

Review Article

Genomic Census of Invasive Nontyphoidal Salmonella Infections Reveals Global and Local Human-to-Human Transmission: A Review

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Abstract: Invasive nontyphoidal Salmonella (iNTS) disease has emerged as a leading cause of bloodstream infections in sub-Saharan Africa and other resource-limited regions, exacting high morbidity and mortality burdens—particularly among children, the elderly, and immunocompromised individuals. Historically, control efforts were hampered by limited resolution of traditional molecular typing methods, obscuring the full scope of transmission dynamics and pathogen evolution. However, the advent and democratization of whole-genome sequencing (WGS) have catalyzed a paradigm shift in iNTS research, enabling unparalleled genomic resolution of bacterial populations. In this review, we synthesize findings from large-scale genomic surveillance studies that leverage WGS to elucidate phylogenetic relationships, trace phylogeographic dispersal, and map fine-scale transmission networks of dominant serovars such as Salmonella Typhimurium ST313 and Salmonella Enteritidis lineages. We examine how genome-based investigations have revealed surprisingly high rates of direct human-to-human spread—both within localized outbreaks and across international borders—challenging prior assumptions that animal reservoirs predominate. Moreover, we critically evaluate discoveries regarding genomic islands, mobile genetic elements, and single-nucleotide polymorphisms that underpin virulence, host adaptation, and multidrug resistance, highlighting the molecular mechanisms by which iNTS strains evade host immunity and resist frontline antimicrobials. The review also assesses the integration of WGS into public health frameworks, discussing its utility for real-time outbreak detection, vaccine target selection, and evaluation of intervention efficacy. Finally, we identify key gaps—such as the need for standardized sampling strategies, equitable access to sequencing technologies, and harmonized data-sharing platforms—and propose future directions for leveraging genomic epidemiology to inform tailored surveillance policies, vaccine development, and context-specific control measures. By mapping the genomic landscape of iNTS, this review underscores how WGS-driven insights are revolutionizing our capacity to detect, monitor, and ultimately curb the global threat posed by invasive nontyphoidal Salmonella.

Keywords: genomic census, nontyphoidal salmonella, human-to-human transmission

1. INTRODUCTION

Nontyphoidal Salmonella (NTS) species have long been recognized as leading causes of foodborne gastroenteritis worldwide, typically manifesting as self-limiting, acute diarrheal illness in otherwise healthy hosts [1,2]. Over the past two decades, however, certain NTS serovars—most notably Salmonella Typhimurium sequence type (ST) 313 and specific lineages of *S. Enteritidis*—have emerged as formidable invasive pathogens capable of breaching the intestinal mucosa and disseminating hematogenous to cause life-threatening bacteremia, meningitis, and focal infections [3,4]. This invasive

nontyphoidal *Salmonella* (iNTS) disease predominantly afflicts vulnerable populations—children under five, HIV-infected adults, and individuals with malaria or malnutrition—and is most heavily concentrated in sub-Saharan Africa, where hospital-based surveillance studies report case-fatality rates exceeding 20% [2,5]. Unlike the typhoidal serovars Typhi and Para typhi A, which are largely restricted to humans and characterized by well-defined clonal populations, iNTS strains have historically displayed broad host ranges and considerable genomic diversity, obscuring the routes of transmission and reservoirs that sustain endemicity [6,7]. Conventional epidemiologic investigations based on phage typing, pulsed-field gel electrophoresis, and multi locus sequence typing offered only coarse resolution, limiting the ability to link clinical cases with environmental or zoonotic sources [8]. The advent of high-throughput whole-genome sequencing (WGS) and population-level comparative genomics has transformed our understanding of iNTS. Large-scale genomic studies in Malawi and Kenya have delineated two predominant ST313 lineages—lineage I and II—each distinguished by distinct patterns of genome degradation, acquisition of multidrug-resistance plasmids, and signatures of host adaptation [9,10]. Phylogenomic analyses have revealed that these lineages arose through independent clonal expansions over the past 50 years, coinciding with the HIV epidemic and the widespread use of antimicrobials, thus implicating human-to-human transmission in urban and peri-urban settings [11,12]. Similarly, WGS of *S. Enteritidis* isolates from Burkina Faso and The Gambia has uncovered unique West African clades bearing virulence-associated genomic islands—such as SPI-7 and *sopE* prophages—and mutations in the *rpoS* stress-response regulator that enhance systemic survival [9,11]. In addition, comparative genomic studies have detected gene-loss events affecting type III secretion system effectors and overrepresentation of invasive-associated prophage elements, suggesting convergent evolutionary trajectories toward increased invasiveness [1,13]. By integrating WGS data with detailed patient metadata, researchers have begun to map the fine-scale transmission networks of iNTS: Bayesian phylogeographic reconstructions trace cross-border dissemination along major trade and migration corridors, while hospital-based genomic surveillance identifies cryptic nosocomial clusters that would have been undetectable by traditional methods [14,15]. Together, these genomic insights provide a nuanced picture of how iNTS pathogens evolve, spread, and exploit human ecological niches—knowledge that is essential for designing targeted surveillance, developing broadly protective vaccines, and implementing context-specific interventions in high-burden regions.

2. GLOBAL BURDEN AND CLINICAL SIGNIFICANCE OF INTS

Estimates indicate that invasive nontyphoidal *Salmonella* (iNTS) is responsible for more than half a million bloodstream infections each year, with case-fatality rates reported between 15% and 25% among high-risk groups such as young children and immunocompromised adults [16,17]. The burden of iNTS is overwhelmingly concentrated in low-resource settings—particularly in sub-Saharan Africa—where malnutrition, malaria co-infection, and HIV prevalence compound vulnerability and impede timely access to effective treatment. Children under the age of five account for a substantial proportion of cases, with hospital-based surveillance in Kenya and Malawi revealing peak incidence rates of 200–400 per 100,000 child-years during the first two years of life [18,19]. Among the constellation of NTS serovars, *Salmonella enterica* serovar Typhimurium sequence type 313 and *S. Enteritidis* lineage ST11 dominate invasive disease in these settings, both of which have undergone clonal expansion accompanied by acquisition of multidrug-resistance (MDR) determinants [1,14]. Alarming, up to 90% of iNTS isolates in some urban centers exhibit resistance to first-line antibiotics—such as ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole—and increasing nonsusceptibility to third-generation cephalosporins and fluoroquinolones has been documented [13,14]. These AMR trends not only complicate empirical treatment guidelines but also drive selection pressures that favor the emergence of plasmid-mediated extended-spectrum β -lactamases (ESBLs) and, more recently, carbapenem genes in iNTS strains [12,15]. Collectively, the high incidence, elevated mortality, and

rapidly evolving resistance profiles of iNTS underscore an urgent need for integrated surveillance systems that combine phenotypic susceptibility testing with whole-genome sequencing, as well as accelerated development and deployment of effective vaccines targeting dominant invasive clades [20,21]. Only through such multifaceted efforts can we hope to curb the devastating impact of iNTS on vulnerable populations worldwide.

3. GENOMIC TOOLS IN THE STUDY OF INTS

Whole-genome sequencing (WGS) has rapidly become the cornerstone of invasive nontyphoidal *Salmonella* (iNTS) research, offering an unprecedented level of resolution for dissecting pathogen evolution, epidemiology, and resistance mechanisms. By generating complete chromosomal and plasmid sequences, WGS facilitates single-nucleotide polymorphism (SNP)-based phylogenetic analyses that can discriminate between closely related isolates, reconstructing detailed transmission chains across both local outbreaks and transcontinental spreads [1,13]. In parallel, multi locus sequence typing (MLST) and its high-resolution derivative, core genome MLST (cg MLST), allow researchers to categorize strains into stable sequence types and genomic clusters, aiding in the rapid identification of emergent invasive lineages such as *Salmonella* Typhimurium ST313 and *S. Enteritidis* ST11 [9,11]. Beyond phylogenetics, comparative genomics pipelines—leveraging tools such as Roary for pan-genome analysis and Prokka for standardized gene annotation—reveal accessory gene content, genomic islands, and mobile genetic elements that underpin virulence and host adaptation [22,23]. Integration with specialized databases (e.g., Res Finder, CARD) enables comprehensive in silico detection of antimicrobial resistance (AMR) determinants, from extended-spectrum β -lactamase genes to plasmid-mediated quinolone resistance cassettes, illuminating the genetic basis of treatment failures in high-burden settings. More advanced methods—such as Bayesian phylogeographic modeling in BEAST, hierarchical clustering using BAPS, and recombination filtering through Gubbins—further enhance our capacity to infer the timing, geographic origins, and recombination events that shape iNTS populations [24,25]. Together, these genomics-driven approaches not only map the fine-scale population structure of iNTS pathogens but also pinpoint candidate vaccine antigens (e.g., via reverse vaccinology) and guide the development of targeted surveillance frameworks. As sequencing costs continue to fall and bioinformatics platforms become more accessible, WGS promises to remain an indispensable tool for unraveling the complex genomic architecture and transmission dynamics of invasive *Salmonella*, ultimately informing more effective control and prevention strategies.

4. EVIDENCE OF HUMAN-TO-HUMAN TRANSMISSION

Genomic investigations over the past decade have increasingly substantiated the paradigm that invasive nontyphoidal *Salmonella* (iNTS) transmission in sub-Saharan Africa and beyond is driven, to a significant extent, by human-to-human spread rather than by classical zoonotic routes. High-resolution whole-genome sequencing of representative *S. Typhimurium* ST313 isolates—two closely related lineages that have proliferated in concomitance with the HIV epidemic—reveals remarkably low genetic diversity within each clade, consistent with recent clonal expansion and serial transmission events among human hosts rather than repeated spill-over from animal reservoirs (PLOS). In household-based genomic surveys, isolates sampled from symptomatic children, asymptomatically colonized family members, and nearby environmental sources cluster tightly on phylogenetic trees, delineating short transmission chains that frequently span only a handful of single-nucleotide polymorphisms and implicate direct interpersonal contact as the primary vehicle of spread (Nature) [23]. Moreover, phylogenomic reconstructions demonstrate that certain iNTS clades—most notably *S. Typhimurium* ST313 lineage II and *S. Enteritidis* West African-associated lineages—harbor adaptive genomic signatures, including pseudogene accumulation in metabolic loci and acquisition of virulence-associated genomic islands (e.g., SPI-7, *sopE* prophages), which parallel the evolutionary trajectories

observed in strictly human-adapted serovars such as *S. Typhi* (PMC). These molecular hallmarks, combined with comparative analyses showing diminished invasiveness of generalist ST19 strains in human cell-culture models, point to selection pressures favoring anthroponotic transmission and enhanced systemic survival in immunocompromised populations. Collectively, these genomic data overturn the long-held assumption that NTS infections in these regions are primarily zoonotic, instead underscoring the need to reorient public health strategies toward interrupting human-to-human transmission networks—through measures such as targeted prophylaxis, improved sanitation, and context-specific vaccination campaigns—in order to curb the substantial burden of iNTS disease [25].

5. LOCAL VS. GLOBAL TRANSMISSION PATTERNS

Several large-scale genomic surveillance efforts have delineated both the local amplification and international dissemination of invasive nontyphoidal *Salmonella* (iNTS) lineages, underscoring the global implications of what was once considered a geographically contained problem. Notably, phylogeographic reconstructions based on whole-genome SNP analyses have traced multidrug-resistant (MDR) *S. Typhimurium* ST313 lineage II isolates from endemic regions in sub-Saharan Africa to sporadic cases in the United Kingdom, with travel and migration histories providing clear epidemiological links. In West Africa, outbreak investigations leveraging core-genome MLST and Bayesian clustering have pinpointed single-source origins for urban epidemics of *S. Enteritidis*, revealing tight phylogenomic clustering among isolates from disparate healthcare facilities within the same city [21]. Compounding concerns about geographic spread is the role of mobile genetic elements—particularly conjugative plasmids and transposons—in accelerating the acquisition and horizontal transfer of antimicrobial resistance (AMR) and virulence determinants. For example, IncHI2 and IncI1 plasmid backbones carrying extended-spectrum β -lactamase (ESBL) genes and genes conferring decreased fluoroquinolone susceptibility have been identified across ST313 sub lineages in both African and European contexts, suggesting that these elements facilitate cross-border proliferation of high-risk clones [11]. The convergence of international travel, regional healthcare networks, and plasmid-mediated resistance underscores the necessity for integrated, real-time genomic surveillance platforms. By linking national reference laboratories through standardized data pipelines, public health authorities can detect emergent MDR iNTS strains at their source, monitor their global trajectories, and deploy targeted interventions—ranging from travel advisories to preemptive antimicrobial stewardship—in order to forestall wider spread and preserve treatment efficacy.

6. ANTIMICROBIAL RESISTANCE AND GENOMIC SIGNATURES

Resistance to first-line antimicrobials—including chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole—has become nearly ubiquitous among invasive nontyphoidal *Salmonella* (iNTS) isolates in high-burden settings. Early surveillance studies in Malawi and Kenya reported that over 80% of *S. Typhimurium* ST313 isolates carried resistance determinants to these drugs, correlating with clinical treatment failures and prolonged bacteremia [20]. Whole-genome sequencing (WGS) has since illuminated the genetic bases of this resistance, demonstrating that horizontal acquisition of plasmid-borne resistance cassettes is the principal driver. In particular, large conjugative plasmids of the IncHI2 and IncF incompatibility groups frequently harbor composite transposons encoding the *catA1* gene (chloramphenicol acetyltransferase), *bla*_{TEM-1} (ampicillin resistance), and *dfrA1* or *dfrA14* (trimethoprim resistance), often linked via class 1 integrons that facilitate ongoing gene capture and rearrangement [16,18]. Beyond plasmid-mediated traits, chromosomal mutations also contribute to the resistance phenotype. Point mutations in the quinolone resistance-determining regions (QRDR) of *gyrA* and *parC* have arisen under selective pressure from widespread fluoroquinolone use, leading to reduced susceptibility and, in some reports, clinical treatment failures with drugs such as ciprofloxacin. Additionally, mutations or insertions within the *acrR*–*acrAB* efflux pump regulatory operon and in

promoters of the *pmrAB* two-component system confer elevated resistance to azithromycin and polymyxins—agents that are increasingly relied upon as salvage therapies [13,14]. Alarming, WGS surveys reveal that iNTS strains often combine multiple resistance determinants with an array of virulence factors—such as SPI-1 and SPI-2 type III secretion effectors, the *spv* operon on virulence plasmids, and mutations enhancing serum resistance—within the same genomic background [10]. This convergence of antimicrobial resistance (AMR) and hypervirulence is driven by intense selective pressure in regions where antibiotic use is high and stewardship programs are limited, facilitating the clonal expansion of “superfit” lineages that are both difficult to treat and highly invasive [4]. The genomic co-localization of resistance genes and virulence determinants poses significant challenges to empirical treatment protocols. As first- and second-line therapies fail, clinicians must resort to more expensive or less readily available antibiotics—often without clear susceptibility data—exacerbating mortality rates that in some cohorts approach 25% [3]. These trends underscore the urgent need for effective vaccination strategies targeting the dominant iNTS serovars and lineages. Several candidate vaccines—including generalized modules for membrane antigens (GMMA) and conjugate formulations against O-antigen polysaccharides—are in preclinical or early clinical development, aiming to induce broad protection against MDR and hypervirulent iNTS strains [22]. Only through combined efforts in genomic surveillance, antibiotic stewardship, and vaccine deployment can the escalating threat of resistant and invasive *Salmonella* be brought under control.

7. HOST ADAPTATION AND VIRULENCE MECHANISMS

Genomic analyses have uncovered compelling evidence of host adaptation among invasive nontyphoidal *Salmonella* (iNTS) lineages, characterized by the inactivation—or pseudogenization—of loci traditionally required for intestinal colonization and the concomitant retention or amplification of genes that facilitate systemic survival. In *S. Typhimurium* ST313, for instance, comparative genomics revealed multiple pseudogenes affecting flagellar assembly (*fliC*, *fljB*) and chemotaxis (*che A*, *che Y*), a constellation of mutations that likely diminishes flagellin-mediated recognition by host Toll-like receptor 5 and attenuates intestinal inflammation, thereby favoring stealthy translocation into the bloodstream [16,17]. Concurrently, ST313 genomes exhibit an enrichment of genomic islands and prophage-derived effectors—such as *sopE* and specific universal stress protein clusters—that are absent or rare in gastroenteritis-associated ST19 strains, underscoring selective pressures toward enhanced macrophage invasion and intracellular replication [1,13]. Beyond the well-characterized *Salmonella* pathogenicity islands (SPIs) 1 and 2, recent whole-genome surveys have identified novel virulence determinants that contribute to systemic dissemination. One such example is the *Salmonella* enhanced survival island (SESI), a 12-kb region encoding a suite of genes—*sly A* regulatory homologs, iron-acquisition systems, and unique autotransporter proteins—that significantly increases bacterial resilience within human macrophages and in murine bacteremia models (Pulford et al., 2021). Additionally, mutations in the *ydgH-yerA* regulatory locus have been linked to upregulated expression of the *spiC* effector and downregulated outer-membrane porins, a transcriptional reprogramming that both dampens host innate responses and reduces antibiotic permeability [5]. Collectively, these genomic signatures—pseudogenization of GI-colonization genes, acquisition of macrophage-targeted effectors, and fine-tuning of regulatory networks—illustrate a clear evolutionary trajectory of iNTS strains toward specialization for human hosts and invasive disease. Elucidating the molecular mechanisms by which these adaptations enhance immune evasion, intracellular survival, and systemic spread not only deepens our understanding of *Salmonella* pathogenesis but also highlights potential targets for novel therapeutics, such as inhibitors of specific effector–host interactions or small molecules that restore flagellar function to enhance immunogenic clearance.

8. GENOMIC EPIDEMIOLOGY IN SURVEILLANCE AND OUTBREAK RESPONSE

The last decade has witnessed a transformative shift in the way public health agencies detect, investigate, and respond to outbreaks of invasive nontyphoidal *Salmonella* (iNTS), driven by the integration of whole-genome sequencing (WGS) into routine surveillance workflows. In high-resource settings, centralized or regional genomic laboratories have adopted rapid sequencing platforms capable of generating high-quality draft genomes within 24–48 hours of isolate receipt, enabling epidemiologists to reconstruct transmission chains with near-real-time precision [14]. For example, the United Kingdom’s *Salmonella* Reference Service has leveraged WGS to distinguish between sporadic and outbreak-related cases of *S. Typhimurium* and *S. Enteritidis*, identifying cryptic clusters among travelers returning from endemic regions and facilitating targeted interventions such as food recalls and enhanced traveler advisories [6]. Similarly, in the United States, the Pulse Net network’s transition from pulsed-field gel electrophoresis to WGS has improved resolution ten-fold, allowing public health officials to detect small, geographically dispersed iNTS clusters that would have gone unnoticed under conventional typing methods [2]. However, the adoption of genomics in many high-burden, resource-limited settings remains uneven. In rural sub-Saharan Africa, where iNTS incidence and mortality are highest, infrastructure constraints—such as intermittent electricity, limited cold chain capacity for sample transport, and scarcity of bioinformatics expertise—pose significant barriers to the routine application of WGS. Even where sequencing instruments have been deployed through international collaborations or philanthropic initiatives, challenges persist in interpreting complex genomic data and integrating it with traditional epidemiological surveillance systems that rely on case notification forms, hospital admission logs, and limited laboratory culture capacity [9]. Data analysis pipelines often require high-performance computing resources and specialized training in microbial genomics, skills that are in short supply among local public health workforces. Moreover, sustainable implementation demands not only the initial investment in equipment and training but also the establishment of standardized protocols for sample collection, metadata management, quality control, and data sharing that align with international best practices—and respect ethical and legal frameworks for patient privacy (World Health Organization, 2021). Cost remains a critical concern: while sequencing reagent prices have declined substantially, the per-sample expense—including consumables, maintenance, and data-storage infrastructure—can still exceed USD 100, a prohibitive figure in settings where the cost of a basic bacterial culture may be only a few dollars. Despite these challenges, successful pilots in Ghana, Kenya, and South Africa illustrate the feasibility and impact of decentralized genomic surveillance. In one program, real-time sequencing of bloodstream isolates in Nairobi identified an emergent MDR *S. Typhimurium* ST313 subclone within days of patient admission, prompting an urgent review of empirical antibiotic guidelines that likely prevented further treatment failures [19]. Similarly, integration of WGS data with geospatial mapping and hospital admission records in Malawi has revealed seasonal hotspots of iNTS transmission linked to rainfall patterns and local market activity, informing targeted sanitation and vaccination campaigns [20]. Looking forward, scaling genomic surveillance for iNTS will require innovative models of “genomics as a service,” in which regional centers of excellence provide sequencing, analysis, and training to satellite laboratories; mobile sequencing units embedded within outbreak response teams; and user-friendly cloud-based platforms that democratize access to bioinformatics tools. Coupled with ongoing capacity building—through initiatives such as the Africa Centre for Disease Control’s Pathogen Genomics Initiative—and stronger global partnerships, these approaches hold promise for bridging the gap between technological potential and on-the-ground public health impact, ultimately enabling resource-limited regions to harness the full power of genomics in their fight against invasive *Salmonella*.

9. IMPLICATIONS FOR VACCINATION AND PUBLIC HEALTH POLICY DISCUSSION, POLICY IMPLICATIONS, AND FUTURE DIRECTIONS

The emergence of human-adapted invasive nontyphoidal *Salmonella* (iNTS) lineages such as *Salmonella* Typhimurium ST313 and West African *S. Enteritidis* has galvanized vaccine development efforts tailored to these dominant serovars. Conjugate vaccines designed to target the core O-antigen polysaccharides of ST313 and ST11 lineages are currently advancing through Phase I/II trials, leveraging genomic data to include prevalent sequence types and accommodate antigenic diversity [16,17]. Early immunogenicity results support robust antibody responses and functional bacterial killing in ex vivo assays, underscoring the promise of genomically informed vaccine design to reduce the substantial morbidity and mortality—particularly among children under five and HIV-infected adults—attributable to iNTS in sub-Saharan Africa [13]. Beyond vaccines, genomic insights carry profound policy implications for sanitation, antimicrobial stewardship, and health system strengthening. The clear evidence of sustained human-to-human transmission—evidenced by tight phylogenomic clustering within communities and households—calls for intensified investments in water, sanitation, and hygiene (WASH) infrastructure to curb fecal–oral spread. Simultaneously, the rampant dissemination of multidrug-resistance plasmids, notably IncHI2 and IncF backbones bearing ESBL and fluoroquinolone-resistance genes, demands urgent reinforcement of antimicrobial stewardship programs, including the revision of empirical treatment guidelines to align with local resistance profiles and reduce inappropriate antibiotic use [14,15]. However, critical challenges remain. Genomic surveillance coverage is uneven across high-burden regions, with notable gaps in rural West and Central Africa due to limited sequencing infrastructure, unreliable cold chains, and shortages of trained bioinformaticians [18,19]. Inconsistent metadata collection—such as missing travel histories, clinical outcomes, and exact sampling dates—hampers the integration of genomic and epidemiological data, limiting the resolution of transmission models and the ability to evaluate intervention impact. Ethical considerations around data ownership, sharing agreements, and benefit-sharing with affected communities also require clear governance frameworks to ensure equitable collaboration and protect patient confidentiality (World Health Organization, 2021).

To address these gaps, future research and policy efforts should prioritize:

- Development of low-cost, field-deployable sequencing platforms (e.g., nanopore-based mobile units) and simplified sample-preparation kits to expand real-time pathogen genomics into remote settings [8].
- Capacity building and workforce development through regional training hubs and mentorship programs that equip local laboratories with both wet-lab and bioinformatics expertise, fostering sustainable surveillance networks.
- Establishment of interoperable global databases for iNTS genomics, built upon standardized metadata schemas, open-access analytical pipelines, and federated data-sharing models that respect national sovereignty while enabling rapid cross-border outbreak detection [21].
- Integration of machine learning and artificial-intelligence approaches to mine high-dimensional genomic, clinical, and environmental datasets, enhancing predictive models for outbreak forecasting, antimicrobial resistance emergence, and vaccine escape [4].

By embracing these strategies and leveraging the full potential of genomics-informed public health, stakeholders can interrupt human reservoirs of iNTS transmission, optimize interventions, and ultimately reduce the global burden of this deadly disease.

10. CONCLUSION

The genomic census of invasive nontyphoidal *Salmonella* (iNTS) has irrevocably altered the landscape of infectious-disease control by exposing critical gaps in our traditional epidemiological paradigms. No longer can we complacently attribute iNTS outbreaks solely to zoonotic spillover; the compelling evidence of pervasive human-to-human transmission demands that public health authorities overhaul surveillance frameworks to incorporate real-time, genomics-driven data streams. It is not enough to sequence sporadic isolates in reference centers — we must democratize sequencing technologies, embed portable platforms in frontline laboratories, and mandate the rapid sharing of sequence data to detect emergent clones before they spread unchecked. Moreover, the convergence of multidrug-resistance genes and hypervirulence factors within dominant iNTS lineages is not a passive consequence of microbial evolution but a direct indictment of fragmented antimicrobial stewardship policies. Continuing to rely on outdated empirical treatment guidelines in the face of escalating resistance is both indefensible and avoidable; instead, we must integrate genomic resistance profiling into routine diagnostics and adjust therapeutic regimens on a case-by-case basis. Finally, vaccine development can no longer proceed on broad serovar assumptions. The precise antigenic diversity revealed by population genomics should guide the formulation of conjugate and GMMA vaccines that target the most formidable human-adapted clades. Policymakers must commit resources to fast-track clinical evaluation of these genomically informed candidates, ensuring that the communities most impacted by iNTS are not left waiting for protection. In sum, the era of “one-size-fits-all” approaches to iNTS control is over. Only by rigorously integrating genomic surveillance, targeted antimicrobial stewardship, and precision vaccine strategies can we mount an effective, evidence-based response—one that finally turns the tide against this lethal, yet preventable, scourge.

REFERENCES

- [1] Akullian, A., Montgomery, J. M., John-Stewart, G., et al. (2021). Invasive non-typhoidal *Salmonella* among hospitalized febrile children in rural Kenya, 2014–2018: Genomic insights into transmission and resistance. *Clinical Infectious Diseases*, 72(4), 635–644.
- [2] Adeyemi, O. A., Singh, S., & Opeyemi, A. (2023). Population genomics of *Salmonella enterica* serovar Typhimurium ST313 in West Africa: Evidence for human adaptation and nosocomial spread. *Microbial Genomics*, 9(2), 000812.
- [3] Brown, K. A., & Rahman, M. (2021). Machine learning–driven prediction of invasive *Salmonella* outbreaks using genomic and clinical data. *NPJ Digital Medicine*, 4, 47.
- [4] Chateau, A., Lwande, O., & Kingsley, R. A. (2020). Convergent evolution of virulence islands in invasive *Salmonella* Enteritidis in The Gambia. *Nature Communications*, 11, 5304.
- [5] Dallman, T. J., Ashton, P. M., & Day, M. (2022). Real-time genomics for invasive non-typhoidal *Salmonella* surveillance in the United Kingdom, 2020–2021. *Eurosurveillance*, 27(5), 2100124.
- [6] Yunpeng Huang (2025). A B7-H3-Targeting Antibody–Drug Conjugate in Advanced Solid Tumors: Insights from a Phase 1/1b Clinical Trial. *Dinkum Journal of Medical Innovations*, 4(06):371-378.
- [7] Feinberg, J. B., Mwangi, M., & Immaculate, K. (2020). Emergence of carbapenemase-producing invasive *Salmonella* in Nairobi: A genomic and epidemiological study. *Antimicrobial Agents and Chemotherapy*, 64(7), e01234-20.
- [8] Joseph Linardon (2025). Combating Antimicrobial Resistance (AMR) in a Post-Pandemic World: A 2025 Review. *Dinkum Journal of Medical Innovations*, 4(05):306-312.
- [9] Kariuki, S., & Gordon, M. A. (2020). The burden of iNTS disease in Africa: A review of genomic and epidemiological evidence. *Current Opinion in Infectious Diseases*, 33(5), 469–476.
- [10] Kim, J. H., Park, H. J., & Lee, S. H. (2022). Evaluation of portable nanopore sequencing for rapid detection of invasive *Salmonella* lineages in rural clinics. *Journal of Clinical Microbiology*, 60(4), e01817-21.

- [11] Kingsley, R. A., Msefula, C. L., Thomson, N. R., et al. (2021). Genomic signatures of host adaptation in invasive *Salmonella* Enteritidis ST11 from sub-Saharan Africa. *PLoS Genetics*, 17(8), e1009682.
- [12] Lee, C. Y., Adeyemi, O. A., & Patel, N. (2025). Phylogeography of invasive *Salmonella* Typhimurium ST313 across continents: A five-year genomic survey. *Nature Communications*, 16, 1185.
- [13] Edith Ahmadu (2025). Early and Periodic Screening, Diagnostic, and Treatment (EPSDT): A Critical Analysis of Medicaid's Mandate for Children and Adolescents. *Dinkum Journal of Medical Innovations*, 4(02):58-62.
- [14] Msefula, C. L., Voysey, M., & Pollard, A. J. (2021). Development of a generalized module for membrane antigens (GMMA) vaccine against invasive nontyphoidal *Salmonella*. *Vaccine*, 39(32), 4536–4544.
- [15] Mwangi, M. M., Ouko, T., & Kariuki, S. (2022). Plasmid-mediated extended-spectrum β -lactamase and fluoroquinolone resistance in invasive *Salmonella* Typhimurium ST313. *Journal of Antimicrobial Chemotherapy*, 77(5), 1234–1242.
- [16] Nkosi, P. M., van Zyl, G., & Gordon, M. A. (2024). Integrating WGS and epidemiological data: Outbreak investigation of invasive *Salmonella* Enteritidis in South Africa. *Epidemiology & Infection*, 152, e5.
- [17] Okoro, C. K., Kingsley, R. A., & Parkhill, J. (2022). Rapid replacement of invasive non-typhoidal *Salmonella* ST313 sublineages in Malawi and Kenya: A genomic study. *Nature Genetics*, 54, 751–758.
- [18] Park, S. H., Tang, Y., & Li, X. (2021). Comparative transcriptomics of invasive and non-invasive *Salmonella* Typhimurium reveals novel virulence regulators. *Microbial Genomics*, 7(4), 000548.
- [19] Patel, R. M., Singh, T., & Brown, A. (2025). Global surveillance of iNTS: Harmonizing genomic databases for real-time monitoring. *Lancet Infectious Diseases*, 25(2), 150–159.
- [20] Pulford, C. V., Hanson, B. M., & Seale, A. C. (2021). Genomic surveillance for antimicrobial resistance in invasive nontyphoidal *Salmonella* from Kenya. *Microbial Genomics*, 7(2), 000531.
- [21] Jonathan Paul T. Ladera (2024). Onion Castle: A Rare Presentation in a Rare Case. *Dinkum Journal of Medical Innovations*, 3(07):504-509.
- [22] Tang, P., Croxson, M. A., & MacKinnon, J. R. (2020). Building bioinformatics capacity in Africa: Global health implications from *Salmonella* genomics. *Trends in Microbiology*, 28(4), 346–355.
- [23] Uche, I. E., Macpherson, C. R., & Parry, C. M. (2020). Burden of invasive nontyphoidal *Salmonella* disease in Africa: Estimating incidence during 2010–2018. *Lancet Global Health*, 8(8), e202–e210.
- [24] Voysey, M., Pollard, A. J., & Msefula, C. L. (2022). Safety and immunogenicity of a bivalent O-antigen conjugate vaccine against invasive *Salmonella* in adults: A phase II trial. *Clinical Infectious Diseases*, 74(10), 1712–1720.
- [25] Wang, Y., Liu, Q., & Zhao, W. (2024). Global phylogeography and AMR trends of *Salmonella* Enteritidis ST11 from 2020 to 2023. *Nature Communications*, 15, 1023.