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Review

The invasive non-typhoidal *Salmonella* vaccine landscape: Innovations and challenges ahead

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ABSTRACT

Invasive non-typhoidal *Salmonella* disease represents a major public health challenge, particularly in sub-Saharan Africa, where it is a leading cause of community-acquired bloodstream infections. Despite its significant morbidity and mortality, no licensed vaccines exist. Recognizing this unmet need, multiple global health initiatives and targeted investments have advanced iNTS vaccine development. These efforts have advanced several promising candidates employing diverse platform technologies, including the first iNTS vaccine candidate to enter clinical trials in more than 15 years in 2019. To date, three additional candidates have entered clinical development—two progressing through Phase 2 trials and one currently in a Phase 1/2 study—while many more remain in preclinical development. Several candidates also incorporate antigens targeting *Salmonella* Typhi or *Salmonella* Paratyphi A alongside iNTS components to broaden coverage and expand market potential. Despite this progress, scientific, regulatory and commercial challenges persist. In response, global health organizations have intensified efforts to support vaccine development, clarify regulatory pathways and foster engagement with key decision-makers, including through the development of Preferred Product Characteristics and a Full Value of Vaccines Assessment. These coordinated efforts mark a significant step toward enabling and accelerating iNTS vaccine development, ultimately aiming to prevent iNTS disease and its associated health burden.

1. Introduction

Invasive disease due to non-typhoidal *Salmonella* (NTS) has been historically underappreciated, largely due to its prevalence in low- and middle-income countries and the to limitations of surveillance efforts that likely underestimate its true burden [1,2]. The majority of cases are observed in sub-Saharan Africa (sSA), where NTS is among the leading causes of community-acquired bloodstream infections in young children [3]. NTS comprises a highly diverse group of Gram-negative *Salmonella enterica* serovars within the *Enterobacteriaceae* family, with more than 2600 serovars described, although only a small subset is associated with invasive disease [4,5]. The most common invasive *S.* Enterica strains identified in Africa belong to *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium) and *Salmonella enterica* serovar Enteritidis (*S.* Enteritidis), which account for more than 80% of iNTS cases [6]. These invasive serovars express antigens and structural components involved in virulence and immune evasion—including O-polysaccharide, flagellin and outer membrane proteins—that are central to disease pathogenesis

Abbreviations: BCH, Boston Children's Hospital; BMGF, Bill & Melinda Gates Foundation; CFR, Case Fatality Rate; CHIM, Controlled Human Infection Model; COPS, Core and O-Polysaccharide; CPS, Capsular Polysaccharide; CVD, Center for Vaccine Development and Global Health; DT, Diphtheria Toxoid; EPI, Expanded Programme on Immunization; GMMA, Generalized Modules for Membrane Antigens; GVGH, GSK Vaccine Institute for Global Health; HIV, Human Immunodeficiency Virus; IVI, International Vaccine Institute; iNTS, Invasive Non-Typhoidal *Salmonella*; MAPS, Multiple Antigen Presenting System; NTS, Non-typhoidal *Salmonella*; OMV, Outer Membrane Vesicle; SEn, *S.* Enteritidis; ST, *S.* Typhi; STm, *S.* Typhimurium; sSA, Sub-Saharan Africa; TCV, Typhoid Conjugate Vaccine; TSCV, Trivalent *Salmonella* Conjugate Vaccine; TT, Tetanus Toxoid; UMD, University of Maryland; WHO, World Health Organization.

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[1,7]. Invasive disease caused by NTS (iNTS disease) is deadly, with a case fatality rate (CFR) estimated at 22–47% in sSA, which is markedly higher than that of other major febrile illnesses such as malaria (CFR 0.2%) and typhoidal *Salmonella* (CFR 2.0%), both of which have approved vaccines currently in use [8–10]. Death from iNTS disease often results from delayed or ineffective treatment, as the disease typically follows a rapid progression. These delays are compounded by misdiagnosis due to non-specific clinical symptoms and reliance on blood culture—which is slow and often inaccessible—for diagnostic confirmation [1,9,11]. The high prevalence of multi-drug resistance, as well as the emergence of extensive drug resistance and resistance to third generation cephalosporins, exacerbates poor outcomes for iNTS disease patients in sSA. These factors limit effective treatment options and increase reliance on alternatives that are often inaccessible or unaffordable [10,12,13]. Together, these attributes demonstrate the significant unmet need for a safe and efficacious vaccine to prevent iNTS disease.

Salmonella vaccines have a long history, with the first effective vaccine being a whole cell, inactivated vaccine against *S.* Typhi developed over 100 years ago [14]. Although the CFR for iNTS disease is higher, the global incidence of typhoid fever is substantially greater than that of iNTS, resulting in a higher absolute number of typhoid-related deaths [15]. A global burden of disease study estimated that typhoid and paratyphoid fevers remain significant causes of morbidity and mortality among children under 15 years, particularly in South Asia and sSA [15,16]. Today, there are three classes of typhoid vaccines recommended by the World Health Organization (WHO): (i) the live attenuated vaccine Ty21a; (ii) Vi capsular polysaccharide (Vi CPS); and (iii) typhoid conjugate vaccines (TCV, e.g., Vi-TT Typbar TCV [Bharat Biotech]; Vi-CRM_{197} TYPHIBEV [Biological E]; Vi-DT SKYTyphoid [SK bioscience], Vi-TT ZyVac TCV [Zydus Life Sciences Ltd]) [17]. TCVs are preferentially recommended by WHO due to their improved efficacy with a single dose, longer-lasting protection of at least 4 years and suitability for children as young as 6 months [18,19]. TCVs have also been shown to be safely co-administered with other routine childhood vaccines including measles-rubella and meningococcal A vaccines, positioning them for inclusion in childhood immunization programs [18,19]. The uptake of the Ty21a and Vi CPS in typhoid-endemic countries has been low, but there has been much greater uptake of TCVs via national immunization programs [17]. While the licensure and large-scale implementation of TCVs represents a major step forward in protection against invasive *Salmonella* disease, there is currently no vaccine available for protection against NTS serovars.

Although an iNTS vaccine is not yet available for use, there is evidence from animal and human studies that support the biological feasibility of iNTS vaccine development. Both antibodies and complement proteins can kill *Salmonella in vitro*, suggesting that at least partial immunity to invasive disease caused by NTS is possible [20]. Children living in NTS-endemic countries develop serum antibodies that have *in vitro* bactericidal activity partly mediated by intracellular oxidation [20,21]. Further, epidemiological studies in sSA have demonstrated that acquisition of antibodies against NTS corresponds with lower invasive disease incidence in an age-dependent manner [20].

There are relatively robust animal models that can be used to evaluate preclinical iNTS vaccine candidates [21]. Mice, for example, are permissive to NTS systemic infection that manifests as invasive disease without gastroenteritis [21]. Proof-of-concept studies in animal models have demonstrated that several different vaccine candidates can induce potent humoral and cellular immune responses [22–24], both of which are critical for full protection against iNTS disease [25]. Murine models of infection have been used to demonstrate the efficacy of live attenuated vaccines [24], glycoconjugate vaccines [23,26] and outer membrane vesicle (OMV)-based vaccines [22,27] against both *S.* Typhimurium and *S.* Enteritidis serovars. Notably, live attenuated vaccine candidates against *S.* Typhimurium or *S.* Enteritidis have demonstrated both homologous (i.e., efficacy within vaccine targets' serogroup) and heterologous (i.e., efficacy outside of the vaccine targets' serogroup) immunity, suggesting that a bivalent formulation may confer broad protection against a diverse range of serovars [28]. In addition, maternal antibodies elicited by immunization with an O-polysaccharide glycoconjugate vaccine enable protection of infant mice against lethal *S.* Typhimurium infection [29]. Building on the success of typhoid conjugate vaccines, these lines of evidence support the biological feasibility of vaccine development against NTS.

A critical consideration in iNTS vaccine design is the selection of target serogroup antigens. Serogroups O:4 and O:9 together account for 90% of all NTS isolated from normally sterile sites, with the serovars *S.* Typhimurium (O:4) and *S.* Enteritidis (O:9) comprising 75% of serotyped isolates [4]. As such, vaccine strategies targeting these dominant serogroups or serovars have the potential to prevent the vast majority of iNTS disease. Therefore, the simplest approach to developing an iNTS vaccine involves a bivalent formulation combining antigens from *S.* Typhimurium and *S.* Enteritidis, though such a vaccine would likely be geographically restricted to Africa, where iNTS disease prevalence is highest [30]. Despite this, bivalent iNTS vaccines have seen limited progress, likely due to limited commercial viability [30,31]. A promising alternative is combining bivalent iNTS vaccines with licensed TCVs, offering a more straightforward regulatory pathway, broader applicability, reduced burden on the immunization schedule, and potential cost savings in manufacturing and distribution compared to standalone options [30,32]. Some developers are exploring this combination strategy, considering the inclusion of *S.* Paratyphi A to expand the vaccine's scope further [33]. Addressing factors such as age of administration, dosing schedule, cost and development timelines will be critical to maximizing the public health impact of these future vaccines [30].

2. Current iNTS vaccine pipeline

While substantial progress has been made in the development of vaccines against *S.* Typhi, efforts to develop vaccines targeting NTS have lagged behind. iNTS vaccine candidates remain in the early stages of development; however, recent partnerships and a growing number of trials reflect increasing momentum and investment in addressing this urgent public health need. The current iNTS vaccine pipeline features a diverse portfolio of promising products in preclinical and early stages of clinical development (Table 1). Five major candidates are advancing across a range of innovative vaccine platforms, including glycoconjugates [34], Generalized Modules for Membrane Antigens (GMMA) [22,35], and Multiple Antigen Presenting Systems (MAPS) (Table 2, Fig. 1) [33,36]. The diversity of approaches may help to increase the probability of successfully developing a safe and efficacious vaccine against iNTS.

2.1. Glycoconjugate vaccines

The Center for Vaccine Development and Global Health (CVD) of the University of Maryland (UMD), in collaboration with their industry partner Bharat Biotech, have developed a trivalent glycoconjugate vaccine candidate targeting *S.* Typhimurium, *S.* Enteritidis and *S.* Typhi (Fig. 1a). The iNTS component comprises a novel combination of Core and O-Polysaccharide (COPS) antigens from *S.* Typhimurium and *S.* Enteritidis, conjugated to the *Salmonella* flagellin protein FliC [37]. The O-Polysaccharide (OPS) component of COPS is consists of a variable chain of repeating sugar units attached to a conserved core backbone and serves as a principal target of protective immune responses [22]. However, in its unconjugated form, OPS is poorly immunogenic and unable to induce strong or durable immunity [34,37]. Conjugation to a carrier protein like FliC, converts OPS into a T cell-dependent antigen, capable of eliciting robust, long-lasting immune responses through CD4+ T-cell activation, memory B-cell generation, and antibody affinity maturation. FliC also acts as a secondary antigen, further enhancing *Salmonella*-specific antibody and T-cell responses [19,38]. The typhoid

Table 1
Overview of major iNTS disease vaccine candidates under development.

Candidate	Developer/ manufacturer	Valency, Serovar Coverage	Platform	Current phase of development	Routine of admin., no. of doses, schedule	Clinical trials
Bivalent iNTS-GMMA	GSK/GVGH	**Bivalent:** *S.* Enteritidis; *S.* Typhimurium	Two-component GMMA (SEnGMMA + STmGMMA)	Two-stage Phase 2 trial with age de-escalation in Ghana (est. completion 2026)	IM; 3 injections at 0, 2- and 6-month intervals	ISRCTN51750695 (Phase 1); NCT06213506 (Phase 2, recruiting)
Bivalent iNTS-MAPS	Boston Children's Hospital (GSK/Affinivax)	**Bivalent:** *S.* Enteritidis; *S.* Typhimurium	Bivalent SEn and STm O-polysaccharide with fusion carrier protein	Not available	IM	Not available
TSCV (CVD 1000, 2000, and 3000)	Center for Vaccine Development and Global Health (CVD), University of Maryland (UMD), Bharat Biotech International Ltd	**Trivalent:** *S.* Enteritidis; *S.* Typhimurium; *S.* Typhi	Trivalent conjugate: SEn and STm O-polysaccharide conjugated to FliC; Vi-TT	Phase 2 trial with age de-escalation in Mali (est. completion 2027)	IM; 1 or 2 injections 28 days apart	NCT03981952 (Phase 1); NCT05525546 (Phase 1); NCT05784701 (Phase 2, recruiting)
Trivalent iNTS-GMMA + TCV	GSK/GVGH (TCV provided by Biological E Ltd)	**Trivalent:** *S.* Enteritidis; *S.* Typhimurium; *S.* Typhi	Two-component GMMA (SEnGMMA + STmGMMA) and TCV (Vi-CRM_{197})	Two-stage Phase 1/2a trial in adults, with Stage 1 in Belgium and Stage 2 in Malawi (est. completion 2024)	IM; 3 injections at 0, 2- and 6-month intervals	NCT05480800 (Phase 1/2a)
Trivalent iNTS conjugate + TCV	International Vaccines Institute, SK Bioscience	**Trivalent:** *S.* Enteritidis; *S.* Typhimurium; *S.* Typhi	Trivalent conjugate: SEn and STm O-polysaccharide conjugated to DT; Vi-DT	Preclinical	IM	No reported clinical trials
Quadrivalent Salm-MAPS	Boston Children's Hospital (GSK/Affinivax)	**Quadrivalent:** *S.* Enteritidis; *S.* Typhimurium; *S.* Typhi; *S.* Paratyphi A	Quadrivalent MAPS: iNTS-MAPS + *S.* Typhi Vi and *S.* Paratyphi A O:2 with fusion carrier proteins	Not available	IM	Not available

component of this vaccine candidate is Typbar TCV, a WHO-prequalified TCV composed of *S.* Typhi Vi capsular polysaccharide conjugated to tetanus toxoid (TT) [17,39]. While Vi polysaccharide can stimulate immune responses on its own, conjugation to TT enhances immunogenicity by inducing T-cell-dependent antibody responses, resulting in higher-affinity antibodies and longer-lasting protection [39].

Non-typhoidal components of this vaccine have been shown to be protective against invasive disease in both infant and adult mice models [23,26]. Further, the trivalent combination with Typbar TCV has demonstrated induction of equivalent anti-polysaccharide IgG levels in rabbits and high levels of protection against invasive disease (88–100%) upon passive transfer of sera to naïve mice [26]. This trivalent *Salmonella* conjugate vaccine (TSCV) entered a first-in-human Phase 1 clinical trial in late 2019 to assess safety and immunogenicity in healthy adult subjects (NCT03981952), representing a major breakthrough in the development of iNTS-containing vaccines [40]. In this dose-escalation study, a single dose of TSCV (6.25 μg, 12 μg, or 25 μg in 0.5 mL buffer and preservative) was administered to healthy volunteers via intramuscular injection [40]. This study reported promising immunogenicity and met all safety endpoints [40]. All TSCV vaccinated participants achieved ≥4-fold increases in serum IgG antibody titers from baseline for each of the three polysaccharides (the two iNTS COPS antigens and Vi antigen for typhoid) [40]. The two iNTS flagellin components also elicited strong responses, with rates of 88% (7/8) and 100% (8/8) among recipients of the 6.25 μg and 12.5 μg TSCV doses, respectively, and no responses in placebo recipients [40]. However, the study was put on hold due to disruptions caused by COVID-19 public health measures, and a follow-up study was subsequently completed in June 2023 (NCT05525546). Building on the success of their Phase 1 study, UMD's CVD has initiated an age-descending (i.e. from adults to children to toddlers to infants), randomized, placebo-controlled Phase 2 trial to evaluate the safety and immunogenicity of TSCV at the Center for Vaccine Development in Mali (NCT05784701), with expected completion in 2027.

The International Vaccine Institute (IVI) has developed a trivalent glycoconjugate vaccine with antigens against *S.* Typhimurium, *S.* Enteritidis, and *S.* Typhi. The iNTS component of this candidate contains OPS from *S.* Typhimurium and *S.* Enteritidis OPS, conjugated to a diphtheria toxoid (DT) carrier protein [41]. In preclinical studies, this optimized bivalent iNTS vaccine formulation, when combined with an existing TCV, demonstrated robust immunogenicity against all included antigens without diminishing the immunogenicity of any individual component [19,42,43].

The typhoid component of IVI's trivalent vaccine candidate is a TCV that consists of a *S.* Typhi Vi capsular polysaccharide also conjugated to DT [19,42,43]. Vi-DT has been found to be safe and immunogenic in children 6–23 months old in Phase 2 clinical trials [19]. A non-inferiority study comparing the Vi-DT vaccine with the WHO-prequalified Vi-TT conjugate vaccine found that single-dose administration of the Vi-DT vaccine was safe, immunogenic, and non-inferior to the Vi-TT vaccine at 4 weeks post vaccination [43]. A study on immune persistence of the Vi-DT vaccine found that anti-Vi IgG seroconversion rate was 88% after 27.5 months and even higher after a booster dose, which demonstrated a safe and robust immune response [42]. Vi-DT (or SKYTyphoid) obtained an export license from the Korean Ministry of Food and Drug Safety in 2022 and was pre-qualified by the WHO in 2024 [44,45].

2.2. Generalized modules for membrane antigens (GMMA) vaccines

The GSK Vaccine Institute for Global Health (GVGH) has developed a bivalent GMMA vaccine targeting *S.* Typhimurium and *S.* Enteritidis and a trivalent formulation that also includes *S.* Typhi in the form of another TCV. The iNTS component of the vaccine consists of outer membrane

Table 2
Comparison of iNTS candidate vaccine platforms across key development and programmatic considerations.

	Live Attenuated	Glycoconjugate	MAPS: Multiple Antigen Presenting System	GMMA: Generalized Modules for Membrane Antigens
Immune Profile & Coverage	• Induces *Salmonella*-specific T-cell responses required for bacterial clearance and mucosal immunity [14] • Whole-cell presentation enables broad immune responses with potential cross-protection across serovars [14] • Achieving optimal attenuation without loss of immunogenicity remains challenging [14]	• Linkage of polysaccharides to carrier proteins enhances immunogenicity through T cell-dependent responses [22] • Improved protection (duration and magnitude) compared with live attenuated [14] • Limited cross-protection across heterologous antigens may constrain serotype breadth [14,26]	• Induces robust B- and T- cell responses through *co*-presentation of polysaccharides and protein antigens [59] • Potential for cross-protection with the inclusion of a conserved protein component [36]	• Presents multiple antigens in their native conformation, similar to live attenuated but without infection risk [14,22] • Induces robust systemic antibody responses with potential for broad antigenic coverage [35] • "Plug-and-play" technology, easily modifiable for targeting different serotypes [35]
Regulatory & Clinical Pathway Risk	• Risk of persistent infection, environmental shedding [95] • Safety concerns in those with underlying comorbidities (e.g. immunodeficiency), in those <6 yrs. and is contraindicated with pregnancy [14,96]	• No possibility of shedding or environmental dissemination [14] • Often requires addition of an adjuvant to achieve acceptable immunogenicity [22]	• No possibility of shedding or environmental dissemination [14] • Platform safety has yet to be established in pediatrics [36] • Efficacy in humans has not yet been demonstrated [36]	• Platform safety has yet to be established in pediatric trials (age-deescalation trial ongoing) [25,97] • Efficacy in humans has not yet been demonstrated [49]
Cost & Manufacturing	• Low theoretical COGS due to fermentation-based production but partially offset by biosafety controls and potency monitoring [98]	• Production can be expensive due to complex and resource-intensive conjugation processes, particularly with multivalent vaccines [14,26] • New, lower-cost approaches (e.g. *in vivo* coupling) are being explored in other gram-negative bacteria [99]	• Potential for lower COGS than traditional glyco-conjugates due to modular affinity-based antigen assembly [36] • Flexible formulation and readily adjustable chemical and physical properties [59]	• Low-cost, high-yield with simpler processes suited to DCVM technology transfer [22]
Programmatic Suitability	• Oral admin could simplify delivery, but cold chain dependence increases risk of potency loss in low-resource settings [14] • Multiple doses and relatively short-lived immunity increase programmatic complexity [100] • Contraindications in immunocompromised complicates deployment in high HIV-burden contexts [31]	• Intramuscular delivery aligns with routine infant immunization infrastructure; standard cold chain required [86] • Affordability in low-resource settings will depend on price and number of doses required [86]	• Intramuscular delivery aligns with routine infant immunization infrastructure; standard cold chain required [86] • Modular design enables inclusion of multiple antigens, leading to broad coverage across serovars, supporting long-term programmatic value and cost-effectiveness [36]	• Intramuscular delivery aligns with routine infant immunization infrastructure; standard cold chain required [86] • Potential for broad serovar coverage supports long-term programmatic value and cost-effectiveness [35]

vesicles (OMVs, termed 'GMMA' by GSK), which are naturally produced spherical nanostructures derived from the outer membrane of Gram-negative bacteria and filled with periplasmic proteins and lipids [35,46]. Mutations in the *tolR* gene in *S.* Typhimurium and *S.* Enteritidis strains induce "hyper-blebbing", enhancing OMV release, while modifications to *msbB* and *pagP* genes reduce lipid A acylation in LPS from hexacylated to pentacylated format, thereby lowering reactogenicity [47]. This process enables antigens to maintain their conformational integrity without laborious purification steps resulting in a more effective and low-cost antigen delivery process [35].

Preclinical studies of the iNTS-GMMA vaccine have shown promising results, with a prototype bivalent formulation (*tolR* deletion only) inducing robust IgG responses to *S.* Typhimurium and *S.* Typhimurium O-antigens, with strong *in vitro* bactericidal activity [22]. In a mouse infection model, immunization with the bivalent iNTS GMMA vaccine significantly reduced the *S.* Typhimurium burden upon infection compared to the corresponding glycoconjugate vaccine [22,48] Additionally, *S.* Typhimurium GMMA immunization demonstrated long-term immunity in mice, with reduced bacterial burden observed 24 weeks post-vaccination [27]. The *Salmonella* Vaccine Study in Oxford was the first-in-human trial to evaluate safety and tolerability of this novel vaccine in healthy adults in the UK, followed by a second phase in an endemic population at the Kenya Medical Research Institute [49]. Interim results showed that the iNTS-GMMA vaccine was well-tolerated in adults, with no safety signals or concerns after three doses, while eliciting robust antibody levels and antibody functional response against the targeted serovars [49]. The bivalent iNTS GMMA vaccine candidate has since advanced to a Phase 2 trial in Ghana (NCT06213506), using an age de-escalation and dose escalation approach, beginning in adult and progressing to children and infants.

In the trivalent format, the typhoid component is the licensed, WHO-prequalified TCV, TYPHIBEV, manufactured by Biological E and developed in collaboration with GVGH [50]. This glycoconjugate vaccine consists of the Vi polysaccharide derived from *Citrobacter freundii* WR7011, which is structurally similar and immunologically indistinguishable to the Vi antigen of *S.* Typhi, conjugated to the CRM_{197} protein, a non-toxic recombinant of diphtheria toxin [48,50]. Vi-CRM_{197} was tested in Phase 1 and 2 trials in adults in Europe and subsequently in Phase 2 trials adults, children and infants in India, Pakistan and the Philippines [51,52]. While found to be safe and considerably more immunogenic than unconjugated Vi after a single dose, a second dose had no incremental effect on antibody levels in children and infants aged 9 to 12 months [53]. The trivalent iNTS-GMMA and TCV vaccine candidate is currently being evaluated in an ongoing Phase 1/2a trial (NCT05480800), with Stage 1 conducted in European adults in Belgium, followed by Stage 2 in Malawi [31].

Beyond GSK's GMMA platform, other OMV-based vaccine approaches have been evaluated in preclinical models as candidates for protection against NTS. These studies demonstrate that OMV-based vaccines can elicit functional immune responses and confer protection against *S.* Typhimurium *and S.* Enteritidis [54,55]. More broadly, OMVs have been explored as antigen delivery platforms in vaccines targeting a

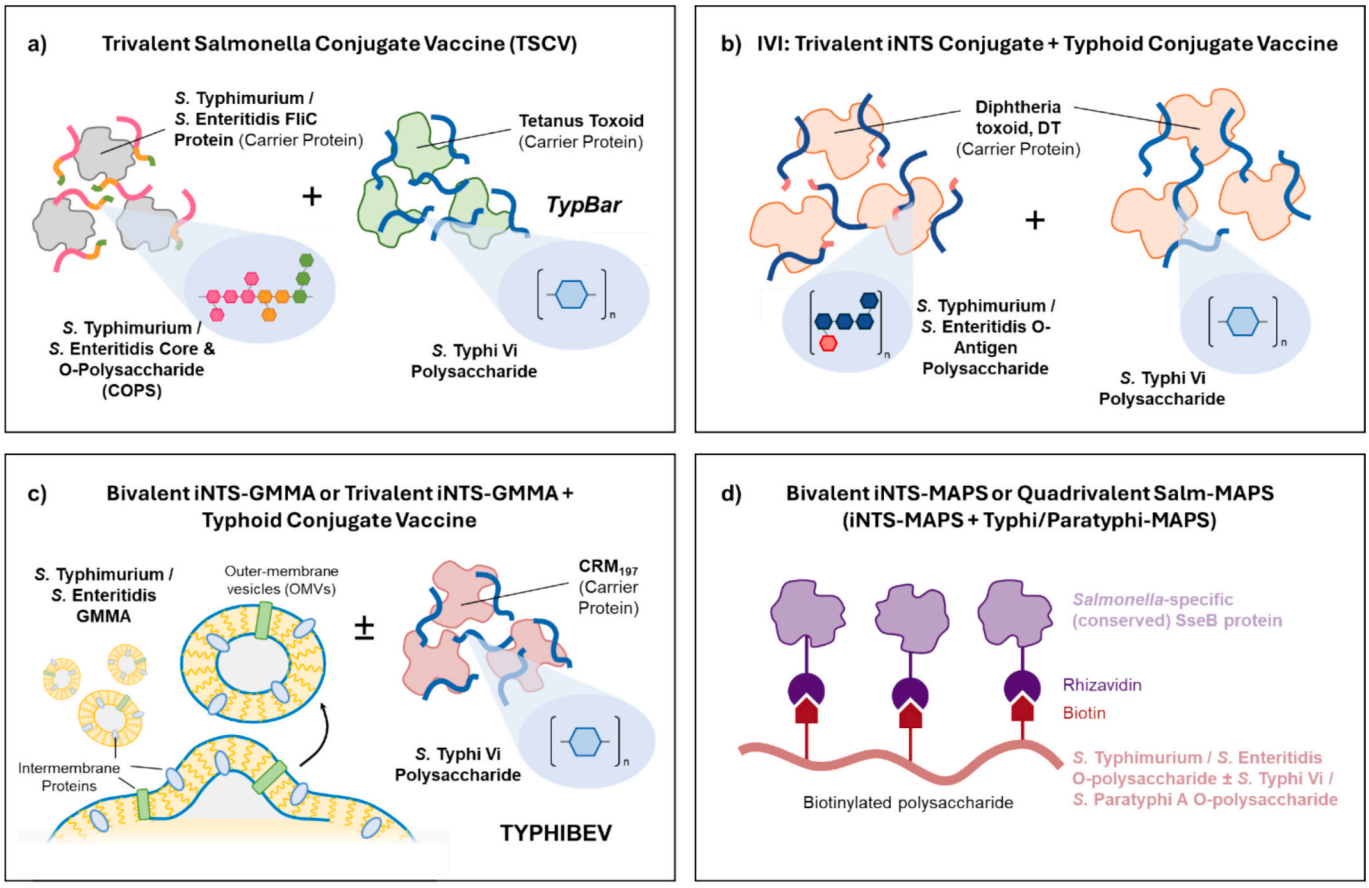

Fig. 1. Overview of vaccine platforms and antigens associated with major iNTS disease vaccine candidates under development. A. Center for Vaccine Development and Global Health, University of Maryland's Trivalent *Salmonella* Conjugate Vaccine (TSCV) consists of *S.* Typhimurium and *S.* Enteritidis FliC flagellin protein conjugated to Core and O-Polysaccharide (COPS), combined with Typbar, tetanus toxoid (TT) conjugated to Vi capsular polysaccharide from *S.* Typhi. **B.** International Vaccine Institute's trivalent iNTS-TCV conjugate consists of diphtheria toxoid (DT) conjugated to O-antigen polysaccharide chains (from either *S.* Typhimurium or *S.* Enteritidis) as well as DT conjugated to Vi capsular polysaccharide *from S.* Typhi. **C.** GSK Vaccine Institute for Global Health's bivalent iNTS-GMMA candidate, consisting of *S.* Typhimurium and *S.* Enteritidis GMMAs or genetically modified outer membrane vesicles, and trivalent formulation with iNTS-GMMA plus TYPHIBEV, CRM197 (detoxified diphtheria toxin conjugated to Vi capsular polysaccharide from *S.* Typhi). **D.** Boston Children's Hospital's MAPS technology, which utilizes high-affinity biotin-rhizavidin binding interaction to present both protein and polysaccharide antigens within a single vaccine, represented here for their bivalent (*S.* Typhimurium/*S.* Enteritidis) and quadrivalent (*S.* Typhimurium/*S.* Enteritidis/*S.* Typhi/*S.* Paratyphi A) formulations.

wide range of pathogens, highlighting their broader applicability as a vaccine technology [56–58].

2.3. Multiple antigen presenting system (MAPS) vaccine

Boston Children's Hospital (BCH), in collaboration with Affinivax (acquired by GSK in 2022 [33]) and with funding from the Bill & Melinda Gates Foundation (BMGF), has been developing preclinical iNTS-containing MAPS vaccines. These include a bivalent formulation targeting *S.* Typhimurium and *S.* Enteritidis, and a quadrivalent vaccine that also targets *S.* Typhi and *S.* Paratyphi A [33]. This technology leverages high-affinity biotin-rhizavidin binding to form integrated macromolecular complexes of polysaccharides and pathogen-specific proteins to achieve high immunogenicity [36]. The platform offers manufacturing ease and flexibility to adapt to different pathogens or in response to changes in disease epidemiology [36,59]. By pairing polysaccharides with pathogen-specific, conserved proteins instead of unrelated carrier proteins, MAPS vaccines have the potential to induce broad immune responses through antibody- and cell-mediated immune responses to both polysaccharide and protein antigens [36,60].

Previous research on a bivalent vaccine against *S.* Typhi Vi and *S.* Paratyphi A O:2 OPS MAPS demonstrated Vi specific memory B cells and the presence of functional antibodies against Vi and OPS postimmunization [61]. Further preclinical studies testing bivalent and quadrivalent formulations incorporating the *Salmonella* type 3 secretion system protein, SseB, as the protein component, showed robust antibody production and functional killing activity, comparable to their monovalent counterparts [33]. With GSK's acquisition of Affinivax and its MAPS platform technology, it remains uncertain whether either of the iNTS-containing vaccine candidates will be further developed. GSK is currently using the MAPS platform for a vaccine against *Streptococcus pneumoniae* which includes 24 pneumococcal polysaccharides [62]. Phase 1 and 2 clinical trials of this vaccine demonstrated the vaccine to be well-tolerated and highly immunogenic in adults and toddlers by inducing a robust immune response at all three dose levels [63,64]. The safety and efficacy of this platform need to be further evaluated in clinical trials for iNTS; however, preclinical iNTS results and clinical results from other infectious diseases support the potential feasibility of the MAPS vaccine platform. In addition to its recently acquired MAPS platform technology, GSK has completed a Phase 1 study in healthy adults in Europe of a bivalent conjugate vaccine targeting typhoid (Vi-CRM_{197}) and paratyphoid A (O:2-CRM_{197}) (NCT05613205).

2.4. Other vaccine candidates

While the vaccine candidates described above show promise for

mitigating iNTS disease, it remains uncertain whether they will confer cross-protection against non-vaccine serotypes or prevent serotype replacement following widespread introduction [37]. Although *S.* Typhimurium and *S.* Enteritidis currently account for the vast majority of iNTS cases, vaccine-mediated suppression of these dominant serovars could theoretically alter serovar distribution over time. Genomic surveillance efforts in sSA have identified sporadic invasive infections caused by other serovars, including *S.* Concord, *S.* Isangi, *S.* Dublin and *S.* Westphalia, underscoring the importance of continued surveillance efforts to detect and monitor potential shifts in circulating serovars [9,65]. O-antigen-based vaccines are highly likely to offer cross-protection against additional *Salmonella* serovars within serogroup B (e.g. *S.* Derby, *S.* Heidelberg, *S.* Stanley and *S.* Paratyphi B) and serogroup D (e.g. *S.* Dublin), as these serovars share the same O-antigens—O:4 and O:9—as *S.* Typhimurium and *S.* Enteritidis, respectively [30]. Other strategies, such as live attenuated vaccines and protein vaccines with highly conserved antigens, are also being explored in preclinical studies as potential solutions to enhance cross-reactivity in vaccine candidates [37].

Over the past decade, UMD's CVD has been optimizing various strains of *S.* Enteritidis and *S.* Typhimurium for use as whole cell, live-attenuated vaccine candidates for protection against iNTS disease [24,28,66]. These candidate strains have been modified with various mutations in genes involved in nucleic acid synthesis (e.g., guaBA, gene responsible for guanine synthesis), flagellar protein synthesis (e.g., clpP and clpX, genes that regulate a master flagellar regulator FlhD/FlhC), and entero-pathogenicity (e.g., pipA, involved in fluid accumulation during infection; htrA, heat shock protein involved in survival in the host) [24,28,66]. As whole-cell vaccines, live-attenuated vaccines present multiple antigens to the immune system and have the potential to induce broad protection against several *Salmonella* serotypes [36]. CVD's live-attenuated vaccine candidates have demonstrated significant immunogenicity and efficacy in mice models, enabling protection against both homologous and heterologous serogroups of NTS [24,28]. Historically, live attenuated vaccines against iNTS have been well-tolerated and provided immunity but development has been prohibited by prolonged fecal shedding [67,68]. Given the possibility of infection from vaccine strains, live attenuated vaccines also present concerns for use in young children and may not be safe for those with underlying comorbidities, such as those living with Human Immunodeficiency Virus (HIV) [14]. CVD's refined live attenuated strains have demonstrated reduced shedding compared to wildtype iNTS strain in animal models; however, it is unclear whether a candidate vaccine containing these strains will be safe and efficacious in humans [69].

Outer membrane proteins (e.g. OmpC, OmpD, OmpF) [70,71], siderophores (enterobactin) [72], and type III secretion system proteins (e.g. SipB, SipD, SseB, SseC, and PrgI) [73–75] have also been investigated as vaccine antigens in preclinical studies. These candidates have shown robust immunogenicity and protective efficacy against homologous strains in mouse models [37]. However, finding an appropriate antigenic component to elicit an effective immune response remains a time-consuming process [76]. Additionally, despite advances in recombinant technology, protein purification can be laborious and costly [14]. Given the need to maintain affordability, this may limit the feasibility of developing such an iNTS vaccine with regional value in low- and middle-income countries.

3. Challenges

While developing a safe and efficacious vaccine to protect against iNTS disease is theoretically feasible and holds significant public health potential in sSA, no vaccine has advanced to late-stage (Phase 2b/3) clinical trials or approval. Despite success in developing vaccines against *S.* Typhi, challenges for iNTS vaccine development persist, including insufficiently granular data on the disease burden in infants, lack of clarity surrounding clinical development plans, in particular regarding age of first administration in infants, age of booster doses, requirement for a large efficacy trial or clarity on using controlled human infection models (CHIM) to guide vaccine licensure and policy, and the absence of established correlates of protection.

3.1. Disease burden data gaps

Over the past decade, expanded surveillance efforts have led to more reliable estimates of NTS disease burden; however, substantial epidemiological gaps remain [2,8,77]. Key uncertainties persist regarding the heterogeneity of disease burden across regions and age groups [8]. Notably, regions with high typhoid incidence often show low iNTS disease burden, and vice versa. As a result, reliance on data from well-established initiatives like the Typhoid Fever Surveillance in Africa Program may skew burden estimates toward areas with limited iNTS disease transmission [5].

Data outside of sSA are especially scarce, with few studies reporting incidence from Asia and other regions [8,11]. Recent surveillance of returning European travelers has revealed a steady increase in antimicrobial resistance among iNTS isolates, highlighting international travel as a potential important driver of global transmission and disease burden [78]. While current iNTS vaccine development justifiably prioritizes protecting young children in sSA, these findings signal a parallel, yet underexplored opportunity: a traveler indication for adolescents and adults, similar to the established travel vaccine market for typhoid [79]. However, this potential use case has yet to be fully characterized and requires additional supporting evidence.

Further challenges include concerns over the quality and completeness of serotyping data, which may hinder a full understanding of the diversity of NTS serovars that cause invasive disease [34]. Improved surveillance of iNTS disease, both in endemic regions and globally, will be essential to inform key aspects of vaccine development, including target population and optimal vaccine serovar coverage [34].

3.2. HIV-positive and other immunocompromised populations

In contrast to the disease burden data gaps described above, iNTS disease is a well-recognized leading cause of bloodstream infection and mortality among immunologically vulnerable groups in sSA, most notably adults living with HIV, but also individuals with severe malnutrition, malaria, or sick cell disease, with estimated incidence ranging from 2000 to 7500 cases per 100,000 HIV-infected adults [2,8]. Despite this substantial burden, current clinical development plans for leading iNTS vaccine candidates have excluded individuals with confirmed or suspected immunosuppression [40,49]. Although such exclusions are common in early-phase trials, it perpetuates a critical evidence gap for populations at highest risk for severe disease and death. Vaccination of immunocompromised populations poses distinct immunological challenges, as underlying immune dysfunction may reduce the magnitude and durability of vaccine-induced protection and influence both immunogenicity and optimal dosing strategies [14]. As iNTS vaccine candidates progress into later-stage clinical development stages of development, inclusion of HIV-positive adults and other immunocompromised populations as a key sub-population will be essential to generate evidence to evaluate safety, immunogenicity, and potential public health impact in these priority high-risk populations.

3.3. Pathway to Licensure

As no iNTS-containing vaccine candidates have advanced beyond early-stage clinical trials, the pathways to licensure remain undefined, emphasizing the importance of early and coordinated engagement with regulators in low- and middle-income countries. Achieving initial regulatory approval will likely require a large-scale Phase 3 trial to establish efficacy based on clinical endpoints, a process that may be difficult to resource and conduct, especially given that most iNTS disease cases are

concentrated in low- and middle-income countries [80]. Further, there remains limited understanding of correlates of protection for NTS to guide incorporation into clinical trial outcomes [1,81]. In response, CHIM studies are being pursued to more directly link vaccine-induced immune responses with clinical outcomes, as CHIMs allow controlled, reproducible assessment of pathogen exposure, immune activation, and disease endpoints in human volunteers. In understanding early signals of vaccine efficacy and generating detailed immunological datasets, CHIMs can accelerate candidate selection and support hypothesis-driven identification of correlates of protection [81,82]. Ongoing efforts to develop an NTS CHIM include foundational work at Imperial College London using well-characterized *S.* Typhimurium challenge strains belonging to pathovars ST19 and ST313, representative of currently circulating isolates implicated in both diarrhoeal and invasive NTS disease [83]. The first CHIM study will be an inpatient safety and dose-escalation study designed to characterize host responses to controlled challenge of healthy individuals 18–50 years of age [34].

However, important limitations affect the translatability of CHIM findings to the intended target populations for iNTS vaccines. Responses observed in healthy, immunocompetent adults may differ substantially from those in young children and immunocompromised individuals, who bear the greatest burden of iNTS disease. Differences in host immunity and comorbidities may influence both disease susceptibility and the magnitude and durability of vaccine-induced protection, such that efficacy observed in adult CHIM may not reliably predict effectiveness in high-risk groups [83]. Therefore, CHIM studies should be viewed as complementary evidence that can inform selection of clinical endpoints and the search for correlates of protection, rather than surrogate measures of field efficacy [34,82]. Further, while CHIM data can de-risk development and support immunological understanding, licensure and policy decisions for iNTS vaccines will likely depend primarily on field efficacy data generated in representative target populations [30].

3.4. Vaccine access and commercial attractiveness

In addition to challenges with vaccine development and licensure, the commercial viability of an iNTS vaccine limited to low- and middle-income countries remains uncertain. In high-income settings, the low incidence of iNTS disease is unlikely to justify routine vaccination, limiting demand among payers, National Immunization Technical Advisory Groups or NITAGs, and healthcare providers [84]. Given the absence of a dual market, development of an iNTS vaccine comes with unique challenges associated with capacity building and investments for clinical trials in low-resource settings and increased costs to generate robust clinical and post-marketing surveillance data [34,85]. Further, a focus in low- and middle-income countries means that vaccine demand is fully dependent on a positive recommendation from the Strategic Advisory Group of Experts on Immunization to WHO for broad use of the vaccine and vaccine procurement-related decisions by organizations such as Gavi and Pan American Health Organization [34,85].

iNTS disease burden is highest among young children in high-burden settings, with incidence peaking between 6 and 36 months of age [77,86]. The WHO preferred product characteristics indicate that protection against NTS should ideally be achieved before 6 months of age [77]. Consequently, iNTS vaccine introduction would need to align with existing Expanded Programme on Immunization (EPI) schedules, with administration coordinated around routine immunization visits (e.g., 6, 10, 14 weeks or 9 months of age). This timing introduces operational considerations related to co-administration with routine pediatric vaccines and the feasibility of adding an additional vaccine to already crowded immunization visits, potentially affecting acceptability and coverage [87]. Lessons learned from the recently developed malaria vaccines, specifically developed for children in sSA, indicate that innovative funding mechanisms and partnerships may be required to support an iNTS vaccine targeted toward low- and middle-income countries [88].

As with other vaccines, commercial attractiveness of an NTS-targeting vaccine may also be influenced by vaccine coverage (i.e., serovar, geography), target population (i.e., high-risk groups, children of expatriates and travelers), and affordability (i.e., vaccine platform and manufacturing process used). Ultimately, affordability will be a key consideration for the introduction of an iNTS vaccine into low- and middle-income countries [34,85]. Therefore, it is important to focus on development of simplified vaccine technologies that minimize the cost of development and ongoing production and delivery costs [85].

4. Conclusion and future directions

iNTS disease continues to be a major global health challenge, causing substantial morbidity and mortality, particularly in low- and middle-income countries in sSA [25]. Despite this burden, no vaccines are currently available. Several promising early-stage vaccine candidates are, however, in development, with the potential to offer safe and effective tools to reduce the burden of iNTS disease and address broader public health challenges, including antimicrobial resistance. In this context, modeling indicates that a hypothetical NTS vaccine, delivered to 70% of infants with 80% efficacy over five years, could avert approximately 1.3 million defined daily doses of antibiotics, highlighting its potential contribution to antimicrobial stewardship [89]. As these candidates progress, it is essential that vaccine manufacturers ensure the iNTS vaccine remains affordable and meets WHO-defined programmatic suitability criteria to drive uptake in the regions that need it most. To support these progress in this space, initiatives such as Vacc-iNTS and PEDVAC-iNTS—supported by the European Commission and the European and Developing Countries Clinical Trials Partnership—along with targeted investments from CARB-X, the Wellcome Trust, the BMGF and other public and private funders are providing critical resources to advance iNTS vaccine development through preclinical and early clinical stages [90–93].

Beyond research and development efforts, global health organizations have enhanced investment in activities to support vaccine development, clarify regulatory pathways and foster engagement with key decision-makers. A Full Value of Vaccines Assessment or FVVA is currently being developed, with funding support from the Wellcome Trust, which will include a business case, global public health investment case and broader societal benefit analysis [1,94]. In parallel, WHO has developed a Preferred Product Characteristics (PPCs) document for bivalent and trivalent iNTS vaccines to better define the value proposition of low- and middle-income country markets and provide guidance on WHO's preferences for new iNTS vaccines [77]. Together, these initiatives will help enable and accelerate vaccine development and represent a major step forward in the journey to prevent iNTS disease and its associated health burden.

All authors attest they meet the ICMJE criteria for authorship.

CRediT authorship contribution statement

Nicole M. Revie: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Matthew Y. Guo:** Writing – review & editing, Investigation. **Anne E. Mullin:** Supervision, Conceptualization. **Jean-Louis Excler:** Writing – review & editing, Supervision, Project administration. **Annelies Wilder-Smith:** Writing – review & editing, Supervision. **Calman A. MacLennan:** Writing – review & editing, Supervision. **Jerome H. Kim:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Donald R. Walkinshaw:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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A.W·S is an employee at the World Health Organization. Any opinions expressed here are hers and do not necessarily reflect those of WHO.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Donald R. Walkinshaw reports financial support was provided by Wellcome Trust. Jerome H. Kim reports financial support was provided by Wellcome Trust. Nicole M. Revie reports financial support was provided by Wellcome Trust. Matthew Y. Guo reports financial support was provided by Wellcome Trust. Anne E. Mullin reports financial support was provided by Wellcome Trust. Annelies Wilder-Smith reports a relationship with World Health Organization that includes: employment. If there are other authors, they 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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Data availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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