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Recent Advancements in Typhoid Fever Vaccination Strategies: A Review

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ABSTRACT

Typhoid fever, caused by *Salmonella Typhi*, continues to be a formidable public health challenge, particularly in low- and middle-income countries where access to clean water and sanitation is limited. This narrative review was conducted to systematically explore and synthesize the recent advancements in typhoid fever vaccination strategies, focusing on the efficacy of next-generation vaccines and the complexity of their real-world implementation. A comprehensive review of academic literature was undertaken to delineate the landscape of current and emerging prophylactic interventions. The major findings indicate that the introduction of Typhoid Conjugate Vaccines (TCVs) represents a paradigm shift, demonstrating superior immunogenicity, longer-lasting protection, and the critical advantage of suitability for use in infants, addressing a significant vulnerability in high-burden settings. Furthermore, these advancements are pivotal in combating the alarming rise of multidrug-resistant *S. Typhi* strains, offering a robust tool to mitigate antimicrobial resistance spread. Major recommendations arising from this synthesis underscore the need for accelerated and equitable TCV deployment integrated with water, sanitation, and hygiene (WASH) improvements, along with continued investment in vaccine development and optimized delivery research, especially in resource-limited contexts. In conclusion, the current trajectory in typhoid vaccination, particularly with TCVs, provides a potent pathway towards disease control and potential elimination. The implications of these findings are substantial, offering evidence-based guidance for policymakers to prioritize TCV introduction as a high-impact public health measure to reduce morbidity, mortality, and the societal burden of this ancient yet persistent disease.

Keywords: Typhoid Fever; Vaccination Strategies; Conjugate Vaccines; *Salmonella Typhi*; Public Health, Immunization

Abbreviations: WASH: Water, Sanitation, and Hygiene; AMR: Antimicrobial Resistance; MDR: Multidrug-Resistant; XDR: Extensively Drug-Resistant; TCVs: Typhoid Conjugate Vaccines; EPI: Expanded Programme on Immunization

Introduction

Typhoid fever, an acute systemic infection caused by the bacterium Salmonella enterica serovar Typhi (*S. Typhi*), remains a significant global health burden, primarily impacting regions with inadequate sanitation and poor access to safe drinking water (Masuet-Aumatell [1]). This bacterial pathogen is transmitted through the fecal-oral route, leading to a spectrum of illness ranging from mild febrile episodes to severe complications and death (Murthy, et al. [2]). The World Health Organization estimates that millions of cases occur annually, resulting in tens of thousands of deaths, disproportionately affecting young children and marginalized populations in endemic areas (Date, et al. [3]). The enduring prevalence of typhoid fever is compounded by rapid urbanization, climate change-related environmental challenges, and the continuous migration of susceptible populations (Ibrahim, et al. [4]). Historically, control efforts have focused on improving water, sanitation, and hygiene (WASH) infrastructure, which, while foundational, have proven insufficient on their own to achieve elimination in many highly endemic settings (Khanam, et al. [5]). The escalating global health threat posed by antimicrobial resistance (AMR) further complicates the management of typhoid fever, as multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *S. Typhi* are increasingly reported, rendering standard antibiotic regimens ineffective (Masuet-Aumatell [1]). This convergence of high disease incidence, inadequate infrastructure, and pervasive AMR necessitates a renewed and vigorous focus on prophylactic strategies (Nampota, et al. [6]).

Vaccination is recognized as a highly cost-effective public health intervention and a critical component of any comprehensive strategy for infectious disease control (Verma, et al. [7]). For typhoid fever, two primary vaccine types-the parenteral Vi capsular polysaccharide vaccine and the live oral Ty21a vaccine-have been available for decades (Date, et al. [3]). The Vi polysaccharide vaccine, based on the surface O-polysaccharide of *S. Typhi*, offers moderate efficacy but is not immunogenic in children under two years of age, and requires booster doses due to short-lived immunity (Verma, et al. [7]). The live oral Ty21a vaccine, a live attenuated strain, requires multiple doses for full efficacy and is also generally not recommended for children younger than six years, which limits its utility in the most vulnerable age group (Verma, et al. [7]). Furthermore, the effectiveness of both older-generation vaccines has been hindered by logistic challenges in mass vaccination campaigns and by the specific age limitations, failing to protect the most susceptible population segment (Date, et al. [3]). These constraints highlighted a substantial gap in the prophylactic toolkit, particularly for the youngest children in high-risk areas (Shakya [8]). The pressing need for a more effective, single-dose vaccine that could be administered to infants, offer durable protection, and be easily integrated into routine immunization programs catalyzed the development of next-generation vaccines (Nampota, et al. [6]). This innovative development led to the advent of Typhoid Conjugate Vaccines (TCVs), which covalently link the Vi capsular polysaccharide antigen to a protein carrier, such as tetanus toxoid or diphtheria toxoid (Shakya [8]). This conjugation process transforms the T-independent Vi antigen into a T-dependent one, fundamentally altering the immune response (Zhang, et al. [9]). TCVs elicit a robust immune response in infants and young children, overcoming the age limitations of the older polysaccharide vaccine (Gloeck, et al. [10]). Furthermore, TCVs induce immunologic memory, suggesting a longer duration of protection and potentially reducing the need for frequent booster doses, which simplifies immunization schedules (Nampota, et al. [6]). The World Health Organization (WHO) prequalification of TCVs and subsequent recommendations for their use in endemic countries marked a pivotal moment in the fight against typhoid fever, positioning these vaccines as the cornerstone of contemporary control efforts (Nampota, et al. [6]).Following the introduction of TCVs, the focus has broadened to include optimal strategies for their real-world deployment, examining cost-effectiveness, programmatic feasibility, and impact in diverse epidemiological settings (Ryckman, et al. [11]). The effective delivery of TCVs is critical, considering the varying national strategies and logistical hurdles across different endemic regions (Ntamwinja, et al. [12]). Cost-effectiveness modeling studies have been instrumental in informing policy decisions, demonstrating that TCV introduction, particularly in high-incidence settings, is a highly economically attractive intervention that can avert substantial morbidity and mortality ((Ryckman, et al. [11]). Furthermore, research is actively exploring the synergistic benefits of combining vaccination with improved sanitation efforts, recognizing that neither measure alone may be sufficient for ultimate elimination (Ibrahim, et al. [4]). The implementation strategies include mass campaigns for rapid disease reduction and integration into the Expanded Programme on Immunization (EPI) for sustainable, long-term control (Carter, et al. [13]). Research is also ongoing to understand the precise immunological correlates of protection and to refine mucosal vaccination strategies for potentially enhanced immunity at the primary site of infection ((Zhang, et al. [9]). The successful integration of TCVs into national immunization programs requires addressing policy priorities, particularly in Asian countries where the disease burden is particularly high (Carter et al., 2025). Moreover, examining the epidemiological models and economic analyses is crucial for tailoring strategies to specific regional needs (Mandaliya, et al. [14]). The impact of TCVs extends beyond direct disease prevention, as their use contributes indirectly to the containment of AMR by reducing the overall number of infections and, consequently, the reliance on antibiotics for treatment (Nampota, et al. [6]).

Given the dynamic nature of *S. Typhi* epidemiology, the recent advances in vaccine technology, and the evolving strategies for vaccine delivery, a comprehensive synthesis of the current state of knowledge is warranted. The landscape of typhoid fever prevention is rapidly changing, driven by new vaccine candidates and evidence-based implementation guidelines. Therefore, the purpose of this review is

to critically examine the recent advancements in typhoid fever vaccination strategies, specifically focusing on the efficacy and delivery of Typhoid Conjugate Vaccines, their role in combating antimicrobial resistance, and the programmatic challenges and opportunities for their widespread and effective adoption.

Statement of the Problem

Despite decades of intervention efforts, typhoid fever persists as a major public health crisis, particularly in developing nations, underscoring fundamental flaws and insufficient reach in current control paradigms (Masuet-Aumatell [1]). The central problem lies in the complex interplay of persistent environmental transmission routes, the inherent limitations of older-generation vaccines, and the rapidly escalating threat of drug-resistant *Salmonella Typhi* (Ibrahim, et al. [4]). Older vaccines, such as the Vi polysaccharide and the oral Ty21a, possess significant programmatic drawbacks that restrict their effective use in the most vulnerable populations (Date, et al. [3]). Specifically, the Vi polysaccharide vaccine is not reliably immunogenic in children under two years of age, precisely the age group facing high incidence rates and significant mortality risk, thereby leaving a crucial susceptibility gap (Verma, et al. [7]). Furthermore, both older vaccines require multiple doses or boosters for sustained protection, creating logistical hurdles and diminishing adherence in resource-constrained settings (Verma, et al. [7]). This failure of older-generation vaccines to adequately protect infants and young children has necessitated a critical re-evaluation of the prophylactic approach to typhoid fever (Shakya [8]). The emergence and global spread of MDR and XDR strains of *S. Typhi* represent an acute and growing crisis that fundamentally challenges the clinical management of the disease (Nampota, et al. [6]). As first-line and increasingly second-line antibiotics become ineffective, treatment options are severely limited, leading to higher rates of complicated illness, prolonged hospitalizations, and increased fatality rates (Masuet-Aumatell [1]). This antimicrobial resistance crisis is a formidable public health security threat, for which vaccination is considered a critical countermeasure, yet its role and the optimal strategies for leveraging it remain insufficiently defined and deployed (Nampota, et al. [6]). The problem is not merely the existence of effective vaccines like the newly introduced Typhoid Conjugate Vaccines (TCVs), but the substantial gap between their proven efficacy in clinical trials and their consistent, widespread, and equitable deployment in real-world endemic settings (Carter, et al. [13]).

While TCVs represent a major scientific advancement, addressing the limitations of older vaccines by being effective in infants and offering durable protection (Gloeck, et al. [10]), significant challenges persist in the operationalization of these new strategies. National strategies and the capacity to integrate TCVs into existing immunization programs vary widely across different countries, leading to uneven coverage and continued disease transmission hotspots (Ntamwinja, et al. [12]). The process of translating evidence on TCV efficacy and cost-effectiveness into concrete policy decisions and implementation roadmaps requires continuous, nuanced research (Ryckman, et al. [11]). Specifically, there is an ongoing need to critically examine the economic analyses and epidemiological models to tailor implementation strategies effectively to diverse local conditions, which often proves difficult due to data scarcity and contextual variation (Mandaliya, et al. [14,15]). Moreover, the synergistic effect of combining TCV introduction with necessary improvements in WASH infrastructure, while logically sound, requires further critical investigation to determine the most cost-effective and impactful combination of interventions (Ibrahim, et al. [4]). The lack of uniform global policy priorities and logistical challenges in Asia and Africa, the regions with the highest burden, further compound the problem of achieving sustained and equitable control (Carter, et al. [13,14]. Therefore, despite the technological breakthrough of TCVs, the persistence of typhoid fever highlights a critical gap in translating scientific advancement into effective, universal public health practice. A comprehensive review is necessary to critically synthesize the most recent advancements, address the residual operational challenges, and delineate clear pathways for accelerated, evidence-based TCV deployment to combat both the disease and the parallel threat of antimicrobial resistance.

Research Objectives

This review aims to achieve the following objectives:

1. To evaluate the comparative efficacy, immunogenicity, and safety profiles of Typhoid Conjugate Vaccines (TCVs) against older-generation typhoid vaccines (Vi polysaccharide and Ty21a) based on the latest clinical and field trial evidence.
2. To examine the role of Typhoid Conjugate Vaccines as a public health intervention in the context of the escalating threat of antimicrobial-resistant *Salmonella Typhi* strains.
3. To identify the programmatic challenges, cost-effectiveness evidence, and optimal strategies for the sustainable and equitable implementation of TCVs within national immunization programs in endemic countries.

Literature Review

The management of typhoid fever, a pervasive bacterial infection, has long been a major global health challenge, requiring a multi-faceted approach involving water, sanitation, and hygiene (WASH) improvements, surveillance, and chemoprophylaxis (Kishore, et al. [16]). Vaccination, in particular, stands out as a critical and highly impactful tool for prevention (Date, et al. [3]). For decades, two conventional vaccines formed the backbone of prophylactic efforts: the Vi capsular polysaccharide vaccine and the live oral Ty21a vaccine (Verma, et al. [7]). The underlying principle of the Vi polysaccharide vaccine is the induction of an immune response against the Vi antigen, an O-polysaccharide covering the surface of *S. Typhi* (Verma, et al. [7]). While effective in older children and adults, this vaccine is T-cell independent, meaning it does not elicit a robust immune response in

children under two years of age and generally requires booster doses due to a lack of long-term immunological memory (Verma, et al. [7,9]) Conversely, the live attenuated Ty21a vaccine is designed to stimulate mucosal immunity in the gut, the primary site of infection, but requires an inconvenient multi-dose schedule and is also unsuitable for infants (Verma, et al. [7,9]). The inherent limitations of these older vaccines-specifically, their inability to protect the most vulnerable infant population and the challenges of sustaining coverage-created a significant gap in the global typhoid control strategy (Date, et al. [3]).

The escalating crisis of antimicrobial resistance (AMR) in *S. Typhi* necessitated a paradigm shift in prophylactic strategies (Masuet-Aumatell [1]). The emergence of multidrug-resistant (MDR) strains, followed by extensively drug-resistant (XDR) strains, has severely constrained treatment options and increased mortality, particularly in highly endemic regions (Nampota, et al. [6]). This realization highlighted that an effective vaccine could serve a dual purpose: preventing disease and, crucially, reducing the need for antibiotics, thereby indirectly mitigating the selection pressure for resistant bacteria (Nampota, et al. [6]). This critical need spurred the development and rapid advancement of Typhoid Conjugate Vaccines (TCVs). TCVs represent a significant immunological innovation where the Vi capsular polysaccharide is covalently linked to a protein carrier (e.g., tetanus toxoid), transforming the antigen from a T-cell independent to a T-cell dependent one (Shakya, et al. [8,10]). This conjugation allows for immunogenicity in infants as young as six months, the induction of robust immunological memory, and potentially longer-lasting protection after a single dose, addressing the core programmatic failings of the older vaccines (Shakya, et al. [8,6]). The advent of TCVs, now prequalified by the WHO, has led to a major focus on evidence generation regarding their efficacy and real-world impact ((Gloeck, et al. [10]). Batool, et al. [17], through a systematic review and meta-analysis, established the high efficacy of TCVs against culture-confirmed *S. Typhi* in endemic countries, providing a strong evidence base for their adoption. This efficacy is particularly vital when considering the high burden of disease and fatality rates in high-incidence areas (Murthy, et al. [2]). The consensus among scholars is that TCVs are a step-change in control efforts, primarily because they can be successfully administered in routine childhood immunization schedules, reaching the most susceptible age group (Nampota, et al. [6,13]). The ability to use TCVs to prevent disease, promote health equity, and actively counter drug-resistant typhoid fever is a pivotal finding in recent literature (Nampota, et al. [6]).

Beyond efficacy, the literature has critically examined the strategic implementation of TCVs. The deployment strategy is often modeled as a combination of mass catch-up campaigns followed by integration into the Expanded Programme on Immunization (EPI) (Carter, et al. [13]). (Ryckman, et al. [11]) conducted a cost-effectiveness modeling study in India, revealing that various TCV introduction strategies are highly cost-effective, with the greatest health and economic benefits generally achieved through early and widespread introduction. Lee, et al. [15] further explored effective strategies for TCV delivery, drawing health and economic insights from outbreak settings, underscoring the vaccine's utility in both routine prevention and emergency response. However, effective implementation is not without its challenges. Ntamwinja, et al. [12] highlight the variability in national strategies and logistical challenges in the fight against typhoid fever in African countries like Kenya, emphasizing the urgency to act and the need for localized solutions. Similarly, Mandaliya et al. (2025) underline the need for further scoping review to examine epidemiological models and economic analyses, which are crucial for tailoring TCV strategies to specific contexts.

The scholarly discussion has also shifted toward integrated control measures, recognizing that vaccination alone may not suffice for elimination. (Ibrahim, et al. [4]) explore the concept of combining vaccination with sanitation methods for better public health policies, asserting that a synergistic approach will yield greater reductions in transmission. This view is supported by the dynamics of typhoid fever transmission models that consider environmental bacteria concentration and emphasize the value of improving immunization initiatives alongside environmental control (Alemneh, et al. [18]). Furthermore, a thorough understanding of localized risk factors for typhoid fever remains essential for targeting interventions effectively (Boakye Okyere, et al. [19]). In summary, the recent literature presents a compelling case for TCVs as a powerful, versatile tool against typhoid fever and AMR. The focus has moved beyond the simple question of 'effectiveness' to the more complex 'how-to' of equitable and sustainable deployment, critically examining programmatic challenges, cost-effectiveness, and the strategic integration of vaccination with foundational WASH improvements to move closer to the goal of typhoid elimination (Khanam, et al. [5,16]).

Results

The synthesis of the literature, guided by the established research objectives, yielded substantial findings regarding the recent advancements in typhoid fever vaccination strategies. These results directly address the comparative performance of TCVs, their pivotal role in combating antimicrobial resistance, and the critical factors influencing their global programmatic implementation.

Comparative Efficacy, Immunogenicity, and Safety Profiles of TCVs

The critical evaluation of the literature confirms a definitive advancement with the introduction of Typhoid Conjugate Vaccines (TCVs) over older-generation options, particularly concerning immunogenicity in the most vulnerable age groups. Studies consistently demonstrate that TCVs elicit a robust immune response in infants as young as six months of age, overcoming the major limitation of the Vi polysaccharide vaccine, which is non-immunogenic in children under two years (Shakya [8,6]). The conjugation of the Vi antigen to a protein carrier fundamentally changes the immunological profile, induc-

ing a T-cell dependent response which results in superior immunogenicity and the establishment of immunological memory, suggesting longer-lasting protection (Zhang, et al. [9,10]). Field trial evidence, synthesized in reviews such as that by Batool, et al. [17], confirms the high efficacy of TCVs against culture-confirmed *Salmonella Typhi* in endemic populations. This contrasts with the older vaccines' shorter duration of protection, which necessitated multiple booster doses, complicating immunization schedules (Verma, et al. [7]). Furthermore, TCVs are well-tolerated, demonstrating safety profiles comparable to other vaccines integrated into routine childhood schedules (Gloeck, et al. [10]). The critical finding is the ability of TCVs to provide protection after a single dose and to be administered concurrently with other routine pediatric vaccines, which significantly simplifies the delivery logistics and increases the potential for higher coverage rates (Nampota-Nkomba, et al. [6]). The collective data strongly supports the TCVs as the superior prophylactic tool due to their capacity to protect infants, provide durability, and simplify administration.

The Role of TCVs in Combating Antimicrobial-Resistant *Salmonella Typhi*

A key finding emerging from the review is the strategic importance of TCVs as a core intervention against the escalating global threat of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *S. Typhi* (Masuet-Aumatell [1])). The literature clearly frames TCV introduction as a high-impact measure to mitigate antimicrobial resistance (AMR) by reducing the overall incidence of typhoid fever (Nampota-Nkomba, et al. [6]). By preventing the infection, TCVs directly decrease the demand for antibiotics used in treatment, thereby reducing the selective pressure that drives the evolution and spread of resistant strains (Nampota-Nkomba, et al. [6]). The research underscores that the impact of TCVs extends beyond mere disease prevention; it is a critical public health strategy to counter the rise of drug-resistant typhoid fever strains, which complicate clinical management and increase mortality (Nampota-Nkomba, et al. [6]). The high rates of AMR are a primary concern in typhoid-endemic regions (Masuet-Aumatell [1]), and the introduction of a highly effective vaccine that targets the most common age group for infection is a powerful, non-antibiotic intervention (Shakya, et al. [8]). This evidence establishes TCVs as an essential tool in global efforts to contain the broader AMR crisis, adding a crucial public health dimension to their primary role as a preventive medicine (Nampota-Nkomba, et al. [6]).

Programmatic Challenges, Cost-Effectiveness, and Implementation Strategies

The analysis of the literature reveals that the successful transition from vaccine development to widespread implementation is highly dependent on addressing complex programmatic and economic challenges. Cost-effectiveness is a major determinant in policy decision-making for endemic countries (Mandaliya, et al. [14]). Ryckman, et al. [11] demonstrated through modeling studies in India that TCV introduction is a highly cost-effective public health strategy, particularly when targeted at high-incidence populations or integrated early into routine immunization. Lee, et al. [15] further emphasize the strong health and economic insights derived from effective TCV delivery strategies in outbreak settings, highlighting the economic justification for early investment. However, the review also highlights significant challenges in translating this evidence into uniform practice. National strategies for the fight against typhoid fever and other invasive salmonellosis vary significantly, leading to non-uniform TCV adoption and coverage (Ntamwinja, et al. [12,13]) identify the need for advancing TCV implementation in Asian countries through regional policy priorities, suggesting that implementation is critically dependent on context-specific policy frameworks. Furthermore, the literature stresses the importance of combining TCV deployment with improvements in water, sanitation, and hygiene (WASH) (Ibrahim, et al. [4]). This integrated approach is viewed as essential for achieving sustained control and movement toward elimination, as modeling studies suggest that vaccination alone may not fully interrupt transmission in highly contaminated environments (Alemneh, et al. [18]). The literature consistently recommends a dual strategy: mass catch-up campaigns to rapidly reduce disease burden, followed by sustainable integration into the routine Expanded Programme on Immunization (EPI) for long-term control (Nampota [6,13]). This strategic integration demands continuous research to optimize delivery, address logistical hurdles, and ensure equitable access to realize the full public health potential of TCVs (Mandaliya, et al. [14]).

Discussion

The results of this narrative review underscore that the development and introduction of Typhoid Conjugate Vaccines (TCVs) represent the most significant advancement in typhoid fever control in recent history, effectively addressing the limitations of older-generation vaccines and providing a potent tool against emerging public health threats. The finding that TCVs demonstrate superior immunogenicity in infants, as highlighted by (Nampota [6,8]), is critically important. This advancement fundamentally alters the disease control landscape by allowing protection of the most susceptible age cohort, which was previously a major vulnerability in high-endemic settings (Verma, et al. [7]). The T-cell dependent mechanism, as discussed by Zhang, et al. [9], is the key to this improved performance, facilitating long-term memory and simplifying the immunization schedule to a single dose, which critically impacts delivery feasibility and coverage rates in resource-limited contexts.

The established role of TCVs in mitigating the pervasive global threat of antimicrobial resistance (AMR) is another pivotal result demanding focused interpretation (Nampota [6]). The escalating prevalence of MDR and XDR *S. Typhi*, as documented by Masuet Aumatell [1], elevates the vaccine from a simple preventive measure to a strategic element of global health security. The critical interpretation is that TCV deployment is not merely a typhoid control measure, but an indi-

rect, yet highly effective, antibiotic-sparing strategy. By averting infections, TCVs systematically reduce the volume of antibiotic consumption for typhoid treatment, thereby dampening the selection pressure for resistance (Nampota [6]). This implication suggests that economic analyses of TCV implementation, such as those by (Ryckman, et al. [11]), should fully incorporate the substantial societal and health system benefits of AMR containment to provide a truly comprehensive picture of their value. Despite the strong evidence base for TCV efficacy and cost-effectiveness, the review highlights significant ongoing programmatic and policy implementation challenges (Ntamwinja, et al. [12]). While studies confirm TCVs are highly cost-effective (Ryckman, et al. [11]), the interpretation of this finding must be balanced against the reality of competing health priorities and varied national policy capacity, especially in high-burden regions (Carter, et al. [13]). The lack of universal, context-specific implementation roadmaps is a major constraint. A crucial implication here is the need for enhanced research into 'implementation science'—focusing on optimizing delivery strategies, logistical adaptation, and the political economy of vaccine introduction, as suggested by Mandaliya. et al. [14].

Furthermore, the emphasis in the literature on the combined approach-TCVs integrated with improvements in water, sanitation, and hygiene (WASH) (Ibrahim, et al. [4])-is a critical point of discussion. This is an explicit recognition that while TCVs offer powerful individual protection and immediate disease reduction, sustainable elimination requires addressing the environmental root cause of transmission (Alemneh, et al. [18]). The successful long-term strategy, therefore, is synergistic: TCVs provide rapid, robust control, buying crucial time for countries to implement fundamental and often slower-paced infrastructural WASH improvements. In conclusion, the current phase of typhoid control is defined by the technical superiority of TCVs; the discussion must now pivot to critical, context-driven strategies for equitable access and sustained integration with environmental controls to realize the full potential of this public health breakthrough.

Conclusion & Recommendations

This comprehensive review of recent advancements in typhoid fever vaccination strategies concludes that the introduction of Typhoid Conjugate Vaccines (TCVs) represents a fundamental and necessary shift in the global control paradigm for *Salmonella Typhi*. TCVs are unequivocally superior to older-generation vaccines, primarily due to their proven immunogenicity and safety profile in infants, suitability for single-dose administration, and the critical establishment of long-term immunological memory. This technological leap addresses the central programmatic flaw of the previous vaccines, which failed to protect the most vulnerable age group. Furthermore, the review establishes TCVs as a vital public health security measure, acting as a crucial intervention in the global effort to mitigate the escalating threat of antimicrobial-resistant *S. Typhi*. While evidence confirms the compelling cost-effectiveness of TCVs, the successful realization of their full public health potential remains contingent on overcoming complex operational and policy challenges in endemic settings. The pathway to sustained control and ultimate elimination is clearly defined as the strategic and simultaneous integration of widespread TCV deployment with foundational improvements in water, sanitation, and hygiene infrastructure.

Based on the critical findings of this review, which highlights the superior efficacy and programmatic advantages of Typhoid Conjugate Vaccines (TCVs) and the urgent need to address antimicrobial resistance, several key recommendations are necessary to accelerate global typhoid control efforts. National governments in all endemic regions must prioritize the rapid and equitable introduction of TCVs into their routine Expanded Programme on Immunization (EPI) schedules. This implementation should be immediately preceded by a catch-up campaign targeting all children up to 15 years, where feasible, to quickly reduce the circulating disease burden and interrupt transmission cycles, which is crucial for reducing infection and subsequent antibiotic use.

Furthermore, international health organizations and national policy bodies must formally recognize and mandate the deployment of TCVs as a core, non-antibiotic intervention within national action plans for Antimicrobial Resistance (AMR) containment. This requires dedicating specific, sustained funding streams to ensure continuous TCV supply and delivery, thereby reducing the selective pressure that drives antibiotic resistance evolution. Achieving high and equitable coverage, particularly among the most vulnerable populations, is essential to realizing the full public health impact of this strategy.

To overcome operational hurdles, there must be a concentrated, multilateral investment in implementation science research. This research should focus on operational optimization, logistical cost analysis, and the development of adaptable, context-specific delivery models to address the programmatic challenges identified in varied endemic settings. Simultaneously, public health policy and funding mechanisms must move away from siloed interventions, instead mandating and funding the strategic integration of TCV deployment with concurrent, substantial investments in community and public water, sanitation, and hygiene (WASH) infrastructure improvement programs. This combined approach is vital to achieving a long-term, synergistic impact on *S. Typhi* transmission and moving toward sustained disease elimination. Finally, post-licensure and post-introduction surveillance systems must be significantly strengthened to continuously monitor the long-term effectiveness, duration of protection, and impact of TCVs on antimicrobial-resistant *S. Typhi* strains in real-world settings. This robust monitoring is essential for providing the critical data needed for future policy adjustments, optimizing booster dose schedules, and strengthening the economic and public health case for the continued TCV funding and utilization globally.

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