PDVAC (virtual) meeting on invasive non-typhoidal *Salmonella* (iNTS) vaccines

07 February 2022, 13h00 -15h15 CET/Geneva time

Summary and outcomes from PDVAC closed discussion

Members present: David Kaslow, Ruth Karron, Jerome Kim, Marian Wentowrth, Gustavo Santos, Gagandeep Kang; Alejandro Cravioto; Raman Rao

Apologies: Sinead Delany-Moretlwe, Sophie Biernaux (present for open session and provided comments on conclusions); Beno Yakubo; Kavita Singh

Question: In PDVAC's opinion, what are the short-, medium- and long-term goals for development of iNTS vaccine(s)

Context/take-aways from open session:

Pipeline:

- The current NTS candidates all target *S.* Typhimurium and *S.* Enteritidis (the leading causes of NTS invasive disease (iNTS) – see additional information under the Epidemiology section) and are based on O-antigens (or OMV in the case of GMMA) expressed by S. Typhimurium (O:4 and O:4,5) and S. Enteritidis (O:9); therefore these vaccines will potentially cross-protect against other NTS serovars, e.g. Dublin, that express O:4 or O:9 antigens.
- Two iNTS (bivalent) candidates are in preclinical development (GVGH and BCH); 3 candidates are in preclinical/early clinical development as an iNTS + TCV (trivalent). Two of the latter trivalent candidates (UMD/BBIL and GVGH) are based on a WHO PQ'd typhoid conjugate vaccine (TCV). One trivalent candidate (UMD/BBIL) has completed a phase I study in adults, in which a single dose elicited strong and durable O-antigen immune responses.
- There are 2 paratyphoid A (PTA) candidates in clinical development, with one (Lanzhou) preparing to enter phase III. The second (UMD/BBIL) is in phase 1 and will be evaluated in a challenge study in 2023 (timeline to be confirmed).
- Hypothetically, it would be possible to develop a quadrivalent vaccine (against iNTS typhoid, and PTA), although development has not been initiated.
- All candidates are expected to require a dose regimen of at least 2 doses for the infant/U5 target population.

Epidemiology:

- Typhoid fever burden is spread across sub-Saharan Africa (SSA), South Asia, and Southeast Asia. Paratyphoid fever is concentrated in South Asia and, to some extent, Southeast Asia. The burden of nontyphoidal Salmonella invasive disease is in sub-Saharan Africa.
- Among NTS serovars (which are defined by O-antigen and H-antigen), *S.* Typhimurium (serogroup O:4) and *S.* Enteritidis (serogroup O:9) account for more than three-quarters of serotyped isolates. It is worth noting that both these O antigens are also expressed by a number of less prevalent NTS serovars, and O:9 is expressed by *S.* Typhi.
- As such, there is an epidemiological rationale for regional vaccines - a iNTS + typhoid conjugate trivalent vaccine for SSA; and potentially a typhoid + PTA bivalent vaccine for South and Southeast Asia. However, the uptake of a standalone TCV continues to be slow, suggesting that achieving high

coverage with a TCV-containing vaccine might also be challenging. Vaccine uptake could be further hampered if a combination vaccine containing a typhoid or PTA component increases vaccine cost, which most likely will be the case.

- The distribution of PTA may evolve to other regions, including SAA, in the coming decades, resulting in a global public health need for a quadrivalent vaccine, although how likely and how fast a global need might arise remains uncertain today.
- Given the best available current epidemiological evidence, a standalone iNTS vaccine would only be implemented in SSA.
- While the conventional key target populations for iNTS vaccines include infants and young children from the age of 6-36 mo, LMIC stakeholders identified the neonatal burden of invasive disease as a key issue.

Potential delivery strategies

- The current iNTS vaccination strategy for neonates focuses on protection through maternal immunization.
- The proposed introduction strategy for an iNTS vaccine for infants is through initial catch-up, followed by routine immunization.
- There appeared to be consensus that introduction of iNTS as a standalone vaccine within the early EPI schedule (6, 10, 14 weeks) would not be feasible.
- Conceivably, a iNTS + typhoid trivalent conjugate vaccine could be introduced from the age of 6 months, particularly if a new visit is established for RTS,S. The potential issues with this strategy are:
    - By the time that a iNTS vaccine is available, TCV may have been more broadly implemented in routine immunization. If so, there may be reluctance, as part of a catch-up campaign, to reimmunize previously TCV-vaccinated children with a trivalent TCV-containing vaccine.
    - The iNTS component of the trivalent vaccine may require a two (or more) dose regimen for infants/young children, while the current recommended schedule for TCV is a single dose regimen. Administering a second iNTS dose as a standalone vaccine would be add significant complexity to vaccine implementation.

Policy and programmatic considerations for combinations:

- Introduction of TCV in AFRO and SEARO has been challenging because of vaccine cost, particularly the cost of delivery. Adding a vaccine component in addition to TCV without compelling disease and economic value will be a significant barrier to uptake.
- TCV is currently licensed for use from the age of 6 months (however early introducer countries have followed the SAGE/WHO recommendation for programmatic use at 9 months or in the 2nd year of life). No boosters are currently included in the schedule; in fact, there is evidence to suggest that boosting within 24 months of the primary series does not increase immunogenicity (i.e., may not provide any additional benefit).

Conclusions of PDVAC:

- The bivalent iNTS and trivalent iNTS+TCV vaccine combinations are all steps along the pathway to a potential global quadrivalent iNTS+PTA+TCV combination; and the quadrivalent may or may not have favourable public health value;
- Full vaccine of value assessments (FVVAs) will be necessary to evaluate ***each*** of these scenarios (iNTS alone, trivalent permutations, and quadrivalent) to assess multiple trade-offs and the incentives for manufacturers;
- There is considerable risk in signalling to vaccine manufacturers that any of these combinations is the preference today, without being informed of a) the relative health, social, and economic value, and b) better understanding the preferences of country and regional level stakeholders, including NITAGs and RITAGs, respectively;
- It should be clear that development of a PPC for either the iNTS or iNTS + TCV trivalent is one of a number of potential salmonella vaccine combinations, and that there will need to be significant parallel effort to determine the likely demand for each, to inform manufacturers. In other words, there needs to be caution that development of a WHO PPC at this early stage is not a signal to manufacturers that there will be uptake of this vaccine.
- In addition, it should also be acknowledged that the epidemiology, and associated need/demand for these iNTS containing vaccines may shift during the course of product development, particularly in the context of emerging data/shifting prevalence of malaria, people living with HIV, awareness of antimicrobial resistance and the potential impact that a vaccine could have; this may warrant revision of the PPC or development of a PPC for an alternate combination;
- Notwithstanding the point above, **a PPC and roadmap for either stand-alone iNTS, or iNTS + TCV trivalent is considered a worthwhile endeavour** as it is a requisite step for assessing vaccine value and potential impact; however, it should be in the context of a broader Salmonella vaccine value assessment co-ordination effort, beyond the scope of the IVI /WHO collaboration.