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Gene Regulation and Antibiotic Response in Human Paratyphoid Fever: Molecular Mechanisms and Clinical Implications

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A B S T R A C T

Paratyphoid fever remains a significant public health challenge in many parts of the world, particularly in regions with limited sanitation and healthcare infrastructure. Caused by *Salmonella enterica* serovars Paratyphi, the disease is characterized by systemic infection resulting from complex host–pathogen interactions. Increasing evidence suggests that gene regulation plays a central role in determining bacterial virulence, host immune response, and clinical outcome. In parallel, antibiotic therapy while essential for disease management exerts profound selective pressure that reshapes gene expression patterns in both the pathogen and the human host. This review synthesizes current knowledge on the regulatory mechanisms governing *Salmonella Paratyphi* pathogenesis and examines how antibiotic exposure modulates bacterial and host gene expression during infection. Key bacterial regulatory networks involved in virulence, stress adaptation, persistence, and antimicrobial resistance are discussed alongside host immune and inflammatory gene responses that influence disease severity and treatment outcomes. The review further highlights how antibiotics act not only as antimicrobial agents but also as modulators of host–pathogen gene regulatory dynamics. By integrating molecular mechanisms with clinical implications, this review provides a comprehensive perspective on antibiotic response in paratyphoid fever and underscores the importance of systems-level approaches for improving diagnosis, treatment optimization, and antimicrobial stewardship. Understanding gene regulation in the context of antibiotic therapy may inform future precision medicine strategies and support the development of more effective interventions for paratyphoid fever management.

Introduction

Paratyphoid fever remains a significant yet underrecognized public health concern, particularly in low- and middle-income countries where access to clean water, sanitation, and timely healthcare remains limited (Crump & Mintz, 2010; Gibani *et al.,* 2018; GBD 2017 Typhoid and Paratyphoid Collaborators, 2019). Caused

primarily by *Salmonella enterica* serovars Paratyphi A, B, and C, paratyphoid fever presents as a systemic febrile illness with clinical features that often overlap with typhoid fever, making accurate diagnosis and targeted management challenging (Xie *et al.,* 2022; Kuehn *et al.,* 2025). Despite advances in antimicrobial therapy, paratyphoid fever continues to contribute substantially to morbidity, prolonged illness, and economic burden in endemic regions (Crump & Mintz, 2010; Xie *et al.,* 2022; Wang *et al.,* 2024). The pathogenesis of paratyphoid fever is a complex, multistage process involving intricate interactions between the invading pathogen and the human host. It is highly similar to typhoid fever, often beginning with a 6–30-day incubation period. Following ingestion, *Salmonella* Paratyphi must successfully survive gastric acidity, invade intestinal epithelial cells, and persist within host immune cells to establish systemic infection (J Barton *et al.,* 2021; Xie *et al.,* 2022; Bhandari *et al.,* 2024). These processes are tightly regulated at the genetic level, with coordinated expression of virulence genes enabling bacterial adaptation to diverse host microenvironments (J Barton *et al.,* 2021; Bhandari *et al.,* 2024). Simultaneously, the host mounts a dynamic immune response characterized by regulated expression of genes involved in innate and adaptive immunity, inflammation, and immune modulation (Wang *et al.,* 2024).

Gene regulation plays a central role in determining both disease progression and clinical outcome in paratyphoid fever. In *Salmonella* Paratyphi, regulatory networks govern the expression of pathogenicity islands, stress response genes, metabolic pathways, and survival mechanisms that allow persistence under hostile host conditions (Pradhan & Negi, 2019). On the host side, transcriptional changes influence susceptibility, immune effectiveness, and the balance between pathogen clearance and tissue damage (Jo, 2019). Understanding these regulatory mechanisms is therefore critical for elucidating disease biology beyond conventional clinical descriptions.

Antibiotic therapy remains the cornerstone of paratyphoid fever management; however, treatment outcomes are increasingly complicated by variable therapeutic responses and the emergence of antimicrobial resistance (Kuehn *et al.,* 2022). Antibiotics not only exert bactericidal or bacteriostatic effects but also induce profound changes in bacterial gene expression, influencing stress adaptation, virulence modulation, and resistance development (Zhang & Cheng, 2022). In parallel, antibiotics can alter host gene expression profiles by modulating immune responses, inflammatory pathways, and host–microbiome interactions (Morgun *et al.,* 2015; Zhang & Chen, 2019). These antibiotic-induced regulatory changes have important implications for treatment efficacy, disease resolution, and long-term clinical outcomes.

Despite growing evidence highlighting the importance of gene regulation in infectious diseases, a comprehensive synthesis focusing specifically on the interplay between gene regulation and antibiotic response in human paratyphoid fever remains limited (Biswas *et al.,* 2022; Xie *et al.,* 2022). Most existing studies address isolated molecular pathways or clinical outcomes without integrating host and pathogen regulatory responses into a unified framework (Näpflin *et al.,* 2019; Yu *et al.,* 2022). This gap hampers the translation of molecular insights into optimized therapeutic strategies and precision medicine approaches for paratyphoid fever.

The present review aims to address this gap by critically examining current evidence on gene regulation in *Salmonella* Paratyphi and the human host, with particular emphasis on antibiotic-induced molecular responses. By integrating mechanistic insights with clinical implications, this review seeks to provide a cohesive understanding of how regulatory pathways shape disease progression, treatment response, and resistance development in paratyphoid fever. Such an integrative perspective is essential for informing future research directions and improving clinical management strategies in endemic and emerging settings.

Epidemiology and Clinical Features of Human Paratyphoid Fever

Paratyphoid fever is a systemic infectious disease caused by *Salmonella enterica* serovars Paratyphi A, B, and C, with Paratyphi A accounting for the majority of reported cases globally. Although often grouped with typhoid fever under the umbrella of enteric fever, paratyphoid fever demonstrates distinct epidemiological patterns and clinical characteristics that warrant independent consideration (Crump & Mintz, 2010; Xie *et al.,* 2022; Wang *et al.,* 2024; Kuehn *et al.,* 2025). The disease remains endemic in many parts of South and Southeast Asia, sub-Saharan Africa, and selected regions of Latin America, where infrastructural limitations and socioeconomic factors facilitate sustained transmission (Centers for Disease Control and Prevention, 2023).

Epidemiological data indicate that paratyphoid fever disproportionately affects adolescents and young to middle-aged adults, particularly those living in densely populated urban environments or regions with inadequate water sanitation and hygiene infrastructure in India (John *et al.,* 2023). International travel to endemic areas has further contributed to the global dissemination of paratyphoid fever, leading to sporadic outbreaks and imported cases in non-endemic, high-income countries (Findlater & Bogoch, 2018; Muresu *et al.,* 2020). Unlike typhoid fever, for which vaccination strategies are increasingly available, effective vaccines targeting *Salmonella* Paratyphi remain limited, posing additional challenges for disease prevention and control (Xie *et al.,* 2022).

Transmission of paratyphoid fever occurs primarily through the fecal–oral route, often via consumption of contaminated food or water. Asymptomatic carriers play a critical role in sustaining transmission cycles, particularly in endemic settings where routine screening is uncommon. Environmental persistence of *Salmonella* Paratyphi and its ability to survive under adverse conditions further contribute to periodic outbreaks, especially during seasons associated with flooding or compromised water supplies (Teh, Chua & Thong, 2014; Liu, Whitehouse & Li, 2018; Bhandari *et al.,* 2024; Jia *et al.,* 2024).

Clinically, paratyphoid fever presents with a spectrum of manifestations ranging from mild febrile illness to severe systemic disease. The incubation period typically spans 6–14 days, after which patients commonly develop prolonged fever, malaise, headache, abdominal discomfort, and anorexia. Gastrointestinal symptoms such as diarrhea or constipation may be present, though these features are often nonspecific and overlap substantially with other febrile illnesses endemic to similar regions (Xie *et al.,* 2022; Kuehn *et al.,* 2025).

As the disease progresses, patients may exhibit hepatosplenomegaly, relative bradycardia, and rose spot–like rashes, although these classical signs are less consistently observed compared with typhoid fever (Northern Territory Government, n.d.; National Centre for Infectious Diseases, n.d.). Laboratory findings frequently include leukopenia, mild anemia, and elevated inflammatory markers, reflecting systemic immune activation and bacterial dissemination (Shrivastava *et al.,* 2015; Etouke *et al.,* 2023). In severe or untreated cases, complications such as intestinal hemorrhage, perforation, encephalopathy, and septicemia may occur, particularly among immunocompromised individuals or those with delayed access to appropriate antimicrobial therapy (Harris & Brooks, 2019).

Diagnosis of paratyphoid fever remains challenging due to the lack of highly sensitive and specific diagnostic tools (Alhaj-Qasem *et al.,* 2020). Blood culture is considered the gold standard; however, its sensitivity is influenced by prior antibiotic exposure and the timing of sample collection. Serological assays and molecular diagnostic methods are increasingly utilized, yet variability in performance and limited availability in resource-constrained settings continue to impede early and accurate diagnosis (Shrivastava *et al.,* 2015; Etouke *et al.,* 2023). These diagnostic limitations contribute to underreporting and misclassification, complicating epidemiological surveillance and burden estimation.

From a clinical perspective, the nonspecific presentation and overlapping symptomatology of paratyphoid fever underscore the importance of understanding underlying molecular and genetic mechanisms that drive disease variability and treatment response (Xie *et al.,* 2022; Wang *et al.,* 2023). Epidemiological patterns and clinical heterogeneity are increasingly recognized as reflections of complex host–pathogen interactions, including gene regulatory processes that influence bacterial virulence, host immunity, and antibiotic effectiveness (Pandit *et al.,* 2012; Kitamoto *et al.,* 2016; Xie *et al.,* 2022).

Integrating epidemiological and clinical insights with molecular data is therefore essential for advancing both diagnostic accuracy and therapeutic strategies in paratyphoid fever management.

Pathogenesis of *Salmonella* Paratyphi Infection

The pathogenesis of *Salmonella enterica* serovar Paratyphi infection involves a highly coordinated sequence of events that enables the pathogen to invade the host, evade immune defenses, and establish systemic disease (Fàbrega & Vila, 2013; Barton *et al.,* 2021). Unlike non-typhoidal *Salmonella* infections, which are typically confined to the gastrointestinal tract, *Salmonella* Paratyphi exhibits a unique ability to disseminate beyond the intestine, resulting in a prolonged systemic illness (Gal-Mor *et al.,* 2014; Soumya *et al.,* 2024). This invasive phenotype is underpinned by tightly regulated virulence mechanisms that are activated in response to host environmental cues.

Following ingestion of contaminated food or water, *Salmonella* Paratyphi must first survive the acidic environment of the stomach, a process facilitated by acid tolerance response systems and stress-induced gene expression pathways (Foster, 1993; Prior *et al.,* 2009; Han *et al.,* 2024). Upon reaching the small intestine, the bacteria adhere to and invade intestinal epithelial cells, particularly through specialized microfold (M) cells overlying Peyer's patches (Jepson & Clark, 2001; Zheng *et al.,* 2022). This invasion is mediated by a suite of virulence factors encoded within Salmonella pathogenicity island 1 (SPI-1), which orchestrates cytoskeletal rearrangements and bacterial internalization (Guiney & Lesnick, 2005; Kombade & Kaur, 2021).

Once internalized, *Salmonella* Paratyphi is engulfed by host phagocytic cells, including macrophages and dendritic cells, where it resides within a modified intracellular compartment known as the Salmonella-containing vacuole (SCV) (Steele-Mortimer, 2008; Hurley *et al.,* 2014; Kurtz *et al.,* 2017; Li, 2022). Survival and replication within this niche are critically dependent on genes encoded by Salmonella pathogenicity island 2 (SPI-2), which regulate intracellular trafficking, nutrient acquisition, and resistance to host antimicrobial mechanisms (Author, Year). The ability to persist within immune cells allows *Salmonella* Paratyphi to disseminate via the lymphatic and circulatory systems to systemic sites such as the liver, spleen, and bone marrow (Chakravortty *et al.,* 2002; Forest *et al.,* 2010; Newson *et al.,* 2025).

Host immune recognition of *Salmonella* Paratyphi is initiated through pattern recognition receptors, including Toll-like receptors and nucleotide-binding oligomerization domain–like receptors, which detect conserved bacterial components such as lipopolysaccharide and flagellin (Franchi, 2011; Bryant, 2021). Activation of these receptors triggers downstream signaling cascades that induce pro-inflammatory cytokine production and antimicrobial effector responses (Kolls *et al.,* 2008; Mogensen, 2009; Stark & Mueller, 2012; Li, 2021). However, *Salmonella* Paratyphi has evolved multiple strategies to modulate and evade these host defenses, including alteration of surface antigens, suppression of antigen presentation, and interference with host signaling pathways (Wang *et al.,* 2020; Schultz *et al.,* 2021; Zhou *et al.,* 2023).

A defining feature of *Salmonella* Paratyphi pathogenesis is the precise temporal and spatial regulation of virulence gene expression (Laughlin *et al.,* 2014; Cohen *et al.,* 2022). Environmental signals such as pH, oxygen tension, osmolarity, and nutrient availability act as cues that modulate transcriptional programs necessary for different stages of infection (Fang *et al.,* 2016; Pasqua *et al.,* 2022). This regulatory flexibility enables the pathogen to transition between extracellular survival, epithelial invasion, and intracellular persistence, optimizing fitness within the human host (Malet *et al.,* 2022).

In addition to bacterial factors, host genetic and immunological variability plays a significant role in shaping disease outcome (Soni *et al.,* 2024). Differences in host immune gene expression, inflammatory responses, and cellular signaling pathways influence susceptibility to infection, severity of clinical manifestations, and the efficiency of bacterial clearance (van der Made., 2022). These host determinants interact dynamically with bacterial regulatory systems, forming a complex host–pathogen interface that governs the trajectory of paratyphoid fever.

Understanding the pathogenic mechanisms of *Salmonella* Paratyphi infection provides a critical foundation for examining how antibiotics influence both bacterial survival strategies and host responses (Harris & Brooks, 2013).

As antibiotic exposure introduces additional selective pressures, it further alters gene regulatory networks involved in virulence, stress adaptation, and persistence, underscoring the importance of integrating pathogenesis with gene regulation and therapeutic response in paratyphoid fever (Geisinger & Isberg, 2017).

Gene Regulation in *Salmonella Paratyphi*

The ability of *Salmonella enterica* serovar Paratyphi to establish infection and persist within the human host is fundamentally dependent on precise and dynamic regulation of gene expression. Rather than constitutive expression of virulence determinants, *Salmonella* Paratyphi employs sophisticated regulatory networks that enable rapid adaptation to fluctuating environmental conditions encountered during different stages of infection (Mark Clements *et al.,* 2001). These regulatory mechanisms coordinate metabolic activity, stress responses, virulence factor production, and immune evasion strategies essential for systemic disease development.

Bacterial Regulatory Systems

Central to gene regulation in *Salmonella* Paratyphi are two-component regulatory systems, which allow the bacterium to sense environmental signals and translate them into appropriate transcriptional responses. These systems typically consist of a membrane-bound sensor kinase and a cytoplasmic response regulator that modulates gene expression in response to stimuli such as pH changes, osmolarity, nutrient limitation, and antimicrobial stress. Key two-component systems implicated in *Salmonella* pathogenesis regulate genes involved in virulence, intracellular survival, and resistance to host-derived antimicrobial peptides (Murret-Labarthe *et al.,* 2020).

In addition to two-component systems, alternative sigma factors play a crucial role in global transcriptional regulation. These sigma factors enable *Salmonella* Paratyphi to redirect RNA polymerase activity toward specific gene sets under stress conditions, including oxidative stress, nutrient deprivation, and stationary-phase growth. Such regulatory flexibility enhances bacterial survival within hostile host environments and contributes to long-term persistence during systemic infection (Park *et al.,* 2024)

Regulation of Virulence-Associated Genes

Virulence gene expression in *Salmonella* Paratyphi is tightly controlled and highly context-dependent. Salmonella pathogenicity islands, particularly SPI-1 and SPI-2, encode key determinants required for epithelial invasion and intracellular survival, respectively. The expression of SPI-1 genes is predominantly induced during the initial stages of infection, facilitating bacterial entry into intestinal epithelial cells, while SPI-2 gene expression is upregulated following intracellular localization within host phagocytes (Lou *et al.,* 2019).

This temporal regulation is achieved through intricate networks involving transcriptional activators, repressors, and regulatory cross-talk between different pathogenicity islands. Environmental cues such as oxygen availability, magnesium concentration, and intracellular pH act as signals that trigger coordinated transcriptional shifts, ensuring that virulence factors are expressed only when beneficial for bacterial fitness. Dysregulation of these pathways has been shown to impair bacterial survival and attenuate virulence, highlighting their central role in disease progression (Kitamoto *et al.,* 2016).

Global Transcriptional Regulators and Stress Response Pathways

Beyond pathogenicity islands, global transcriptional regulators orchestrate broad gene expression programs that influence metabolism, stress adaptation, and survival. These regulators integrate multiple environmental signals and coordinate responses to oxidative stress, nitrosative stress, and nutrient limitation encountered within host immune cells. Such stress response pathways are essential for maintaining cellular homeostasis and preventing bactericidal damage during infection.

Small regulatory RNAs and post-transcriptional control mechanisms further refine gene expression in *Salmonella* Paratyphi. By modulating mRNA stability and translation efficiency, these regulatory elements allow rapid and reversible adjustments to protein production, enhancing bacterial adaptability under fluctuating host conditions. Emerging evidence suggests that these post-transcriptional mechanisms also contribute to antibiotic tolerance and persistence phenotypes, linking gene regulation directly to therapeutic response.

Epigenetic and Adaptive Regulatory Mechanisms

In addition to classical transcriptional regulation, epigenetic mechanisms such as DNA methylation have been implicated in controlling gene expression patterns in *Salmonella* species. These modifications can influence promoter accessibility and regulatory protein binding, leading to heritable yet reversible changes in gene expression.

Such epigenetic regulation enables population-level heterogeneity, allowing subsets of bacteria to adopt alternative phenotypic states that enhance survival under selective pressures, including antibiotic exposure.

Collectively, the gene regulatory architecture of *Salmonella* Paratyphi provides the molecular foundation for its pathogenicity, adaptability, and resilience within the human host. Understanding these regulatory systems is critical for interpreting how antibiotics perturb bacterial transcriptional networks and drive adaptive responses that influence treatment outcomes and resistance development (Liu *et al.,* 2007). This knowledge forms a crucial bridge between molecular microbiology and clinical management of paratyphoid fever.

Host Gene Expression and Immune Regulation during Paratyphoid Fever

The outcome of *Salmonella* Paratyphi infection is determined not only by bacterial virulence strategies but also by the host's capacity to mount an effective and regulated immune response. Infection triggers widespread changes in host gene expression, reflecting activation of innate and adaptive immune pathways aimed at pathogen recognition, containment, and clearance. However, excessive or dysregulated immune activation can contribute to tissue damage, systemic inflammation, and disease severity, highlighting the need for tightly controlled host gene regulatory mechanisms (Kurtz *et al.,* 2017).

Innate Immune Gene Responses

The innate immune system constitutes the first line of defense against *Salmonella* Paratyphi infection and is characterized by rapid transcriptional activation of genes involved in pathogen recognition and inflammatory signaling. Pattern recognition receptors, including Toll-like receptors and intracellular sensing molecules, detect conserved microbial components and initiate signaling cascades that culminate in the production of pro-inflammatory cytokines and chemokines. These gene expression changes promote recruitment and activation of immune cells at sites of infection and facilitate early containment of the pathogen (Mogensen, 2009).

Macrophages and dendritic cells play a central role in orchestrating innate immune responses, with gene expression programs that regulate phagocytosis, antigen processing, and antimicrobial effector functions. Infection-induced transcriptional changes include upregulation of genes associated with oxidative burst, nitric oxide production, and autophagy-related pathways, all of which contribute to intracellular bacterial killing. However, *Salmonella* Paratyphi has evolved mechanisms to manipulate host transcriptional responses, dampening antimicrobial gene expression and promoting intracellular survival (Cohen *et al.,* 2022).

Adaptive Immune Gene Regulation

Adaptive immune responses are critical for sustained control and eventual clearance of *Salmonella* Paratyphi infection. T lymphocytes exhibit distinct transcriptional profiles during paratyphoid fever, with differential expression of genes involved in T-cell activation, differentiation, and cytokine production. These responses influence the balance between cell-mediated immunity and immune regulation, shaping disease resolution and long-term protection (Chowdhury *et al.,* 2023).

B-cell activation and antibody-mediated responses are also governed by tightly regulated gene expression programs. Transcriptional changes associated with immunoglobulin production, class switching, and memory formation contribute to humoral immunity against *Salmonella* Paratyphi (Lopez-Medina *et al.,* 2014). Variability in these adaptive gene responses may partially explain differences in disease severity, relapse rates, and susceptibility to reinfection among individuals.

Host Genetic and Transcriptomic Determinants of Disease Outcome

Host genetic variation has emerged as a significant determinant of susceptibility and clinical outcome in paratyphoid fever. Polymorphisms in genes encoding immune receptors, signaling molecules, and cytokines can influence transcriptional responsiveness to infection, thereby modulating immune effectiveness (Ma *et al.,* 2021). Transcriptomic studies have identified host gene expression signatures associated with severe disease, prolonged fever, and treatment failure, underscoring the role of host regulatory pathways in disease heterogeneity (Mejias *et al.,* 2021).

In addition to immune-related genes, infection-induced transcriptional changes affect metabolic pathways, stress response genes, and regulatory networks involved in maintaining cellular homeostasis. These broader host responses reflect systemic adaptation to infection and inflammation and may influence both pathogen control and recovery. Understanding these transcriptomic patterns provides valuable insights into host–pathogen interactions and highlights potential biomarkers for disease progression and therapeutic response (Eisenreich *et al.,* 2013).

Interaction between Host Gene Regulation and Antibiotic Treatment

Antibiotic therapy introduces an additional layer of complexity to host gene regulation during paratyphoid fever. Beyond their direct antimicrobial effects, antibiotics can modulate host immune gene expression

by altering inflammatory signaling pathways and host–microbiome interactions. Such changes may enhance or suppress immune responses, influencing treatment outcomes and recovery trajectories (Newson *et al.,* 2025).

The interplay between host gene regulation and antibiotic exposure is increasingly recognized as a critical factor in determining clinical efficacy and adverse outcomes. Integrating host transcriptional responses with bacterial regulatory adaptations offers a more comprehensive understanding of therapeutic dynamics and underscores the importance of personalized and context-specific treatment strategies in paratyphoid fever management (Geisinger *et al.,* 2017)

Antibiotic Therapy in Paratyphoid Fever

Antibiotic therapy remains the cornerstone of clinical management for paratyphoid fever and has significantly reduced disease-related morbidity and mortality since its introduction. Effective antimicrobial treatment shortens the duration of fever, limits systemic dissemination of *Salmonella* Paratyphi, and reduces the risk of severe complications and chronic carriage. However, therapeutic success is influenced by multiple factors, including antimicrobial susceptibility patterns, timing of treatment initiation, host immune status, and pathogen-specific adaptive responses (Sahai *et al.,* 2025).

Historically, first-line antibiotics such as chloramphenicol, ampicillin, and trimethoprim–sulfamethoxazole were widely used for the treatment of enteric fever, including paratyphoid fever. The emergence of multidrug-resistant *Salmonella* strains, however, has led to declining efficacy of these agents and necessitated shifts in treatment guidelines.

As a result, fluoroquinolones, third-generation cephalosporins, and macrolides have become commonly employed alternatives in many clinical settings (Parry *et al.,* 2023).

Fluoroquinolones act by inhibiting bacterial DNA gyrase and topoisomerase IV, leading to impaired DNA replication and bacterial cell death. These agents have demonstrated high clinical efficacy in paratyphoid fever; however, reduced susceptibility and resistance have increasingly been reported, particularly in endemic regions. Third-generation cephalosporins exert their antibacterial effects by inhibiting cell wall synthesis and are often preferred in cases involving fluoroquinolone resistance or severe disease presentations. Macrolides, which inhibit bacterial protein synthesis, are frequently used as oral treatment options, especially in uncomplicated cases or pediatric populations (Crump *et al.,* 2010).

The choice and duration of antibiotic therapy are guided by clinical severity, local resistance patterns, and patient-specific factors. Inappropriate antibiotic selection or suboptimal treatment duration can result in treatment failure, relapse, or prolonged bacterial shedding. Moreover, prior antibiotic exposure may reduce the sensitivity of diagnostic cultures, complicating confirmation of infection and antimicrobial susceptibility testing (Khilnani *et al.,* 2019).

Beyond their direct bactericidal or bacteriostatic actions, antibiotics exert selective pressures that influence bacterial physiology and gene expression. Exposure to antimicrobial agents can trigger stress response pathways, alter metabolic activity, and modulate virulence gene expression in *Salmonella* Paratyphi. These antibiotic-induced changes may contribute to transient tolerance, persistence, or the emergence of resistance, even in the absence of classical resistance mutations (Hassanin *et al.,* 2025).

From a clinical perspective, the increasing complexity of antibiotic response in paratyphoid fever underscores the limitations of treatment strategies based solely on antimicrobial susceptibility profiles. Integrating molecular insights into how antibiotics influence bacterial and host gene regulation offers the potential to improve therapeutic decision-making and optimize treatment outcomes (The *et al.,* 2014).

Such an approach is particularly relevant in endemic settings, where evolving resistance patterns and resource constraints pose ongoing challenges to effective disease control.

Understanding antibiotic therapy within the broader context of gene regulation provides a critical foundation for examining how antimicrobial exposure reshapes host–pathogen interactions during paratyphoid fever. This perspective sets the stage for exploring antibiotic-induced gene regulatory responses in *Salmonella* Paratyphi, which are discussed in the following section (Punchihewage-Don *et al.,* 2024).

Antibiotic-Induced Gene Regulation in *Salmonella Paratyphi*

Exposure to antibiotics imposes strong selective and physiological pressures on *Salmonella* Paratyphi, leading to rapid and often complex alterations in bacterial gene expression. Beyond their primary antimicrobial targets, antibiotics act as environmental stressors that trigger global transcriptional reprogramming, enabling the pathogen to adapt, survive, and in some cases persist under therapeutic conditions (Pradhan *et al.,* 2019).

These antibiotic-induced gene regulatory responses play a pivotal role in shaping treatment outcomes and the emergence of resistance.

Transcriptional Responses to Antibiotic Exposure

Antibiotic exposure activates stress response pathways that are tightly regulated at the transcriptional level. Genes involved in DNA repair, oxidative stress management, protein quality control, and metabolic adaptation are frequently upregulated in response to antimicrobial challenge. Such responses enhance bacterial resilience by mitigating antibiotic-induced damage and maintaining cellular integrity (Brand *et al.,* 2025).

Different classes of antibiotics induce distinct transcriptional signatures in *Salmonella* Paratyphi. Agents targeting DNA replication, cell wall synthesis, or protein translation elicit class-specific gene expression changes that reflect their mechanisms of action. These responses often include downregulation of energy-intensive processes and redirection of metabolic resources toward survival pathways, enabling transient tolerance during antibiotic exposure (Goh *et al.,* 2002).

Regulation of Virulence under Antibiotic Pressure

Antibiotic treatment can significantly influence the expression of virulence-associated genes in *Salmonella* Paratyphi. In some contexts, exposure to sub-inhibitory antibiotic concentrations has been shown to modulate the expression of genes encoded within Salmonella pathogenicity islands, potentially altering bacterial invasiveness and intracellular survival capacity. Such regulatory shifts may impact disease severity and persistence, particularly when antibiotic concentrations fluctuate during treatment (Holman *et al.,* 2018).

The repression or activation of virulence genes under antibiotic stress reflects a strategic trade-off between pathogenicity and survival. By downregulating energetically costly virulence functions, *Salmonella* Paratyphi may enhance survival under hostile conditions, while retaining the capacity to reactivate these pathways once antibiotic pressure is relieved. This regulatory plasticity underscores the adaptive advantage conferred by tightly controlled gene expression networks (Bader *et al.,* 2003).

Antibiotic Resistance–Associated Gene Regulation

The development of antibiotic resistance in *Salmonella* Paratyphi is closely linked to gene regulatory mechanisms that control the expression of resistance determinants. Antibiotic exposure can induce the expression of efflux pumps, membrane transporters, and modifying enzymes that reduce intracellular drug concentrations or inactivate antimicrobial agents. These regulatory responses may be transient or stabilized through genetic or epigenetic changes under sustained selective pressure (Chowdhury *et al.,* 2023).

Regulatory pathways governing resistance gene expression often intersect with global stress response networks, allowing coordinated adaptation to multiple environmental challenges. In addition to chromosomal mechanisms, plasmid-borne resistance genes are subject to transcriptional regulation that influences their expression and transmission dynamics. Such regulatory complexity contributes to heterogeneity within bacterial populations, enabling subsets of cells to survive antibiotic treatment and seed recurrent infection or transmission (Dawan & Ahn, 2022).

Persistence, Tolerance, and Regulatory Adaptation

Antibiotic-induced gene regulation also underlies the formation of persistent and tolerant bacterial subpopulations. These phenotypes are characterized by altered transcriptional states that reduce metabolic activity and growth rate, rendering bacteria less susceptible to antibiotics that target active cellular processes. Importantly, persistence is often reversible and

does not rely on stable resistance mutations, highlighting the central role of regulatory plasticity (Eisenreich *et al.,* 2022).

The existence of such regulatory adaptations has significant clinical implications, as persistent bacteria can contribute to prolonged infection, relapse, and chronic carriage. Understanding the gene regulatory mechanisms that drive persistence and tolerance is therefore essential for developing therapeutic strategies that effectively eradicate *Salmonella* Paratyphi and prevent treatment failure (Gunn *et al.,* 2014).

Collectively, antibiotic-induced gene regulation in *Salmonella* Paratyphi represents a dynamic and multifaceted process that influences virulence, resistance, and survival under therapeutic pressure. Integrating these molecular insights with host responses and clinical data provides a more comprehensive framework for understanding antibiotic efficacy and failure in paratyphoid fever (Chowdhury *et al.,* 2023).

Impact of Antibiotics on Host Gene Expression

Antibiotic therapy in paratyphoid fever influences not only bacterial survival but also host biological processes through modulation of gene expression. Increasing evidence suggests that antibiotics can directly and indirectly alter host transcriptional programs, shaping immune responses, inflammatory pathways, and tissue homeostasis during infection. These host-directed effects contribute to therapeutic efficacy, adverse outcomes, and interindividual variability in clinical response (Tosi *et al.,* 2024).

Modulation of Immune and Inflammatory Gene Pathways

Antibiotics can affect host immune gene expression by altering the magnitude and duration of inflammatory responses. Successful antimicrobial treatment is often associated with downregulation of pro-inflammatory cytokine genes and normalization of immune signaling pathways as bacterial burden decreases. This transcriptional shift supports resolution of inflammation and tissue repair, contributing to clinical recovery (Venditto *et al.,* 2021).

Conversely, certain antibiotics have been reported to exert immunomodulatory effects independent of bacterial clearance. These effects include altered expression of genes involved in cytokine signaling, antigen presentation, and immune cell activation, which may enhance or suppress host defenses depending on the context. Such modulation can influence disease severity, risk of complications, and susceptibility to secondary infections (Sauer *et al.,* 2021).

Antibiotic–Host–Microbiome Interactions

The human microbiome plays a critical role in shaping host gene expression, particularly within the gastrointestinal tract. Antibiotic-induced disruption of commensal microbial communities can lead to significant changes in host transcriptional profiles related to barrier function, immune regulation, and metabolic processes. These alterations may persist beyond the duration of antibiotic therapy and influence long-term health outcomes (Patangia *et al.,* 2022).

In the context of paratyphoid fever, microbiome perturbations may modify host susceptibility to infection, immune recovery, and risk of relapse. Changes in microbial-derived signaling molecules and metabolites can impact host gene regulatory networks, further complicating the host response to antibiotic treatment. Understanding these interactions is essential for interpreting host gene expression patterns observed during and after antimicrobial therapy (Ashton *et al.,* 2025).

Host Gene Expression and Treatment Outcomes

Host transcriptional responses to antibiotic therapy exhibit considerable interindividual variability, reflecting differences in genetics, immune status, and prior microbial exposures. Specific gene expression signatures have been associated with favorable treatment outcomes, rapid fever clearance, and reduced risk of complications. Conversely, persistent inflammatory or dysregulated immune gene expression may correlate with treatment failure, prolonged illness, or relapse (Shahid, 2025).

Identification of host gene expression biomarkers predictive of therapeutic response holds promise for personalized treatment approaches in paratyphoid fever. Such biomarkers could aid in optimizing antibiotic selection, dosing, and duration, thereby improving clinical outcomes and minimizing unnecessary antimicrobial exposure (Alhaj-Qasem *et al.,* 2020).

Table.1 Antibiotics commonly used in paratyphoid fever and their associated gene regulatory responses in *Salmonella Paratyphi*

Antibiotic Class	Representative Drug(s)	Primary Molecular Target / Mechanism	Bacterial Gene Regulatory Effects	Host / Clinical-Level Effects	Clinical Implications	Reference
Fluoroquinolones	Ciprofloxacin	DNA gyrase and topoisomerase IV inhibition	Altered DNA repair and stress response gene expression; modulation of SPI-1/SPI-2 virulence genes	Reduced bacterial load with immune activation	Rapid clinical response; increased resistance risk with prolonged or sub-therapeutic exposure	Teichmann *et al.,* 2025
Third-generation cephalosporins	Ceftriaxone	Cell wall synthesis inhibition	Downregulation of virulence-associated genes; selection pressure on β-lactam resistance pathways	Immune stabilization and infection control	Effective clearance in susceptible strains; failure in resistant isolates	15th European Congress of Clinical Microbiology and Infectious Diseases, 2005
Macrolides	Azithromycin	Inhibition of bacterial protein synthesis	Altered virulence and quorum-sensing gene regulation	Immunomodulatory effects; reduced excessive inflammation	Useful in uncomplicated cases; persistence possible if intracellular bacteria survive	Leroy *et al.,* 2021
Combination therapy	Multiple agents	Multi-target inhibition	Broad suppression of adaptive regulatory networks	Balanced innate and adaptive immune responses	Reduced relapse risk but higher selective pressure if misused	Li *et al.,* 2010
Trimethoprim–sulfamethoxazole	Co-trimoxazole	Folate synthesis inhibition	Upregulation of alternative metabolic pathways; stress-induced regulatory adaptation	Reduced efficacy due to widespread resistance	Limited current use; regulatory plasticity supports bacterial survival and persistence (Minato *et al.,* 2018)	Minato *et al.,* 2018

Figure.1 Antibiotic-Driven Host–Pathogen Gene Regulatory Interactions in Paratyphoid Fever

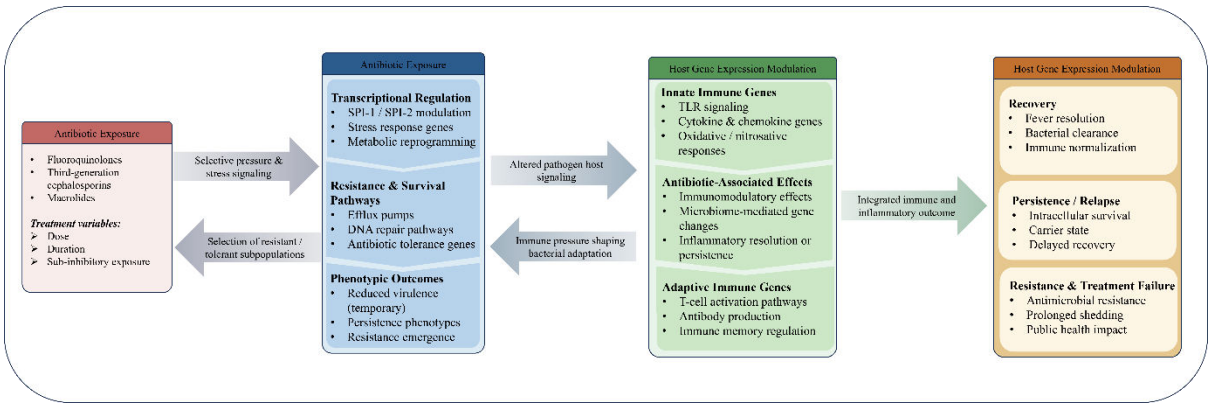
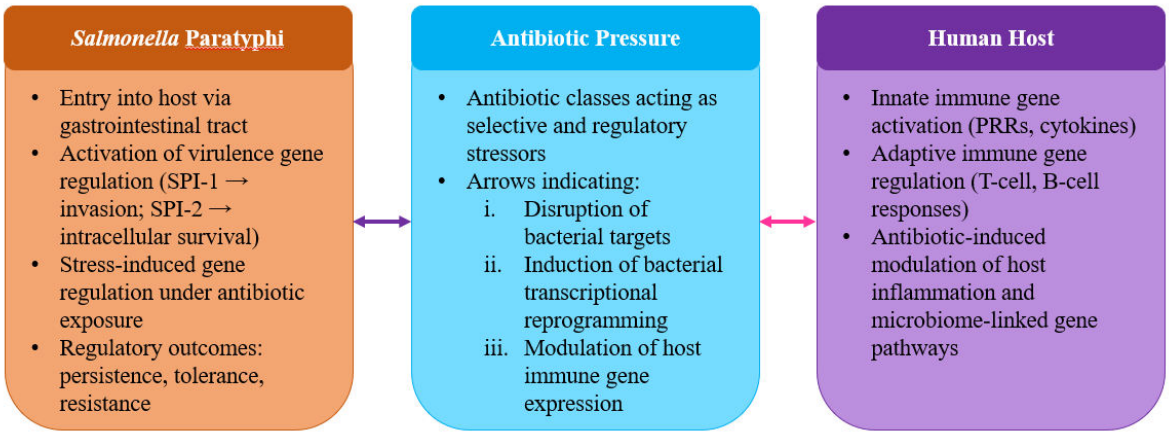


Figure.2 Integrated model of host–pathogen gene regulation and antibiotic response in human paratyphoid fever.



Clinical and Translational Implications

The impact of antibiotics on host gene expression highlights the need to consider therapeutic strategies beyond pathogen eradication alone. Integrating host transcriptional data with bacterial regulatory responses offers a more comprehensive understanding of treatment dynamics and disease resolution.

This systems-level perspective may inform the development of adjunctive therapies aimed at modulating host immune responses to enhance recovery and reduce complications (Morgun *et al.,* 2015).

Overall, antibiotic-induced modulation of host gene expression represents a critical but often underappreciated aspect of paratyphoid fever management. Recognizing and characterizing these effects can contribute to more effective, personalized, and sustainable treatment strategies in the face of evolving antimicrobial resistance (Weir *et al.,* 2008).

Clinical Implications of Gene Regulation and Antibiotic Response

Advances in understanding gene regulation and antibiotic-induced molecular responses in paratyphoid fever have important implications for clinical practice. Integrating insights from bacterial and host gene expression studies provides a more nuanced framework for interpreting disease progression, treatment response, and variability in clinical outcomes (Sheikh *et al.,* 2010).

Such integration moves beyond traditional pathogen-centric approaches and supports more precise and adaptive management strategies.

One of the most significant clinical implications relates to optimization of antibiotic therapy. Knowledge of antibiotic-induced gene regulatory responses in *Salmonella* Paratyphi can inform the selection of antimicrobial agents that minimize the induction of stress pathways, persistence phenotypes, and resistance-associated gene expression (Wójcicki *et al.,* 2021). Understanding these molecular effects may also guide decisions regarding antibiotic dosing and treatment duration, reducing the risk of relapse and chronic carriage.

Gene regulation studies also offer opportunities for improving diagnostic and prognostic capabilities. Host and bacterial transcriptional signatures associated with disease severity, treatment response, or resistance development may serve as biomarkers for early risk stratification and therapeutic monitoring. Such biomarkers could enable timely adjustments in treatment strategies, particularly in cases of suboptimal clinical response or suspected antimicrobial resistance (Mejias *et al.,* 2021).

From a public health perspective, insights into gene regulation and antibiotic response have implications for antimicrobial stewardship. By elucidating how inappropriate or excessive antibiotic use drives adaptive gene regulatory changes in *Salmonella* Paratyphi, these findings reinforce the importance of rational antibiotic prescribing practices. Incorporating molecular evidence into stewardship programs may help curb the emergence and spread of resistant strains in endemic settings (Chowdhury *et al.,* 2023).

Understanding host gene regulatory responses also opens avenues for adjunctive and host-directed therapies. Modulating immune and inflammatory gene expression through supportive or targeted interventions may enhance pathogen clearance while minimizing tissue damage and systemic complications. Such approaches are particularly relevant for vulnerable populations, including individuals with comorbidities or altered immune function (Jeong *et al.,* 2022).

Finally, integrating molecular insights into clinical guidelines requires careful consideration of feasibility and resource constraints, especially in low- and middle-income countries where paratyphoid fever is most prevalent. Translating gene regulation research into accessible diagnostic tools and treatment strategies will be critical for ensuring equitable clinical impact. Continued collaboration between basic scientists, clinicians, and public health practitioners is essential to bridge the gap between molecular discovery and practical application in paratyphoid fever management (The *et al.,* 2014).

This figure illustrates the coordinated gene regulatory mechanisms operating in *Salmonella* Paratyphi and the human host during infection and antibiotic treatment. Following ingestion, bacterial virulence genes are differentially regulated to enable invasion, intracellular survival, and systemic dissemination. Antibiotic exposure imposes selective pressure that induces bacterial stress responses, modulates virulence gene expression, and promotes persistence or resistance phenotypes. Concurrently, host gene expression programs governing innate and adaptive immunity are dynamically regulated in response to infection and antimicrobial therapy. Antibiotics further influence host transcriptional pathways through immunomodulatory effects and microbiome disruption. The interplay between bacterial adaptation and host immune regulation ultimately determines clinical outcome, therapeutic efficacy, and disease resolution.

Emerging Technologies and Future Directions

Rapid advances in molecular biology, high-throughput sequencing, and computational analytics have significantly expanded the scope of research on gene regulation and antibiotic response in paratyphoid fever. These emerging technologies provide unprecedented opportunities to dissect host–pathogen interactions at multiple biological levels and to translate molecular insights into clinically actionable strategies (Hooda *et al.,* 2023). Leveraging such tools is essential for addressing persistent challenges related to antimicrobial resistance, treatment failure, and disease heterogeneity.

High-throughput transcriptomic approaches, including bulk and single-cell RNA sequencing, have enabled comprehensive profiling of gene expression changes in both *Salmonella* Paratyphi and infected host cells. These techniques allow identification of regulatory networks that govern virulence, immune evasion, and antibiotic tolerance at high resolution. Single-cell technologies, in particular, can reveal transcriptional heterogeneity within bacterial populations and host immune cells, shedding light on persistence phenotypes and variable immune responses that are obscured in bulk analyses (Bumann, 2019).

Integrative multi-omics approaches represent a promising direction for future research. Combining transcriptomics with proteomics, metabolomics, and epigenomics can provide a more holistic understanding of how gene regulatory processes translate into functional outcomes during infection and antibiotic exposure (Cohen *et al.,* 2015). Such systems-level analyses are critical for mapping complex regulatory interactions and identifying key molecular nodes that may serve as therapeutic or diagnostic targets.

Advances in bioinformatics and artificial intelligence have further enhanced the capacity to analyze and interpret large-scale molecular datasets. Machine learning algorithms can identify patterns and predictive signatures within host and pathogen gene expression data, enabling stratification of patients based on risk, treatment response, or likelihood of resistance development (Chen *et al.,* 2025). These computational tools hold promise for supporting precision medicine approaches in paratyphoid fever, particularly when integrated with clinical and epidemiological data.

Emerging experimental models also offer new avenues for investigating gene regulation and antibiotic response. Improved in vitro infection systems, organoid models, and humanized animal models can better recapitulate host–pathogen interactions and facilitate functional validation of regulatory pathways identified through omics studies. Such models are essential for translating molecular findings into therapeutic strategies with clinical relevance (Aguilar *et al.,* 2021; Sun *et al.,* 2025).

Looking ahead, future research should prioritize longitudinal and context-specific studies that capture dynamic changes in gene regulation over the course of infection and treatment. Greater emphasis on studies conducted in endemic regions will be critical for ensuring that molecular insights reflect real-world disease patterns and resistance landscapes. Collaborative, interdisciplinary efforts that integrate molecular biology, clinical medicine, and public health will be key to advancing the understanding and management of paratyphoid fever in the coming years (Xie *et al.,* 2022).

Challenges, Knowledge Gaps, and Research Priorities

Despite significant advances in understanding the molecular and clinical aspects of paratyphoid fever, several challenges continue to limit comprehensive interpretation and effective translation of gene regulation and antibiotic response research (Pandit *et al.,* 2012, Neupane, 2022). A major constraint lies in the relative scarcity of studies focusing specifically on *Salmonella* Paratyphi, as much of the current knowledge is extrapolated from research on *Salmonella* Typhi or non-typhoidal *Salmonella* species (Näsström *et al.,* 2014; Sajib *et al.,* 2023). While informative, such extrapolation may overlook serovar-specific regulatory mechanisms and clinically relevant differences (Gal-Mor *et al.,* 2014).

Another critical challenge is the limited availability of high-quality human data linking gene expression profiles to clinical outcomes. Many molecular studies rely on in vitro systems or animal models that do not fully recapitulate the complexity of human infection and immune responses (Schaub, *et al.,* 2025). The absence of longitudinal human studies capturing dynamic changes in host and bacterial gene regulation during infection and antibiotic treatment further constrains mechanistic understanding (Hakansson *et al.,* 2018).

Methodological heterogeneity represents an additional barrier to synthesis and comparison across studies. Variations in experimental design, antibiotic exposure conditions, sequencing platforms, and analytical pipelines can yield inconsistent findings and hinder reproducibility (Sun *et al.,* 2024; Yang *et al.,* 2025). Standardization of study protocols and reporting frameworks is therefore essential for improving comparability and cumulative knowledge generation in this field.

Significant knowledge gaps also exist in understanding host–pathogen regulatory interactions under real-world treatment conditions. The effects of subtherapeutic antibiotic exposure, treatment interruptions, and co-infections on gene regulatory networks remain poorly characterized (Hantabal *et al.,* 2026). Furthermore, the role of host genetic diversity and environmental factors in shaping transcriptional responses and treatment outcomes has not been adequately explored, particularly in endemic populations (Nguyen *et al.,* 2025).

From a translational perspective, the clinical application of gene regulation research faces practical and ethical challenges. Limited access to advanced molecular diagnostics, especially in resource-constrained settings, restricts the feasibility of implementing gene

expression–based biomarkers in routine clinical practice (Wagner *et al.,* 2024). Addressing these disparities will require development of cost-effective, scalable technologies and integration with existing healthcare infrastructure.

Future research priorities should focus on generating robust, context-specific evidence that bridges molecular insights with clinical relevance. Key priorities include conducting longitudinal human studies, expanding research in endemic regions, and integrating multi-omics data with clinical and epidemiological information (Zhao *et al.,* 2025). Strengthening interdisciplinary collaboration and promoting data-sharing initiatives will be critical for accelerating progress and translating gene regulation research into meaningful improvements in paratyphoid fever prevention and treatment.

In conclusion, Paratyphoid fever represents a complex infectious disease in which clinical outcome is shaped by dynamic interactions between *Salmonella* Paratyphi and the human host.

This review highlights that disease progression, treatment response, and therapeutic failure cannot be fully understood without considering the regulatory mechanisms governing gene expression on both sides of the host–pathogen interface. Gene regulation emerges as a central determinant linking bacterial virulence, host immune responses, and antibiotic efficacy.

At the pathogen level, *Salmonella* Paratyphi relies on finely tuned transcriptional and post-transcriptional regulatory networks to adapt to diverse host environments and antibiotic pressure. Antibiotic exposure induces widespread changes in bacterial gene expression, influencing stress responses, virulence modulation, persistence, and resistance development. These adaptive responses underscore why antimicrobial susceptibility alone may be insufficient to predict clinical outcomes.

Concurrently, host gene expression plays a critical role in shaping immune defense, inflammation, and recovery during paratyphoid fever. Antibiotic therapy further modifies host transcriptional programs through immunomodulatory effects and microbiome-mediated pathways, contributing to interindividual variability in treatment response. Integrating host transcriptional dynamics with bacterial regulatory adaptations provides a more comprehensive framework for understanding therapeutic success and failure.

By synthesizing current evidence on gene regulation and antibiotic response, this review emphasizes the need for a systems-level perspective that bridges molecular biology and clinical practice. Future advances in transcriptomics, multi-omics integration, and computational analysis hold promise for identifying predictive biomarkers and informing precision treatment strategies. Ultimately, translating insights from gene regulatory studies into accessible diagnostic and therapeutic tools will be essential for improving the management and control of paratyphoid fever, particularly in endemic and resource-limited settings.

Reporting Standards Statement

Not applicable. This manuscript is a narrative review article and does not involve original experimental data, human participants, or animal experimentation.

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Author Contributions

Hirdesh Gour: Investigation, formal analysis, writing—original draft. Rimpa Manna: Validation, methodology, writing—reviewing.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Conflict of Interest The authors declare no competing interests.

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