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Review Article

Vaccine adjuvants: Insights into development, present and future perspective

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Abstract

Vaccination offers a reliable biological defence against a particular infection or malignant disease. Vaccines are made up of certain substances that mimic a series of events that prompt the body defence system to identify and eradicate the sustance as a threat. Adjuvants are compounds that are included into vaccines in order to improve or strengthen the defence mechanism towards infectious diseases. Through the yrs. adjuvant development has witnessed a number of notable advancements. Adjuvants are divided into four types: delivery systems, immune-stimulating mucosal adjuvants, and combinations of adjuvants. These categories are further divided into mineral salt, Emulsions, microscopic particles, and agonists of receptors 1/2, 3, 4, 5, 7/8, 9, and NOD. This overview covers the adjuvant s' history, various kinds, licensed adjuvants, and other related topics. which are under clinical trials or clinical developments and Various type of adjuvants use for vaccine developments.

Keywords: Vaccines, Adjuvants, Immunomodulators, Delivery system, Clinical research

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1. Introduction

1.1. Vaccine

Via actively gained immunity, vaccination offers a reliable biological defence against a particular infection or cancer-causing illness. Vaccines effectiveness and safety have been rigorously examined, verified, and validated. Usually, it consists of weakened or killed forms of the organism i.e., the infectious agent's enzymes or its surface proteins. It consists of a substance that imitates a bacterium that becomes the source of illness. The agent sets off a chain reaction that causes the defence system to identify the agent as a threat, get rid of them, and subsequently identify and get rid of any associated germs the body gets encounter with. To put it another way, they are biological preparations that encourage the production of memory T cells, a subset of immune cells that "remembers" previous infections and may mount a strong and quick defense when the same pathogen is encountered again.[1-3]

1.2. Vaccine adjuvant

An adjuvant is an additive used in immunology that either boosts or modifies the defence mechanism of the body. The word adjuvant means to help or sustain. Any material that, when combined with particular vaccination antigens, works to speed up, extend, or improve antigen-specific immune responses is known as an immunologic adjuvant. Manufacturing of vaccines in early phase was rightly believed that substantial differences in the success of several batches of the same vaccine were due to adulteration. Nevertheless, it was soon discovered that some pollutants actually boosted the immune response, and more meticulous cleaning appeared to decrease the efficiency of vaccines.[4- 5]

1.3 History of vaccine adjuvants

Brief history of various vaccine adjuvants is elaborated in **Table 1**.

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Table 1: Timeline of vaccine adjuvants

Year	Adjuvants	Status	Brand Name	References
1885	SSRNA	Not licensed	-	6
1921	DNA, Lipoprotein	Not licensed	-	6
1926	Alum	-	-	6-7
1932	Aluminium potassium sulfate	Licensed	Pentacel, Quadracel, Adacel, TENIVAC, TDVAX	6
1937	IFA	Not licensed	-	8
1939	Aluminium hydroxide	Licensed	Havrix, Vaqta, Engerix-B, Recombivax HB, Infanrix, Pediarix, PedvaxHIB, ActHIB, Prevnar 13 and Pneumovax 23	9
1994	Virosome	Licensed	Invivac, Inflexal, Epaxal, Isiflu and viroflu,	10-11
1997	MF59	Licensed	Fluad, Focetria and Celtura	12
2000	Calcium phosphate	Licensed	Comvax, IPOL, BCG Vaccine, Stamaral, MMR, Hepavax	13-14
2005	AS04	Licensed	Fendrix, Cervarix	15-16
2006	Amorphous aluminium Hydroxy phosphate sulfate	Licensed	Recombivax, PedvaxHIB, Gardasil and Vaxelis	6,17
2009	AS03	Licensed	Pandemrix, Prepandrix and Arepanrix	18-19
2009	AF03	Licensed	Humenza	20
2017	AS01B	Licensed	Shingrix	6
2017	CpG 1018	Licensed	Heplisav-B	6,15
2018	GLA-AF	Not licensed	-	21
2020	LNP*	Licensed	Moderna/Spikevax	22,23
2021	Alhydroxiquim-II*	Licensed	COVAXIN	24-25
2022	Matrix M*	Licensed	Novavax	26-27

2. Classification of Adjuvants

Types of Vaccine adjuvants can be classified broadly into Delivery systems, Immunomodulators, Combined and Mucosal adjuvants. **Figure 1** depicts classification of vaccine adjuvants.

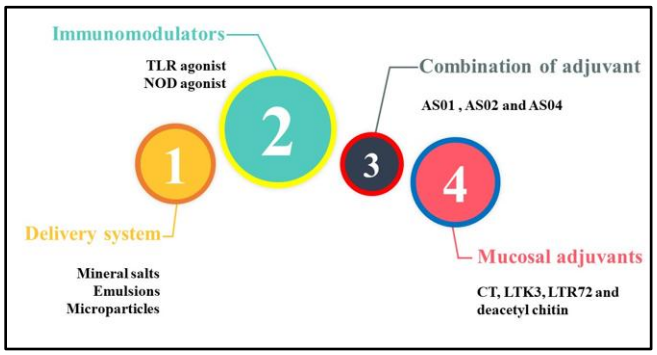

Figure 1: Classification of vaccine adjuvants

2.1. Delivery systems

A DS for vaccine adjuvants are a carrier material that facilitates antigen presentation and prolongs the bioavailability of antigens, enhancing adaptive immune responses. Different types, such as emulsions, liposomes, VLP, and microspheres, are integral components of immunization strategies. These systems enhance antigen uptake by APCs, which are essential in initiating body defence mechanism. DS are essential for enhancing antigen immunogenicity, eliciting a more robust immune response, and possibly lowering vaccination dosages and manufacturing expenses. These technologies improve vaccine efficiency and aid in the creation of more precise and successful vaccination regimens. Crucially, delivery systems ensure that adjuvants reach the appropriate mucosal surfaces, thereby eliciting a robust immune response.[28-30] **Figure 2** illustrates types of Delivery systems.

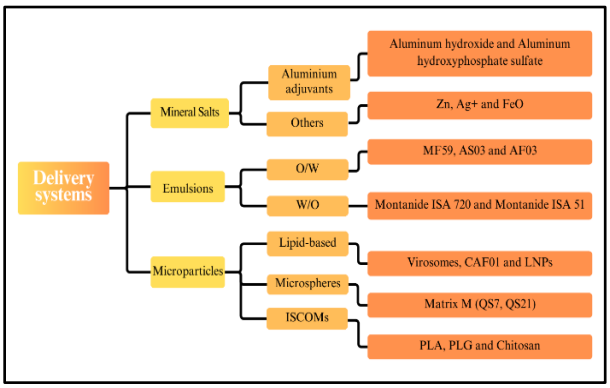

Figure 2: Classification of delivery systems

***2.2.** Immunomodulators*

An Immunomodulators (**Figure 3**) is a substance that boosts the body defence mechanism by prompting the innate

immunity to react robustly. These stimulants are molecules that signal danger, leading to APCs' development and activation by binding to specific sites on APCs. They can originate from various sources, including bacterial cell walls, internalized nucleic acids, and DNA containing unmethylated CpG dinucleotides. Immunomodulators are pivotal in augmenting vaccine efficacy by:

1. Expediting the development of strong and enduring responses over an extended period.
2. Triggering local mucosal immune reactions.
3. Producing antibodies with heightened avidity/affinity and increased neutralization capability.
4. Stimulating the production of killer T cell.
5. Boosting immunological responses in those with weakened immune systems.[31-33].

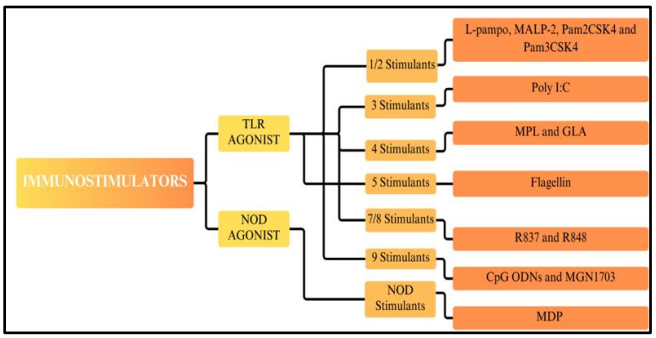

Figure 3: Classification of immunostimulators

2.3. Combination of adjuvant

Combination adjuvants are formulations comprising multiple molecules that work together synergistically to modulate, amplify, or prolong the immune response. These combination adjuvants have been created after a thorough testing process on human and animals. They are already approved for several vaccines in both human and animal health, with new combination adjuvants under development. The study highlights that any combination of adjuvants, including helper T cells type 1, 2, or 17, is sufficient to both augment and guide the immune responses toward the intended outcomes given a better understanding of the precise immunological responses required for successful disease prevention. The use of a range of adjuvants is thought to be crucial for the creation of vaccinations against serious. The use of a range of adjuvants is thought to be crucial for the creation of vaccinations against serious illnesses, as different disease targets and populations necessitate distinct adjuvant strategies[34-36]

2.4. Mucosal adjuvants

Mucosal adjuvants refer to compounds that heighten the body defence mechanism specifically at mucus regions, like those in the digestive or respiratory systems. These adjuvants are pivotal in eliciting both local and systemic immune defences, crucial for crafting potent mucosal vaccines. Employed alongside antigens and delivery systems, they serve to bolster vaccine effectiveness and fortify the immune reaction against pathogens.[37-39]

2.5. Adjuvants' function in delivery of vaccines

Figure 4 describes mechanisms of adjuvants in delivery of vaccines.

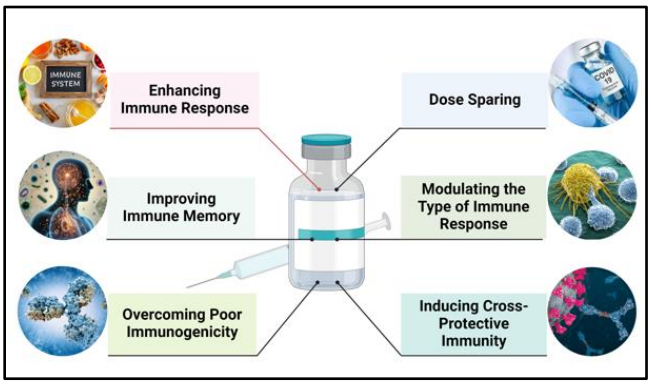

Figure 4: Adjuvants function in the delivery of vaccines

3. Licenced Vaccine Adjuvant for Human Use

A licensed vaccine adjuvant is a substance other than active pharmaceutical ingredient that has been approved for human use by regulatory agencies such as the FDA(**Table 2**).

Table 2: Licensed vaccine adjuvants

Adjuvants	Description	Mechanism of Action	Application	References
Alum	Particles of aluminium hydroxide, phosphate, or hydroxy phosphate sulphate salts that are hydrophobic	The partly characterised Extended-release system and a number of DAMPS and PRRs, such as IL-1α, IL-33, STING, and uric acid, have been linked. Enhances the generation of IgE and IgG antibodies	HAV, HBV, DTP, HPV, HIB	40-45
MF59	primarily oil-dispersed, squalene-based nano emulsions stabilized with citrate buffer, sorbitan trioleate, and polysorbate 80	It induces the generation of natural warning signals and operate via an ASC activation mechanism that is NLRP3-independent.	Influenza and flu	12,46-47

AS03	Polysorbate 80-based oil-dispersed Nano emulsions mostly containing squalene, α-tocopherols, and saline with phosphate buffering	Enhancing cytokine production. α-Tocopherol also recruits immune cells and induces high antibody titers. NF-κB activation	Swine flu and Influenza	48-52
AF03	Distributed oil-based Nano emulsions(primarily squalene)sorbitan, mannitol, phosphate-buffered saline, and polyoxymethylene–Ceto stearyl ether	Unknown. probably results in cell damage or death, which releases DAMP.	Influenza	53
AS01	Scattered lipids in vesicles include cholesterol, saponin QS-21, and TLR4 ligand.	MPL activates the TLR4 signalling process. QS-21 stimulates the release of HMGB1 and caspase-1 activation. Both act together to enhance IL-12, IL-18, and early IFN-γ production.	Malaria , HZV and Shingles	54-55
AS04	Aluminium hydroxide-adsorbed synthetic TLR 4 ligand.	MPL initiates the signalling of TLR4. Alum increases the MPL signalling's duration, or the Depot effect.	Human papilloma virus (HPV) ,HBV	56-57
Virosomes	Made up of viral glycoproteins and membrane lipids from reconstituted viral envelopes that serve as adjuvants or a vehicle for antigens.	Function by the generation of cytokines and in addition to stimulating CD8+ and CD4+ T cell proliferation.	Hepatitis A and influenza	10,11,58
CpG ODN (1018)	These synthetic ODNs are artificial short DNA sequences containing 18–25 bases. They are designed to interact with Toll-like Receptor 9 (TLR9) and consist of unmethylated cytosine-phosphate-guanine (CG) motifs.	MyD88, IRAK, and TRAF-6 transmit TLR9 engagement signals, which in turn enhance the proinflammatory cytokines and costimulatory molecules.	SARS-CoV-2, HBV	59-66
LNP (Lipid nanoparticles)	Ionisable lipids, PEG, and triglycerides incorporated in spherical vesicles	It activates NLRP3 inflammatory signals 1 and 2.	Covid 19	67
Matrix M	Particles containing phospholipids, cholesterol, and quillaja saponins.	Unknown. The suggested mechanism entails activating the NLRP3 inflammatory and increase production of MHC and co-stimulatory components.	Covid 19	26,67-68
Alhydroxiquim-2	IMQ adsorbed on alum	Alum shows Extended-release effect. IMQ is a tiny chemical that targets the signalling pathways of TLR7 and TLR8.	Covid 19	69-71

Table 3: Clinical research of immunomodulators platforms

Platform Type	Platform Name	Mechanism of Action	Tested Diseases and Age Group	NCT No.	Location	Phase
Synthetic double stranded RNA	Poly-ICLC	It activates TLR3 and MDA5.[74-75]	Tubular adenoma (40 Yrs to 70 Yrs)	NCT02134925	US	2
			Low grade glioma (up to 22 Yrs)	NCT04544007	US	2
			Hepatocellular Carcinoma (20 Yrs and older)	NCT05281926	Taiwan	1
			Grade IV astrocytoma (18 Yrs and older)	NCT03665545	Switzerland	1/2

			HIV-1 Infection (18 Yrs to 55 Yrs)	NCT02071095 NCT04672291	US	1/2
			COVID – 19 (18 Yrs to 69 Yrs)		Canada	1
GLA	GLA-SE	Activates TLR4.75-79	Merkel Cell Carcinoma (18 Yrs to 80 Yrs)	NCT02035657	US	1
			Schistosomiasis (18 Yrs to 49 Yrs)	NCT03041766	Senegal	2
			HIV Infections (0 Days to 5 Days	NCT04607408	SA	1
			Colorectal Cancer Metastatic (18 Yrs and older)	NCT03982121	France	1
			Schistosomiasis (18 Yrs to 50 Yrs)	NCT03110757	Brazil	1
	GLA-AF		Schistosomiasis (18 Yrs to 50 Yrs)	NCT02337855	US	1
IMQ	Imiquimod	Activates TLR7 and TLR8.[75,80-82]	Hepatitis B (18 Yrs and older)	NCT04083157	China	2/3
			Newly Diagnosed H3-mutated Glioma (18 Yrs nd older)	NCT04808245	Germany	1
			Cervical Dysplasia (18 Yrs and older) Renal Failure (21 Yrs and older)	NCT02864147	US	2
			Influenza (18 Yrs and older)	NCT02621112	Hong Kong	2/3
			Leukemia (18 Yrs and older)	NCT02960815	Switzerland	2
			Acute Lymphoblastic Leukemia (1 Year to 30 Yrs)	NCT02802943	Germany	2
			Grade IV astrocytoma (18 Yrs and older)	NCT03559413	Germany	1/2
			Melanoma (18 Yrs and older)	NCT02078648	US	1/2
	Resiquimod			NCT02126579	US	1/2
CpG ODNs	CpG ODN 1018	MyD88, IRAK, and TRAF-6 transmit Toll Like Receptors 9 engagement signalling[59-64]	Plague (18 Yrs. to 55 Yrs.)	NCT05506969	US	2
			COVID- 19(18 Yrs. and older)	NCT05012787	Ukraine	3
			SARS-COV-2(18 Yrs. to 70 Yrs.)	NCT05228613	Indonesia	1
			COVID- 19(12 Yrs. and older) COVID- 19(18 Yrs. to 75 Yrs.)	NCT04672395 NCT04405908	Belgium	2/3
			Malaria (18 Yrs. to 50 Yrs.)	NCT01351948	Australia	1

	CpG ODN 7909 IC31	Sustained-release antigens and TLR- 9 activation to improve antigen presentations[75,83]		NCT03512249	UK	1
			Tuberculosis (18 Yrs. to 60 Yrs.)	NCT03265977	SA	2
			Tuberculosis (12 Yrs. to 17 Yrs.)	NCT02378207	SA	2
			Tuberculosis (12 Yrs. to 17 Yrs.)	NCT02503839	SA	1
			Tuberculosis (18 Yrs. to 70 Yrs.)	NCT02496897	Norway	1
			Hepatitis B (18 Yrs. to 65 Yrs.)		Korea	1
CDNs	c-di-AMP	cGAS-STING pathway activation to produce CTLs and a robust Th1-type cellular response[75,84-85]	HPV (18 Yrs. to 45 Yrs.)	NCT05208710	Germany	1

Table 4: Clinical research of delivery systems

Type	Name	Mechanism of Action	Tested Diseases and Age Group	NCT No.	Location	Phase
W/O emulsion	MOT ISA 51	Sustained-release of antigens[75,86]	Melanoma (18 Yrs. and older)	NCT02334735	US	2
			Multiple Sclerosis (5 Yrs. to 17 Yrs.)	NCT02200718	US	1
			Melanoma (18 Yrs. and older)	NCT02425306	US	1/2
			Carcinoma (18 Yrs. and older)	NCT02955290	US	1/2
			Malaria (18 Yrs. to 45 Yrs.)	NCT04739917	Colombia	2
	MOT ISA 720		Yellow Fever (18 Yrs. to 45 Yrs.)	NCT02743455	US	1
LNPs	LNP	It activates NLRP3 inflammatory signals 1 and 2.[67,75]	COVID- 19(18 Yrs. and older)	NCT05658523	Australia	3
			HIV (18 Yrs. to 55 Yrs.)	NCT05903339	US	1
			COVID- 19(18 Yrs. to 99 Yrs.)	NCT04889209	US	1/2
			COVID- 19(18 Yrs. and older)	NCT05289037	US	1/2
			COVID- 19(18 Yrs. and older)	NCT04860258	Belgium	3
VLPs	VLP	Function through production of cytokines and co-stimulatory.[10,11,58,75]	Equine Encephalitis (18 Yrs. to 50 Yrs.) COVID- 19(18 Yrs. to 49 Yrs.)	NCT03879603	US	1

			Norovirus (18 Yrs. to 64 Yrs.)	NCT05040789	Canada	3
			Norovirus (6 Weeks to 8 Yrs.)	NCT02038907	Belgium	2
			Rheumatic fever (65 Yrs. and older)	NCT02153112	Finland	2
				NCT05349617	US	3

4. Clinical Research of Vaccine Adjuvants (2014-2025)

Clinical experiments are studies carried out on individuals to assess a treatment, operations, or change in behaviour. These are the main method used by investigators to evaluate the effectiveness and safety of new medications. There are a number of purposes for research studies, such as:

1. Evaluating techniques for early illness diagnosis, often prior to symptoms
2. Assessing novel medicines' safety and efficacy.
3. Comparing the effectiveness of different therapies

Clinical trials often involve volunteers from many countries as well as multiple medical and research institutions. Before they can begin, they must be accepted after being thoroughly planned, examined, and finished. Clinical trial participation is available to individuals of all ages, including minors.[72-73]

4.1. Clinical research of immunomodulators

An immunomodulators is a substance that enhances the defence mechanism to a vaccination by inducing a stronger immunological response. Immunomodulators are substances that act as warning signs and stimulate ACPs. Table 3 gives summary of clinical research on Immunomodulator platforms.

4.2. Clinical research of delivery systems under investigation

A DS for vaccine adjuvants are a carrier material that facilitates antigen presentation and prolongs the bioavailability of antigens, enhancing adaptive immune responses. **Table 4** gives summary of clinical research on Immunomodulator platforms.

5. Future Prospective of Vaccine Adjuvants

The future of vaccine adjuvants lies in the development of novel, targeted, and safe formulations that can enhance immunogenicity while minimizing side effects. Here are recent studies describe about future prospects, new findings of vaccine adjuvants:

5.1. Nanotechnology and molecular biology in adjuvant development

Modern technologies like nanotechnology and molecular biology have significantly enhanced the effectiveness of adjuvants. Novel adjuvants such as microparticles and emulsions are being developed to address safety concerns while maintaining efficacy.[87]

5.2. Synthetic and biosynthetic adjuvants

The future of adjuvant development lies in synthetic and biosynthetic materials, which offer more robust supply chains, reduced heterogeneity, and improved safety profiles. This transition is necessary for creating novel vaccines for emerging pathogens.[88]

5.3. Outer membrane vesicles

Outer Membrane Vesicles are emerging as promising adjuvants with low toxicity and the ability to boost innate as well as adaptive immunity. They also show potential as advanced mucosal delivery vehicles.[89]

5.4. Adjuvant systems for diverse populations

Advances in combination of adjuvant have made it possible to create vaccinations specifically designed for certain groups of population, including the older population and immunocompromised, with high safety and efficacy.[90].

5.5. Pandemic preparedness

Novel adjuvants are critical for improving pandemic preparedness. Antigen-agnostic platforms and adjuvants like aluminium salts and TLR agonists play key roles in rapid vaccine development during health crises.[91]

5.6. Polysaccharide adjuvants

Polysaccharides like chitosan have gained attraction for their biocompatibility, low toxicity, and potential applications in nano vaccine formulations.[92].

5.7. Systems vaccinology

Adjuvant molecular pathways have been enhanced because of innovations in systems biology, facilitating the development of vaccines that produce immune responses that are long lasting and specific.[93]

5.8. Multiple adjuvant combination techniques and cancer vaccines

Multiple adjuvant combination techniques are being investigated to overcome tumour immune evasion and improve antigen presentation, hence addressing problems in cancer immunotherapy.[94]

5.9. Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

5.10. Code availability

This article does not involve the use of any software or custom code.

6. Conclusion

Adjuvants are vital components that boost vaccination efficacy because they act as immune system stimulators, transporters, and depots. Among its many advantages are reduce in the dose, reduce in the number of vaccination sessions, and enhancing the antigen's immunogenicity and durability. Adjuvants of many kinds, such as mineral salts, aluminium salts, emulsions, and liposomes, are currently accessible for use in the manufacturing of vaccines; however, certain adjuvants have limits related to their toxicity and safety. Adjuvant research is essential for developing vaccines, particularly in anticipation of future epidemics.

Toxicological and safety considerations must be addressed in order to increase vaccination efficacy with innovative adjuvants. These limitations restrict the number of adjuvants that are compatible with humans. The major goals are to develop new and better vaccines, recognize the traits and workings of adjuvants that are compatible with humans, evaluate the state of adjuvant development today, and explore potential avenues for future adjuvant developments. Analyse the current state of adjuvant development and acknowledge the characteristics and mechanisms of adjuvants that are compatible with people. These investigations can identify unique molecular fingerprints that assist in overcoming the limitations of outdated adjuvants. Preclinical study has shown the potential of complicated adjuvant concepts, but there are limitations to how they might be used in preventive vaccination. New prospects may present themselves, though, if problems with the robustness, reproducibility, and mass production of therapeutic vaccinations are resolved.

7. Abbreviations

yrs. – years, NOD – Nucleotide-binding oligomerization domain, SsRNA – Single-stranded ribonucleic acid, DNA – Deoxyribonucleic acid, IFA – Incomplete Freund's adjuvant,GLA-AF – Glucopyranosyl lipid A aqueous formulation,LNP – Lipid nanoparticles, CpG – Cytosine phosphoguanine, AS – Adjuvant System, BCG – Bacillus Calmette-Guerin, DS – Delivery system, VLP – Virus-like particle, APCs – Antigen-presenting cells, FDA – Food and Drug Administration, IL – Interleukin, DAMP – Damage-associated molecular patterns, PRRs – Pattern Recognition Receptors, STING – Stimulator of interferon genes, Ig – Immunoglobulin, ASC – Apoptosis-associated speck-like protein containing a caspase recruit domain,HAV – Hepatitis A virus, HBV – Hepatitis B virus, DTP – Diphtheria, tetanus toxoids and pertussis, HPV – Human papillomaviruses, HiB – Haemophilus influenzae type B, NF-κB – Nuclear factor kappa-light-chain-enhancer of activated B cells,QS – Quillaja saponaria.,HMGB – High mobility group box,TLR – Toll-like receptors, IFNγ – Interferon gamma, HZV – Herpes zoster, CpG OND – Cytosine-phosphorothioate-guanine oligodeoxynucleotides, My D88 – Myeloid differentiation primary response 88, IRAK – Interleukin receptor associated kinase, TRAF – Tumour necrosis factor receptor associated factor, SARs CoV2 – severe acute respiratory syndrome coronavirus 2, IMQ – Imiquimod, MHC – Major histocompatibility complex, GLA-SE – Glucopyranosyl lipid adjuvant formulated in a stable emulsion, GLA-AF – Glucopyranosyl lipid adjuvant aqueous formulation, MDA – Maternally derived antibodies, Poly ICIC – Polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose, US – United States, cGAS – Cyclic GMP-AMP synthase, CTLs – Cytotoxic T-Lymphocytes, MOT ISA – Montanide Incomplete Seppic Adjuvant, W/O – Water in oil emulsion, VLP – Virus-like particle.

8. Authors' Contributions

All authors contributed equally to the conception, drafting, and critical revision of the manuscript. AM was responsible for literature collection and review. PP contributed to the drafting of the manuscript and provided critical feedback. All authors read and approved the final manuscript.

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10. Conflicts of Interest

The authors declare that they have no conflicts of interest or competing interests related to this work.

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