

**Review Article****Open Access****A review of vaccine adjuvants in modern immunology: Mechanisms, classes, and advances in next-generation vaccine design**

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Abstract:

Vaccines are biological preparations that stimulate the immune system to prevent infectious disease without causing illness. By delivering weakened or inactivated pathogens, purified antigens, or genetic material encoding specific proteins, vaccines induce antibody production and generate memory B and T cells, enabling rapid, protective responses upon later exposure. Vaccination is among the most effective public health measures, leading to the eradication of smallpox in human and rinderpest in ruminants, and control of many infectious diseases. Advances such as recombinant and mRNA platforms have broadened applications to emerging infections and cancer immunotherapy. Adjuvants enhance vaccine immunogenicity, particularly in subunit and inactivated formulations. They activate innate immune pathways, including pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), triggering inflammatory signaling and cytokine release. This promotes recruitment and maturation of antigen-presenting cells, especially dendritic cells, improving antigen presentation and T-cell activation. Adjuvants also shape adaptive immunity by directing T-helper cell polarization and strengthening cytotoxic T-lymphocyte responses. Major adjuvant classes include aluminum salts (alum), which primarily elicit strong antibody (T_{H2}) responses; emulsion-based systems such as MF59 and AS03, which enhance antigen uptake and promote balanced humoral and cellular immunity; and TLR agonists such as monophosphoryl lipid A and CpG oligodeoxynucleotides, which drive T_{H1}-biased responses. Saponin-based and liposomal formulations further augment both antibody and cellular immunity, supporting vaccines against complex pathogens and cancer. Ongoing advances in molecular immunology and nanotechnology are enabling next-generation adjuvants designed to achieve precise, durable, and safe immune protection, underscoring their central role in future vaccine development and global disease prevention.

Keywords: Vaccines, adjuvants, immunological mechanisms, challenges and future

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Adjuvants vaccinaux en immunologie moderne: Mécanismes, classes et avancées dans la conception des vaccins de nouvelle generation

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Résumé:

Les vaccins sont des préparations biologiques qui stimulent le système immunitaire afin de prévenir les maladies infectieuses sans provoquer la maladie. En administrant des agents pathogènes atténués ou inactivés, des antigènes purifiés ou du matériel génétique codant pour des protéines spécifiques, les vaccins induisent la production d'anticorps et génèrent des lymphocytes B et T mémoire, permettant des réponses rapides et protectrices lors d'expositions ultérieures. La vaccination figure parmi les mesures de santé publique les plus efficaces, ayant conduit à l'éradication de la variole et au contrôle de nombreuses maladies infectieuses. Les avancées telles que les plateformes recombinantes et à ARNm ont élargi les applications aux infections émergentes et à l'immunothérapie du cancer. Les adjuvants renforcent l'immunogénicité des vaccins, en particulier dans les formulations sous-unitaires et inactivées. Ils activent les voies de l'immunité innée, notamment les récepteurs de reconnaissance des motifs (PRR) comme les récepteurs Toll-like, déclenchant des signaux inflammatoires et la libération de cytokines. Cela favorise le recrutement et la maturation des cellules présentatrices d'antigènes, en particulier les cellules dendritiques, améliorant ainsi la présentation de l'antigène et l'activation des lymphocytes T. Les adjuvants modulent également l'immunité adaptative en orientant la polarisation des lymphocytes T auxiliaires et en renforçant les réponses des lymphocytes T cytotoxiques. Les principales classes d'adjuvants comprennent les sels d'aluminium (alun), qui induisent principalement de fortes réponses humores (Th₂) ; les systèmes à base d'émulsions tels que MF59 et AS03, qui améliorent la capture de l'antigène et favorisent une immunité humorale et cellulaire équilibrée; ainsi que les agonistes des récepteurs Toll-like comme le monophosphoryl lipid A et les oligodésoxynucléotides CpG, qui stimulent des réponses de type Th₁. Les formulations à base de saponines et les systèmes liposomaux renforcent davantage l'immunité humorale et cellulaire, soutenant le développement de vaccins contre des agents pathogènes complexes et le cancer. Les progrès continus en immunologie moléculaire et en nanotechnologie permettent le développement d'adjuvants de nouvelle génération conçus pour assurer une protection immunitaire précise, durable et sûre, soulignant leur rôle central dans la conception future des vaccins et la prévention mondiale des maladies.

Mots-clés: Vaccins, adjuvants, mécanismes immunologiques, défis et perspectives d'avenir

Introduction:

Vaccines are biological preparations designed to stimulate the immune system to recognize and defend against specific infectious agents, such as bacteria, viruses, or toxins. They work by introducing an antigen either a weakened or inactivated form of a pathogen, a fragment of it (such as a protein or polysaccharide), or genetic material encoding it into the body without causing the disease itself (1). This controlled exposure triggers the immune system to produce antibodies and activate immune cells, including memory B and T lymphocytes. As a result, if the vaccinated individual later encounters the actual pathogen, the immune system can respond rapidly and effectively, preventing illness or significantly reducing its severity (2).

Vaccination is one of the most successful and cost-effective public health interventions in history. It has led to the eradication of smallpox, near-eradication of polio, and dramatic reductions in diseases such as measles, diphtheria, tetanus, and whooping cough. Beyond individual protection, vaccines contribute to herd immunity, whereby high levels of immu-

nization in a population reduce the spread of infectious diseases, protecting vulnerable individuals who cannot be vaccinated (3). With advances in biotechnology, modern vaccines including recombinant, vector-based, and mRNA platforms continue to expand the scope of disease prevention, addressing emerging infections and even non-communicable diseases such as cancer (4). This review aims to provide a comprehensive overview of vaccines, examining their mechanisms of action, types, and public health impact, while highlighting recent advances and future directions in vaccine development.

Methodology:

This is a narrative review of the scientific literature designed to provide a comprehensive synthesis of existing knowledge on vaccine adjuvants, their mechanisms of action, types, and safety profiles. Relevant data were obtained from peer-reviewed scientific literature sourced from major electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. Additional information was gathered from authoritative reports by global

health organizations such as the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC).

The search strategy involved the use of key terms including "vaccine adjuvants," "immunological mechanisms," "aluminum salts," "emulsion adjuvants," "TLR agonists," and "vaccine safety," with the use of Boolean operators, "AND" and "OR", to refine the results. Only articles published in English were considered, with priority given to recent and high-impact studies. The review primarily covers literature published between 2000 and 2025, while also incorporating seminars of earlier studies where necessary to provide historical context. Articles were screened for relevance based on titles, abstracts, and full-text evaluation, and selected findings were synthesized qualitatively to present a coherent and up-to-date overview of the field.

Immunological mechanisms of adjuvant action:

The mechanisms of adjuvant action begin with the activation of the innate immune system, which serves as the foundation for effective adaptive immunity. Most adjuvants function by stimulating pattern recognition receptors (PRRs) expressed on innate immune cells such as dendritic cells, macrophages, and monocytes. These receptors including Toll-like

receptors (TLRs), NOD-like receptors (NLRs), and others recognize molecular patterns associated with pathogens or cellular stress. Engagement of these receptors triggers intracellular signaling pathways such as NF- κ B and interferon regulatory factors (IRFs), leading to the production of pro-inflammatory cytokines (e.g. IL-1 β , IL-6, TNF- α) and type I interferons. This localized inflammatory response creates an immunostimulatory environment at the injection site that is essential for initiating strong immune responses (5,6).

A critical consequence of innate immune activation is the recruitment and maturation of antigen-presenting cells (APCs), particularly dendritic cells. Adjuvants enhance the uptake and processing of vaccine antigens and promote dendritic cell maturation, characterized by increased expression of major histocompatibility complex (MHC) molecules and costimulatory molecules such as CD80 and CD86 (7). Mature dendritic cells migrate to draining lymph nodes, where they present antigen-derived peptides to naïve T cells.

Effective T-cell activation requires three signals; antigen presentation via MHC (signal 1), co-stimulation (signal 2), and cytokine-mediated differentiation cues (signal 3) (Fig 1). By strengthening these signals, adjuvants prevent immune tolerance and ensure robust priming of antigen-specific T lymphocytes (7,8).

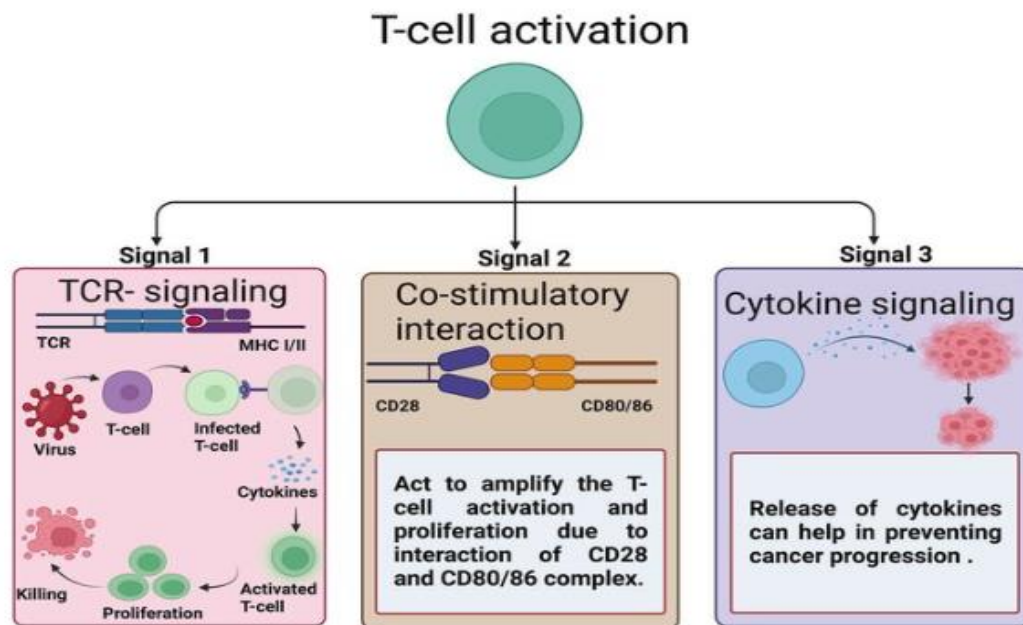


Fig. 1 Three signal hypotheses for T-cell activation: Signal 1-TCR-signaling; Signal 2-Co-stimulatory interaction between CD28 and CD80/86; Signal 3-Cytokine signaling ([CC BY 4.0](#))

Adjuvants also shape the quality and polarization of adaptive immune responses. Depending on their composition and the innate pathways they activate, adjuvants can direct T-helper cell differentiation toward distinct functional subsets. For example, aluminum salts typically promote T_{H2} -biased responses that favor strong antibody production, whereas TLR agonists tend to induce T_{H1} responses associated with cellular immunity and cytotoxic T-cell activation. Some adjuvants facilitate cross-presentation, allowing exogenous antigens to enter the MHC class I pathway and stimulate CD8+ cytotoxic T lymphocytes, which are essential for protection against intracellular pathogens and cancer. Through these mechanisms, adjuvants tailor immune responses to match the nature of the targeted pathogen (9).

Finally, adjuvants enhance the magnitude and durability of humoral immunity by promoting germinal center formation and B-cell maturation. They support the development of T follicular helper (T_{FH}) cells, which assist B cells in undergoing affinity maturation, isotype switching, and differentiation into long-lived plasma cells and memory B cells. This results in higher antibody titers, improved antibody quality, and sustained immunological memory (10). By coordinating innate activation, antigen presentation, T-cell differentiation, and B-cell maturation, adjuvants act as essential immune modulators that transform weakly immunogenic antigens into highly effective and long-lasting vaccines (11).

Types of vaccine adjuvants:

Vaccine adjuvants can be broadly classified into several major categories based on their composition and mechanism of action. The oldest and most widely used adjuvants are mineral salts, particularly aluminum-based compounds such as aluminum hydroxide and aluminum phosphate, collectively referred to as alum (12). These adjuvants primarily enhance humoral immunity and are known to promote T_{H2} -type immune responses. Alum has been used for nearly a century in vaccines such as hepatitis B, diphtheria-tetanus-pertussis (DTaP), and human papillomavirus (HPV) vaccines. While highly effective at stimulating antibody production, aluminum salts are less efficient at inducing strong cellular (T_{H1} or cytotoxic T-cell) responses (13).

Another important category includes emulsion-based and combination adjuvants, such as MF59, AS03, and AS01. Emulsion adjuvants are typically oil-in-water formulations that enhance immune responses by recruiting

antigen-presenting cells to the injection site and promoting antigen uptake. They are widely used in influenza vaccines, particularly for the elderly populations where stronger immune stimulation is required (6). Combination adjuvants, such as AS01 (which contains monophosphoryl lipid A and QS-21 in a liposomal formulation) are designed to activate multiple innate immune pathways simultaneously. These systems generate both strong antibody and cellular immune responses and are used in vaccines such as recombinant zoster vaccine (14).

A more targeted group of adjuvants includes pattern recognition receptor (PRR) agonists and saponin-based adjuvants. PRR agonists, such as monophosphoryl lipid A (a TLR4 agonist) and CpG oligodeoxynucleotides (TLR9 agonists), directly stimulate innate immune receptors, promoting T_{H1} -biased and cytotoxic T-cell responses. Saponin-based adjuvants, including QS-21 and Matrix-M, enhance both humoral and cellular immunity and are used in newer vaccines such as malaria and COVID-19 vaccines (15). In addition, emerging adjuvant technologies such as nanoparticle systems, liposomes, and STING agonists are being developed to provide more precise immune modulation. Together, these diverse types of adjuvants enable the design of vaccines tailored to specific pathogens and population needs (16).

Aluminum salts (Alum):

Aluminum salts are the most widely used adjuvants in human vaccines, commonly referred to collectively as "alum." The principal forms used in licensed vaccines are Aluminum hydroxide, Aluminum phosphate, and historically Potassium aluminum sulfate. Since their introduction in the 1920s, aluminum-based adjuvants have been incorporated into numerous vaccines to enhance immune responses to purified antigens that would otherwise be weakly immunogenic. Their long record of clinical use, established safety profile, and relatively low cost have made them foundational components of many routine immunization programs worldwide (17).

The mechanisms by which aluminum salts act as adjuvants are multifactorial. Traditionally, they were thought to function mainly through a "depot effect," in which the antigen adsorbed onto the aluminum particles is retained at the injection site and released slowly, prolonging immune exposure. More recent research shows that their activity also involves activation of innate immune pathways (18).

Aluminum salts promote local inflammation, recruit antigen-presenting cells such as dendritic cells, and enhance antigen uptake. They can stimulate the release of danger-associated molecular patterns (DAMPs) and activate inflammasome pathways, leading to cytokine production that supports adaptive immunity. Importantly, aluminum adjuvants tend to skew immune responses toward a T_{H2} -type profile, promoting strong antibody (humoral) responses rather than cytotoxic T-cell responses (19).

In terms of applications, aluminum salt adjuvants are included in many widely used vaccines, such as diphtheria vaccine, tetanus vaccine, hepatitis B vaccine, and certain formulations of the human papillomavirus vaccine. In these vaccines, aluminum salts adsorb protein antigens (such as toxoids or recombinant surface proteins), increasing their immunogenicity and enabling protective antibody titers with fewer doses or lower antigen quantities. They are especially effective for inactivated or subunit vaccines, where the pathogen is not live and requires immune enhancement to achieve adequate protection (12).

The characteristic features of aluminum salt adjuvants include their particulate nature, positive surface charge (depending on pH and formulation), and strong capacity for antigen adsorption through electrostatic interactions and ligand exchange. They are generally administered intramuscularly and are considered safe, with common side effects limited to mild local reactions such as pain, redness, or swelling at the injection site (20). Unlike newer adjuvants designed to elicit strong cellular immunity, aluminum salts are less effective at inducing robust T_{H1} or cytotoxic T lymphocyte responses, which limits their use in certain modern vaccines (e.g., some viral or cancer vaccines). Nevertheless, due to their stability, safety, affordability, and proven efficacy in stimulating durable antibody responses, aluminum salt adjuvants remain central to contemporary vaccinology (21).

Emulsion-based adjuvants:

Emulsion-based adjuvants are vaccine adjuvants formulated as mixtures of two immiscible liquids typically oil and water stabilized by surfactants to enhance immune responses to antigens. They are usually oil-in-water (O/W) emulsions, where small droplets of oil are dispersed within an aqueous phase. Prominent examples include MF59, AS03, and montanide ISA 51. MF59 and AS03 are squalene-based O/W emulsions widely used in human vaccines, whereas montanide formula-

tions are often water-in-oil (W/O) emulsions used in veterinary and experimental vaccines. These systems are designed to improve immunogenicity, particularly for subunit or inactivated vaccines that may otherwise elicit weak immune responses (22).

The mechanisms of emulsion-based adjuvants involve both innate immune activation and enhancement of antigen delivery. Unlike traditional depot-forming adjuvants that simply retain antigen at the injection site, O/W emulsions such as MF59 actively recruit immune cells. They induce local production of chemokines and cytokines, which attract monocytes, macrophages, and dendritic cells to the injection site (23). These antigen-presenting cells (APCs) then uptake the antigen more efficiently and migrate to lymph nodes, where they prime T and B lymphocytes. Components such as squalene and α -tocopherol (in AS03) can further amplify immune signaling pathways, leading to stronger antibody titers and improved cellular immunity. The small droplet size and large surface area of the emulsion enhance antigen dispersion and interaction with immune cells (24).

Emulsion-based adjuvants are widely applied in human and veterinary vaccines. MF59 has been used in licensed influenza vaccines, particularly for older adults, to enhance immunogenicity against seasonal strains. AS03 gained prominence during influenza pandemics, including H1N1, due to its capacity to induce strong and cross-reactive immune responses with antigen-sparing effects (25). In veterinary medicine, Montanide emulsions are commonly used for vaccines against parasitic and viral infections in livestock. These adjuvants are especially valuable in pandemic preparedness, dose-sparing strategies, and in populations with weaker immune responses, such as the elderly. They are also under investigation for emerging infectious diseases and therapeutic cancer vaccines (26).

The characteristic features of emulsion-based adjuvants include their physical stability, biocompatibility (particularly when using metabolizable oils like squalene), and capacity to induce balanced humoral and cellular immunity (27). Oil-in-water emulsions are generally less reactogenic than older water-in-oil formulations, which were associated with stronger local inflammation and granuloma formation. They are typically manufactured with controlled droplet sizes (often in nanometer range) to ensure consistency, safety, and efficacy. While they may cause mild local reactions such as pain or swelling at the injection site, they have demonstrated strong safety profiles in licensed

vaccines (28). Overall, emulsion-based adjuvants represent a significant advancement in vaccine formulation by combining immunostimulatory capacity with acceptable tolerability and broad applicability (12).

Toll-like receptor (TLR) agonists:

Toll-like receptor (TLR) agonist adjuvants are immunostimulatory substances that enhance vaccine efficacy by specifically activating Toll-like receptors, a family of pattern recognition receptors expressed on innate immune cells such as dendritic cells, macrophages, and B cells. These receptors recognize conserved pathogen-associated molecular patterns (PAMPs), thereby initiating rapid immune activation. Notable examples of TLR agonists include monophosphoryl lipid A (a TLR4 agonist), CpG oligodeoxynucleotides, and imiquimod.

Each of these molecule mimics microbial components to safely trigger innate immune signaling without causing full-blown infection, making them powerful tools in modern vaccine design (29,30).

The mechanism of TLR agonist adjuvants centers on receptor-specific activation of intracellular signaling cascades. Upon binding to their respective TLRs, these agonists stimulate adapter proteins such as MyD88 or Toll-interleukin receptor (TIR)-domain containing adapter-inducing interferon- β (TRIF), which then activate series of cytoplasmic kinases, leading to subsequent activation of transcription factors like nuclear factor kappa B (NF- κ B) and interferon regulatory factors (IRFs). This results in the production of pro-inflammatory mediators (cytokines, chemokines), and type I interferons (Fig 2) (31).

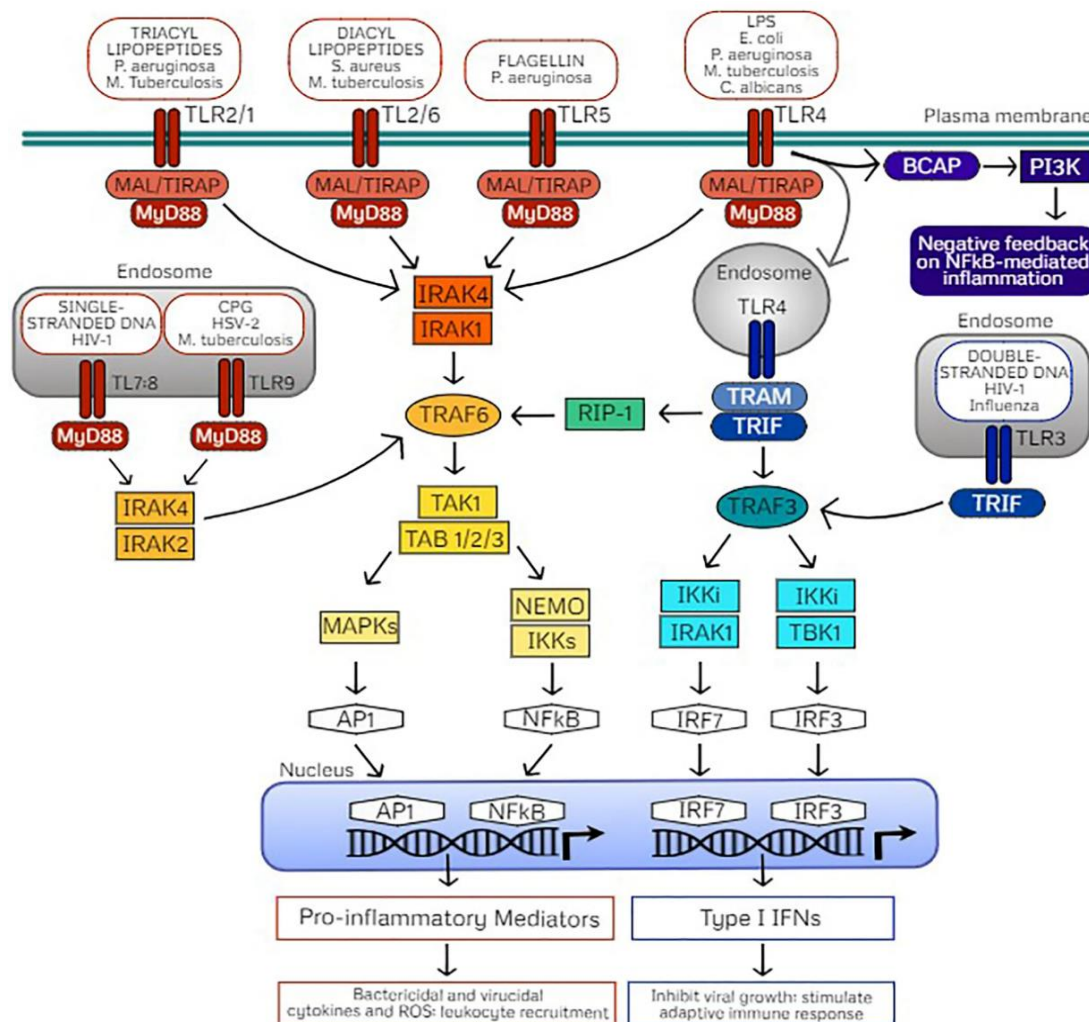


Fig 2: TLR signaling pathways mediated through MyD88- or TRIF-dependent cascades (31).

Consequently, antigen-presenting cells upregulate co-stimulatory molecules (e. g., CD80/CD86) and enhance antigen processing and presentation to T cells. For example, monophosphoryl lipid A promotes a balanced T_{H1} -biased immune response via TLR4 signaling, while CpG oligodeoxynucleotides stimulate strong T_{H1} and cytotoxic T-lymphocyte responses through TLR9 activation. This targeted engagement bridges innate and adaptive immunity efficiently (32).

In terms of application, TLR agonists are widely incorporated into licensed and experimental vaccines. Monophosphoryl lipid A is a component of the AS04 adjuvant system used in certain human vaccines, including those targeting viral infections. CpG oligodeoxynucleotides have been approved in specific hepatitis B vaccines to improve sero-protection rates, particularly in populations with weaker immune responses (33). Although primarily used topically for certain dermatological conditions, imiquimod has demonstrated adjuvant properties in therapeutic vaccine strategies and cancer immunotherapy. Beyond infectious diseases, TLR agonists are being explored in cancer vaccines and allergy immunotherapy due to their ability to skew immune responses toward desired T_{H1} or cytotoxic profiles (34).

The characteristic features of TLR agonist adjuvants include high specificity, potent immune activation, and the capacity to tailor immune polarization. They are often used in combination with other adjuvants (such as aluminum salts or emulsions) to create synergistic effects. Compared with traditional adjuvants, TLR agonists provide a more mechanistically defined mode of action, allowing rational vaccine design. However, because they strongly stimulate innate immunity, careful dose optimization is required to balance efficacy and reactogenicity (35). Overall, TLR agonist adjuvants represent a sophisticated generation of immune enhancers that leverage molecular insights into host-pathogen recognition to produce robust, durable, and targeted immune protection (29).

Saponin-based adjuvants:

Saponin-based adjuvants are immunostimulatory compounds derived primarily from plant glycosides known as saponins, which possess amphiphilic (both hydrophilic and hydrophobic) properties. These natural compounds are commonly extracted from the bark of the Chilean soapbark tree, *Quillaja saponaria* (36). One of the most studied purified saponins is QS-21, which has been incorporated into seve-

ral advanced vaccine formulations. Saponins can also be formulated into more complex structures such as ISCOMs (immune-stimulating complexes), which combine saponins with cholesterol and phospholipids to create cage-like nanoparticles. Due to their potent immunostimulatory capacity, saponin-based adjuvants are widely investigated for both infectious disease and cancer vaccines (37).

The mechanisms of saponin-based adjuvants involve multiple immunological pathways. They enhance antigen uptake by antigen-presenting cells (APCs), promote dendritic cell maturation, and stimulate cytokine production. A key feature is their ability to induce strong cellular immunity, particularly cytotoxic CD8+ T-cell responses, which are essential for combating intracellular pathogens and tumors (38). QS-21 and related saponins are known to promote both T_{H1} -type immune responses, characterized by interferon- γ production and robust antibody production. Mechanistically, they may activate inflammasomes and facilitate antigen cross-presentation through membrane interaction and pore-forming activity. Their amphiphilic structure allows them to associate with cell membranes, enhancing antigen delivery and immune cell activation (37).

In terms of application, saponin-based adjuvants have been incorporated into licensed and experimental vaccines. QS-21 is a key component of the AS01 adjuvant system used in vaccines such as the malaria vaccine and certain herpes zoster vaccines. These formulations have demonstrated high efficacy by generating strong humoral and cellular immune responses (39). Beyond infectious diseases, saponin adjuvants are widely explored in therapeutic cancer vaccines due to their capacity to stimulate cytotoxic T lymphocytes. They are also under development for veterinary vaccines and emerging infectious diseases, particularly when a balanced and durable immune response is required (36).

The characteristic features of saponin-based adjuvants include their potent immunogenicity, ability to stimulate both arms of adaptive immunity (humoral and cellular), and compatibility with nanoparticle delivery systems. However, crude saponin extracts can be reactogenic or hemolytic, which is why purified fractions like QS-21 and formulated systems such as ISCOMs are preferred for human use. They are typically used at carefully optimized doses to minimize local and systemic side effects. Overall, saponin-based adjuvants represent a highly effective class of modern vaccine enhancers, valued for their strength, vers-

atility, and suitability for next-generation vaccine platforms (39).

Liposomal and combination adjuvants:

Liposomal adjuvants are vaccine delivery systems composed of phospholipid bilayer vesicles (liposomes) that encapsulate or adsorb antigens and immunostimulatory molecules. Their structure mimics biological membranes, allowing efficient fusion with or uptake by antigen-presenting cells (APCs). A prominent example is AS01, which contains monophosphoryl lipid A and QS-21 incorporated into liposomes. Another example is CAF01, a cationic liposomal formulation designed to induce strong cellular immunity (40). Liposomes can vary in size, charge (neutral, cationic, or anionic), and composition, allowing customization of immune responses. Their versatility makes them suitable for delivering protein subunits, peptides, nucleic acids, and even mRNA-based antigens (41).

The mechanisms of liposomal adjuvants involve enhanced antigen delivery, protection from degradation, and immune activation through co-delivered immunostimulants. Liposomes facilitate efficient uptake by dendritic cells and macrophages, promoting antigen processing and presentation via both MHC class I and II pathways. Cationic liposomes, in particular, form electrostatic interactions with negatively charged cell membranes, improving cellular uptake and depot formation at the injection site. When combined with immunostimulatory molecules such as monophosphoryl lipid A (a TLR4 agonist) or QS-21 (a saponin), liposomal systems can synergistically enhance cytokine production, dendritic cell maturation, and T-cell activation. This dual function serving as both a delivery vehicle and an immune enhancer distinguishes liposomal adjuvants from simpler adjuvant systems (42).

Combination adjuvants integrate two or more immunostimulatory components to achieve broader and more potent immune responses than single agents alone. For example, AS04 combines aluminum salts with monophosphoryl lipid A to enhance both antigen presentation and innate immune activation. Such systems are used in licensed vaccines against infectious diseases and are being explored for cancer immunotherapy and emerging pathogens (43). Characteristically, liposomal and combination adjuvants provide balanced humoral and cellular immunity, dose-sparing effects, and adaptable immune polarization (e.g., T_H1 -biased responses). While formulation complexity and stability considerations require

careful manufacturing control, these advanced adjuvant platforms represent a significant evolution in rational vaccine design, offering enhanced efficacy with acceptable safety profiles (44).

Emerging and experimental adjuvants:

Emerging and experimental adjuvants represent the next generation of immune-enhancing systems designed to improve vaccine efficacy, precision, and durability. Unlike traditional adjuvants such as aluminum salts, these novel platforms often target specific innate immune pathways or use advanced delivery technologies. Examples include cyclic GMP-AMP (a STING agonist), poly I:C (a TLR3 agonist), and CpG 1018 (45). In addition, nanoparticle-based systems, virus-like particles (VLPs), and RNA-based platforms are being investigated as both delivery vehicles and intrinsic adjuvants. These approaches aim to generate stronger cellular immunity, cross-protection against variants, and long-lasting memory responses (46).

The mechanisms of emerging adjuvants often involve precise activation of innate immune sensors such as STING, RIG-I-like receptors, and various Toll-like receptors. For example, cyclic GMP-AMP activates the STING pathway, leading to robust type I interferon production and enhanced dendritic cell maturation. Poly I:C mimics viral double-stranded RNA and stimulates TLR3, inducing antiviral cytokines and promoting T_H1 -skewed immune responses (47). Many nanoparticle-based adjuvants enhance lymphatic trafficking and improve antigen cross-presentation, facilitating cytotoxic CD8⁺ T-cell activation. Some experimental systems are designed to co-deliver antigen and immune stimulators within the same particle, ensuring synchronized uptake by antigen-presenting cells. This targeted immune modulation allows fine-tuning of immune polarization, whether toward antibody-dominant (T_H2), cell-mediated (T_H1), or balanced responses (48).

Applications of emerging and experimental adjuvants span infectious diseases, cancer immunotherapy, allergy desensitization, and personalized vaccines. They are particularly valuable for subunit, peptide, and nucleic acid vaccines that lack intrinsic immunogenicity. In oncology, STING agonists and nanoparticle-based systems are being evaluated to stimulate tumor-specific cytotoxic T lymphocytes (49). In pandemic preparedness, RNA vaccines inherently possess self-adjuncting properties through innate immune recognition

pathways, offering rapid scalability and adaptability. Characteristically, these novel adjuvants emphasize specificity, modularity, and synergy with advanced vaccine technologies. Although many remain under clinical evaluation due to concerns about reactogenicity and manufacturing complexity, they represent a transformative frontier in vaccinology, aiming for safer, more potent, and highly targeted immune protection (50).

Safety profiles and side effects of vaccine adjuvants:

The safety profiles of vaccine adjuvants are evaluated through extensive preclinical testing, phased clinical trials, and continuous post-licensure surveillance to ensure that their benefits outweigh potential risks. Historically used adjuvants such as aluminum salts (alum) have demonstrated decades of safe use in millions of doses worldwide, primarily causing mild and transient local reactions such as pain, redness, or swelling at the injection site (51). Modern adjuvants including emulsions, liposomal systems, saponin-based formulations, and Toll-like receptor (TLR) agonists undergo rigorous toxicological assessment to evaluate local reactogenicity, systemic effects, biodistribution and long-term safety. Regulatory agencies require detailed evaluation of dose, formulation stability, and immunostimulatory intensity to minimize adverse effects while preserving efficacy (52).

Most adjuvant-related adverse events are mild to moderate and reflect the intended activation of the innate immune system. Common effects include localized inflammation, low-grade fever, fatigue, or muscle aches, which are typically short-lived and resolve without intervention. Rare but more significant reactions such as severe allergic responses are carefully monitored during clinical trials and pharmacovigilance programs (53). Importantly, modern adjuvants are often designed to reduce systemic exposure and limit excessive inflammatory signaling. For example, detoxified derivatives of microbial components are used instead of native toxins to maintain immunostimulatory capacity while minimizing toxicity. Dose optimization and formulation strategies, such as nanoparticle encapsulation or liposomal delivery, further improve tolerability by controlling how and where immune activation occurs (54).

Long-term safety monitoring is a critical component of adjuvant evaluation, involving global surveillance systems and large-scale epidemiological studies. Extensive data from

licensed vaccines show no consistent evidence linking approved adjuvants to chronic autoimmune diseases or long-term systemic harm (51,55). The biological mechanisms of adjuvants primarily transient activation of innate immunity support their short-lived action rather than persistent immune dysregulation. Nonetheless, continuous research aims to refine adjuvant design to balance potency with safety, especially for vulnerable populations such as infants, pregnant individuals, the elderly, and immunocompromised patients. Overall, the safety profiles of vaccine adjuvants reflect careful scientific design, stringent regulatory oversight, and decades of real-world evidence demonstrating that their benefits in preventing infectious diseases far exceed their risks (56).

Challenges in adjuvant development:

The development of vaccine adjuvants faces multiple scientific and regulatory challenges that make the process both complex and high-stakes. One of the primary scientific hurdles is achieving the optimal balance between immunogenicity and safety. Adjuvants must be potent enough to enhance immune responses to weak or subunit antigens but must not induce excessive inflammation or systemic toxicity. Overstimulation of the immune system can lead to adverse events, including local tissue damage, fever, or, in rare cases, autoimmune reactions. Designing adjuvants that consistently elicit the desired type of immune response whether humoral, cellular, or balanced is particularly challenging for diseases requiring specific immune polarization, such as intracellular pathogens or cancer (12,17).

Another major challenge in adjuvant development is variability in immune responses across populations. Factors such as age, sex, genetics, nutrition, microbiome composition, and prior exposure to pathogens can significantly influence how an individual responds to a given adjuvant. For example, older adults may have immunosenescence that reduces vaccine responsiveness, while infants have developing immune systems that are more sensitive to inflammatory stimuli. This variability complicates dose selection, formulation optimization, and safety assessment during clinical trials. It also necessitates large, diverse study populations and carefully tailored clinical trial designs to ensure that the adjuvant performs safely and effectively across demographics (57,58).

Regulatory and manufacturing hurdles

add additional layers of complexity. New adjuvants must undergo rigorous preclinical toxicology studies, phased human clinical trials, and post-licensure surveillance to demonstrate safety, efficacy, and batch-to-batch consistency. Manufacturing adjuvants with stable physical and chemical properties such as emulsions, liposomes, or nanoparticle formulations requires specialized facilities, precise quality control, and scalable production methods (59). Furthermore, combination or experimental adjuvants must meet even stricter standards due to their novel mechanisms of action. Regulatory agencies are cautious with new adjuvants because even minor formulation changes can impact immunogenicity or reactogenicity, making approval processes lengthy and resource-intensive (60).

A final challenge is the lack of universally predictive preclinical models. Animal models often fail to fully replicate human immune responses, leading to discrepancies between preclinical and clinical results. This is particularly true for adjuvants that act on specific innate immune pathways, such as Toll-like receptors or STING, where receptor expression and signaling differ between species. As a result, developers must rely on a combination of *in vitro* human immune cell assays, computational modeling, and carefully designed clinical trials to bridge this gap (61). Overall, these scientific, regulatory, and logistical challenges mean that adjuvant development is a slow, expensive, and highly iterative process, but overcoming them is essential for advancing vaccines against challenging or emerging infectious diseases (62).

Future perspectives of adjuvants:

The future of vaccine adjuvants is poised for transformative advances, driven by a deeper understanding of immunology, molecular biology, and materials science. Next-generation adjuvants aim to provide highly tailored immune responses, enhancing both efficacy and safety. One major direction is the rational design of adjuvants that selectively target specific innate immune receptors, such as TLRs, STING, or RIG-I-like receptors, to elicit precisely calibrated T_{H1} , T_{H2} , or cytotoxic responses. For example, synthetic TLR agonists and cyclic dinucleotide STING activators are being developed to boost cellular immunity for vaccines against intracellular pathogens or cancer, offering unprecedented specificity compared to traditional adjuvants (57).

Another emerging trend is the integration of advanced delivery platforms, including

nanoparticles, liposomes, virus-like particles, and microneedle patches, which allow controlled release of antigens and adjuvants directly to immune cells. These technologies not only improve the magnitude and duration of immune responses but also reduce systemic reactogenicity (63). Combination adjuvants are likely to become more sophisticated, where multiple immunostimulatory signals are delivered simultaneously within the same formulation to achieve synergistic effects. Such systems can potentially overcome challenges posed by immunosenescence in elderly populations or hypo-responsive immune systems in certain patients (64).

Personalized and precision vaccinology is also expected to influence adjuvant development. Advances in genomics, transcriptomics, and immune profiling may allow vaccines to be tailored to individual immune profiles, optimizing both the type and strength of the response while minimizing adverse effects (65). Additionally, with the rapid expansion of mRNA and other nucleic acid vaccines, adjuvants that safely enhance these platforms by stabilizing RNA, improving delivery, or stimulating innate immunity will be crucial (66). Overall, the future perspectives of adjuvants revolve around precision, modularity, and synergistic design, combining immunological insights with innovative formulation technologies to create safer, more effective, and adaptable vaccines for a wide range of infectious diseases, cancers, and emerging global health threats (21).

Conclusion:

In summary, vaccine adjuvants play a critical role in enhancing immune responses, bridging the gap between antigen presentation and effective immunological memory. By modulating innate immunity and influencing the adaptive response, adjuvants improve vaccine efficacy and durability, which is especially important for subunit, recombinant, or inactivated vaccines that may be poorly immunogenic on their own. Understanding the mechanisms of action has led to the development of diverse adjuvant types, ranging from traditional aluminium salts to novel lipid-based and immunostimulatory compounds, each with distinct advantages and safety considerations. The careful evaluation of these adjuvants' immunological profiles ensures a balance between potency and tolerability, ultimately guiding safe and effective vaccine formulation.

Looking forward, the future of adjuvant research lies in designing highly targeted, pathogen-specific, and personalized adjuvants

capable of eliciting robust and durable protection with minimal side effects. Addressing challenges such as rare adverse events, regulatory hurdles, and variability in individual immune responses will be crucial to expanding their application. Advances in immunology, molecular biology, and nanotechnology hold promise for next-generation adjuvants that not only improve vaccine efficacy but also enable rapid responses to emerging infectious diseases. Ultimately, continued innovation in adjuvant science is pivotal to enhancing global vaccination strategies and strengthening public health outcomes worldwide.

Contributions of authors:

CPE conceptualized the study; MEN, CPE, CCA, and OVA conducted the literature search and data collection; CPE and MEN drafted the initial manuscript, while FE, OOO and JTA contributed to critical revision for intellectual content. All authors read and approved the final version of the manuscript.

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