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WHO Research and Development Technology Roadmap for Non-Typhoidal *Salmonella* vaccines against invasive disease

Covering priority activities for the research, development, testing, licensure, and use of vaccines
against invasive non-typhoidal *Salmonella* disease

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84 Acronyms

AMR	antimicrobial resistance
ELISA	enzyme linked immunosorbent assay
EPI	expanded programme on immunization
iNTS disease	invasive non-typhoidal <i>Salmonella</i> disease
GCP	good clinical practice
LMIC	low- and middle-income country
MDR	multi-drug resistance, multidrug resistant
NRA	national regulatory authorities
NTS	non-typhoidal <i>Salmonella</i>
PDVAC	Product Development for Vaccines Advisory Committee
R&D	research and development
SAGE	Strategic Advisory Group of Experts (on Immunization)
S. Ent	<i>Salmonella</i> Enteritidis
SETA	Severe Typhoid Fever in Africa study
S. Tm	<i>Salmonella</i> Typhimurium
sSA	sub-Saharan Africa
TCV	typhoid conjugate vaccine
TSAP	Typhoid Fever Surveillance in Africa Program
WASH	water, sanitation, and hygiene
WHO	World Health Organization
XDR	extensively drug-resistance, extensively drug-resistant
YLL	years of life lost

85

86

87 **Executive summary**

88 In 2019, over half a million cases of invasive non-typhoidal *Salmonella* (iNTS) disease and over 79,000
89 deaths were estimated to have occurred. Cases of iNTS disease disproportionately affect infants and
90 young children and the majority occur in sub-Saharan African countries. There are currently no
91 licensed NTS vaccines but the typhoid conjugate vaccine (TCV) which protects against invasive disease
92 caused by another serovar of *Salmonella enterica* has shown to be highly effective in children.

93 This roadmap sets out the WHO Vision and strategic goals for the research and development of NTS
94 vaccines against invasive disease for use in low- and middle-income countries. It is designed for use
95 by key stakeholders to outline activities that should be prioritized. The WHO vision is for the
96 development of safe, affordable, and effective vaccine(s) to protect children against invasive disease
97 caused by *Salmonella enterica* for use in high-burden countries. In order to meet this vision the near
98 term goal is to demonstrate safety, immunogenicity, and efficacy of a candidate NTS vaccine caused
99 by serovars Typhimurium and Enteritidis, ideally as a combination vaccine, including in combination
100 with TCV. There is some international consensus that a vaccine against iNTS disease as a stand-alone
101 vaccine may have limited market potential., and therefore vaccine development in combination with
102 other appropriate vaccines is encouraged.

103 The roadmap is divided into three levels: themes, actions and key capacities. Actions are organized
104 into 3 themes: addressing evidence gaps, accelerating vaccine development and maximizing public
105 health impact.

106 The first theme identified is **addressing evidence gaps** regarding fundamental aspects of iNTS disease.
107 Improved epidemiological data are required to understand the distribution and burden of iNTS
108 disease. This will facilitate the modelling estimates for areas where data are not available and to
109 forecast the impact of external factors on iNTS disease. It is critical to characterize the role of enteric
110 NTS colonization events in the development of immunity and to identify the modes and sources of
111 transmission to inform preventive efforts. Greater understanding of how host risk factors confer
112 susceptibility to iNTS disease will be key to ensuring NTS vaccines protect those most vulnerable to
113 iNTS disease. NTS isolates are associated with antimicrobial resistance (AMR), the extent and drivers
114 of which need more broadly describing. NTS vaccination may have potential to help combat AMR and
115 the potential impact of NTS vaccines on antimicrobial use should be modelled. Describing the direct
116 and indirect economic burdens of iNTS disease are needed to establish the full public health value of
117 NTS vaccination.

Clinical trials will be essential in **accelerating vaccine development**. Trial design and endpoints should be planned to deliver the information required for licensure and programmatic implementation including immune non-interference studies. Standardized immunoassays will facilitate comparison of data and the characterization of the immunological correlates of risk and protection. A NTS human challenge model may offer great potential to investigate the pathogenesis and immunobiology of NTS disease.

Finally, **maximizing public health** impact is the ultimate goal by focussing on the successful implementation of an efficacious vaccine to target populations. This will require a clearly defined regulatory pathway to licensure and a safe, affordable, secure supply of vaccine manufactured to cGMP standards. It will be critical to understand the funding landscape for both research and vaccine doses as well as the demand from national stakeholders and their inclination to implement. It will be important to understand at the national, regional, local, and individual level, the drivers and barriers to NTS vaccines and to identify vaccine advocates within endemic countries. Reflection following TCV introduction may be useful to identify key barriers and factors contributing to successful programmes.

The roadmap ends with a consideration of the key capacities that will be required in order to complete the actions identified. Sustainable funding and the engagement of stakeholders are central to success.

Background on Vaccine R&D Technology Roadmaps

Vaccine R&D technology roadmaps produced by the World Health Organization (WHO) aim to provide a strategic framework outlining priority activities for global stakeholders - vaccine researchers, funders, industry, regulatory authorities, policy makers and the wider community - to accelerate availability of effective vaccines from development through licensure and policy recommendations and ultimately to reach the people with the greatest burden of disease, in particular in low- and middle-income countries.

This R&D roadmap describes the areas of work and specific activities that WHO considers as priorities to support the development of vaccines targeting invasive disease caused by non-typhoidal *Salmonella enterica* (NTS), which may be addressed by standalone or combined vaccine products against antigens from multiple invasive *Salmonella enterica* serovars. This document has been compiled with inputs from academic groups, industry, funding bodies, public health agencies and national stakeholders from endemic areas. The document is not product- or product-type specific. WHO encourages implementation of the roadmap, which will be updated as necessary if the vision, goal, or priority activities evolve as new information becomes available.

Introduction

The species *Salmonella enterica* is a common cause of invasive disease in low- and middle-income countries (LMICs). Over 2600 serovars have been identified and include typhoidal serovars such as Typhi and Paratyphi A which cause enteric fever. Non-typhoidal *Salmonella enterica* (NTS) is recognized as a frequent cause of self-limiting enterocolitis worldwide but NTS can also cause invasive disease (iNTS) such as bloodstream infections and focal infections such as meningitis. There are limited global incidence data on iNTS disease but invasive disease is less common in high-income settings. It is most commonly seen in LMICs, with the majority of cases occurring in sub-Saharan Africa (sSA) (1–3). This is likely due to the presence of host risk factors such as current or recent malaria, severe acute malnutrition, HIV disease and moderate to severe anaemia (4). Globally over half a million cases of iNTS disease are estimated to have occurred in 2019, with approximately 80% occurring in sSA (5,6). This severe disease phenotype particularly affects infants and young children, occurring from birth through the first year of life with peak incidence occurring at early in the second year of life before declining and becoming much less common beyond 3 years of age (7–9). Invasive NTS disease has a high case fatality ratio and is estimated to have resulted in over 79,000 deaths across all ages, with almost 50,000 of these deaths occurring in children under 5 in sSA (5,6). The majority of iNTS disease is caused by two serovars, *Salmonella* Typhimurium and *Salmonella* Enteritidis and these serovars are therefore the focus for vaccine development (10,11).

The typical presentation of iNTS disease is a severe, non-specific febrile illness which is clinically indistinguishable from other common childhood infections including malaria. Diagnosis is further hindered by the lack of a point-of-care test, inadequate access to diagnostic laboratories, low sensitivity of blood cultures, and delay in getting results from blood cultures. There is increasing prevalence of antimicrobial resistance (AMR) in NTS. Multi-drug resistance (MDR) is common in many isolates (2), increasing prevalence of fluoroquinolone resistance noted by surveillance systems and extensively drug-resistant isolates (XDR) have been observed (12–15). For clinicians, this means that there may be very limited effective treatment options available, particularly in LMICs. Increasing AMR is a global threat and is likely to result in significant morbidity, mortality, pressure on healthcare systems and economic loss (16). Vaccination against iNTS disease offers the potential to combat AMR by preventing infection and transmission of strains (regardless of antimicrobial susceptibility) and thereby reducing antibiotic use (17). Vaccination may also avert economic burden associated with AMR. There are limited data on the direct and indirect economic burden of iNTS disease. Studies of cost-of-illness and the long-term economic effects are underway, which will inform stakeholders, including funders, of the potential cost-effectiveness of vaccination (18).

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185 Access to adequate water, sanitation, and hygiene (WASH) facilities as well as improvements in food
186 safety are crucial to prevent invasive *Salmonella* disease as evidenced by the elimination of typhoid
187 from present-day high-income settings in the 20th century. Interventions at individual, household,
188 community and population levels may all help to prevent disease. The infrastructure to fully deliver
189 large-scale WASH strategies to LMICs is expensive and requires unwavering and long-term political
190 will to bring projects to fruition whilst household and community level interventions may be more
191 feasible to implement more quickly. For typhoid fever, there is clear evidence of the benefit of access
192 to clean water and sanitation (19), however whilst it seems likely that this would also apply to iNTS
193 disease, research is required to better understand NTS transmission and the potential impact of
194 specific WASH improvements on iNTS disease incidence in high-burden countries. Vaccination against
195 iNTS disease offers a complementary strategy to prevent morbidity and mortality in infants and young
196 children that may be achieved in the medium-term.

197 In 2018, the WHO recommended the programmatic use of typhoid conjugate vaccine (TCV) in endemic
198 countries, as part of routine childhood immunization in children aged less than 2 years for the control
199 of typhoid fever, an invasive bloodstream infection caused by *Salmonella enterica* serovar Typhi (S.
200 Typhi) (20). TCVs are in the process of being introduced into a number of high-burden countries and
201 have demonstrated high levels of effectiveness, highlighting the potential for other vaccines targeting
202 invasive *Salmonella* disease (21,22). This progress has galvanized the field of *Salmonella* vaccination
203 with focus on the development of vaccines against *Salmonella* Typhimurium and *Salmonella*
204 Enteritidis, and exploration of the feasibility of combination vaccines including non-typhoidal and
205 typhoidal (i.e., S. Typhi and S. Paratyphi A) antigens in a single product (11).

206 Currently there are no licensed vaccines to prevent iNTS disease. Current vaccine development
207 strategies include O-antigen-based glycoconjugates and novel, innovative approaches that allow
208 presentation of multiple antigens to the immune system. Combination products may permit a single
209 vaccination to protect against multiple serovars and therefore decrease the delivery costs within the
210 Expanded Programme on Immunization (EPI) schedule.

211 **WHO Vision and Strategic Goals**

212 **Vision**

213 The WHO vision is for the development of safe, affordable, and effective vaccine(s) to protect children
214 against invasive disease caused by *Salmonella enterica* for use in high-burden countries.

Licensed safe and effective vaccines currently only exist for a single *Salmonella* serovar (*S. Typhi*), but these suggest that the development of effective vaccines for other serovars may be feasible. There are multiple potential options for vaccine formulations targeting one or more of the four leading serovars causing invasive disease (including bivalent *S. Typhi*/*S. Paratyphi A*, bivalent *S. Typhimurium*/*S. Enteritidis* and trivalent *S. Typhi*/*S. Typhimurium*/*S. Enteritidis* candidates that are already in clinical development). Quadrivalent vaccines targetting invasive disease caused by four *Salmonella* serovars (*S. Typhi*/*S. Paratyphi A*/*S. Typhimurium*/*S. Enteritidis*) are in preclinical development. Vaccination against iNTS disease is a central component of this vision and at this stage, development of bivalent and combination NTS vaccines may have a positive value proposition. An incremental and parallel approach to NTS containing vaccines is anticipated considering the current understanding of epidemiology, the status of candidates in development, and the complex regulatory process for a multivalent product. Further data are required to define the most appropriate strategies for any NTS-containing combination vaccines which may differ by geography and by country context. This R&D technology roadmap addresses vaccines that protect against invasive disease caused by non-typhoidal serovars, *S. Typhimurium* and *S. Enteritidis* which may include combination vaccines.

Strategic Goals

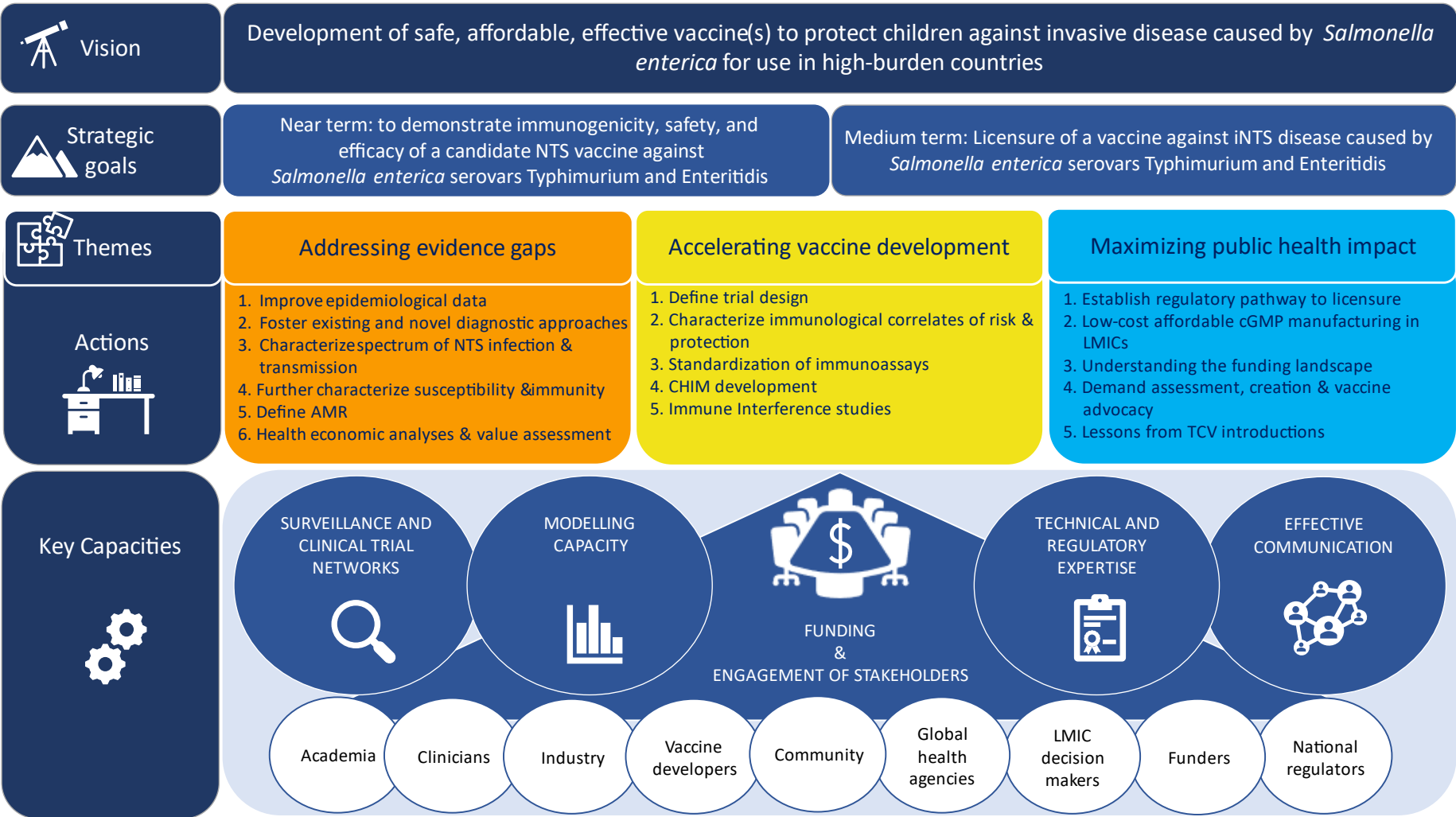
Near term: to demonstrate safety, immunogenicity, and efficacy of a candidate NTS vaccine or vaccines against *Salmonella* serovars Typhimurium and Enteritidis which may or may not be in combination with other serovars causing invasive disease.

Medium term: the licensure of a vaccine against iNTS disease caused by serovars Typhimurium and Enteritidis (which may be as part of a combination vaccine with vaccines targetting other *Salmonella* serovars or other pathogens).

Long-term: programmatic inclusion of vaccine(s) for the prevention of invasive disease in infants and young children caused by non-typhoidal *Salmonella enterica* serovars (which may be as part of a combination vaccine with vaccines targetting other *Salmonella* serovars or other pathogens).

An overview of the R&D Roadmap is presented in **Figure 1**.

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244 Figure 1: Overview of R&D Roadmap for NTS vaccines

Priority Activities

The following themes are identified as the major areas into which activities contributing towards the strategic goals can be divided. It is acknowledged that the themes are intrinsically interconnected and many actions are interdependent with others. Activities should be conducted concurrently wherever possible. Key capacities are necessary to address these actions across all themes.

1. Theme 1: Addressing evidence gaps

There is limited information on some of the central features of iNTS disease. It is critical to develop a better understanding of the epidemiology, including the geographical and temporal heterogeneity of disease burden. It is also important to evaluate the impact that external factors such as the rollout of malaria vaccination and climate change may have on the epidemiology of iNTS disease. It is unlikely that this will be possible for all endemic countries therefore a network approach accompanied by modelling may be useful to provide data for national decision-makers in those countries where local data do not exist. Fundamental understanding of the pathogenesis and immunity to iNTS disease will support vaccine development. AMR is a global problem and observed in invasive *Salmonella* disease, for which few novel antimicrobials are in a development pipeline. In addition to the substantial burden of disease, the threat of AMR, the potential impact of vaccination against iNTS disease on AMR and impact of the introduction of malaria vaccines on iNTS disease incidence should be modelled.

1.1. Improve epidemiological data to support global estimates of burden and model the impact of external factors on burden.

Further research is recommended to support accurate estimates of the burden and define the epidemiology of iNTS disease. Priorities include understanding incidence and case fatality ratios in children in the first year of life, associations with co-morbidities, defining the geographical distribution of iNTS disease both at a national and sub-national level, and relative contribution of different serovars to confirm appropriate vaccine antigens.

Current incidence data on iNTS disease is derived from relatively few locations in sSA and from multi-centre surveillance studies which may have been established with broader aims than to assess iNTS disease hence there may be intrinsic sampling bias in the available epidemiological data. Regional and international multi-site surveillance networks using standardized surveillance protocols and case definitions are recommended. Surveillance methods should include molecular epidemiology and standardized antimicrobial susceptibility testing. Selection of sites for such surveillance should reflect both known epidemiology of iNTS disease and, where this is not available, understanding of the host

and environmental risk factors to give a range of locations with differing risk-profiles to give a more complete picture of iNTS disease burden across sSA. Surveillance data from regions other than sSA will provide greater insight as to the global burden of iNTS disease. Serosurveillance methods to investigate the seroprevalence and seroincidence of NTS transmission within communities will complement understanding on acquisition of naturally-derived immunity, the relationship between exposure and disease incidence and help to define correlates of protection (see sections 1.2, 1.4, 2.2) (23). Ongoing microbiological and clinical surveillance will also be important post-vaccine introduction to assess for serovar replacement and impact on antimicrobial use. Currently there are few data to understand the impact of acute severe illness in early childhood on longer-term health, developmental and educational parameters in LMICs. Longitudinal follow-up of iNTS disease patients will demonstrate if serious illness is associated with morbidity beyond the acute illness.

Actions to address modifiable host risk factors for iNTS disease such as malaria, malnutrition and anaemia, could affect iNTS disease epidemiology and interact with the assessment of the impact of NTS vaccination (24–26). Malaria is recognized as a major host risk factor for iNTS disease in young children and introduction of effective malaria vaccines soon may modify the incidence of iNTS disease in some settings. Environmental factors such as climate change have the potential to influence iNTS disease epidemiology, by influencing host susceptibility and environmental transmission patterns. For example, changing patterns of rainfall may impact malaria epidemiology and food security, and affect iNTS transmission. The development of models to estimate the impact of changes in these host and environmental factors on iNTS disease burden, and will inform the value assessment for vaccination against iNTS disease.

1.2. Foster existing and novel diagnostic approaches

Diagnostics for invasive *Salmonella* disease remain imperfect and access to existing diagnostics is limited in many areas. The current practical reference standard diagnostic test is the blood culture which has limited sensitivity due to the low bacterial burden in bloodstream infections and antibiotic treatment prior to presentation. Blood cultures require considerable infrastructure and trained personnel to deliver which means that such facilities are often not present in high-burden areas. Support for implementation of existing diagnostics in LMICs and the development of novel diagnostics including point-of-care testing are essential to provide individual patient care and surveillance information including antimicrobial susceptibilities. Promoting communication between diagnostic laboratory facilities and clinicians is also important.

The seroepidemiology of iNTS disease is not well understood and is complicated by the large number of NTS serovars representing a large number of antigens. Further understanding of the natural

exposure to NTS over a life course in relation to exposure and both dNTS and iNTS disease is required to establish if seroepidemiology can be used as a tool for estimates of population exposure or protection.

Novel approaches should be encouraged to develop diagnostic tests, with specific use cases integral to their design (27).

1.3. Characterize the spectrum of NTS infection and transmission.

A comprehensive understanding of the following is needed:

- the pathogenesis of colonization, diarrhoeal and invasive disease and the relationship of pathogen and host factors to pathogenesis;
- the relationship between NTS enteric infection and the acquisition and maintenance of immunity (including the role of exposure to NTS not commonly associated with iNTS disease); and
- the modes and sources of transmission of NTS with reference to serovar and serogroup and the contribution of WASH and unsafe food on disease burden.

Asymptomatic shedding of NTS is described in endemic areas, however prevalence of faecal NTS carriage is observed to be lower in areas with a high iNTS disease incidence suggesting that natural enteric NTS exposure may induce immunity (28). It is unknown if NTS serovars that have a lower pathogenic potential and are from the O:4 and O:9 serogroups can induce immunity and confer cross-protection to those serovars which are associated with iNTS disease. NTS isolates from cases of iNTS disease are often highly related to NTS isolates collected from asymptomatic household contacts but unrelated to NTS isolates from household animals, suggesting humans may be an important reservoir for iNTS-associated serovars though there may be other non-human reservoirs which need defining (29–31). Modes of transmission need to be established; NTS serovars associated with invasive disease may be transmitted similarly to typhoidal serovars, via water or food sources.

Longitudinal studies of NTS stool carriage, sero-epidemiology and disease are required to improve understanding of stool shedding of NTS in different demographic, disease, and treatment groups as well as in asymptomatic individuals within the community setting. Such studies are crucial to understand how NTS immunity develops and is maintained over a life course. These studies will also help define the role of different groups as potential reservoirs of iNTS-associated serovars and how transmission of these serovars occurs. It is unknown what the impact of NTS vaccination may have on the spectrum of NTS infection. Current vaccine candidates are focused on protection against iNTS disease but elucidating the impact of vaccination on diarrhoeal disease and colonization will be

important to understand the potential for indirect vaccine effects. This information will help to inform both trial design to measure the interaction with and impact of vaccination on these parameters, and other preventive methods. Providing an evidence based understanding of transmission and relationship with access to WASH facilities and the food chain are required to holistically understand prevention. Identified preventative interventions could be instituted to complement vaccination and protect at-risk groups for whom programmatic vaccination is not feasible.

1.4. Further characterize susceptibility and immunity

Incidence of iNTS disease is relatively lower in the first 6 months of life, increases from approximately 4-6 months of age and declines from approximately 3 years of age. This suggests that there may be some maternally-mediated protection in the early months of life which wanes (32) and infants and young children may have gastrointestinal exposures that contribute to the development of immunity with increasing age. *Salmonella* specific T-cells are acquired during the first year of life but are not sufficient to provide protection from disease (33). Functional IgG is detectable with increasing age, which suggests that immunity likely results from natural exposure. However, high levels of antibody may inhibit complement-mediated killing of *Salmonella* in patients co-infected with HIV emphasizing that the quantity and quality of antibody function may be critical (9,32,34). Understanding the relative contribution of humoral and cellular immunity will inform vaccine platform selection, assessment of vaccine immunogenicity and identification of correlates of protection.

Host risk factors for iNTS disease such as HIV infection, current and recent malaria, severe acute malnutrition, and moderate to severe anaemia have been identified. The possible mechanisms conferring susceptibility to iNTS disease include impairment of the gut mucosal barrier, complement deficiency, and impaired humoral and cellular immunity (34–37). Understanding the impact of these co-morbidities on the immune response will be important to anticipate immune response to vaccination and help plan how patients with these host risk factors may be included in clinical trials. It will also be necessary to understand the relationship between immune parameters and the kinetics of enteric NTS events and stool shedding.

1.5. Understand the extent of AMR and potential impact of iNTS vaccination on AMR

AMR in NTS is prevalent, meaning that there are limited treatment options available for the most resistant strains in LMICs in addition to considerable challenges in dosing and administration of existing antibiotics in children (38). Multi-drug resistant (MDR) NTS isolates are common and extensively drug-resistant (XDR) strains have been reported from the Democratic Republic of Congo, having emerged independently in multiple hotspots (12,14,39). Concerningly, a small number of pan-

drug-resistant (PDR) isolates have also been reported from the Democratic Republic of Congo (13). A recent large study of *S. Typhimurium* genomes from sSA showed that drug-resistant phenotypes were caused by a combination of different and independent genetic mechanisms suggesting NTS may be a reservoir for AMR genes (14). AMR studies often rely on data from centres with specialist interest and expertise. Systematic antimicrobial susceptibility surveillance and local antibiograms will contribute to a wider understanding of the prevalence, transmission, and genetic mechanisms of AMR. Accurate national and sub-national data on prevalence of AMR may lead to more bespoke empiric treatment guidelines and aid antimicrobial stewardship. It is necessary to better understand the most appropriate empiric and targeted treatment strategies in susceptible populations for antimicrobials currently in use, to inform those in development and encourage innovation with respect to novel antimicrobials. Estimates on the impact of NTS vaccination on antimicrobial use, and AMR-related morbidity and mortality plus the potential to mitigate AMR-associated healthcare pressure and economic loss through vaccination are critical to inform the wider value assessment of NTS vaccines.

1.6. Conduct health economic analyses to inform investment case and value assessment

A thorough understanding of the cost-of-illness of iNTS disease, the overall economic burden of iNTS disease, broader societal socioeconomic benefits and potential cost-effectiveness of NTS vaccines (including combination vaccines targeting other *Salmonella* serovars) is vital for the investment case and value assessment for NTS vaccines. Cost-of-illness and economic burden will vary between settings based on parameters such as the healthcare funding model, costs of wage loss or substitute labour required. Defining these will allow countries to understand the threshold at which NTS vaccines become cost-effective to introduce.

Establishing the most cost-effective target age for delivery of NTS vaccines in the context of other vaccine introductions is relevant information for selecting the optimal age of vaccination. Other factors, such as the introduction of malaria vaccines may affect the public health impact and cost-effectiveness of NTS vaccines. *Salmonella* combination vaccines including two or more serovars could be envisaged within a global or a regionalized strategy and evaluation of willingness to pay and cost-effectiveness for different strategies could be modelled. Evaluation of different vaccine campaign scenarios especially for the high-burden areas of sub-Saharan Africa will inform decision-making about roll-out strategy. The contribution of vaccines containing NTS antigens to combat the socio-economic burden of AMR should be considered.

The WHO SAGE (Strategic Advisory Group of Experts on Immunization) provides a leadership role for global immunization by making evidence-based recommendations for a diverse range of immunization stakeholders including National and Regional Immunization Technical Advisory Groups (NITAGs and

RITAGs, respectively). High-quality research and data are fundamental to the SAGE process and equally important for follow-on policy decisions at the regional or national levels. Funding decisions, whether national or through external donor support such as Gavi, will rely on articulation of the health impact and value of NTS vaccine introduction, for which sufficient data and modelling are required.

2. Theme 2: Accelerating Vaccine Development

Several bivalent (NTS antigens from *S. Typhimurium* and *S. Enteritidis*) and trivalent (typhoid conjugate vaccine combined with antigens from *S. Typhimurium* and *S. Enteritidis*) candidates are in early clinical stage development (11).

Vaccine candidates that are successful in early phase studies will take time to progress through age-de-escalation and efficacy trials. Clinical efficacy endpoints are highly desirable and likely to be feasible given high incidence of iNTS disease in some areas. However, substantial sample sizes may be required in target populations in endemic areas. Inclusion of children in clinical trials with co-morbidities, particularly those that confer susceptibility to iNTS disease such as malnutrition will be important to establish safety, immunogenicity and efficacy in these susceptible groups.

Human challenge models can offer unique insights, particularly where animal models are limited in their translation to human disease for a given pathogen. There is no established human challenge model for iNTS disease although progress towards a human challenge model involving NTS is currently underway. Hence at this stage, NTS vaccines require traditional stepwise progression through clinical trial stages. Vaccine combination strategies (such as combining TCV with antigens from NTS serovars) offer potential to add value to and increase uptake of each component but may also add potential complexity to the process of licensure. Robust immune interference studies will be required for confidence in this approach. Co-formulation of vaccines into a combination product may increase cost-effectiveness.

2.1. Define appropriate trial design including safety monitoring, immunological, and clinical endpoints

The high incidence of iNTS disease in target populations of infants and young children up to 36 months of age suggests that clinical efficacy trials are likely to be feasible and desirable from a licensure and policy-making standpoint. The approach to efficacy trial design should be defined, including case definition, standardised sampling and diagnostic procedures. Standards of care for trial participants and consent processes should accord with local guidelines and the trial should meet WHO ICTRP

Registry Criteria. Clinical trials should have appropriate ethical and regulatory oversight. Primary and secondary clinical endpoints should be agreed, as well as safety endpoints, including adverse events of special interest where applicable. Given the unknowns in iNTS disease and therefore the assumptions needed for the planning of clinical trials, the potential for using adaptive trial design may be explored. Consideration should be given as to whether enteric infection endpoints in participants and contacts can be assessed within trials. Community engagement should start early to inform approaches throughout the trial design, recruitment and conduct.

Host risk factors often confer susceptibility via impairment of innate immunity and/or cellular immunity which may suggest that even if NTS vaccines are demonstrably immunogenic in terms of eliciting antibodies, protection from iNTS disease may not assured. For this reason, trials must be designed to permit inclusion of participants with comorbidities during immunogenicity studies and also capture co-infections and other host risk factor parameters at trial clinical efficacy endpoints.

2.2. Characterize correlates of protection

Defining the humoral and cellular immunogenicity of vaccine candidates that use shared O-antigens presented by different platforms will contribute to the WHO vision of a multivalent vaccine for invasive disease caused by *Salmonella*. Identifying correlates of protection for different clinical endpoints such as bloodstream infection, bacterial intracellular clearance, and faecal shedding are important. Other analyses of vaccine-mediated immunity such as antibody profiling of isotypes and Fc-glycosylation, as well as assessment of antibody-mediated functionality using serum bactericidal assays (SBA) and systems serology may offer additional insights to the functional basis of immunity to iNTS disease (40).

Inclusion of participants with co-morbidities in clinical trials will need to be carefully planned to assess if immunogenicity, efficacy and identified correlates are maintained across different patient groups. Defining the longevity of vaccine-mediated immune responses across age ranges will be relevant to decision-making surrounding the need for and timing of booster doses. Correlates of protection may become increasingly important if the epidemiology of iNTS disease changes in the face of other factors (such as the introduction of malaria vaccination) which may make efficacy trials for multiple vaccine candidates more challenging to perform.

2.3. Develop standardization and validation of immunological assays for human samples

With several O-antigen based potential vaccine candidates in early phase development, standardized and validated immunoassays are important to be able to measure immunogenicity using reproducible and reliable methods. An international standard serum and enzyme linked immunosorbent assays (ELISAs) are already available for *S. Typhi* (41) but do not yet exist for NTS. Establishing a panel of O-

antigen international reference standards and reference serum for use in assays is an essential element in NTS vaccine development. Quantification of antigen-specific antibody titres following vaccination using ELISA will be required. Functional assays such as SBA are likely to be important as exploratory endpoints. As information accrues that helps inform surrogates or correlates of protection, there should be coordinated efforts to create the appropriate immunoassay(s) for use in later stage vaccine development with reference standards and reagents to allow comparisons between high and low income settings where responses may differ (42). A standardized approach adopted by trials provides comparable data to help with the identification of thresholds of protection, and may contribute to licensure (particularly for subsequent generation vaccine candidates) and facilitate immunobridging for groups in which efficacy trials are not feasible.

2.4. Develop a human challenge model to help define disease pathogenesis, correlates of protection and deselection of vaccine candidates

Human challenge models involve the deliberate exposure of healthy volunteers to pathogens under carefully controlled conditions. Human challenge models have been used as a tool in vaccine development to help understand the pathogenesis and immunobiology of a disease, identify correlates of protection, and evaluate vaccine efficacy, thereby providing data to allow further investment in specific vaccine candidates. There may be barriers to performing large-scale field trials of multiple NTS vaccine candidates in children in endemic areas, and a human challenge trial may offer preliminary evidence to support a large-scale and expensive efficacy trial and gather preliminary data on possible immune correlates of protection (43).

A human challenge model seeking to reproduce iNTS disease is likely to have ethical, safety and practical concerns, and may be technically difficult to achieve in immunocompetent adults. A non-invasive model of colonization and/or diarrhoeal disease to study pathogenesis and immunity may still be informative and provide insight into aspects that are more difficult to study in natural infection. Of particular interest is the immune response to gastrointestinal colonization, the duration of faecal shedding, the immune parameters that relate to shedding and the identification of diagnostic biomarkers. The target group for NTS human challenge trials will be adults rather than infants in LMICs, who are the target population for NTS vaccines. It should be noted that a human challenge model (and vaccines tested within such a model) may perform differently in different settings in terms of dose, attack rate, clinical endpoints and efficacy, particularly for enteric diseases (44). This may be due to host factors such as genetic susceptibility and pre-existing immunity from exposure or host/environmental factors such as diet and microbiome. Therefore, careful consideration of endpoints will be necessary to maximize the utility of a human challenge trial performed in adults to

inform vaccine development. Adoption of standardized methodologies for immunoassays by both vaccine trials and human challenge trials will permit comparison. Human challenge trials can provide key and supporting information for regulatory authorities. For other pathogens such as cholera and typhoid, data from human challenge trials have contributed towards the regulatory approval for vaccines (20,45).

The first study involving a NTS human challenge model is currently underway using two serotypes of *S. Typhimurium* (46). The clinical endpoints observed will help determine how best a human challenge model may contribute to NTS vaccine development, however there is high potential for these models to provide a large amount of valuable information which is otherwise difficult to achieve in field studies. Human challenge models may also identify the most relevant immune parameters for testing in clinical trials which can be important with limited clinical samples particularly from target populations of infants and young children.

2.5. Support immune interference studies with vaccines that may be combined or co-administered

Vaccines against iNTS disease will ultimately be co-administered with other vaccines, during the same immunization visit and potentially in co-formulation with other antigens (mostly pertinently TCV) as part of a combination vaccine. It is key that immune interference studies are performed in target populations to ensure co-administration and co-formulation of vaccine antigens do not impair the anticipated immune response to individual antigens or cause safety concerns. Consideration should be given to the varying vaccine schedules in different settings and to vaccines that are imminently being introduced for the same target population, such as the RTS,S and R21 vaccines against *P. falciparum* malaria, to ensure maximum flexibility for the introduction of a NTS vaccine (47).

3. Theme 3: Maximizing public health impact

Understanding the potential pathway to vaccine licensure ensures that the relevant data are available from preclinical and clinical trials for regulatory authorities, regional decision-makers, and funders. Vaccines targeting iNTS disease are likely to be delivered within routine immunization schedules to protect those most vulnerable to iNTS disease. Programmatic challenges include co-administration and timing of vaccination visits compared with disease-specific epidemiology to ensure target populations are protected at ages of peak risk, particularly for combination NTS vaccines. Identification of high-quality GMP manufacturing capabilities and planning for technology transfer will be essential for licensure and the WHO prequalification process. Experiences with COVID-19 vaccine programmes have highlighted the complexity of the social determinants of acceptability and uptake

which will need to be explored further for any new vaccine introduction. Specific lessons may be gleaned from the experience of TCV introduction.

3.1. Establish regulatory pathway to licensure in LMICs

Trial design, safety, immunogenicity, efficacy and clinical endpoints and standardized, validated assays should be aligned to ensure that trial data generated will meet the anticipated requirements for regulatory approval. A regulatory expert consultation to delineate these requirements involving key stakeholders will help align vaccine development activities. Data from clinical trials, particularly clinical efficacy data, will also be required to provide policy-makers with the evidence required for robust policy recommendations and communication at both global and country levels. Post-licensure effectiveness studies will be required. Evaluation of the interaction of NTS vaccines with other vaccination programmes such as those planned for malaria vaccines is anticipated.

3.2. Low-cost vaccine manufacturing under Good Manufacturing Practices

Access to high-quality, low-cost vaccine manufacturing under cGMP (and capacity building for manufacture within LMIC countries) for late-stage clinical development and commercial production should be supported. This will require technology transfer from developer to manufacturer(s) or between manufacturers. This must be supported by personnel equipped with the relevant professional expertise to ensure safe transfer of all relevant information including development, production, quality control and regulatory requirements. National regulatory authorities (NRAs) also play an important role in ensuring vaccine quality.

Consistent supply of affordable, safe vaccine will be critical for implementation and is likely to require multiple manufacturers in different locations with secure supply chains. In particular, manufacturing expertise, capacity, infrastructure and policy development should continue to be supported and developed in LMICs. Strengthening LMIC (in particular African) vaccine manufacturing capacity should include production of the antigen component to complement formulation, fill and finish capacity, promoting access to technology transfer and optimizing commercial approaches (48). Regional collaborations may also increase vaccine security and make investments more sustainable.

High-quality manufacturing is a pre-requisite for WHO pre-qualification which facilitates, in principle, Gavi financing and procurement by UN agencies.

3.3. Understanding the funding landscape

A clear articulation of the value proposition for NTS vaccines will be crucial to attract funding, for basic research, for vaccine development, to support manufacturing and ultimately to deploy vaccine doses.

As the cost of vaccine delivery has been noted to increase over recent years, understanding the cost-benefit ratio for vaccine programmes by geographical area will be important to inform vaccination strategies, programmatic planning and approaches to combination vaccines such as those for invasive *Salmonella* serovars. Some countries with endemic iNTS disease may be evolving economically, placing them in a different position for vaccine funding strategies which may require distinct solutions to promote access.

3.4. Demand assessment, creation, and vaccine advocacy

Evaluation for each country of the perceived public health need of NTS vaccines is required in the context of regional and if available, national data. Due to limited data available, the burden of iNTS disease is at risk of being under-appreciated and engagement with country-level decision-makers is important to raise awareness and gain an understanding of how iNTS disease, and typhoid in the case of trivalent vaccines, is viewed in the context of other public health priorities for individual countries. Awareness of factors that may alter the burden of iNTS disease such as increasing AMR and malaria vaccine introduction may contribute to decision-making about demand. Demand predictability is important to inform manufacturers and to provide confidence to investors. The acceptability of the trivalent NTS vaccine approach amongst stakeholders will need to be assessed in the context of variable geographic burden for iNTS disease and typhoid as well as the cost-effectiveness of this approach.

For successful implementation of NTS vaccines it is essential to understand the key drivers and barriers that country decision-makers face with respect to the feasibility of vaccine introduction. There may be common themes such as higher vaccine delivery costs, the congested EPI schedule, multiple new vaccine introductions and reduced healthcare capacity requiring prioritization. There may also be population- or country-specific barriers that need to be acknowledged and may require more tailored approaches.

Community engagement involving caregivers to educate about the risk of iNTS disease and understanding attitudes to immunization both in general and with respect to specific vaccinations is likely to be important. Seeking to understand how iNTS disease is perceived by caregivers, and the acceptability of vaccination to protect against diseases that do not have a name in local language(s) will be relevant to inform the planning and design of vaccine campaigns.

The rise of misleading and incorrect information about vaccines has led to vaccine hesitancy and, in combination with the COVID-19 pandemic, contributed to a reduction in routine vaccination coverage. Vaccine advocacy is essential to support vaccines in development including those for iNTS disease.

Raising awareness of NTS disease at every level, including the identification of ‘vaccine champions’ as advocates to promote vaccines and empowerment of national decision-makers (including Ministries of Health and Finance, RITAGs and NITAGs) and clinicians will be critical to successful vaccine implementation.

3.5. Lessons from TCV introduction

Lessons learnt from the implementation of TCV in early introducer countries may be useful for the introduction of NTS vaccines (and other *Salmonella* vaccines) in the future (49). Data demonstrating the potential impact, cost-effectiveness and feasibility of TCV roll-out have contributed to successful implementation. Countries that participated in surveillance studies of typhoid and clinical trials of TCV were key front runners in the introduction of TCV. Awareness of typhoid as a public health problem at the community level was identified as important. High coverage of TCV (as well as coverage or catch up of other routine childhood vaccines such as measles) has been challenged by the COVID-19 pandemic which disrupted healthcare systems and was associated with prevalent misinformation and vaccine hesitancy. The introduction landscape may be different when NTS vaccines are ready for roll-out. Vaccine confidence and routine attendance at vaccine appointments may need to be restored. Effective communication and engagement at each level, from government, healthcare workers (including the private sector) and the community have been identified as essential for success (49).

Key capacities

a. Engagement with key stakeholders to optimize implementation and maximize uptake

Engagement with stakeholders is essential to understand the demand and barriers to vaccine development and implementation. Each group of stakeholders plays a key role in the steps towards vaccinating the target population and seeking to collaborate effectively throughout the process of vaccine development is essential, similarly to what was done for the Meningitis Vaccine Project (50). Approaches in this area could include organization of forums for stakeholders to explore shared areas of interest, promotion of NTS disease awareness, learning from other vaccine implementation initiatives and understanding the drivers and barriers at the national and individual levels for vaccination both in general and specifically for NTS vaccines.

b. Funding

Sustainable longer-term funding can facilitate efficient progress through the phases of vaccine development by preventing delays generated by lengthy rounds of competitive grant applications. Collaborative or partnership funding arrangements should be explored. Investment in manufacturing

infrastructure, technical expertise and commercial scale-up is an important factor in being able to produce high-quality vaccine products in sufficient volumes to support large-scale campaigns.

- c. Multi-site surveillance (pre and post licensure) and trial capacities in multiple sub-Saharan countries

There is a paucity of evidence available from endemic areas and the heterogeneity of iNTS disease incidence that needs to be better understood. Surveillance and good clinical practice (GCP) trial networks using aligned laboratory techniques and methodology are essential to improve the quality of data available for understanding the incidence of iNTS disease and evaluating vaccine candidates in clinical efficacy trials which will require large sample sizes.

- d. Modelling

Estimates of disease burden and vaccine impact, including health economic endpoints, rely on modelling capability to maximize the value of the data as it becomes available, and the quality of modelled estimates relies on the quality of inputs. Due to multiple factors (for example, non-specific disease presentation, imperfect diagnostics, lack of laboratory resources in endemic settings) there are inevitable uncertainties in iNTS disease evidence. By using mathematical modelling as a tool, these uncertainties can be effectively included in estimates of incidence and burden and contribute to assessment of impact. Models are critical to inform cost-effectiveness decisions both by national and regional decision makers and funding bodies.

- e. Technical and regulatory expertise

Establishing an anticipated regulatory pathway will facilitate licensure of NTS vaccines (whether as bivalent or trivalent formulations in combination with TCV). NTS vaccines are likely to be included in EPI schedules for endemic areas and therefore high volumes of vaccine will be required. Affordable and high-quality products will be essential for cost-effectiveness to be maximized and for product confidence to be established. Technology transfer to support regional manufacturing may be important in improving access, reducing costs, and promoting supply confidence, all of which support successful implementation.

- f. Effective communication

Communication between stakeholders is a vital foundation for vaccine development.

Involvement of communities is essential throughout the vaccine development process and is likely to build public trust and encourage both demand and uptake.

At a community level, demand creation and vaccine advocacy require understanding of existing knowledge, health beliefs, attitudes, and prevailing external influences on vaccine uptake. Expertise

660 in health promotion, effective messaging and the local use of traditional and digital/social media are
661 essential. Engaging community members and caregivers of potential recipients to appreciate concerns
662 will allow effective planning and trialling of communication materials ahead of implementation.
663 Equally, by listening to the access barriers for vaccination, local programmes can respond
664 appropriately to make access easy and thereby encourage uptake.

665 Vaccine hesitancy is a complex multifaceted issue with many determinants. Understanding vaccine
666 hesitancy within local populations and providing healthcare workers with strategies to address this
667 are likely to be important.

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DRAFT

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