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Commentary

Landscape analysis of invasive non-typhoidal salmonella (iNTS) disease and iNTS vaccine use case and demand: Report of a WHO expert consultation

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ABSTRACT

Invasive disease caused by non-typhoidal *Salmonella* serovars (iNTS) occurs with increased risk in the presence of other comorbidities such as malaria, HIV, malnutrition, anaemia and sickle cell disease. While infection with non-typhoidal (NTS) serovars often results in self-limited enterocolitis in high-income settings, in sub-Saharan Africa (SSA) where these risk-comorbidities are common, an invasive (iNTS) disease phenotype is seen, associated with up to 20 % case-fatality ratio, and antimicrobial resistance is both significant and growing. The need to evaluate the potential public health value of vaccines against iNTS disease is increasingly being recognized, and several candidate vaccines are in early development. A better understanding of the global burden and epidemiology of iNTS disease, as well as the potential public health and socio-economic benefits that iNTS vaccines may offer is fundamental to support and justify the investments in vaccine development. In addition, the pathways for licensure, policy recommendations and eventual vaccine prioritization and use in low- and middle-income countries (LMICs) need to be defined.

Here, we report on the proceedings of an expert consultation held on 29 November – 1 December 2021 as part of an overall project to develop a Full Value of Vaccines Assessment (FVVA) for iNTS vaccines and in addition to more recent iNTS vaccine developments. Experts at the consultation reviewed the current evidence on iNTS disease and discussed knowledge gaps to be addressed to accelerate vaccine development, licensure and introduction, as well as LMIC perspectives on potential iNTS vaccine use and demand. The learnings from this consultation are critical inputs to inform remaining work under the iNTS FVVA project.

1. Background and objectives of the consultation

Salmonella enterica is a leading cause of community-acquired bloodstream infections in both Africa and Asia with non-typhoidal serovars, in particular *S. typhimurium* and *S. enteritidis*, contributing to a significant burden of invasive disease in young children and immune-compromised hosts in sub-Saharan Africa (SSA) [1–5]. While several candidate vaccines against invasive non-typhoidal *Salmonella* (iNTS) disease are in development [6], the potential public health and socio-economic value of these vaccines is not well defined. Starting in 2021, the International Vaccine Institute (IVI), the World Health Organization (WHO), Shift Health, and the London School of Hygiene and Tropical Medicine (LSHTM) initiated a collaboration to develop a Full Value of Vaccines Assessment (FVVA) to better articulate the value of investment

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in an iNTS vaccine from a multi-stakeholder perspective. The long-term goal of this project is to accelerate the development and licensure of safe and efficacious iNTS vaccines, and their future use through policy recommendations by the WHO Strategic Advisory Group of Experts on Immunization (SAGE), WHO prequalification, and Gavi financing.

An expert consultation was convened under the FVVA project on 29 November – 1 December 2021 with the objectives to (a) examine the current evidence on iNTS disease and knowledge gaps to be addressed to accelerate vaccine development, licensure and use; and (b) understand low- and middle-income country (LMIC) perspectives on potential iNTS vaccine use and demand. The consultation was planned to inform additional work packages of the FVVA project, including development of WHO Preferred Product Characteristics (PPC), a Research and Development (R&D) Technology Roadmap, a clinical development plan and regulatory pathway, and the overall rationale for development of an iNTS vaccine. Consultation participants were drawn from key stakeholder groups: public health agencies (including country level policymakers and programme managers), academia, vaccine developers and industry, regulatory authorities, funding bodies, and the WHO's Product Development for Vaccines Advisory Committee.

2. Global burden and epidemiology of iNTS disease

A recent systematic review and meta-analysis of the prevalence of community-acquired bloodstream infections among febrile inpatients found that non-typhoidal Salmonellae are the leading cause of community-onset bloodstream infections in SSA, accounting for almost one-third of isolates, followed by *Streptococcus pneumoniae*, and *Escherichia coli* [4]. By contrast in Asia, *S. typhi*, the aetiological agent of typhoid fever, is the leading cause of community-onset bloodstream infections [7]. In Europe and the Americas, *Salmonella* is not among the leading causes of community-onset bloodstream infections. Notably, there is a low incidence of iNTS disease in LMICs in regions outside SSA, such as Asia and Oceania [4,8].

The Institute for Health Metrics and Evaluation (IHME) estimated 590,000 illnesses, 6.1 million disability adjusted life years, and 79,000 deaths (excluding deaths with HIV as underlying cause) in 2019 [9]. Sources of variation between existing estimates include limited data sources and differences in extrapolation methods, however the IHME figures and previous estimates conducted for 2010, showed the highest iNTS disease incidence, DALYs, and deaths in Africa (with highest incidence in West, Central, and Southern Africa) [9–11]. Data underlying estimates of burden are limited and improvements are needed to address uncertainties and to understand the heterogeneity in epidemiology of iNTS disease in place and time. Specific data-gaps include the need for a better range of country-level and regional incidence surveillance data. Since iNTS disease is highly driven by host susceptibility, there is a need for a better epidemiological understanding of the relationship of disease incidence to risk factors for exposure and susceptibility, including better understanding of longitudinal patterns of disease incidence in relation to epidemiological risks. More granular data on disease incidence and associated mortality in early childhood is of particular importance, since this is critical to vaccination scheduling decisions. The exclusion of deaths due to iNTS disease among HIV-infected persons from global estimates disguises its importance as a cause of death in HIV-infected persons, an important consideration for vaccination strategies.

In high-incidence settings, iNTS disease has a bimodal peak among infants and young children, and in adults aged 25–50 years, likely driven by host risk factors such as malaria in infants and young children in areas of high malaria transmission intensity and HIV infection in younger adults [8]. This contrasts with a peak of iNTS disease in older adults in high-income settings. Neonatal and postnatal iNTS illnesses are reported from multiple settings but estimates of burden in these groups are based on limited number of studies that provide age-stratified incidence of iNTS disease and mortality by month of life [12–14]. A decline in cases at approximately 4 months is reported, coinciding with a decline of maternal *Salmonella*-specific antibody, followed by an increase in cases with a variable peak around 1 year of age followed by a decline to low incidence levels by 3 years of age [8,14,15].

Trends in iNTS disease incidence over time show a peak in DALYs per 100,000 in 2006 [8] with a well-described intra-continental epidemic spread of iNTS disease caused by a multidrug resistant (MDR) sequence type, ST313, followed by settling to more stable endemic pattern of transmission and incidence [16]. This was likely moderated by the development of a degree of natural immunity within populations, in addition to public health interventions in malaria, nutrition and the rollout of HIV care and treatment. A significant association between increased use of antiretroviral therapy (ART) and a decrease in incident iNTS disease has been reported in a number of settings, particularly among adults [17–19]. Because ART does not completely abolish the risk of iNTS disease, a burden of disease likely remains in persons living with HIV following roll out of ART in high prevalence HIV settings [17]. The initial decline in DALYs due to iNTS disease has levelled off in recent years, particularly among children, despite HIV and malaria interventions [8].

Global data on culture-confirmed iNTS disease from 1971 through 2019, shows *S. typhimurium* (45.7 %) and *S. enteritidis* (31.7 %) were the most prevalent serovars reported, accounting for more than three-quarters of serotyped isolates [20]. Serogroups O:4 and O:9 accounted for more than 80 % of isolates and serogroups O:4, O:9 and O:7 accounted for the top five isolates in five of the six UN regions.

Modelling estimates of iNTS disease burden were presented. The first model examined the probability of iNTS disease occurrence and its spatial distribution in SSA based on published data on iNTS disease occurrence and geospatial covariates of established host risk factors for iNTS disease such as malaria, HIV, and malnutrition. It also included access to safe water, an environmental factor, which may be inversely associated with iNTS disease. This model reported a high correlation between the composite iNTS risk factor index and the proportion of iNTS disease cases from blood culture surveillance studies. Further calibration of this model is anticipated to allow estimation of the probability of iNTS occurrence in sub-national areas and thereby to identify low- versus high-risk settings to inform site selection for surveillance and clinical trials as well as delivery of public health interventions such as vaccination [21].

A second unpublished model was also presented which explored immunization impact by campaign strategy, vaccine efficacy and coverage. In a scenario where vaccination with a bivalent iNTS vaccine (against *S. enteritidis* and *S. typhimurium*) was introduced through a catch-up campaign targeting children aged 13–60 months plus routine vaccination of 2 doses (at 6 weeks and 9 months) over a 10-year period, the model showed a significant impact on the burden of iNTS disease (cumulative deaths averted and percent case reduction) depending on the country size and vaccination coverage. The reduction projected in the number of cases and deaths was found to be inversely proportional to the vaccination coverage (data in open access manuscript deposit archive pending peer review [22]).

3. Risk factors, disease transmission and carriage of iNTS

While there are data gaps regarding the sources and transmission of NTS serovars, accumulating evidence shows genetic overlap between iNTS disease-causing strains and stool isolates from asymptomatic household members. Conversely, there is evidence for lack of genetic overlap between strains causing invasive disease in humans with animal strains, as well as limited evidence of environmental reservoirs of NTS suggesting humans as a possible reservoir of strains associated with invasive disease [23–28]. Poultry and red meat have been reported as sources of *S. enteritidis* ST11 sub-lineage and *S. typhimurium* ST19 (but not the African invasive pathovar, *S. typhimurium* ST313) [29] while pigs are also a possible reservoir for *S. typhimurium* closely associated with

diarrhoeal NTS (dNTS) but not of ST313 strains associated with iNTS disease [30].

Moderate-severe diarrhoeal NTS disease (dNTS) and iNTS disease appear to be distinct disease phenotypes in Africa and diarrhoea is generally not a prominent feature of iNTS disease. While the presence of *Salmonella* in the stool has been shown to be a pre-requisite for dNTS and likely iNTS disease, understanding of the range of NTS serovars/genotypes causing diarrheal disease compared to invasive disease remains limited [31–33]. Case-controlled aetiological studies show that the attributable fraction of moderate-severe diarrhoea that is caused by *Salmonella* spp. is very low (approximately 1–2 % in African sites) compared to other diarrhoeal pathogens such as rotavirus, *Shigella*, crytosporidium and norovirus [26–28].

The peak of iNTS disease varies by geography, and can be in the first or second year of life and declines thereafter [14]. It is likely that natural, asymptomatic exposure (enteric eNTS) gradually leads to natural immunity and reduced susceptibility to invasive infection, despite ongoing exposure to risk factors in the community [15]. Cross-sectional household data from Malawi shows a much wider range of varied NTS serovars found in the stool of asymptomatic healthy adults and children in Africa, than are known to cause either iNTS or dNTS disease [27]. It remains unclear what the frequency and duration of these eNTS events is, and which factors might affect the ways in which eNTS events result in effective acquired immunity, but participants noted that asymptomatic enteric carriage may be an exploratory clinical endpoint in vaccine trials. It may be feasible to study the immune response to asymptomatic enteric carriage in a controlled human infection model (CHIM) of NTS.

There is substantial evidence suggesting that key risk factors for iNTS disease include age, recent or current malaria, haemolysis or anaemia, malnutrition, HIV infection, sickle cell disease, and other immunocompromising disorders. Understanding the attribution of each risk factor to disease will be important in the assessment of vaccine efficacy and effectiveness in different settings.

Preliminary (unpublished) results from an ongoing systematic review and meta-analysis of attributable risk factors for iNTS were shared with participants, showing malaria as the single largest overall host risk factor for iNTS disease. This analysis also found HIV to be a substantial contributor to the burden of iNTS disease, particularly among adults. These data support other previously published evidence that 50–60 % of iNTS cases are linked to malaria as an underlying cause of susceptibility [34,35].

Several studies have reported a strong seasonal pattern of iNTS disease in the rainy season; seasonality may be directly related to NTS exposures as well as indirectly via the seasonality of other risk factors such as malaria [35–38]. Further data are needed to better understand the sources and modes of transmission, NTS reservoirs, the relationship between gut carriage of NTS serovars and protection against invasive disease, and the potential impact of malaria vaccine use on iNTS disease prevalence.

4. Diagnostics, treatment and AMR trends

In hospital-admitted children, iNTS disease presents as a severe febrile illness commonly accompanied by respiratory symptoms and signs [38,39]. Limited access to laboratories with blood culture facilities in SSA means a high risk of misdiagnosis and undertreatment of cases. Blood culture, the most practical reference method for diagnosing iNTS disease, has several associated challenges including low sensitivity (approximately 60 %), slow results (after 2–3 days), limited laboratory capacity in most endemic settings, as well as limited access and use among clinicians and low acceptability among patients. Alternate diagnostic approaches such as molecular testing, non-pathogen-specific point-of-care (POC) tests distinguishing bacterial from viral or malaria infections or *Salmonella*-specific POC tests, are limited for a variety of reasons related to test-accuracy, technical and human resource requirements [40,41].

There is a lack of supranational or evidence-based guidelines and no clinical studies available to inform the efficacy or safety of antimicrobial treatment of iNTS disease. Antimicrobial treatment recommendations for suspected iNTS disease are necessarily empiric due to the lack of diagnostics, and in most settings the antimicrobial choice for confirmed iNTS disease is extrapolated from treatment for enteric fever. Ceftriaxone, ciprofloxacin and azithromycin are therefore recommended as the first-choice antimicrobials. This makes biological sense, since iNTS disease is believed to have both intracellular and extracellular pathogenesis, enabling persistence and recrudescent disease, so antibiotics with intracellular penetration are appropriate [42–44]. However, pharmacodynamic and pharmacokinetic data for the antimicrobial treatment of iNTS disease in children are lacking, precluding reliable decisions about doses, formulation and duration of treatment. In addition, paediatric formulations of antibiotics are frequently not available or accessible in LMICs [45].

As with other bacterial infections, the need for empirical treatment of suspected iNTS disease is a major factor in the emergence and increase in AMR among NTS strains. Multidrug resistance (co-resistance to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol) is widespread among NTS clinical isolates in SSA, and third-generation cephalosporin resistance and fluoroquinolone non-susceptibility have now been reported in various countries including the Democratic Republic of Congo (DRC), Kenya and South Africa [46]. Azithromycin resistance has been observed in the DRC and in some settings proportionally higher rates of MDR, third-generation cephalosporin resistance and fluoroquinolone non-susceptibility in NTS strains have been observed compared to co-existing *S. typhi* strains [46–49].

5. iNTS vaccine development

An overview of the iNTS vaccine pipeline was presented followed by brief summaries on the most advanced candidates (Fig. 1, updated since the consultation from [6]). Bivalent iNTS vaccine candidates, targeting *S. typhimurium* and *S. enteritidis*, include a Generalized Modules for Membrane Antigens (GMMA) outer membrane vesicle O-antigen-based candidate vaccine from GSK Vaccines Institute for Global Health (GVGH) in clinical phase development [50,51] and a Multiple Antigen Presenting System (MAPS)-based vaccine in preclinical development by the Boston Children's Hospital [52]. Due to the uncertain market potential of standalone iNTS vaccine products, one approach has been to combine iNTS vaccine candidates with vaccines for other pathogens to maximize commercial viability. One such approach is trivalent combination iNTS vaccines, combining a bivalent iNTS candidate with a typhoid conjugate vaccine (TCV), are under development by University of Maryland (UMD) and Bharat Biotech International Limited (BBIL); the GSK GVGH; and by SK Bioscience in partnership with IVI [6]. The former two trivalent vaccines are in or have completed Phase 1 clinical trials [53,54].

The GVGH bivalent vaccine candidate (*S. typhimurium* GMMA and *S. enteritidis* GMMA) is targeting children under 2 years of age with a primary dose schedule from 6 weeks of age consisting of two intramuscular doses two months apart (plus a booster at 9 months and at school entry), or catch-up vaccination from 9 months of age. This candidate completed clinical follow-up in the Phase 1 trial in 2023 [55]. Plans were noted for the start of a Phase 2a age de-escalation study in Ghana which started in 2024 [56,57]. The GVGH trivalent (iNTS-TCV) candidate vaccine combines the bivalent iNTS-GMMA with a licensed and WHO-prequalified TCV (TyphiBEV® produced by Biological E Ltd). It was noted that preclinical data had been generated to support Phase 1 trials in Europe and Africa [54]. Development of the GVGH vaccine candidates were reported to include GMP manufacturing of vaccine lots and current Phase 1/2a clinical trial in adults in Europe and Malawi through the Vacc-iNTS consortium (https://cordis.europa.eu/project/id/815439) as well as production of vaccine lots, in-depth immunological studies and epidemiological studies on AMR through the PEDVAC-

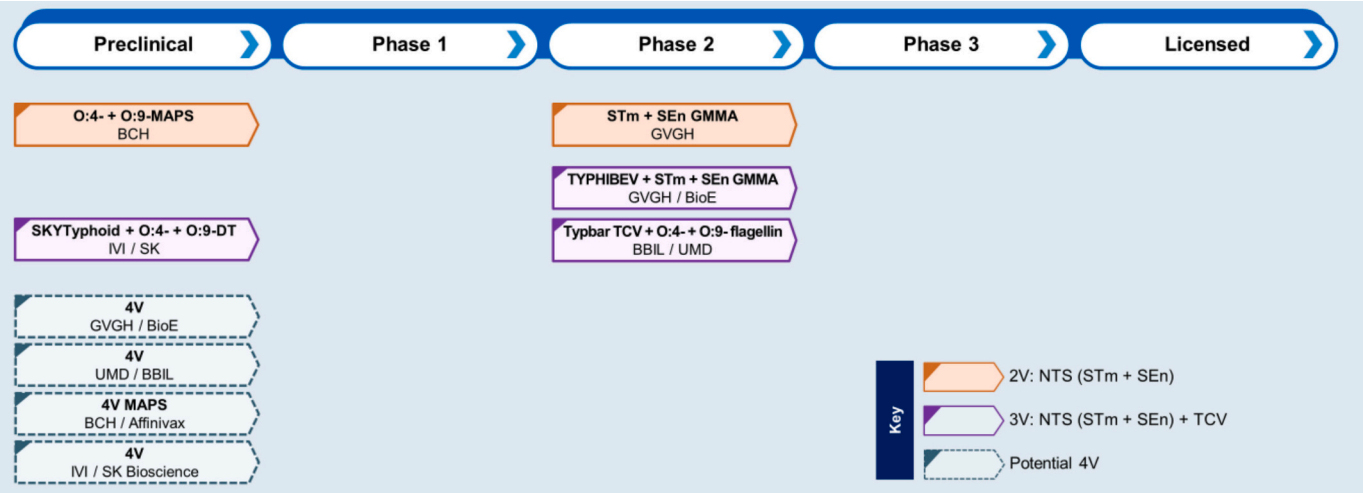

Fig. 1. iNTS Vaccine Pipeline. Reproduced and adapted from MacLennan et al. (2023) [6]. Updated May 2024, note TYPHIBEV+STm + SEn GMMA is in Phase 2a in Malawian adults. Arrowed boxes indicate ongoing development. Abbreviations: 2 V, bivalent; 3 V, trivalent; 4 V, quadrivalent; BBIL, Bharat Biotech International Ltd.; BCH, Boston Children's Hospital; BioE, Biological E; GMMA, generalized modules for membrane antigens; GVGH, GlaxoSmithKline Vaccines Institute for Global Health; IVI, International Vaccine Institute; NTS, non-typhoidal Salmonella; SEn, *Salmonella Enteritidis*; STm, *Salmonella Typhimurium*; TCV, typhoid conjugate vaccine; UMD, University of Maryland.

iNTS consortium (https://pedvac-ints.eu/). A Phase 2 age de-escalation dose-finding study is also planned.

The trivalent *Salmonella* conjugate vaccine by UMD/BBIL consists of 25 μg of each polysaccharide by weight (*S. typhimurium* conjugate – Group B Core O-Polysaccharide (COPS) linked to Typhimurium Phase 1 flagellin subunits [FliC]; *S. enteritidis* conjugate – Group D COPS linked to Enteritidis Phase 1 flagellin [FliC]; combined with a licensed, WHO-prequalified Vi-conjugate vaccine Typbar-TCV®). This candidate uses serovar-homologous FliC (phase 1 flagellin subunits) as the carrier protein which provides an additional target for antibodies and cell-mediated immunity [58]. Results from a Phase 1 randomized, placebo-controlled, dose-escalation study of the safety, reactogenicity, and immunogenicity in healthy US adults were presented demonstrating safety and favourable immune response to a single parenteral dose of quarter-strength (6.25 μg of polysaccharide per conjugate) or half-strength (12.5 μg of polysaccharide per conjugate) vaccine. Further clinical development plans were presented which included an additional Phase 1 trial with 25 μg dose in US adults which has now been completed and Phase 2 age de-escalation trials of a two-dose schedule including infants aged 12–18 weeks in SSA [59–61].

A third trivalent candidate vaccine, by SK BioScience and IVI, was noted to be in preclinical development with a toxicology study in progress [62]. The target population for this candidate is infants between 2 and 4 months of age, with an aim to integrate intramuscular administration of 1 or 2-dose schedule into the early Expanded Programme on Immunization (EPI) schedule (e.g., 6 to 14 weeks) or at 9 months concomitant with measles-containing vaccines.

Based on the pipeline information presented, all the current iNTS vaccine candidates were noted to be O-antigen-based, with the UMD/BBIL candidate using flagellin as carrier protein, and the GVGH candidate utilizing OMV technology additionally incorporating outer membrane proteins. It was noted that immune responses are likely to be elicited by antibody to O-antigen, which is a well-characterized effector of protection, and/or antibodies and T cells to pathogen-specific proteins. One important consideration is the requirement for protection in different target populations. For example, antibody may protect against fatal bacteraemia in immune naïve children, however more research is required to understand whether T-cell immunity is required for clearance of NTS, particularly from the intracellular niche in macrophages, and whether vaccine-acquired immunity would protect in the context of comorbidities. As a result of immune dysregulation in HIV, excessive levels of IgG to O-antigen in some HIV-infected persons have been shown to prevent killing of NTS in vitro [63]. In the context of malaria, phagocyte blockade may mean a different type of immune response must be elicited to protect individuals [64]. None of the existing candidates are currently being developed for maternal vaccination.

An important next step is to review whether current candidates are safe and immunogenic in Phase 1 studies, and whether the development of an NTS CHIM may inform pathogenesis, immunity, potential correlates of protection and provide proof of concept for protective efficacy [65]. The consultation was informed about plans for the development of a non-typhoidal *Salmonella* human challenge model, led by researchers at the Imperial College London [61]. The model proposes to use two cGMP Typhimurium challenge strains belonging to ST19 and ST313 sequence types. This CHIM may help to evaluate the pathogenesis of intestinal colonization and invasion and the immune responses to these events. The CHIM study could be a valuable means to understand correlates of protection and potential efficacy of iNTS vaccines, although disease presentation in the model may be mucosal or diarrhoeal rather than fully recapitulating invasive disease. The CHIM will also shed light on any clinical phenotypic differences in pathogenic potential between "African" ST313 and ST19 sequence types in relation to carriage, diarrhoea and invasion. As with established challenge models with strains of *S. typhi* and *S. paratyphi* A (and other pathogens), key ethical and clinical safety concerns such as prolonged shedding and/or chronic carriage in challenged volunteers, and how severe clinical manifestations should be managed have been duly considered in the study design.

6. Cost effectiveness analysis and health economics

Recent and planned iNTS disease cost-of-illness (COI) and cost-effectiveness analysis (CEA) studies were presented to inform the iNTS FVVA. A COI analysis completed in four African countries (Burkina Faso, Ghana, Madagascar and Ethiopia), under the Severe Typhoid Fever in Africa (SETA) study [66], included out-of-pocket patient costs for laboratory confirmed iNTS disease cases (through a patient survey with measurement of direct and indirect costs), however facility costs or third-party costs were not collected and the sample size was limited. A separate COI analysis as part of the Vacc-iNTS project (using methodology similar to the SETA study), is expected to provide data from Malawi, Burkina Faso and Ghana on both out-of-pocket expenses and facility costs. Also, under the Vacc-iNTS, a CEA study will examine

productivity losses, direct and indirect medical costs, and treatment costs in addition to assumptions on the vaccine impact, efficacy impact, vaccine costs and disease burden..

Finally, as part of the iNTS FVVA an investment case analysis on the trivalent iNTS-TCV vaccine, consisting of a CEA and policy-makers survey will be conducted. The CEA will focus on estimation of economic burden based on literature review and existing data while the policy-makers survey is planned to understand the drivers of need and demand of iNTS vaccines by country decision makers and global health partners.

7. Considerations for iNTS vaccine use case

Given the concerns that a standalone iNTS vaccine may not be sufficiently attractive to policy-makers the focus for use case has been on iNTS vaccines in combination. This was echoed at this consultation where LMIC stakeolders expressed a strong general preference for multivalent combination formulations. The principle focus of combination vaccine development thus far has been on combination with TCV though increasingly since this consultation potential combinations with other pathogens are being considered.

The potential age of administration for a trivalent typhoid/iNTS vaccine was discussed at length due to concerns about potential incompatibility of the target ages for protection against iNTS disease and typhoid. The age distribution of iNTS disease in children shows the highest incidence of disease to be in early life and decreases fairly rapidly to a low level by about 24–36 months, likely as a result of the acquisition of natural immunity through exposure. In comparison, the age-distribution of typhoid is notably broad: typhoid incidence is low in the first year of life, rising during the second year of life, especially in high-incidence settings, [67]. Peak incidence of typhoid typically occurs at the age of 5–9 years but may be at younger ages in highly endemic settings, or at higher ages in areas of low endemicity [67–69]. Typhoid incidence remains appreciable into adulthood in endemic settings, suggesting that the acquisition of natural immunity is considerably less effective than for iNTS disease. Typhoid and paratyphoid are also observed in international travelers [70,71].

Thus, an iNTS vaccine needs to illicit protective antibodies by 6 months of age ideally, and provide durable protection to 3 years of age (making a reasonably tight time window for duration of vaccine efficacy) while TCV will need to protect for much longer, from the second year of life into adulthood. The currently WHO prequalified TCVs (and licensed TCVs in general) are approved for use from six months of age and introduction of the malaria vaccines (RTS,S at the time of the consultation, and more recently R21), is planned for visits during the first year of life including at approximately 6 months of age which may make y 6 months of age a convenient and appropriate delivery timepoint for a trivalent vaccine to be co-administered with malaria vaccines. Combination of iNTS vaccine with malaria vaccines are less likely to be feasible An earlier dose(s) at 6–14 weeks with the aim of establishing protection at a younger age, may be an alternative, followed by a dose at 9–12 months of age, as is currently planned for some trivalent iNTS-TCV vaccine candidates in development. Theoretically different iNTS containing vaccines may given a successive ages however practically the development, manufacture and delivery of multiple products for the same pathogen is challenging.

A hypothetical, unpublished valuation exercise, conducted by the Bill and Melinda Gates Foundation's (BMGF) Integrated Portfolio Management programme, looked at different iNTS disease burden scenarios and vaccine characteristics to explore the potential public health impact and cost-effectiveness of an iNTS-containing vaccine, as a standalone vaccine or in combination with TCV. The optimal hypothetical scenario, using an introduction year of 2028, 80 % efficacy, and 5-year duration of protection to model expected impact and cost-effectiveness, showed that a combination iNTS-TCV vaccine would offer cost-saving benefits.

8. LMIC perspectives on the value of iNTS vaccines

LMIC perspectives on the public health needs and goals for iNTS vaccines largely reflected the issues raised in the expert consultation, with specific points as summarized in Table 1. Among these, the burden of disease at an early age; importance of AMR; co-infection of NTS with HIV and malaria were highlighted as important contributors to perceived value. LMIC stakeholders strongly expressed the need for raising awareness of iNTS disease and advocacy on the potential value of an iNTS vaccine (including the added benefit of inclusion of TCV in a trivalent product) to maximize acceptability, given a general perception among decision-makers as well as healthcare workers that NTS is primarily a foodborne pathogen for which WASH and other control measures may suffice. Introducing an iNTS vaccine into routine immunization in the early EPI schedule or at six months were both considered feasible, with a need to consider the potential challenges of adding to a busy early EPI schedule, balanced against the substantial observed neonatal/early burden of iNTS disease.

If the decision is to administer the iNTS-TCV vaccine in early EPI, TCV immunobridging studies in infants less than 6 months of age would be required. It was felt that if not combined or co-administered, early administration of an iNTS vaccine could possibly delay decisions for TCV introduction in countries that have not yet introduced TCV. Modelling of the impact of different delivery schedules on mortality would be helpful to assess trade-offs between an early versus later administration timepoint for either one or both of iNTS and TCV vaccines from an epidemiological as well as a coverage perspective.

LMIC preferences were also articulated for an iNTS vaccine to be given as a single dose (as for TCV currently). Notably, the age-window for high incidence of iNTS is relatively narrow. Data presented from the BBIL/UMD iNTS/TCV vaccine indicates that the vaccine is highly immunogenic, although two doses might be required, particularly if administered at an early age. If an iNTS vaccine is to be delivered as a combination or co-administered with TCV and/or malaria vaccines, evidence will be needed on duration of protection, non-interference, compatibility of schedules, route of administration and number of doses.

Key end-user perspectives on potential drivers and barriers to iNTS vaccine uptake were addressed in the context of integration in the EPI, country-specific cost-effectiveness and risk-benefit ratios, resources required for supply and distribution, and communication strategies for partially effective vaccines and effectiveness in the context of other potential public health interventions such as WASH initiatives. Key end-users include in-country decision-makers (e.g., Ministries of Health including EPI and National Immunization Technical Advisory Groups), immunization providers and caregivers. Specific drivers identified included the potential to integrate iNTS vaccines in the EPI schedule at approximately 6-months of age as several countries start to introduce the malaria vaccine, RTS,S; having robust data on disease burden, cost effectiveness and potential impact on AMR; and practical and appropriate strategies and language for timely advocacy and communication. Country-specific cost-effectiveness modelling may be required to convince decision-makers in each country. A partially effective vaccine could be a potential barrier as would programmatic challenges such as cold chain requirements, however these were not seen as insurmountable barriers (e.g., they could be addressed by leveraging experiences from other routine vaccines and existing cold chain logistic management).

Interest was expressed by end-users and developers for a quadrivalent *Salmonella* combination vaccine containing *Salmonella Typhi*, Paratyphi A, Typhimurium and Enteritidis components even if epidemiology in a given setting is low for an individual vaccine component (e.g., potential acceptability in Africa for a vaccine containing an *S. paratyphi* A component, despite Paratyphi A being uncommon in Africa). Increased cost of a quadrivalent formulation would, however, likely be a consideration. Potential combinations of iNTS vaccines with other pipeline vaccines such as *Shigella* or a next-

Table 1
Summary of LMIC perspectives on public health needs and goals for iNTS vaccines (based on the 2021 WHO expert consultation).

Topic	Key discussion points
Key considerations (by regional and country stakeholders) for iNTS disease as a public health priority	• iNTS disease is an important cause of death in neonates, infants and young children. However, a crowded EPI immunization schedule is a key issue, especially if multiple doses are required in the primary schedule and if boosters are needed. Countries are facing multiple planned and potential vaccine introductions in the first year of life for other pathogens, such as malaria vaccines. • AMR in NTS strains has required changes to empiric antimicrobial guidelines. • Co-infection of NTS in persons living with HIV represents a secondary immunization target group of interest. • Co-infection of NTS in persons with recent or current malaria, as well as residual iNTS disease in the context of progress with malaria elimination are also of interest in defining target populations for immunization. • Preliminary engagement with decision-makers in a high burden country (in SSA) found that they were not convinced that NTS is a major cause of moderate or severe diarrhoea, whereas it is perceived to be an important cause of invasive bacterial disease. It is important to understand what other knowledge or evidence will be required for policy-makers to make decisions regarding iNTS vaccine use. • Raising awareness and acceptability of iNTS vaccines among affected populations will be critical, especially for a disease not well characterized even for clinicians, and for which there is no specific name in many local languages. Communicating the value of iNTS vaccines will need to factor in that NTS is viewed as a foodborne pathogen for which alternative interventions (e.g., WASH) are available. Advocacy, stakeholder engagement and political support will be required to clearly articulate the need for iNTS vaccines and call for their **introduction**. • The case for iNTS vaccine use will need to be made beyond disease burden. While AMR was seen as insufficient by itself to win political interest, it was felt that it will likely be an important consideration for financing decisions. The travelers' market may present a favourable business case for iNTS vaccines, although of lower potential and priority.
Knowledge/evidence gaps for policy and decision-makers on future iNTS vaccine use	• Data exist on age-specific occurrence of iNTS disease showing a high disease burden in early childhood, however the data need to be age-stratified and made more accessible by country or region. • Selecting a 6-month vaccination timepoint versus a timepoint earlier in life will have implications for lives saved; evidence will be needed to inform key considerations such as potential compromises to be made over a crowded immunization schedule in early life as well as considerations for iNTS combination with typhoid (or paratyphoid) vaccine. • Better understanding is needed on whether and how the epidemiology of iNTS disease might change with progress in malaria elimination. Observational data from malaria elimination in combination with invasive bacterial disease surveillance might provide useful insights to policy makers. • Policymakers will be interested to have information on whether iNTS vaccines are immunogenic and effective early in life and in those with co-morbidities like malnutrition, malaria and HIV.
Potential value of iNTS vaccine combination with typhoid and/or paratyphoid A vaccines, including perceived benefits and potential issues of acceptability and/or cost	• There was support for multi-valent vaccines due to potential efficiencies. This included combination with a Paratyphi A vaccine seen as of potential value in case of a future rise in paratyphoid A fever in Africa. • Some participants were of the view that there might be better acceptability and demand for larger combinations. The precedence of Meningococcal ACWY vaccine was cited, where a single quadrivalent vaccine is currently provided for the meningitis endemic region regardless of the local epidemiological situation. However, it is also worth noting that the Meningitis A epidemic in SSA was first tackled with monovalent Meningococcal A vaccine catch-up campaigns. • Understanding the complex financing scenario and feasibility of combination vaccines can help shape the market.
Feasibility of introducing iNTS vaccine to routine vaccination (based on current knowledge)	• Introducing iNTS vaccines is feasible given the evidence on the burden of disease but implementation will require careful planning. Overall, it would be preferable to introduce the vaccine earlier than six months of age to maximize reduction in the burden of febrile illness, morbidity and mortality. However, adding a new vaccine visit at six months is feasible and the malaria vaccine schedule may be an important anchoring point. • Typhoid conjugate vaccine is currently recommended to be administered in routine immunization at nine months, which was considered to be late for a potential iNTS vaccine combined with TCV. Therefore, TCV administration (currently licensed for use from 6 months) may need to be scheduled at six months to better meet the demands of iNTS vaccine administration. • Despite the above, it was noted that there are potential pros and cons of introducing iNTS vaccine at each of the timepoints considered - in the early EPI schedule, at six months of age or in the 2nd year of life - and clinical trial data will be critical for decisions on the recommended age of immunization. • It will be important to educate the target population and engage them early in the decision-making process for iNTS vaccine use.
Anticipated broader health system benefits or added burden of iNTS disease	• NTS is perceived by some as simply a foodborne disease and a cause of diarrhoea. This can be confusing to some stakeholders; and a more appropriate explanatory narrative is needed to explain the similarity between typhoid fever and iNTS disease.

(*continued on next page*)

Table 1 (*continued*)

Topic	Key discussion points
Key considerations to best meet the public health needs of key target populations through a vaccination programme	• Advocacy to healthcare workers in LMICs to explain the added value of an iNTS vaccine in the immunization schedule, particularly in settings where healthcare workers have been overwhelmed by the incidence of typhoid fever, was highlighted. • Access to appropriate diagnostics is important in order to support vaccine uptake and maximize the public health benefits of an iNTS vaccine. • Meningitis as a complication of iNTS disease is a contributor to the burden of iNTS disease, albeit at a lower incidence than bacteraemia, and leads to an even higher case fatality than invasive bloodstream disease. Providing iNTS vaccine in the early EPI schedule to reduce deaths caused by meningitis will likely appeal to policymakers for whom reduction of mortality is an important concern. • Strategies will need to be clearly defined to make the vaccine available for use especially in countries with a high burden of iNTS disease.

generation rotavirus vaccine were briefly noted but not explored in detail in this consultation.

9. Conclusions

This stakeholder consultation convened under the iNTS FVVA project identified the current evidence and knowledge gaps on iNTS disease and vaccine pipeline as well as end-user perspectives on the potential vaccine use case and demand. This consultation informed the development of the PPC and research and development roadmap for iNTS vaccines, and the outcomes will also provide critical inputs to inform other components of the iNTS FVVA project such as the COI and CEA analyses.

Importantly, a clear case was made for the public health value of a vaccine against iNTS disease, recognizing the significant morbidity and mortality in SSA among infants and young children particularly in areas of high malaria transmission intensity, and in young adults living with HIV infection. Modelling efforts to date have projected a positive impact of iNTS vaccination in reducing the burden of disease. Nonetheless, future modelling and research will be needed to address remaining knowledge gaps. One of the key current limitations for iNTS vaccine development and policy-making is the knowledge gap due to the heterogeneous and incomplete epidemiological data from LMICs in SSA, particularly on the age-stratified incidence and mortality of iNTS disease during the first year of life as well as the factors driving geographic and temporal variation in disease. Other areas where shortfalls are recognized include diagnostics, AMR, potential vaccine impact in reducing transient shedding and transmission, and potential vaccine impact in the context of improved control of the main risk factors of malaria and HIV.

A robust iNTS vaccine development pipeline was reported, including bivalent iNTS and trivalent iNTS-TCV vaccine candidates. Combination vaccines may be more cost-effective to deliver, promote uptake and coverage for multiple pathogens and be preferred by stakeholders. The relative health, social, and economic value of the different vaccine formulations will be further assessed through the iNTS FVVA project led by IVI and WHO, and from clinical trial data as the pipeline advances. Policy-makers, donors and end-users will all need to be assured of a clear health and economic value for a preferred formulation with considerations for the age distribution of risk (iNTS disease versus typhoid), geographic incidence and mortality rates. As further data are required to define the optimal dose scheduling for vaccine administration in relation to potential pathogen combinations, at this stage in vaccine development pursuit of both bivalent and trivalent iNTS-TCV vaccines appear warranted, and this informed the PPC and R&D Roadmap. Vaccine advocacy and raising awareness of iNTS disease in high-burden areas will be important for demand creation and successful implementation. Remaining questions with respect to the vaccination strategy include timing and schedule of vaccination, duration of protection for each pathogen included in a multi-pathogen vaccine and whether further TCV doses might be required to protect against a risk of typhoid in older children.

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Data Statement.

This manuscript summarizes the proceedings of an expert consultation as part of an overall project to develop a Full Value of Vaccines Assessment (FVVA) for iNTS vaccines and in addition to more recent iNTS vaccine developments. There are no specific data to be shared.

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Kate Emary: Writing – review & editing, Writing – original draft. **Adwoa D. Bentsi-Enchill:** Writing – review & editing, Writing – original draft, Conceptualization. **Birgitte K. Giersing:** Writing – review & editing, Conceptualization. **Melita Gordon:** Writing – review & editing. **Helen Dale:** Writing – review & editing. **Esmelda B. Chirwa:** Writing – review & editing. **Peter Johnston:** Writing – review & editing. **Calman A. MacLennan:** Writing – review & editing, Conceptualization. **Samuel Kariuki:** Writing – review & editing. **Jean-Louis Excler:** Writing – review & editing. **Jerome H. Kim:** Writing – review & editing, Funding acquisition, Conceptualization. **Robert W. Kaminski:** Writing – review & editing. **Annelies Wilder-Smith:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The views, findings, and conclusions contained within are those of the authors and do not necessarily represent the position or policies of the World Health Organization, the Wellcome Trust or other institutions to which speakers and participants are affiliated.

Data availability

No data was used for the research described in the article.

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