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Adjuvant strategies to improve vaccination of the elderly population

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Immunosenescence contributes to increased incidence and severity of many infections in old age and is responsible for impaired immunogenicity and efficacy of vaccines. Adjuvants are one strategy to enhance immunogenicity of vaccines. The oil-in-water emulsions MF59TM and AS03, as well as a virosomal vaccine have been licensed in seasonal or pandemic influenza vaccines and are/were used successfully in the elderly. AS01, a liposome-based adjuvant comprising two immunostimulants has recently been approved in a recombinant protein vaccine for older adults, which showed very high efficacy against herpes zoster in clinical trials. Several adjuvants for use in the older population are in clinical and preclinical development and will hopefully improve vaccines for this age group in the future.

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Introduction

Historically, incidence and severity of infections were particularly high in children, but wide-spread vaccination programs have dramatically reduced this burden of disease [1]. The outstanding success of childhood vaccination is undoubted, but the importance of vaccination for other age groups is frequently underestimated. Many infectious diseases, such as influenza, pneumonia, herpes zoster, urinary tract infections and infections of the skin and soft tissue are more frequent in the elderly than in younger adults [2]. The reasons for this increased risk are diverse and include anatomical changes, underlying chronic diseases, medical procedures, as well as altered immune function in old age, referred to as immunosenescence [3]. A serious challenge for public health systems is the fact that many of these infections can have long-term consequences for older patients, such as impairment of daily living activities, onset of frailty and ultimately, the loss of independence [4,5]. Prevention of infectious diseases is therefore an important measure to improve the quality of life and to ensure healthy aging, particularly as the number of persons older than 60 years of age is steadily increasing [6]. Many countries have established vaccination schedules for adults frequently including specific recommendations for older adults regarding vaccination against influenza, *Streptococcus pneumoniae* and in some cases herpes zoster. Unfortunately, the immunogenicity and clinical efficacy of most current vaccines is lower in older compared to younger adults due to immunosenescence. One strategy to enhance immunogenicity of vaccines is the addition of adjuvants in order to develop vaccines for populations and pathogens for which traditional vaccines do not provide adequate protection. The first adjuvants used in human vaccines were aluminum salts, which are administered in various vaccines since the 1920s [7]. Most studies evaluating novel adjuvants for the elderly focus on influenza in order to achieve one or more of the following improvements: Firstly, higher antibody responses and thereby protective antibody responses in a higher percentage of vaccines; secondly, broader antibody recognition, which confers cross-protection against strain variants not included in the vaccine. This aspect is relevant for seasonal influenza vaccines, but particularly for pandemic vaccines enabling the development of prepandemic vaccines (vaccines for potentially pandemic strains, which might evolve until they cause a pandemic); thirdly, antigen dose sparing, which is also particularly relevant for pandemic situations, when it is crucial to produce a large number of doses in a very short period of time; and finally, induction of protective mucosal immunity. The ultimate goal of next-generation adjuvanted influenza vaccines is to confer higher clinical efficacy and effectiveness, particularly for vulnerable populations, such as the elderly.

This review gives an overview of adjuvant technologies currently used in vaccines specifically targeting older adults, and highlights the potential of novel adjuvants to improve influenza and other vaccines for the older population. Most of these adjuvants can be categorized into a few major classes, namely, emulsions, virosomes and immune-stimulatory complexes, liposomes, saponins, and Toll-like receptor (TLR) agonists. Combination adjuvants, which contain more than one class of adjuvants, have also been extensively studied over the last years and have been successfully implemented (Table 1).

Table 1

Adjuvants used or developed for the older population

Pathogen	Adjuvant	Adjuvant class	Components	Stage of development	Reference
Influenza (seasonal)	MF59®	Oil-in-water emulsion	Squalene, Tween 80, Span85	Licensed	[18••]
Influenza (seasonal)	Virosomes	Virosomes	Reconstituted influenza envelopes	Licensed	[24]
Influenza (seasonal, intradermal)	Imiquimod (topical)	TLR agonist	Imiquimod	Phase IIb/III	[43]
Influenza (seasonal)	Matrix-M™	Saponin ISCOM	Saponin, cholesterol, phospholipids	Phase I/II (ongoing)	NCT03293498
Influenza (seasonal)	Advax™	Microparticles	Polyfructofuranosyl-D-glucose (delta inulin)	Phase I	[52]
Influenza (seasonal)	GLA-SE	Oil-in-water emulsion + TLR agonist	GLA, squalene	Preclinical	[32,33]
Influenza (seasonal)	IC31®	TLR-agonist + antimicrobial peptide	d(IC) ODN (ODN1a), KLKL(5) KLK-peptide	Preclinical	[64]
Influenza (seasonal)	CAF01	Cationic liposomes	Dimethyl dioctadecylammonium, trehalose dibehenate	Preclinical	[55–57]
Influenza (seasonal)	CCS/C	catIonic liposomes	Polycationic sphingolipid, cholesterol	Preclinical	[54]
Influenza (seasonal)	CLDC/JVRS-100	Cationic liposomes + DNA	DOTIM, cholesterol, plasmid DNA	Preclinical	[59,60]
Influenza (seasonal, intranasal)	Endocine™	Anionic liposomes	Mono-olein, oleic acid	Preclinical	[61]
Influenza (seasonal, intranasal)	CpG ODN + Flt3 ligand	TLR-agonist, DC stimulation	Plasmid DNA encoding for CpG ODN + Flt3 ligand	Preclinical	[63]
Influenza (seasonal, tetravalent)	MF59®	Oil-in-water emulsion	Squalene, Tween 80, Span85	Phase III (ongoing)	NCT02587221 NCT03314662
Influenza (H1N1/ pdm2009)	AS03	Oil-in-water emulsion	Squalene, polysorbate 80, α-tocopherol	Licensed during the pandemic	[20]
Influenza (pandemic)	MF59®	Oil-in-water emulsion	Squalene, Tween 80, Span85	Phase III	[17]
Influenza (pandemic)	AS03	Oil-in-water emulsion	Squalene, polysorbate 80, α-tocopherol	Phase II	[22,23]
Influenza (pandemic)	Matrix-M™	Saponin ISCOM	Saponin, cholesterol, phospholipids	Phase I	[49–51]
Influenza (universal)	Montanide™	Oil-in-water emulsion	Mineral oil, mannide mono-oleate surfactant	Phase I	[45,46]
Varicella-zoster-virus	AS01	Liposomes + TLR agonist + saponin	Liposomes, MPL, QS-21	Licensed	[29••,30••]
RSV	GLA-SE	Oil-in-water emulsion + TLR agonist	GLA, squalene	Phase II	[39••]
Streptococcus pneumoniae (PhtD protein)	AS02	Oil-in-water emulsion + TLR agonist + saponin	Squalene, MPL; QS-21	Phase II	[44]
Streptococcus pneumoniae (PspA protein, intranasal)	CpG ODN + Flt3 ligand	TLR-agonist, DC stimulation	Plasmid DNA encoding for CpG ODN + Flt3 ligand	Preclinical	[63]
Streptococcus pneumoniae (PspA protein, intranasal)	Flagellin	TLR-agonist	Flagellin	Preclinical	[65]
Hepatitis B virus	Advax™	Microparticles	Polyfructofuranosyl-D-glucose (delta inulin)	Phase I (ongoing)	NCT01951677

DOTIM: 1-[2-(oleoyloxy)ethyl]-2-oleyl-3-(2-hydroxyethyl)imidazolinium chloride.
Flt-3: Fms-like tyrosine kinase 3.
GC: germinal center.
GLA: glucopyranosyl lipid A.
ISCOM: immune stimulatory complex.
MPL: 3-O-desacyl-4′-monophosphoryl lipid A.
ODN: oligodeoxynucleotide.
PhtD: polyhistidine triad D.
PspA: pneumococcal surface protein A.
QS-21: *Quillaja saponaria* Molina, fraction 21.