could produce bacteraemia). This is not the current approach in the only iNTS CHIM being studied at present. The risk was acknowledged that using an imperfect model that didn't resemble the disease could risk down selecting a vaccine candidate that could have been successful in the field. Even if an iNTS CHIM was developed the feeling was that efficacy studies would be required.
- CHIM data may support clinical efficacy data for iNTS vaccines and generate confidence but are not a gatekeeper of true randomized clinical efficacy trials in high-incidence populations.

**Immunological assay standardization (qualification for early clinical development and validation for pivotal studies to licensure): who would provide standard reagents and reference serum, particularly for iNTS and paratyphoid A? Do we need a reference lab for iNTS and paratyphoid A assays?**

- The need for standardized assays has gained significant attention, particularly as vaccines advance into later-stage clinical trials. To address this need, BMGF and NIBSC are organizing a workshop on standardization of assays which is scheduled for 2024.

3. **Marketability and acceptability (perspectives of manufacturers, policy makers at all levels, end users/target populations, COGs, pricing)**

   **Lessons learned from TCV introduction; would a combination vaccine be more easily introduced?**

   - Increasing vaccine hesitancy requires a proactive effort to boost vaccine confidence, not only among parents but also among healthcare workers who need support in addressing questions and concerns.
   - Many countries face growing financial pressure to fund their vaccines, and while Gavi graduation may be on the horizon for some, co-financing remains a challenge for many.
   - Caregivers often lack complete information when making vaccination decisions, which can lead to scepticism, particularly with numerous new vaccine introductions.
   - Community-level vaccine hesitancy calls for close collaboration with EPI program managers to gain insights and effective communication, particularly regarding combination vaccines, is crucial.
   - Combination vaccines may be more attractive for their efficiency, but they can raise safety and interaction questions that need reassurance.
   - Vaccine introduction fatigue is a real concern, emphasizing the importance of managing public expectations and maintaining trust in immunization programs.

**What are the risks to develop a combination *Salmonella* vaccine for manufacturers?**

- Regional vaccines may face challenges in smaller markets, and it is crucial to determine how many vaccines a market can support. Manufacturers need clear market data to make informed decisions.
- Pricing is a critical consideration, especially as many countries move up the ladder in terms of economic development. The price point becomes increasingly important.
- Despite having two PQ products for TCV, supply constraints have been an issue, and there is often a lead time from funding requests to production. Combining vaccines, even in a dual-market scenario, may not involve a single manufacturer capable of producing both types.
- Demand forecasting is challenging, and more thought is needed on how to provide data to support manufacturers and country-level decision-making, with a focus on ensuring a secure and consistent supply.
- TCV is not yet a mature market, and differentiated products may be beneficial for different developers. Timing considerations are important, especially if manufacturers are producing both TCV and iNTS vaccines. iNTS vaccines may not involve large catch-up campaigns like TCV, and therefore will have different implications for demand.

**What would drive developers to invest in a combination *Salmonella* vaccine?**

- There is a consensus that combinations should not be pursued merely for the sake of it. Developers require guidance that take into account factors such as the target age group, disease burden, and immune parameters to make informed decisions.

**What are the potential requirements to support policy at both global and national levels?**

- To support policy development at both global and national levels, it is essential to recognize and address the risks associated with iNTS disease in infants and typhoid in older children.
- Providing support during the transition from Gavi funding to national financing is a crucial requirement to facilitate policy implementation at the national level.
- Meeting the demand for additional data, including post-introduction effectiveness data for TCV, is essential to inform evidence-based policies both globally and within individual countries.
- Ensuring the sustainability of TCV beyond Gavi funding is a key consideration for policy support, as it impacts both global and national vaccination strategies.

**Other points**

- One conceptual idea is to establish a global consortium dedicated to conducting phase three trials for iNTS-containing vaccines. While it is understood that some companies may have reservations about this approach, it is worth noting the historical precedent from the 1950s and 1960s when multiple vaccines were assessed within the same trial using shared control groups, particularly with typhoid vaccines. Similarly, the NIH funded a comparable approach for acellular pertussis vaccines. Regulatory authorities may be receptive to this method, given its potential cost-efficiency compared to running multiple separate efficacy trials. Considering that the target population comprises the youngest children in the poorest countries, there exists a strong case for collaboration to ensure the effective development and accessibility of these vaccines. However, it is important to recognize that funding could pose a significant challenge for this model, as the associated costs could be substantial.
- Considering the multitude of questions, uncertainties, and challenges that span across developers, manufacturers, regulators, and various stakeholders worldwide, a coordinated consortium approach appears to be a compelling need for iNTS work.
- While our primary focus remains on vaccines, it is equally important to recognize that in some areas, WASH (Water, Sanitation, and Hygiene) conditions are deteriorating. This highlights the need for a holistic approach that encompasses other preventive measures alongside vaccination efforts.

List of Participants

| No. | Affiliation | Name | Email address |
|---|---|---|---|
| 1 | Biological E. | Ganesh Mishra | ganesh.mishra@biologicale.com |
| 2 | Biological E. | Nupur Sengupta | nupur.sengupta@biologicale.com |
| 3 | BMGF/Wellcome Trust | Calman MacLennan | calman.maclennan@gatesfoundation.org |
| 4 | BMGF | Duncan Steele | duncan.steele@gatesfoundation.org |
| 5 | BMGF | Jessica Long | Jessica.long@gatesfoundation.org |
| 6 | BMGF | Kirsten Vannice | kirsten.vannice@gatesfoundation.org |
| 7 | BMGF | Tanya Shewchuk | tanya.shewchuk@gatesfoundation.org |
| 8 | University of the Witwatersrand/Emory University | Rob Breiman | rfbreiman@emory.edu |
| 9 | EU Biologics | Rachel Park | rachel.park@eubiologics.com |
| 10 | Gavi | Allyson Russell | arussell@gavi.org |
| 11 | GSK Vaccines Institute for Global Health | Ashwani Kumar Arora | ashwani.k.arora@gsk.com |
| 12 | GSK Vaccines Institute for Global Health | Dalia Ibrahim | dalia.i.ibrahim@gsk.com |
| 13 | GSK Vaccines Institute for Global Health | Rocio Canals Alvarez | rocio.x.canalsalvarez@gsk.com |
| 14 | GSK Vaccines Institute for Global Health | Simona Rondini | simona.x.rondini@gsk.com |
| 15 | Institute for Molecular Bioscience, University of Queensland | Ian Henderson | i.henderson@uq.edu.au |
| 16 | IVI | Hyonjin Jeon | hyonjin.jeon@ivi.int |
| 17 | IVI | Jean-Louis Excler | jeanlouis.excler@ivi.int |
| 18 | IVI | Jerome Kim | jerome.kim@ivi.int |
| 19 | IVI | Jungseok Lee | jungseok.lee@ivi.int |
| 20 | IVI | Tarun Saluja | tarun.saluja@ivi.int |
| 21 | Kenya Medical Research Institute | Sam Kariuki | skariuki@kemri.go.ke |
| 22 | PATH | Aziza Mwisongo | amwisongo@path.org |
| 23 | PATH | Emmanuel Mugisha | emugisha@path.org |
| 24 | PATH | Farzana Muhib | fmuhib@path.org |
| 25 | Preventive Health Services, Ministry of Health and Population | Mike Nenani Chisema | nchisema@gmail.com |
| 26 | Sabin Vaccine Institute | Denise Garrett | denise.garrett@sabin.org |
| 27 | Sclavo Foundation | Gianluca Breghi | breghi@sclavo.org |

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|---|---|---|---|
| 28 | Swiss TPH | Branwen Owen | branwennia.owen@swisstph.ch |
| 29 | University of Birmingham | Adam Cunningham | a.f.cunningham@bham.ac.uk |
| 30 | University of Liverpool | Helen Dale | helen.dale@liverpool.ac.uk |
| 31 | University of Liverpool | Melita Gordon | magordon@liverpool.ac.uk |
| 32 | University of Liverpool | Tonney Nyirenda | tnyirenda@kuhes.ac.mw |
| 33 | University of Maryland | Kathy Neuzil | kneuzil@som.umaryland.edu |
| 34 | University of Maryland | Myron M. Levine | mlevine@som.umaryland.edu |
| 35 | University of Otago | John Crump | john.crump@otago.ac.nz |
| 36 | University of Otago | Shruti Murthy | shruti.murthy@otago.ac.nz |
| 37 | University of Oxford | Andrew Pollard | andrew.pollard@paediatrics.ox.ac.uk |
| 38 | Wellcome Trust | Deborah King | d.king@wellcome.org |
| 39 | Wellcome Trust | Pierre Balard | p.balard@wellcome.org |
| 40 | WHO | Adidja Amani | amaniad@who.int |
| 41 | WHO | Adwoa Bentsi-Enchill | bentsienchilla@who.int |
| 42 | WHO | Ana Ibarz Pavon | ibarza@who.int |
| 43 | WHO | Annelies Wilder-Smith | wildersmitha@who.int |
| 44 | WHO | Jenny Walldorf | walldorfj@who.int |
| 45 | WHO | Kate Emary | emaryk@who.int |