Al-Qadisiyah J. Vet. Med. Sci. 2025; 24 (3): 10.29079/qjvms.2025.166141.1125
The 1st National and International Scientific Conference November 26 / 2025
ISSN P: 1818-5746
E: 2313-4429
qjvms@qu.edu.iq

Lipopolysaccharide-Adjuvant Vaccination and Immune Response Against Antibiotic Resistance Salmonella: modulation Toll-Like Receptors and Virulence determinants

Husain Ali Khalaf [1] Alaa Abdulaziz Abed [2]
[1]Dept. of Veterinary Microbiology, College of Veterinary Medicine, University of Al-Qadisiyah, Iraq
[2]Dept. of Pathology and Poultry Diseases, College of Veterinary Medicine, University of Al-Qadisiyah, Iraq

Submitted: October 13, 2025
Revised: November 10, 2025
Accepted: November 11, 2025

Correspondence:
Husain Ali Khalaf
Husseinsraer8@gmail.com

Abstract Salmonella remains a major global pathogen causing significant morbidity and mortality, particularly in low- and middle-income regions, with global rise of antimicrobial resistance in Salmonella underscores the urgent need for effective vaccines. Lipopolysaccharide (LPS), the major glycolipid of the outer membrane, is a potent immunogen capable of stimulating both innate and adaptive immunity. When combined with complete or incomplete adjuvants, LPS-based vaccines enhance antigen presentation, cytokine release, and protective antibody responses, The integration of lipopolysaccharide in vaccine formulations represents a promising strategy to enhance the immune response against antibiotic-resistant Salmonella strains. Developing an effective lipopolysaccharide-adjuvant vaccine against antibiotic-resistant Salmonella presents numerous challenges, including ensuring safety, enhancing immunogenicity, and overcoming bacterial variability. Toll-like receptor 4 (TLR4) plays a central role in recognizing LPS and initiating protective immunity, though host genetic variation influences the response. This review highlights the role of LPS in immunity and vaccination in reduced dependence on antibiotic interventions and of combating antibiotic resistance through novel vaccine strategies.

Keywords: Lipopolysaccharide, Salmonella, Toll-Like Receptors, Antibiotic Resistance, Virulence determinants, immune modulation

Introduction Salmonella enterica serovars, such as Typhimurium and Enteritidis, are among the most frequent causes of gastroenteritis worldwide (1). The increasing emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Salmonella strains presents a serious public health challenge (2). Vaccination regardea crucial strategyto control Salmonella transmission and infection (3). While inactivated and attenuated vaccines have been widely studiedto reduce safty safety, risk of reversion to virulence, and inconsistent immune protection (4). Recent attention has been interested to the development of adjuvant-based vaccines, which induce immune responses through immunomodulators (5). The LPS molecule is an a glycolipid of Gram negative bacterial outer membrane (OM), has emerged as adjuvant candidate because its interaction with innate immune receptors (6). Lipopolysaccharide, a component of Gram-negative bacterial cell walls, has emerged as a promising adjuvant candidate due to its interaction with innate immune receptors (6). LPS activates innate immunity via Toll-like receptor 4 (TLR4), leading to downstream signaling cascades such as NF-κB activation, cytokine production, and enhanced antigen presentation. This stimulation both humoral and cellular immunity will be induced, which are crucial for controlling intracellular pathogens like Salmonella (3). LPS-adjuvant vaccines could reduce the need for therapeutic antibiotics, thereby alleviating the selective pressure driving antimicrobial resistance (7). Salmonella enterica serovars cause widespread foodborne infections with diverse manifestations from gastroenteritis to invasive diseases. Their pathogenesis involves virulence genes clustered in Salmonella pathogenicity islands (SPIs) and plasmids that confer antimicrobial resistance, complicating therapeutic efficacy (8). Lipopolysaccharides (LPS) are potent immunostimulants but also contribute to endotoxicity; thus, extraction and detoxification of LPS, coupled with adjuvants such as Freund's Complete and Incomplete Adjuvants containing Mycobacterium components, have been employed to boost protective, T-cell mediated immunity (9). Toll-like receptors (TLRs),

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particularly TLR4 recognizing LPS and TLR5 recognizing bacterial flagellin, initiate crucial innate immune signaling including cytokine release and inflammasome activation, shaping vaccine responses. However, the global rise of multi-drug resistant (MDR) Salmonella strains, coupled with variable vaccine efficacy and outbreak control challenges, necessitates a multidimensional approach integrating vaccine innovation, therapeutic modulation of immune pathways, and strengthened public health measures (10). The aim of this study is to investigate the immune responses induced by lipopolysaccharide (LPS) extracted from local isolate and study lipopolysaccharide immunomodulating effects in animal model and to study resistance pattern of plasmid in local salmonella spp. in chickens.

This aim will be achieved through the following objectives:

1- Extraction of LPS from salmonella spp (local isolates)
2-use conjugated protein mixed with LPS and Study effect its on the immune responses
3- Study the effect of lipopolysaccharide (LPS) on the immune responses include (TLR4 and CD4 gene expression) .
4- Study the effect of lipopolysaccharide (LPS) on some cytokines related to innate immune , antibody immune responses and cellular immunity.
5- Study the effect of lipopolysaccharide (LPS) on antibody level and cellular picture
6- Study bacterial resistance plasmids profile .

Overview of salmonella

Salmonella is a genus of gram-negative, facultative intracellular bacteria from the family Enterobacteriaceae that causes a wide spectrum of diseases in humans and animals, ranging from self-limited gastroenteritis to severe systemic infections such as typhoid fever (Lamichhane, 2024). The genus comprises over 2600 serovars classified primarily into Salmonella enterica and Salmonella bongori, with S. enterica responsible for the vast majority of human infections. The transmission of Salmonella occurs mainly through the ingestion of contaminated food and water, with poultry and poultry products being the most common sources, followed by beef, pork, fish, fruits, and vegetables (11).

Antibiotic resistance of salmonella

Typical Resistance Patterns.

Salmonella species exhibit resistance to a wide range of commonly used antibiotics, with some serovars showing multidrug resistance (MDR). especially against antibiotics such as tetracycline, ampicillin, nalidixic acid, trimethoprim/sulfamethoxazole, and azithromycin. Resistance percentages vary by serovar and region:

Salmonella Typhimurium and S. enterica show resistance rates around 60–90% for tetracycline and ampicillin. Resistance to quinolones such as nalidixic acid and fluoroquinolones ranges between 60–75%. Lower resistance rates are reported for ceftriaxone and ciprofloxacin but rising trends are noted. These resistance patterns complicate treatment as first-line antibiotics become less effective (12).

Molecular Mechanisms of Antibiotic Resistance in Salmonella

1. Enzymatic Inactivation: Production of β-lactamases that hydrolyze β-lactam antibiotics, including penicillins and cephalosporins.
2. Efflux Pumps: Active expulsion of antibiotics from bacterial cells, reducing intracellular drug concentration. Efflux pump systems like AcrAB-TolC are critical in multidrug resistance.
3. Target Modification: Mutation or protection of antibiotic targets such as DNA gyrase and topoisomerase IV in fluoroquinolone resistance (13).
4. Reduced Permeability: Changes in membrane porins decrease antibiotic entry.
5. Biofilm Formation: This phenotype enhances antibiotic tolerance and facilitates horizontal gene transfer of resistance plasmids.

Virulence determinants

Plasmid Profiles and Salmonella Pathogenicity Islands

SPIs encode secretion systems and effector proteins facilitating host invasion and immune subversion. Concurrently, plasmids carry antimicrobial resistance genes, increasingly conferring multidrug resistance across Salmonella serotypes (14; 15).

SPI-1: Encodes a Type III secretion system (T3SS-1) that injects effector proteins into intestinal epithelial cells, triggering their uptake of Salmonella. This is critical for initiating infection and causing intestinal inflammation. Deletion or targeting of SPI genes reduces virulence, making them key candidates for live-attenuated vaccines. SPI-encoded proteins also serve as antigen targets to improve vaccine-induced protective immune (16, 17).

SPI-2: Encodes a second Type III secretion system (T3SS-2) essential for survival and replication inside macrophages by preventing phagosome-lysosome fusion. SPI-2 facilitates systemic dissemination and persistence within host tissues (14, 16).

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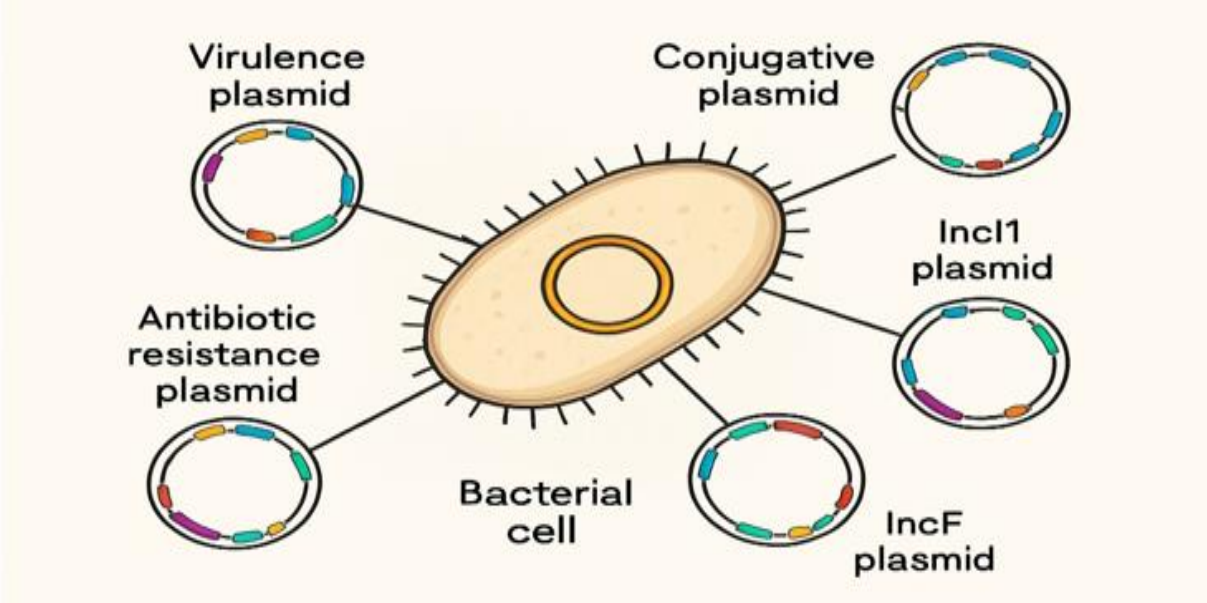
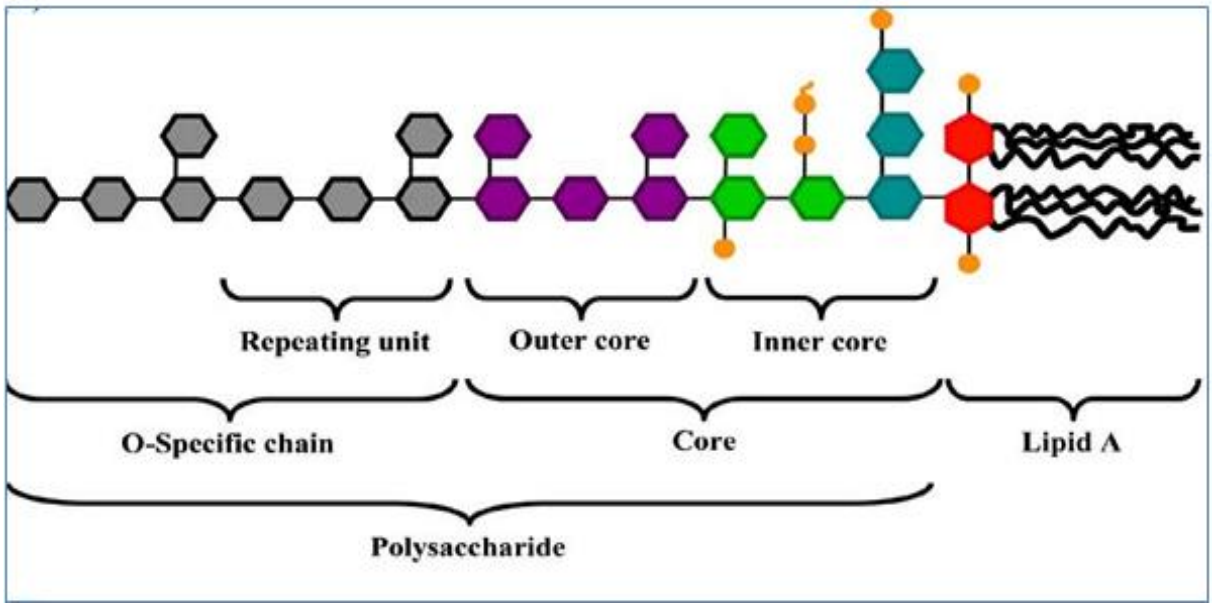


Key virulence genes commonly linked to pathogenicity islands (SPIs) were detected, including:
tviA (Typhi Vi antigen gene) detected in 94.1% of isolates, critical for bacterial invasiveness and systemic spread. ctdB, associated with typhoid toxin. sipA/sspA, spiC, and orfL, genes involved in invasion, intracellular survival, and toxin secretion, respectively (17).

Lipopolysaccharides

Structure and function of Lipopolysaccharides

Lipid A: The anchor and toxic moiety embedded in the outer membrane. Core Oligosaccharide: Central region with heptose, KDO, and hexose residues. O-antigen: Distal polysaccharide chain, species- and strain-specific, with repeating sugar unbound Below is a schematic image showing the three main components of lipopolysaccharide: Lipid A, core oligosaccharide, and O-antigen. (18).



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Functional of lipopolysaccharides

Immune Evasion

LPS with long O-antigen allows Salmonella to avoid complement-mediated killing and enhances survival during infection (19; 20).

Resistance and Antibiotic Protection

LPS modifications increase resistance to antimicrobial peptides (e.g; LL-37, colistin), protect against host immune mechanisms, and affect sensitivity to antibiotics (21).

Inflammasome and Cytokine Modulation

Altering LPS composition helps Salmonella inhibit inflammasome activation, resulting in decreased secretion of inflammatory cytokines (IL-1β, IL-18, IFN-λ) (16, 14).

Biofilm Development

LPS structure impacts biofilm formation, supporting persistence and environmental survival. The structure of Salmonella LPS, espicially the lipid A region and the variable O-antigen polysaccharide chain, have been recognizedby innate immune receptors such as (TLR4) (16). Recent study of how it activates pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and promotes immune cell recruitment and activation (14, 21).

Role of LPS in immune response

Lipopolysaccharide (LPS) extracted from Salmonella is a fundamental molecule used to elucidate the mechanisms of immune activation and host-pathogen interactions. The structure of Salmonella LPS, espicially the lipid A region and the variable O-antigen polysaccharide chain, have been recognizedby innate immune receptors such as (TLR4) (16)., recent study of how it activates pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and promotes immune cell recruitment and activation (14, 21).Purified LPS from Salmonella contributes to vaccine formulation as an adjuvant or antigen, Modifications in LPS structure, including O-antigen length and composition,abcence of o antigen as in soft lps promote Salmonella's ability to evade complement-mediated killing and resist phagocytosis, impacting the effectiveness of immune responses (20, 22).

Adjuvant in vaccination

Types and mechanism of action of adjuvants

Adjuvants enhance vaccine immunogenicity mainly through innate immune activation, leading to improved antigen presentation and adaptive immune responses. This involves cytokine and chemokine induction, immune cell recruitment, antigen depot formation, and inflammasome activation (23). Freund's adjuvants are water-in-oil emulsions. Complete Freund's adjuvant (CFA) contains killed mycobacteria, which strongly activate innate immunity via pattern recognition receptors (like NOD2 and NLRP3 inflammasomes), producing inflammatory cytokines and robust Th1/Th17 responses. CFA acts both as an immunostimulant and delivery system by creating a depot and providing microbial molecules as adjuvants (23). Incomplete Freund's adjuvant (IFA) is similar in composition minus the mycobacteria. It primarily acts as an antigen depot, allowing slow release and persistent antigen presentation, but lacks potent innate immune activation seen with CFA. IFA alone produces weaker immune responses and may even induce tolerance if not combined with immunostimulants (24)

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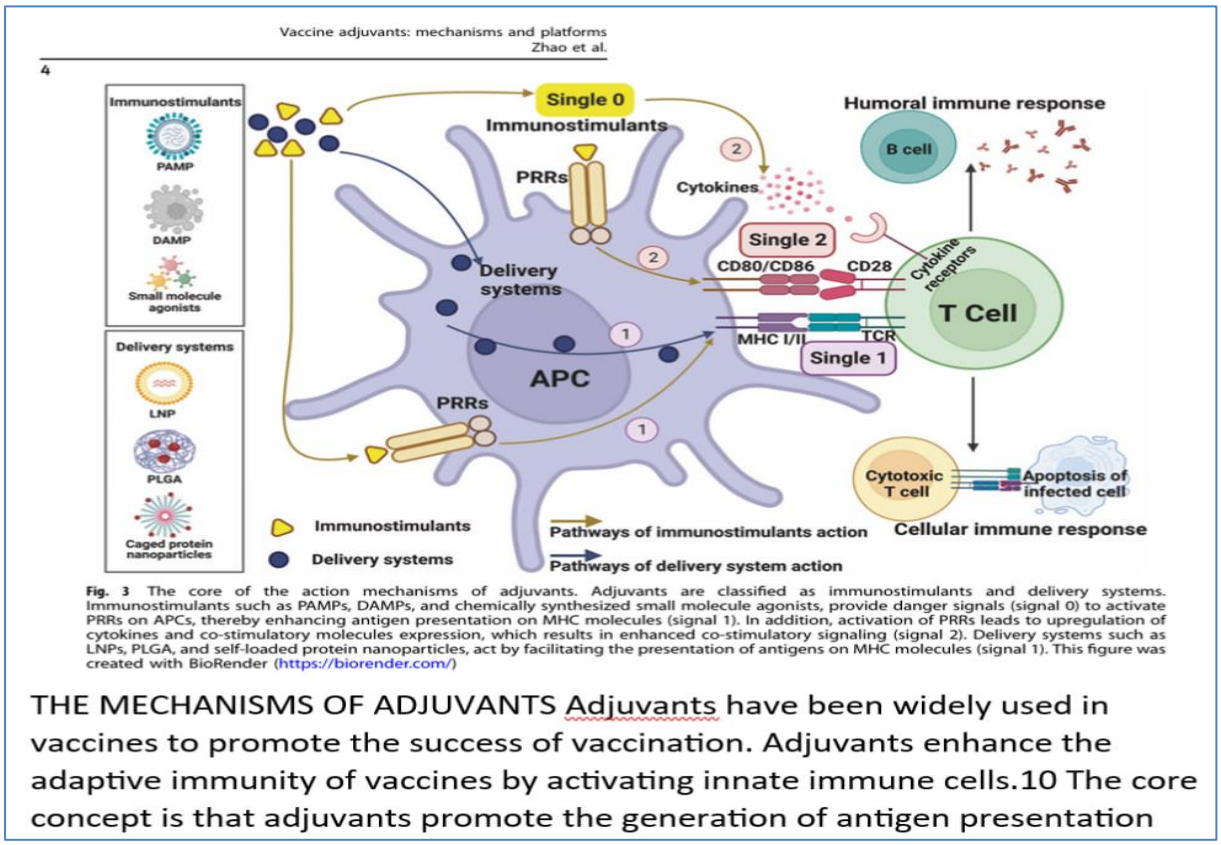

Fig. 3 The core of the action mechanisms of adjuvants. Adjuvants are classified as immunostimulants and delivery systems. Immunostimulants such as PAMPs, DAMPs, and chemically synthesized small molecule agonists, provide danger signals (signal 0) to activate PRRs on APCs, thereby enhancing antigen presentation on MHC molecules (signal 1). In addition, activation of PRRs leads to upregulation of cytokines and co-stimulatory molecules expression, which results in enhanced co-stimulatory signaling (signal 2). Delivery systems such as LNPs, PLGA, and self-loaded protein nanoparticles, act by facilitating the presentation of antigens on MHC molecules (signal 1). This figure was created with BioRender (https://biorender.com/)

THE MECHANISMS OF ADJUVANTS Adjuvants have been widely used in vaccines to promote the success of vaccination. Adjuvants enhance the adaptive immunity of vaccines by activating innate immune cells.10 The core concept is that adjuvants promote the generation of antigen presentation

TLRs in Salmonella Infection

(TLRs) are evolutionarily conserved pattern recognition receptors (PRRs) critical for detecting pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), Two phosphate groups positioned at 1′ and 4′ in lipid A are recognized and bind to the Toll-like receptor 4 (TLR4)-myeloid differentiation factor 2 (MD-2 innate immune responses that initiate and shape adaptive immunity. Humans express 10 TLRs (TLR1-10), The first TLR, identified in an insect (Drosophila), was a molecule with a critical role in antifungal responses localized either on the cell surface or intracellular compartments, capable of recognizing diverse microbial components such as lipopolysaccharides, nucleic acids, and flagellin (15).

Structurally, TLRs contain extracellular leucine-rich repeats for binding intracellular Toll/IL-1 receptor (TIR) domain that mediates signaling. Signaling primarily occurs via the MyD88-dependent or MyD88-independent (TRIF) pathways,resulting in transcription factors such as NF-κB and IRFs toenhence pro-inflammatory cytokines, interferons, and antimicrobial peptides (15). Structurally, TLRs contain extracellular leucine-rich repeats for ligand binding and a conserved intracellular Toll/IL-1 receptor (TIR) domain that mediates downstream signaling. Signaling primarily occurs via the MyD88-dependent or MyD88-independent (TRIF) pathways, activating transcription factors such as NF-κB and IRFs to induce pro-inflammatory cytokines, interferons, and antimicrobial peptides (15).

Modulation of TLRs by LPS

Lipopolysaccharide (LPS) is a key molecule that modulates Toll-like receptor 4 (TLR4) signaling, crucial for initiating innate immune responses against Gram-negative bacterial infections. The binding of LPS to the TLR4/MD-2 complex triggers a cascade of intracellular signaling pathways, leading to activate of transcription factors such as NF-κB and IRFs, and subsequent production of pro-inflammatory cytokines and type I interferons (14). This modulation plays a central role in tight regulation to avoid excessive immune activation that leads to pathology (16, 21).

Innate and Adaptive Immune Response

Innate Immunity

The innate immune system is the first line of defense against Salmonella infection, involving macrophages, dendritic cells (DCs), neutrophils,. These cells detect and attempt to eliminate Salmonella through phagocytosis, production of proinflammatory cytokines, and cell-intrinsic defenses like xenophagy (autophagic

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degradation of pathogens) 20; 18Recent advances highlight the dual roles of TLRs not only in infection control but also in trained immunity, a form of innate immune memory characterized by epigenetic and metabolic reprogramming that enhances responsiveness upon secondary challenges. This broadens TLRs' impact in long-term immune protection and immunotherapy development (25).

Immune Evasion Strategies by Salmonella

Salmonella secretes effector proteins via T3SSs that manipulate host cellular mechanisms, including autophagy inhibition and Rab GTPase modulation, to establish intracellular infection and avoid immune detection (26).

Adaptive Immunity

Adaptive immune responses are crucial for controlling and clearing Salmonella infection. CD4+ T cells produce cytokines that activate macrophages and support B cell responses, which produce antibodies neutralizing Salmonella and its toxins. CD8+ T cells contribute by lysing infected cells, limiting bacterial dissemination (27). Salmonella evades adaptive immunity by altering antigen expression and interfering with antigen-presenting cells such as DCs, modulating T cell activation (27).

Cytokine Production and Signaling

Cytokines are key regulators in host responses to Salmonella infection. Upon recognition of bacterial components like LPS by innate immune receptors, macrophages and dendritic cells release pro-inflammatory cytokines such as TNF-α, IL-1β, and IFN-γ, which activate antimicrobial pathways (28). Interleukin-6 (IL-6) triggers acute-phase responses and supports T and B cell activation. On the other hand, IL-10 and TGF-β are regulatory cytokines that help prevent tissue damage by suppressing excessive inflammation. The cytokine balance is critical in determining the progression or resolution of infection (20, 21).

Vaccination Strategies

Prioritizing high-risk populations while considering transmission dynamics to optimize herd immunity. Use of booster doses to sustain long-term immunity against evolving pathogens. Leveraging novel vaccine platforms like mRNA and viral vectors for accelerated development and adaptability Addressing vaccine hesitancy and ensuring equitable vaccine access to improve coverage. Integrating advances in immunology, structural biology, and bioinformatics for rational vaccine design. Implementing targeted and selective vaccination campaigns based on risk assessment and resource availability (14, 28).

LPS-Adjuvant Vaccination Protocols

Despite Monophosphoryl lipid A (MPL) is a detoxified form of lipopolysaccharide (LPS) extracted from Salmonella species and widely used as a vaccine adjuvant. It activates the immune system through Toll-like receptor 4 (TLR4), promoting strong and balanced immune responses while reducing the toxicity of native LPS (16, 22, 23).

Efficacy in Animal Models

Animal models are vital during vaccine discovery and development stages by providing the required information on safety, immunogenicity, and protective efficacy (29, 30). Choosing the suitable animal species that most closely mimics human infection and immune response is essential (31). The goal of these studies is optimizing efficacy by exploring appropriate doses and routes of administration while monitoring important immune correlates such as antibody production and cellular immunity (32, 33).

Challenges associated with animal models include differences in immune responses, ethical issues, and sometimes their limited ability to predict vaccine effectiveness in humans. On the other hand, the development, and advancement of genetically engineered models and humanized models increases translatability (34). In different animal species such as rodents, non-human primates, and other models the understandings for how vaccines work and benefits for us poor humans in the informatics of many aspects of clinical trial design. Limitations are clear, but animal models are instrumental to understanding the induction of vaccines and vaccine assessment (35).

Challenges in Vaccine Development

Though technology has improved vaccine production, challenges remain in managing infectious disease. The major challenges in vaccine production are the diversity of pathogens and mutating quickly, the multifaceted immune responses needed for protective immunity, , producing on a large scale, fear of adverse side effect of vaccine. additionally The uncertainty of the specific immune correlates of protection can make vaccine development typically not rational regarding vaccine development. The recognition that different pathogens may require triggering distinctive but arguably (or even completely) antagonistic immune response pathways creates a complex framework to develop broadly protective vaccines. The emergence of both new pathogens and variants of viral pathogens serves as an quickly reminder that we need to may have existing new platforms for the production of vaccines, which are still under development (13).

Conclusion

Lipopolysaccharide-adjuvant vaccination provides robust immune activation, effective protection, and a potential

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means of mitigating antibiotic resistance in Salmonella infections. By enhancing both humoral and cellular responses through TLR4 signaling, these vaccines reduce bacterial virulence and dependence on antibiotic interventions. Continued optimization of detoxified LPS formulations and translational studies in human populations are essential for realizing their full potential in next-generation vaccines.Efforts to mitigate Salmonella's global health burden require advancements in vaccine development harnessing detoxified LPS with Freund mycobacterial adjuvants to stimulate TLR-mediated protective immunity. Understanding plasmid-mediated resistance and SPI-driven virulence informs therapeutic innovation and surveillance. Integrated control strategies encompassing immunization, antimicrobial stewardship, food safety, and outbreak management are essential to address the multifaceted challenges posed by this pathogen.

Conflict of interest

Authors declare no conflict of interest.

Funding source

This research had no specific fund; however, it was self-funded by the authors.

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