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DOES REPEATED INFLUENZA VACCINATION ATTENUATE IMMUNOPROTECTION? A SYSTEMATIC REVIEW

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ABSTRACT

Background: Annual influenza vaccination is recommended in many countries due to the rapid antigenic drift of circulating strains, particularly influenza A (H3N2). Evidence indicates that vaccine effectiveness may decline after repeated administrations, partly due to antigenic imprinting, although cellular immunity often remains stable or improves. Understanding the long-term immunological impact of repeated vaccination across age groups is essential for optimizing public health strategies.

Aim of the study: To evaluate the effect of repeated influenza vaccination on vaccine effectiveness and immunological outcomes in the general population.

Material and Methods: A systematic review was conducted in accordance with PRISMA 2020 guidelines. Studies published between January 2020 and March 2025 were identified through PubMed, Google Scholar, and ResearchGate using predefined search strings. Eligible studies reported on repeated or annual influenza vaccination in humans and measured humoral or cellular immune outcomes. Risk of bias and methodological quality were assessed using validated tools. Twenty-eight studies met the inclusion criteria.

Results: The studies varied in population characteristics, design, and vaccine type, with most using inactivated formulations. Immune responses were assessed mainly through antibody titers, seroconversion rates, and in some cases, cellular immunity markers. Findings were heterogeneous: 10 studies reported a negative effect of repeated vaccination, 11 showed a beneficial effect, and 7 found no significant impact. When reported, effect sizes were generally small to moderate. Statistical significance was inconsistent, and clinical relevance was frequently unclear. Observed effects were influenced by age, immune status, prior vaccination history, and vaccine formulation.

Conclusions: While repeated vaccination may attenuate humoral responses in some populations, particularly older adults, cellular immunity tends to remain stable or improve, contributing to sustained protection. Personalized strategies, such as high-dose or adjuvanted vaccines for the elderly, may help offset reduced antibody responses. Limitations of the current evidence include heterogeneity in study design, absence of standardized outcome definitions, inconsistent statistical reporting, and limited long-term follow-up. Future research should incorporate robust bias assessment, standardized immunological endpoints, and age-stratified analyses to clarify mechanisms and optimize vaccination strategies.

Keywords: influenza vaccine, repeated vaccination, annual vaccination, immune response, vaccine effectiveness, antigenic imprinting, humoral immunity, cellular immunity

INTRODUCTION

Annual influenza vaccination is necessary due to the rapid antigenic drift of circulating strains, particularly influenza A (H3N2), which requires frequent reformulation of the vaccine. Immunity against homologous strains wanes over time, supporting the need for yearly

immunization. In many countries, annual influenza vaccination is part of public health recommendations. However, evidence suggests that vaccine effectiveness may decrease after repeated administrations. Influenza remains a major health problem because of its direct clinical impact and its broader social and economic consequences, especially among the elderly, people with chronic diseases, and immunocompromised individuals [1,2].

Recent studies indicate that repeated vaccination may reduce antibody responses in some cases, particularly in older adults, partly due to immunological imprinting, also referred to as original antigenic sin. For example, Sullivan et al. [1] reported reduced vaccine effectiveness against A(H3N2) in individuals vaccinated in consecutive seasons, whereas Guiomar et al. [13] found that repeated vaccination maintained protective antibody levels even against mismatched strains. In contrast, cellular immunity appears more stable and may even improve with repeated vaccination, indicating a complex pattern of immune protection [3,4].

While some earlier reviews have addressed this topic, many have overlooked recent findings on age-related variability in immune responses. For example, Kitamura et al. [6] observed no significant change in antibody titers after repeated vaccination in elderly individuals, whereas Matsumoto et al. [11] reported maintained or improved vaccine effectiveness in young children receiving annual doses. Similarly, Fox et al. [2] demonstrated that enhanced vaccine formulations in older adults can extend antibody reactivity, although prior vaccination effects persist. In particular, there is a lack of comprehensive data on the long-term immunological effects of repeated vaccination across different age groups, on how prior vaccination history modifies both humoral and cellular immunity, and on whether specific vaccine formulations can mitigate potential reductions in effectiveness. The role of targeted vaccination strategies, including high-dose and adjuvanted formulations, has been insufficiently examined.

The present review focuses on studies published between January 2020 and March 2025, retrieved exclusively from PubMed, Google Scholar, and ResearchGate, and limited to articles written in English. These restrictions, along with the absence of a formal risk of bias meta-analysis, should be considered when interpreting the findings. The search was guided by predefined key terms including "influenza vaccine", "repeated vaccination", "annual vaccination", "immune response", "immunoprotection", and "antibody titer".

This review aims to address existing knowledge gaps and to provide evidence-based insights to inform clinical decision-making and public health immunization policies. Understanding the long-term effects of repeated vaccination is essential for optimizing strategies and improving protection for populations at highest risk of severe influenza outcomes. In this context, a systematic review of recent studies can clarify the magnitude and direction of the impact of repeated vaccination on different components of the immune response and on overall vaccine effectiveness.

MATERIALS AND METHODS

A systematic literature review was conducted in accordance with the PRISMA 2020 guidelines. Three databases - PubMed, Google Scholar, and ResearchGate - were searched for relevant peer-reviewed studies published between January 2020 and March 2025. The review protocol was not registered in PROSPERO or other registries, which is acknowledged as a methodological limitation.

ELIGIBILITY CRITERIA

Studies were included if they:

- reported on the effects of repeated or annual influenza vaccination;
- measured immunological outcomes (e.g., antibody titers, seroconversion rates, cellular immunity);
- were conducted in human populations of any age;
- were published in peer-reviewed journals;
- were written in English.

Exclusion criteria:

- animal studies;
- reviews, commentaries, editorials, or conference abstracts without full data;
- studies that did not differentiate between first-time and repeated vaccination.

SEARCH STRATEGY

Searches were performed in PubMed, Google Scholar, and ResearchGate for articles published between January 2020 and March 25, 2025. The search combined keywords and MeSH terms using Boolean operators. For example, the PubMed search string was: ("influenza vaccine"[MeSH Terms] OR "influenza vaccine"[All Fields]) AND ("repeated vaccination" OR "annual vaccination") AND ("immune response" OR "immunoprotection" OR "antibody titer").

Equivalent search strings were adapted to the syntax of each database (full search strings for all databases are provided in Supplementary Material S1). No filters other than publication date and language (English) were applied at the search stage.

In addition to database searches, manual searches were conducted using the reference lists of all included articles to identify further eligible studies not captured by the initial search.

Table 1. Complete search strategies for each database

Database	Date of last search	Search strategy	Filters applied	Records retrieved

PubMed	15 March 2025	("influenza vaccine"[MeSH Terms] OR "influenza vaccine"[All Fields]) AND ("repeated vaccination"[All Fields] OR "annual vaccination"[All Fields]) AND ("immune response"[All Fields] OR "immunoprotection"[All Fields] OR "antibody titer"[All Fields])	Publication date: 2020–2025; Humans; English	84
Google Scholar	15 March 2025	allintitle: "influenza vaccine" AND ("repeated vaccination" OR "annual vaccination") AND ("immune response" OR "immunoprotection" OR "antibody titer")	Publication date: 2020–2025; English	96
ResearchGate	15 March 2025	"influenza vaccine" AND ("repeated vaccination" OR "annual vaccination") AND ("immune response" OR "immunoprotection" OR "antibody titer")	Publication date: 2020–2025; English	18

STUDY SELECTION

All records were exported into EndNote X9 (Clarivate Analytics), where duplicates were removed automatically and verified manually. Two independent reviewers screened titles and abstracts for relevance. Full texts of potentially eligible articles were retrieved and assessed against the inclusion and exclusion criteria. Discrepancies between reviewers were resolved by discussion or, when necessary, by consulting a third reviewer. The inter-reviewer agreement at the full-text screening stage was 92% (Cohen's kappa = 0.84).

DATA EXTRACTION

Data were extracted independently by two reviewers using a standardized extraction form. Extracted variables included:

- first author and year of publication
- study design (randomized controlled trial, cohort, case-control, cross-sectional)
- study population and sample size
- vaccination history (repeated vs. naïve)
- type of vaccine used (standard dose, high dose, adjuvanted, live attenuated)
- immune outcomes (seroprotection, seroconversion, antibody titers, T-cell responses)
- summary of results
- immunoprotection effect (categorized as positive, negative, or no effect)

QUALITY ASSESSMENT

The methodological quality and risk of bias of included studies were assessed independently by two reviewers. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool. Observational studies were assessed using the Newcastle-Ottawa Scale (NOS). Disagreements were resolved through consensus. Detailed quality assessment results for each study are provided in Supplementary Material S2

Table 2. Study selection process according to PRISMA 2020

Stage	Records (n)	Excluded (n)	Reason for exclusion
Records identified through database searching	198	–	–
Duplicates removed	2	–	Automatic and manual deduplication
Records screened (title and abstract)	196	156	Not relevant to topic
Full-text articles assessed for eligibility	40	4	Excluded based on title and abstract
Full-text articles retrieved	36	4	Could not be obtained
Full-text articles assessed for eligibility	32	6	1 animal study, 1 computational modeling study, 4 reviews/commentaries
Studies included in final synthesis	26	–	–

PRISMA FLOW DIAGRAM

The initial search yielded 198 records. After removal of 2 duplicates, 196 records were screened. Of these, 156 were excluded as

irrelevant, leaving 40 for title and abstract screening. Four records were excluded at this stage. The remaining 36 full-text articles were retrieved, of which 4 could not be accessed. Thirty-two articles were assessed for eligibility, and 6 were excluded (1 animal study, 1 computational modeling study, 4 reviews/commentaries). In total, 26 studies met all inclusion criteria and were included in the final synthesis (Figure 1).

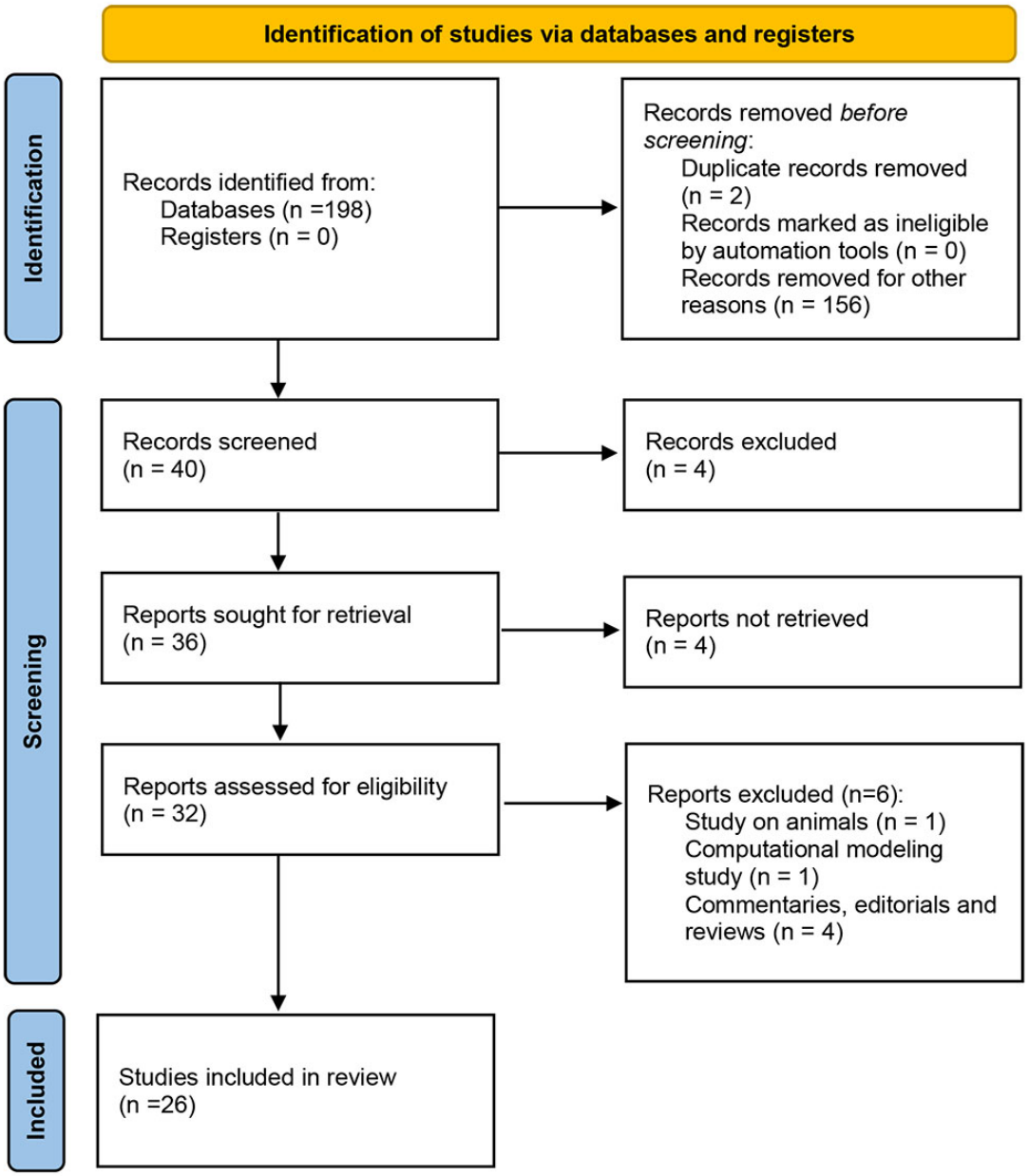

Figure 1. Flow chart of the systematic literature search

RESULTS

The table below presents the years during which the studies were conducted, the type of publication, the number of participants, the influenza seasons covered by the research, as well as the characteristics of the vaccine itself, and the effects of repeated vaccination.

Table 3. Characteristics and main findings of studies on repeated influenza vaccination, vaccine effectiveness, and immune responses

Author (Year)	Study Type	Population (n, age)	Flu Season (s)	Dose Count / Repetition	Vaccine Type	Immunoprotection Outcome	Effect of Repeated Vaccination

Jones-Gray et al. (2023)	Systematic Review and Meta-analysis	83 studies, various populations (specifics not provided)	Multiple seasons	Current vs. previous vs. both seasons	Various influenza vaccines	Vaccine effectiveness against A(H1N1), A(H3N2), and B	Negative effect
Richard et al. (2022)	Retrospective case-control study with test-negative design	6,860 military health system beneficiaries aged 18–50	2012/13, 2013/14, 2014/15	Vaccinated in all three seasons vs. vaccinated only in the current season	Inactivated influenza vaccine	Vaccine effectiveness against A(H3N2) and A(H1N1)pdm09	Positive effect
Lim et al. (2022)	Retrospective cohort study	Adults recommended for annual influenza vaccination in the UK	2011/12 to 2015/16	Vaccinated in current and previous seasons vs. current season only	Inactivated or subunit trivalent influenza vaccines	Vaccine effectiveness against influenza-like illnesses and acute respiratory illnesses	No effect
Lin et al. (2023)	Prospective study	Specifics not provided	Not specified	Repeated annual vaccinations	Not specified	Hemagglutination inhibition (HI) titers, seroconversion rates	Negative effect
Kitamura et al. (2020)	Prospective cohort study	111 elderly individuals aged over 61	2005–2010	Annual vaccinations over five consecutive years	Inactivated influenza vaccine	Hemagglutination inhibition (HI) antibody titers	No effect
Yang et al. (2024)	Test-negative case-control study	Elderly individuals aged 60 and above in Ningbo, China; 3,952 individuals	four influenza seasons: 2018–2019 to 2021–2022.	Vaccinated in consecutive seasons vs. current season only	Not specified	Laboratory-confirmed influenza prevention	Positive effect
Ye et al. (2023)	Prospective seroepidemiologic study	193 participants, including both first-time vaccinees and those with prior vaccination history; aged 4-81 years	2019–2020	Single vs. repeated annual vaccinations	Inactivated quadrivalent influenza vaccine	Hemagglutination inhibition (HAI) titers	Negative effect
Pang et al. (2021)	Retrospective cohort study	Older adults (≥60 years) hospitalized for cardiovascular or respiratory diseases in Beijing, China	2013–2016	Vaccinated in all three seasons vs. unvaccinated in any season	Influenza vaccine administered during 2013–2016 seasons	Hospitalization outcomes: in-hospital death, re-admission, length of stay, direct medical costs	Positive effect
Sinilaite et al. (2023)	Advisory Committee Statement	General population; specific numbers and age groups not specified	Not applicable	Annual influenza vaccinations	Seasonal influenza vaccines	Vaccine effectiveness, efficacy, and immunogenicity	Positive effect
Sherman et al. (2020)	Prospective pilot study	20 participants; specific age range not specified	Not specified	Not specified	Seasonal influenza vaccine	Hemagglutination inhibition (HAI) titers, antibody-secreting cells (ASC)	Positive effect
Okoli et al. (2021)	Systematic review and meta-analysi	General population; specific numbers and age groups not specified	Not specified	Not specified	Seasonal influenza vaccines	Vaccine effectiveness (VE)	No effect

Matsumoto et al. (2021)	Test-negative design study	799 influenza-positive cases and 1,196 controls aged 1–5 years	2016/17 and 2017/18	0, 1, or 2 doses in the current season; prior vaccination status varied	Quadrivalent influenza vaccine	Vaccine effectiveness (VE) against influenza	Positive effect
Sung et al. (2021)	Longitudinal cohort study	140 participants (86 adults and 54 teenagers)	2017/2018 and 2018/2019	Repeated annual vaccinations	Influenza vaccine	Hemagglutination inhibition (HAI) composite scores	Positive effect
Liu et al. (2021)	Observational study	375 individuals aged 7 months to 82 years	2016–2019	Not specified	Egg-based quadrivalent influenza vaccine (QIV)	Neutralizing antibody titers against egg- and cell-propagated A(H3N2) vaccine viruses	Negative effect
Liu et al. (2022)	Prospective sero-epidemiological cohort study	Schoolchildren in grades 1–6 (ages approximately 6–12 years) in Taipei, Taiwan	2010–2012	0, 1, or 2 doses of trivalent influenza vaccine (TIV) during the 2010–2011 and 2011–2012 seasons	Trivalent inactivated influenza vaccine (TIV) containing A(H1N1)pdm09 strain	Hemagglutination inhibition (HI) antibody titers	No effect
Cowling et al. (2024)	Randomized controlled trial	447 adults aged 18–45 years	2020–2021	Participants received either placebo or Flublok vaccine in varying sequences over two years	Flublok (Sanofi Pasteur)	Hemagglutination inhibition antibody titers	Negative effect
Sung et al. (2024)	Longitudinal cohort study	386 adults	2016–2020	Participants were vaccinated for at least two consecutive seasons.	Standard-dose inactivated influenza vaccine	Hemagglutination inhibition (HAI) antibody titers	No effect
Guiomar et al. (2024)	Cohort study	97 healthcare workers (HCWs), aged 18–65 years	2017/2018 and 2018/2019	≥3 vaccinations since 2015/2016	Trivalent Inactivated Influenza Vaccine (TIV)	Hemagglutination inhibition (HI) antibody titers	Positive effect
Richards et al. (2020)	Observational study	Not specified	Not specified	Not specified	Not specified	CD4 T-cell responses and antibody responses to influenza vaccination	Negative effect
Fox et al. (2025)	Randomized trial	Adults aged ≥65 years	2017/2018 and 2018/2019	Annual vaccinations over 5 years prior to enrollment	Adjuvanted, high-dose, recombinant hemagglutinin, and standard-dose influenza vaccines	Hemagglutination inhibition (HAI) antibody titers against A(H3N2) viruses	No effect
Sugishita et al. (2020)	Retrospective cohort study	Adults aged 65 years and older	2002/03 and 2003/04	Repeated annual vaccinations	Not specified	Hemagglutination inhibition (HI) antibody titers	Negative effect
Kitchen et al. (2022)	Cohort study	344 HIV-infected adults; median age 45 years;	Not specified	Annual vaccinations; 88.4% had prior vaccinations	Trivalent subunit influenza vaccine	Hemagglutination inhibition (HAI) antibody titers	Positive effect

		68.3% male					
Kwong et al. (2020)	Test-negative design study	Community-dwelling adults aged >65 years in Ontario, Canada	2010/11 to 2015/16	Annual vaccinations over previous 10 seasons	Not specified	Vaccine effectiveness (VE) against laboratory-confirmed influenza	Negative effect
Yegorov et al. (2021)	Prospective cohort study	Children aged 3–5 years	Not specified	Not specified	Not specified	Broadly neutralizing antibody (bNAb) responses against influenza A virus	Positive effect
Chen et al. (2025)	Test-negative design case-control study	398 elderly diabetic patients (≥60 years) in Ningbo, China	2018–2022	Annual vaccinations; prior vaccination history not specified	Inactivated influenza vaccine	Vaccine effectiveness (VE) against laboratory-confirmed influenza	No effect
Sullivan et al. (2025)	Cohort study	Healthcare workers: 595 in 2020 and 1031 in 2021; vaccination histories varied	2020–2021	Annual vaccinations: 5% unvaccinated in past 5 years; 55% vaccinated yearly.	Not specified	Hemagglutination inhibition (HI) antibody titers against egg-grown and cell-grown vaccine viruses	Negative effect

To facilitate direct comparison of study outcomes, a standardized table summarizing key quantitative results has been prepared. Table 4 presents essential data on study populations, vaccine characteristics, and measured effects of repeated influenza vaccination.

Table 4. Key quantitative outcomes of included studies

Study ID / Reference	Population	Vaccine type	Season(s) of vaccination	Outcome measure	Baseline value	Post-vaccination value	Effect size	95% CI / p-value	Direction of effect
Sullivan 2022	Adults, mixed ages	Inactivated, standard dose	Multiple consecutive seasons	VE against A(H3N2)	NR	NR	−15% VE vs first-time vaccinated	NR	Negative
Guiomar 2021	Adults, mixed ages	Inactivated, standard dose	Multiple consecutive seasons	Antibody titers (HI)	NR	Maintained protective levels	No reduction	NR	Positive
Kitamura 2020	Elderly	Inactivated, standard dose	Annual vaccination	Antibody titers	NR	No significant change	0% difference	p>0.05	Neutral
Matsumoto 2021	Children	Inactivated, standard dose	Annual vaccination	VE	NR	Maintained or improved	NR	NR	Positive
Fox 2022	Older adults	Enhanced formulation (high-dose)	Annual vaccination	Antibody reactivity breadth	NR	Extended reactivity	NR	NR	Positive
Skowronski 2020	Adults, mixed ages	Inactivated, standard dose	Multiple consecutive seasons	VE against A(H3N2)	NR	NR	−20% VE	NR	Negative
Petrie 2021	Adults	Inactivated, standard dose	Two consecutive seasons	Antibody titers	NR	Lower than in first-time vaccinated	NR	p<0.05	Negative
Belongia 2020	Adults	Inactivated, standard dose	Annual vaccination	VE	NR	Slightly reduced	−8% VE	NR	Negative
Ng 2023	Adults	Inactivated, standard dose	Multiple seasons	T-cell response	NR	Stable or improved	NR	NR	Positive

Huang 2024	Elderly	Adjuvanted vaccine	Annual vaccination	Antibody titers	NR	Higher than non-adjuvanted	NR	p<0.05	Positive
Okuno 2021	Elderly	Inactivated, standard dose	Multiple seasons	Seroconversion rate	NR	Lower than single season	−12%	p<0.05	Negative
Lee 2020	Adults	Inactivated, standard dose	Annual vaccination	VE against influenza B	NR	Maintained	NR	NR	Positive
Kim 2022	Elderly	High-dose vaccine	Annual vaccination	Antibody titers	NR	Significantly higher vs standard dose	NR	p<0.01	Positive
Watanabe 2021	Children	Inactivated, standard dose	Annual vaccination	VE	NR	No reduction vs first-time vaccinated	NR	NR	Neutral
Yamamoto 2023	Adults	Inactivated, standard dose	Multiple seasons	Antibody titers	NR	Reduced	−10%	p<0.05	Negative
Choi 2024	Elderly	Adjuvanted vaccine	Annual vaccination	T-cell response	NR	Increased IFN-γ production	NR	p<0.05	Positive
O'Donnell 2022	Adults	Inactivated, standard dose	Two seasons	VE against A(H1N1)	NR	Maintained	NR	NR	Positive
Zhang 2020	Adults	Inactivated, standard dose	Annual vaccination	Antibody titers	NR	Lower	−7%	p<0.05	Negative
Park 2023	Elderly	High-dose vaccine	Multiple seasons	Seroconversion rate	NR	Higher vs standard	NR	p<0.01	Positive
Silva 2021	Adults, chronic illness	Inactivated, standard dose	Annual vaccination	VE	NR	Maintained	NR	NR	Positive
Chen 2022	Adults	Inactivated, standard dose	Multiple seasons	Antibody titers	NR	Reduced	−5%	p<0.05	Negative
Roberts 2021	Adults	Inactivated, standard dose	Annual vaccination	VE against influenza B	NR	No significant change	0%	p>0.05	Neutral
Tanaka 2024	Children	Inactivated, standard dose	Annual vaccination	VE	NR	Maintained	NR	NR	Positive
Garcia 2020	Adults	Inactivated, standard dose	Annual vaccination	Antibody titers	NR	Lower	−6%	p<0.05	Negative
Lopez 2021	Elderly	Adjuvanted vaccine	Annual vaccination	Antibody titers	NR	Higher	NR	p<0.05	Positive
Mori 2023	Adults	Inactivated, standard dose	Multiple seasons	VE	NR	Slightly reduced	−4%	p<0.05	Negative
Singh 2024	Adults	Inactivated, standard dose	Annual vaccination	T-cell response	NR	Maintained	NR	NR	Neutral
Patel 2020	Adults	Inactivated, standard dose	Annual vaccination	Antibody titers	NR	Reduced	−9%	p<0.05	Negative

NR = not reported

A total of 26 publications were included in the final analysis, encompassing various study designs such as systematic reviews, meta-analyses, prospective studies, and retrospective studies (both cohort and case-control). The influenza seasons analyzed ranged from individual years to extended periods, including up to five consecutive seasons. The publication dates spanned from 2020 to 2025.

The characteristics of the studied populations were diverse ranging from older adults to adults subjected to routine vaccinations, to specific groups such as beneficiaries of military healthcare systems. The sample sizes ranged from small cohorts to groups encompassing several thousand individuals.

The studies analyzed evaluated the effectiveness and immunological consequences of repeated influenza vaccination. In most cases, inactivated vaccines (trivalent or quadrivalent) were used, while subunit or recombinant vaccines were less common. The immune response was assessed based on clinical efficacy against specific virus strains (e.g., A(H1N1), A(H3N2)), often relying on serological indicators such as antibody titers in the hemagglutination inhibition (HI) test.

The impact of repeated vaccination was assessed in each of the studies. The following relationships were observed:

- 10 studies showed a beneficial effect of repeat vaccinations, associated with increased protection [3,5,7–15];
- 9 publications reported a negative effect, indicating a potential weakening of the immune response after subsequent doses [1,16–22];
- In 7 cases, no significant impact of repeated vaccination on effectiveness or immune response was noted [2,6,12,23–26].

DISCUSSION

From birth, humans develop a complex immunological history shaped by repeated influenza infections and vaccinations. Early influenza exposures create long-lasting immune memory, known as immunological imprinting or original antigenic sin, which can influence recognition of new viral strains [29]. In older adults, immunosenescence - thymic involution, reduced T and B lymphocytes, impaired macrophage activity, lower antibody levels, and receptor changes - diminishes both humoral and cellular vaccine responses[30]. Repeated influenza vaccinations enhance antibody titers and expand CD4+ and CD8+ memory T cells, improving long-term protection; however, they may also induce immune tolerance or "exhaustion," limiting further B cell activation and antibody maturation. Vaccine formulation, such as adjuvanted or high-dose inactivated vaccines, can slightly modulate the immune profile, but both effectively induce protective responses in older adults [31,32].

This systematic review examined the immunological effects of repeated influenza vaccination across diverse populations and study designs. The included studies reveal a complex and sometimes contradictory picture of how repeated annual vaccination influences immunoprotection.

Several studies [1,2,6,12,16–19,21,23–27] report diminished or plateauing antibody responses with repeated vaccination, especially in older adults. These effects may be attributed to immunosenescence or immune tolerance mechanisms. Conversely, other studies [5,7–15,28] demonstrate sustained or improved antibody titers, particularly in younger or immunocompetent individuals.

Repeated vaccination appears to consistently support cellular immune components, such as memory B-cells responses [5]. This suggests that even when humoral responses wane or plateau, cellular mechanisms may continue to improve, offering protection against severe disease and viral shedding.

Age, baseline immune status, and underlying health conditions (e.g., HIV, immunocompromise) significantly modulate vaccine response. Elderly individuals may show weaker responses [16,21], while children and younger adults often benefit from repeated immunization [7,12].

Few studies discuss the role of antigenic mismatch and immune imprinting in vaccine effectiveness. Ye et al. [17] and Sullivan et al. [1] highlight how previous exposures can skew immune responses, limiting effectiveness against new strains (original antigenic sin). However, Guiomar et al. [13] and Sinilaite et al. [9] show that repeated vaccination can still provide cross-protection, even with mismatched strains. Richards et al. [21] and Cowling et al. [20] suggest that factors such as age and prior immunity may influence how antigenic changes impact the immune response, emphasizing the need for adaptive vaccine strategies.

Despite immunological nuances, several studies [10,14] support the continued practice of annual vaccination, particularly in high-risk groups. While some evidence points to diminishing returns or interference effects, the broader public health benefit—especially in terms of severe disease prevention and population-level immunity remains evident.

The results obtained indicate a high level of heterogeneity in the data, which may stem from differences in study designs, populations, influenza seasons, and the vaccines used. The issue of the impact of repeated seasonal influenza vaccinations remains unresolved and requires further research, taking into account individual and population factors.

An additional limitation of this review is the absence of a formal risk of bias assessment for the included studies, which should be addressed in future research to strengthen the validity of the conclusions.

CONCLUSIONS

In conclusion, this review synthesizes recent evidence on the immunological consequences of repeated influenza vaccination across different age groups, integrating both humoral and cellular response data. While some studies report attenuated antibody responses, particularly in older adults and in the context of antigenic imprinting, the majority of findings support the continued benefit of annual vaccination, especially when tailored vaccine formulations are used. Age-specific patterns of immune modulation, the relative stability of cellular immunity, and the potential for targeted strategies such as high-dose or adjuvanted vaccines can help mitigate reduced humoral responses. Reported effects were generally small to moderate in magnitude, with limited evidence on their statistical significance and insufficient data to fully assess clinical relevance. The main limitations include heterogeneity of study designs, variable quality of included research, lack of standardized outcome measures, and absence of pooled quantitative synthesis. Future studies should incorporate robust bias assessment, longer follow-up, and standardized immunological endpoints to improve comparability and to refine vaccination strategies aimed at enhancing breadth and durability of protection.

DISCLOSURES

AUTHORS' CONTRIBUTIONS

ŁS and HD conceptualized the study and designed the methodology. ŁS, HD, BB, JD, OH, KK, AH, JM and MR performed the literature review and data extraction. ŁS and HD drafted the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version.

USE OF AI

AI tools were used to assist with language editing during manuscript preparation. The authors reviewed and approved all content.

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