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SYSTEMATIC REVIEW

Efficacy of influenza vaccine in adults. Systematic review

Eficacia de la vacuna antigripal en adultos. Revisión sistemática

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ABSTRACT

This study addresses the challenges and advances in the vaccination of older adults in a context of global population aging, evaluating its effectiveness in the prevention of serious infectious diseases. Immunosenescence and comorbidities in this population may affect the response to vaccines, decreasing their efficacy. Through a systematic review, we analyzed recent studies evaluating various vaccine formulations and strategies such as high doses, natural adjuvants (e.g., probiotics and nondigestible polysaccharides), and vaccine coadministration to optimize immunogenicity in the elderly. The results show that high-dose quadrivalent vaccines (QIV-HD) and formulations with natural adjuvants improve immune response and reduce hospitalizations compared to standard doses. Coadministration of vaccines, such as influenza and COVID-19, is a safe practice that does not compromise the efficacy of each vaccine and facilitates vaccination in this high-risk population. The findings support the use of tailored vaccination strategies and underscore the need for additional studies to establish evidence-based recommendations for immunization in older adults.

Keywords: Aged; Adults; Influenza Vaccines; Vaccine Efficacy.

RESUMEN

Este estudio aborda los desafíos y avances en la vacunación de adultos mayores en un contexto de envejecimiento poblacional global, evaluando su efectividad en la prevención de enfermedades infecciosas graves. La inmunosenescencia y las comorbilidades en esta población pueden afectar la respuesta a las vacunas, disminuyendo su eficacia. Mediante una revisión sistemática, se analizaron estudios recientes que evalúan diversas formulaciones de vacunas y estrategias como dosis altas, adyuvantes naturales (por ejemplo, probióticos y polisacáridos no digestibles) y coadministración de vacunas para optimizar la inmunogenicidad en personas mayores. Los resultados muestran que las vacunas cuadrivalentes de alta dosis (QIV-HD) y las formulaciones con adyuvantes naturales mejoran la respuesta inmune y reducen hospitalizaciones en comparación con dosis estándar. La coadministración de vacunas, como la de influenza y COVID-19, es una práctica segura que no compromete la eficacia de cada vacuna y facilita la vacunación en esta población de alto riesgo. Los hallazgos respaldan el uso de estrategias de vacunación adaptadas y subrayan la necesidad de estudios adicionales para establecer recomendaciones basadas en evidencia para la inmunización en adultos mayores.

Palabras clave: Ancianos; Adultos; Vacunas Antigripales; Eficacia de las Vacunas.

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INTRODUCTION

Population aging is one of the most important and rapid demographic phenomena of the 21st century. The World Health Organization (WHO) estimates that by 2050, the number of people over 60 will double, reaching nearly 2,1 billion globally.[1,2] This change in population structure poses significant challenges for public health systems, especially in preventing and controlling infectious diseases. One of the most effective and impactful preventive interventions in reducing morbidity and mortality associated with infectious diseases is vaccination. However, the effectiveness of vaccines in the elderly population is not uniform and can be affected by multiple factors related to aging, such as immunosenescence and comorbidities.[3,4]

Immunosenescence, defined as the gradual deterioration of the immune system associated with age, represents an obstacle to the effectiveness of vaccines in older adults. This process involves a decline in innate and adaptive immune responses, reducing the ability of older individuals to generate effective and lasting immune responses after vaccine administration.[5,6] In addition, the coexistence of chronic diseases such as diabetes, cardiovascular disease, and chronic obstructive pulmonary disease (COPD) is common in this population, which can further complicate the response to vaccination and, in some cases, limit the effectiveness of preventive interventions.[6,7,8]

In recent years, research on vaccine efficacy in the elderly population has gained prominence, especially in the context of diseases such as seasonal influenza, pneumococcus, and, more recently, COVID-19.[4] Studies suggest that although vaccines may be less effective in older adults than in younger adults, they continue to offer significant benefits in terms of reducing hospitalizations, serious complications, and mortality.[9,10,11] However, immune response rates and levels of protection vary considerably between different types of vaccines and between older individuals, making it necessary further to analyze vaccine efficacy specific to this age group.[12,13]

The present study aims to systematically review the literature on vaccine efficacy in older adults to provide an updated overview of the immune response and protection conferred in this population.

One of the emerging areas in the field of immunization in older adults is the use of vaccines with adjuvants and high-dose formulations, which have been shown to improve immunogenicity in older people, offering enhanced protection compared to conventional vaccines. Likewise, strategies such as revaccination or periodic booster doses have also been explored in some studies as possible measures to optimize vaccine efficacy in this age group. However, evidence is still limited, and additional studies are needed to establish more straightforward, evidence-based guidelines.[14]

As healthcare systems face pressure from an aging population and an increase in the prevalence of chronic diseases, it is essential to have robust, evidence-based guidelines for vaccine administration in older adults and to design more effective vaccination policies tailored to the needs of this population, promoting a better quality of life and reducing the burden of infectious diseases on healthcare systems.

METHOD

A search was conducted in the PubMed databases to identify studies evaluating the efficacy of vaccines in adults, especially older adults (≥65 years), published between 2020 and 2024. The search terms included combinations of keywords such as “Influenza Vaccines” and “Vaccine Efficacy.” Peer-reviewed clinical trials in English and Spanish that reported results on efficacy, vaccine characteristics, population, and clinical outcomes, with full-text access and conducted in populations over 65 years of age, were included.

This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, ensuring transparency and rigor in each process phase.

RESULTS AND DISCUSSION

The workflow and main results are presented. Nineteen clinical studies were obtained for analysis.

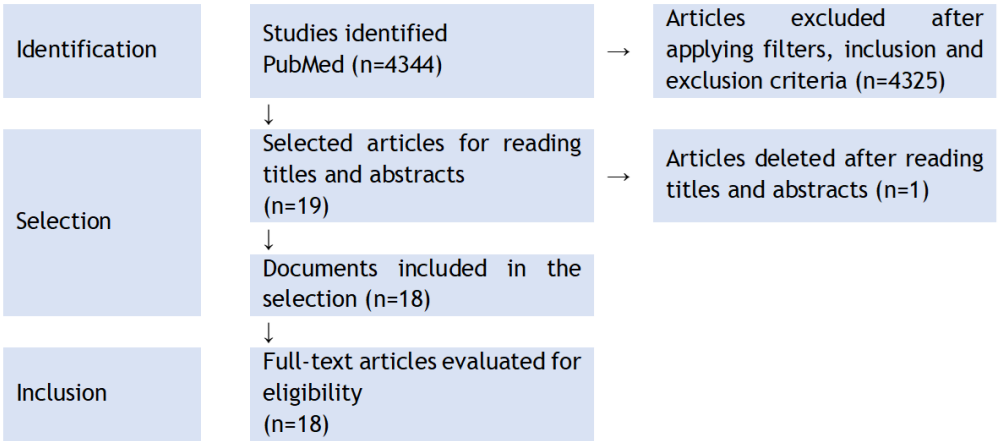

Figure 1. Flowchart of state-of-the-art review according to PRISMA methodology

Table 1. Main results of the interventions

Author, year	Country	Vaccine	Population	Key findings
Curran, 2024[15]	Multicenter	RSVPreF3 OA (Respiratory Syncytial Virus Prefusion Protein F) Single dose for older adults, intended to prevent ARI and ETRI	Adults ≥60 years old 12 466 vaccinated, 12 494 placebo	71,7 % efficacy against ARI due to RSV; 82,6 % against ETRI due to RSV
Ison, 2024[16]	Multicenter	RSVPreF3 OA (RSV Prefusion Protein F) Single dose with optional revaccination; adjuvanted to enhance immunity in older adults	Adults ≥60 years old 24 967 in combined groups of 2 doses and placebo	67,2 % efficacy against ETRI by VSR; revaccination did not improve efficacy.
Toback, 2022[17]	Reino Unido	NVX-CoV2373 (COVID-19) and seasonal influenza vaccine Co-administration of COVID-19 and influenza vaccines in adults	Adults (18-64 age subgroup in sub-study) 431 in co-vaccination sub-study	No significant impact on response to influenza vaccine; COVID-19 efficacy maintained
Shimada, 2021[18]	Japón	TIV (Trivalent Influenza Vaccine) + PPSV23 (Pneumococcal Vaccine) Combined influenza and pneumococcal vaccine for patients with CAD	Adults ≥50 years with coronary artery disease 40 patients with CAD, randomized	Safe dual vaccine; no significant change in markers after vaccination
Gögenur, 2023[19]	Dinamarca	Intratumoral vaccine against Intratumoral, seeks to increase the infiltration of immune cells into tumors	Patients with colorectal cancer, stages I-III 10 patients with pMMR colorectal tumors	Increased CD8+ T cell infiltration and PD-L1 expression in tumors
Johansen, 2024[20]	Dinamarca	QIV-HD (Quadrivalent High-Dose Influenza) vs QIV-SD (Standard Dose) Comparison of efficacy between high dose and standard dose	Adults aged 65–79 years 12 477 participants, randomized	QIV-HD reduced hospitalization rates by 13 % compared to QIV-SD.
Hadigal, 2022[21]	Europa	IIV4HD (Quadrivalent High-Dose Influenza) Improves immunogenicity in elderly populations	Adults ≥60 years old Elderly, without significant comorbidities	Superior immunogenicity and effectiveness in elderly populations
Leroux-Roels, 2022[22]	Bélgica	OVX836 (Nucleoprotein-based influenza vaccine)	Adults aged 18–65 years 300 healthy adults Nucleoprotein-based, targeting broad-spectrum cellular immunity	Increased T-cell response; reduction in episodes of influenza-like illness
Alvarez, 2023[23]	Bélgica, Finlandia, Portugal	QIV-HD (Quadrivalent High Dose for Influenza) High-dose vaccine for older adults, designed to improve cost-effectiveness and reduce hospitalizations.	Adults ≥60 years old 3 European countries, ICER and PSA analysis for efficacy and cost	Cost-effective in older adults; significant reduction in hospitalizations
Shimizu, 2022[24]	Japón	Immucise™ Intradermal Vaccine for Influenza Intradermal injection system to maximize immunity with reduced doses in older adults	Adults ≥65 years old 600 healthy adults, efficacy at 90 and 180 days	Comparable efficacy to subcutaneous; greater immunity in B strains in ID group
Christensen, 2024[25]	Dinamarca	QIV-HD vs QIV-SD Quadrivalent High Dose for Influenza High dose quadrivalent vs standard, relationship between vaccination timing and efficacy	Adults aged 65–79 12 477 participants, association between ToV and hospitalization	Early vaccination with QIV-HD reduces hospitalization for pneumonia
Wall, 2021[26]	Reino Unido	TIV (Trivalent Influenza) and PPSV23 (Pneumococcal) Vaccines for CKD in people over 65, varied immune responses	Adults ≥65 years with CRF 65 participants with CRF and healthy controls	Low immune responses, impact of previous CMV and PPV23
Uthoff, 2023[27]	Alemania	Complex Intervention to Improve Vaccination Rates in General Medicine Training in communication and vaccination processes for general practitioners treating patients over 60 years of age	Adults ≥60 years old in general medical practices 1057 general medical practices, training interventions	Increased vaccination rates, improved health literacy

Eto, 2024[28]	Japón	Ad26.RSV.preF for VSR Adenovirus-based vaccine for adults ≥60 years of age, evaluating safety and immune response	Adults ≥60 years old 36 Japanese elderly adults, immunogenicity analysis	High tolerability and immune efficacy for RSV up to 183 days
Tuthill, 2023[29]	EE. UU.	Thymalfasin (Ta1) as an adjunct for COVID-19 Adjuvant for COVID-19 in patients with ESRD, improves immune response	Hemodialysis patients ≥60 years old 194 hemodialysis patients in Kansas City, compared with a control group	3 deaths in Ta1 compared to 7 in control; 91 % vaccinated against COVID-19 in group A
Yu, 2020[30]	EE. UU.	Experimental adjuvanted vaccine for RSV Adjuvanted vaccine with symptom-based evaluation and virological confirmation	Adults ≥60 years old 1900 participants, with self-reported symptoms	Definition of ARI showed good reliability and increased detection with self-sampling.
Sandionigi, 2022[31]	Italia	Influenza vaccine + Multi-strain probiotic Seasonal influenza vaccine, administered together with probiotics as a natural adjuvant.	Adults aged 60 to 80 50 elderly participants vaccinated against influenza	Significant reduction in infectious symptoms in the probiotic group at 28 and 56 days
Laue, 2021[32]	Alemania	Influenza Vaccine + Non-Digestible Polysaccharides Influenza vaccine with polysaccharide adjuvant, in a preparation of β-glucans and arabinoxylans.	Adults aged 50 to 79 years 239 healthy adults divided into 5 adjuvant groups	Increase in antibody titers and protection with arabinoxylan; trend toward lower incidence of colds

Legend: ARI Acute respiratory infection, LRTI Lower respiratory tract infection, RSV Respiratory syncytial virus, CAD Coronary artery disease, ICER Incremental cost-effectiveness ratio, PSA Probabilistic sensitivity analysis, CKD Chronic kidney disease, CMV Cytomegalovirus.

The RSVPreF3 OA and Ad26.RSV.preF vaccines are designed for older adults and show significant effectiveness in reducing acute respiratory infections associated with RSV (ARI-RSV) and lower respiratory tract diseases. In the case of RSVPreF3 OA, 71,7 % effectiveness against ARI-RSV and 82,6 % against ETRI was observed, while Ad26.RSV.preF achieved high tolerability and maintained a long-term immune response up to 183 days post-vaccination.[31] These vaccines are especially relevant for older adult populations due to their efficacy in preventing serious respiratory diseases, which often significantly impact this population. Revaccination, however, did not show additional improvements in some studies, suggesting that immunity induced by a single dose is adequate in most cases.

The studies included several high-dose quadrivalent (QIV-HD) and trivalent vaccine formulations with different adjuvants and approaches to increase immunogenicity in older adults. QIV-HD, used in multiple studies, has been shown to reduce hospitalizations by 13 % compared to standard doses. Adding multistrain probiotics or non-digestible polysaccharides (such as β-glucans and arabinoxylans) significantly improved the immune response and reduced symptoms of common infections, such as colds and flu.[31,32] The increased response regarding immunogenicity and prolonged protection is consistent with growing efficacy in immunosenescent populations. Combinations of QIVs with natural adjuvants, such as probiotics and β-glucans, offer immunomodulatory benefits without the side effects of synthetic adjuvants, making these options attractive for individuals with increased susceptibility to infections and comorbidities.

Co-administration of vaccines, such as NVX-CoV2373 for COVID-19 and influenza vaccines, has been shown not to compromise the efficacy of COVID-19 immunization, indicating that the combination is safe and practical. In addition, no interference with the influenza vaccine response was observed.[31] The ability to administer combination vaccines without diminishing their efficacy is advantageous from a logistical and public health perspective. It facilitates vaccination in high-risk populations during high incidences of respiratory infections. This co-administration represents a practical option for maximizing protection without increasing the number of medical visits.

Intratumoral vaccines (influenza) were tested in patients with colorectal cancer, and other adjuvanted formulations were tested in older adults with special conditions (e.g., chronic renal failure and dialysis treatments). Natural adjuvants, such as Thymalfasin (Ta1) and non-digestible polysaccharides, were safe and positively affected immunity and reduced symptoms of common respiratory infections.[32] In populations with compromised immune conditions, such as dialysis patients, adjuvants may play a key role in improving the response to vaccination without overburdening the immune system. Specific adjuvants such as Ta1 are particularly beneficial, as they facilitate an adaptive immune response without significantly increasing the risk of chronic inflammation.

A systematic comparison of these vaccines highlights that adjuvanted and high-dose formulations, as well as the inclusion of probiotics and non-digestible polysaccharides, have improved vaccine efficacy and immunogenicity in older adults and vulnerable populations. Vaccine co-administration strategies also offer logistical benefits without compromising immunity. The optimal formulation choice should consider the target population's immunological characteristics, with natural adjuvants and high doses recommended for older adults and people with comorbidities.

CONCLUSIONS

High-dose quadrivalent vaccines (QIV-HD) are more effective than standard doses in preventing hospitalizations and severe respiratory illness in older adults, suggesting their preferred use in at-risk populations during seasons of high influenza circulation. In addition, natural adjuvants, such as probiotics and non-digestible polysaccharides, enhance the immune response without significant adverse effects, making it a safe and beneficial option for boosting immunity in older adults with immunosenescence.

Co-administration of vaccines, such as the combination of COVID-19 and influenza vaccines, does not adversely affect immunogenicity and facilitates immune coverage without needing multiple appointments. Likewise, specific adjuvants, such as Thymalfasin (Ta1), show great potential for improving immunity in immunocompromised individuals. Overall, this review supports the use of high doses and natural adjuvants in vaccine formulations and strategic co-administration to maximize immune protection in vulnerable populations, highlighting the importance of further research into personalized combinations to improve effectiveness in high-risk settings.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Conceptualization: Yasmin González.
Data curation: Yasmin González.
Formal analysis: Yasmin González.
Research: Yasmin González.
Methodology: Yasmin González.
Project management: Yasmin González.
Resources: Yasmin González.
Software: Yasmin González.
Supervision: Yasmin González.
Validation: Yasmin González.
Visualization: Yasmin González.
Writing – original draft: Yasmin González.
Writing – review and editing: Yasmin González.

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