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REVIEW

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Systematic review of the efficacy, effectiveness and safety of high-dose seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥18 years of age

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Abstract

This review sought to assess the efficacy, effectiveness and safety of high-dose inactivated influenza vaccines (HD-IIV) for the prevention of laboratory-confirmed influenza in individuals aged 18 years or older. A systematic literature search was

Abbreviations: CDC, Centres for Disease Control and Prevention; CI, Confidence interval; FEM, Fixed-effect model; GRADE, Grading of recommendations assessment, development and evaluation; HD-IIV, High-dose inactivated influenza vaccine; HIQA, Health Information and Quality Authority; ICD, International classification of diseases; ILI, Influenza-like illness; NITAG, National immunisation technical advisory group; NRSI, Non-randomised studies of intervention; PICO, Participants, intervention, comparison, outcomes; PRISMA, Preferred reporting items for systematic reviews and meta analyses; RCT, Randomised controlled trial; REM, Random-effects model; ROBINS-I, Risk of bias in non-randomised studies of interventions; RR, Risk ratio; SAE, Serious adverse event; SD-IIV, Standard-dose inactivated influenza vaccine; VE, Vaccine effectiveness; WHO, World Health Organization.

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conducted in electronic databases and grey literature sources up to 7 February 2020. Randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSIs) were included. The search returned 28,846 records, of which 36 studies were included. HD-IIV was shown to have higher relative vaccine efficacy in preventing influenza compared with standard-dose influenza vaccines (SD-IIV3) in older adults (Vaccine effectiveness (VE) = 24%, 95% CI 10–37, one RCT). One NRSI demonstrated significant effect for HD-IIV3 against influenza B (VE = 89%, 95% CI 47–100), but not for influenza A(H3N2) (VE = 22%, 95% CI −82 to 66) when compared with no vaccination in older adults. HD-IIV3 showed significant relative effect compared with SD-IIV3 for influenza-related hospitalisation (VE = 11.8%, 95% CI 6.4–17.0, two NRSIs), influenza- or pneumonia-related hospitalisation (VE = 13.7%, 95% CI 9.5–17.7, three NRSIs), influenza-related hospital encounters (VE = 13.1%, 95% CI 8.4–17.7, five NRSIs), and influenza-related office visits (VE = 3.5%, 95% CI 1.5–5.5, two NRSIs). For safety, HD-IIV were associated with significantly higher rates of local and systemic adverse events compared with SD-IIV (combined local reactions, pain at injection site, swelling, induration, headache, chills and malaise). From limited data, compared with SD-IIV, HD-IIV were found to be more effective in the prevention of laboratory-confirmed influenza, for a range of proxy outcome measures, and associated with more adverse events.

KEYWORDS
high-dose, human, influenza, influenza vaccines

1 | INTRODUCTION

Seasonal influenza is an infectious respiratory disease which circulates in annual epidemics worldwide, with the period of circulation typically occurring from November to April in the Northern hemisphere and from June to October in the Southern hemisphere.[1] Influenza viruses are from the *Orthomyxoviridae* family of ribonucleic acid viruses and are classified as four specific types, with influenza A and influenza B providing the primary focus when discussing seasonal influenza.[1,2] In adults, influenza A(H1N1), influenza A(H3N2) and influenza B generally co-circulate each year in varying proportions depending on the season.[1]

The World Health Organization (WHO) estimates that annual seasonal influenza epidemics result in 3–5 million severe cases and 290,000–650,000 respiratory deaths worldwide.[3] All-cause influenza-attributable mortality was estimated to be 25.4 (95% CI 25.0–25.8) per 100,000 population and 118.2 (95% CI 116.4–119.9) per 100,000 for adults aged 65 and older in the 2017–2018 influenza season in Europe.[4] In 2019, influenza was reported to have the highest burden of all infectious diseases in Europe in terms of disease-adjusted life years (DALYs), with 81.1 DALYs per 100,000 population (95% uncertainty interval 76.9–86.5) representing 30% of the total burden of all included diseases.[5]

The most effective means to prevent influenza infection is through strain-specific vaccination.[3] To facilitate strain-specific vaccination, the WHO issues recommendations to vaccine manufacturers regarding vaccine strain inclusion. However, due to antigenic drift, whereby genetic changes arise from ongoing evolution of the virus, antigenic mismatch between the virus strains contained in the vaccine and those in circulation in the seasonal epidemic can occur. Accurate predictive matching of vaccine strains to those that circulate is a key determinant of Vaccine effectiveness (VE).[3,6,7]

Beyond strain-specific matching, an additional consideration for VE is the generation of a sufficient immune response. The response to traditional influenza vaccines can be suboptimal.[7] Enhanced influenza vaccines have been developed in an attempt to improve VE, particularly in the elderly for whom there is evidence of immunosenescence.[8] One such enhanced technique is the use of high-dose vaccines to increase the immune response generated.[9] High-dose influenza vaccines contain a fourfold increase of haemagglutinin (HA) per strain,[9] that is, 60 μg of HA per strain instead of 15 μg of HA typically included in standard dose vaccines.[10] The increase in HA dose is intended to induce a larger overall immune response, thereby improving VE.[11] A high-dose trivalent influenza vaccine, Fluzone®, has been licenced in the United States, and similarly a trivalent high-dose influenza vaccine was available for use in Europe for the 2019/2020 season, with both recommended in adults aged 65 years and older.[9,12]

A series of systematic reviews was undertaken to investigate the efficacy, effectiveness and safety of newer and enhanced influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged 18 years or older.[13,14] The aim of this current review

was to determine the efficacy (i.e., how well a vaccine performs in the context of a controlled trial), effectiveness (i.e., how well a vaccine performs in real world settings) and safety of high-dose trivalent (HD-IIV3) and quadrivalent (HD-IIV4) egg-based seasonal influenza vaccines by influenza type, subtype, age and risk group.

2 | METHODS

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[15] The proposed methodology for this systematic review was registered on PROSPERO (ID = CRD42020156800).

2.1 | Eligibility criteria

The population for this study was adults (persons age 18 years and older), irrespective of health status or setting. The interventions of interest were HD-IIV3 and HD-IIV4 high-dose egg-based seasonal influenza vaccines. The main efficacy and effectiveness outcomes were laboratory-confirmed influenza and influenza-related mortality and hospitalisation. Safety outcomes included local and systemic events. Eligible studies included randomised controlled trials (RCTs), non-randomised controlled trials, quasi-experimental, prospective and retrospective cohort, case control, test-negative design and analytical cross sectional studies. The population, intervention, comparison, outcomes and study (PICOS) design (PICOS) criteria for inclusion of studies in this systematic review are provided in the Supplementary Appendix 1.1. No restrictions were placed on language or date of publication.

2.2 | Exclusion criteria

Animal studies, case studies, immunogenicity studies, studies conducted during pandemic periods and studies that included pandemic, prepandemic or zoonotic vaccines were excluded. As no high-dose intradermal seasonal influenza vaccine was licenced and available for use for the 2019/2020 season in the EU/EEA, they were excluded as an intervention, but could be included as a comparator.

2.3 | Search strategy

Electronic searches were conducted in Embase, MEDLINE (via PubMed), Cumulative Index to Nursing and Allied Health and The Cochrane Library. The search terms and detailed search strategy are provided in the Supplementary Appendix 1.2. The search strategy was designed to identify a range of influenza vaccines including high-dose influenza vaccines. Searches were conducted on the 26 September 2019 and updated on 7 February 2020 prior to analyses. Forward citation searching was applied to included studies. A search of grey literature sources was conducted in an attempt to source any unpublished or ongoing studies which may be relevant to future iterations of this systematic review.

Two reviewers independently reviewed the titles and available abstracts in Covidence® to identify studies for full-text review. Full texts were evaluated and data extracted by two reviewers independently. Data extraction was carried out using an agreed data extraction form. Where disagreements occurred in study identification or data extraction, discussions were held to reach consensus and where necessary, a third reviewer was involved. Where additional data were required, study authors were contacted by email. For safety outcomes, data relating to the influenza season, vaccine strains and circulating strains were not deemed to be relevant and therefore were not extracted.

2.4 | Assessment of risk of bias in included studies

Two reviewers independently assessed the included studies for risk of bias using validated critical appraisal tools. Disagreements were resolved through discussion and, where necessary, the assistance of a third reviewer was involved.

The Cochrane Risk of Bias tool was used to assess RCTs.[16] Certain domains within the risk of bias tool were designated as key domains to enable a summary assessment of risk of bias within and between studies.[17] For efficacy studies, the designated key domains were: funding sources (other bias), random sequence generation, and incomplete outcome data. For safety studies, the designated key domains were: funding sources (other bias), blinding of participants and personnel, blinding of outcome assessment, and incomplete outcome data.

Non-randomised studies of interventions (NRSIs) were assessed for risk of bias using the Risk Of Bias In Non-randomised Studies-of Interventions (ROBINS-I) tool.[18] Results were presented in tabular form with the agreed consensus of risk of bias for each of the seven included domains and the overall risk of bias for each study denoted by the highest risk of bias score in any singular domain, as per the ROBINS-I methodology.[18] Where adjusted and unadjusted estimates were extracted from a study, the risk of bias was assessed for each outcome.

Studies that did not possess a comparator were not assessed for risk of bias as no suitable tool was identified.

2.5 | Measures of treatment effect

For test-negative design (case-control) studies, the outcome was defined as VE which was uniformly expressed as (1-Odds Ratio)*100%, where a value of 100% indicates prevention of all cases of influenza and 0% indicates prevention of no cases of influenza. For cohort studies, the outcome was defined as VE expressed using either a risk ratio, incidence risk ratio, or hazard ratio in place of the odds ratio. Where studies reported both unadjusted and adjusted VE, the adjusted figure

was used in the results as it was considered the less biased estimate of treatment effect.

For safety studies, numbers of events were extracted and the risk ratio was used as the preferred measure of treatment effect.

2.6 | Data synthesis

Where two or more studies reported an outcome, pooling was considered. Meta-analysis was conducted using the Mantel–Haenszel method for fixed effect and the Sidik–Jonkman estimator combined with the Hartung and Knapp adjustment for random effects.[19,20] Given the clinical heterogeneity across studies, preference was for a Random-effects model (REM). As the estimate of between study variance is considered to be unreliable when there are few studies available for pooling,[21,22] a Fixed-effect model (FEM) was used when less than four studies were available for pooling. For adjusted VE, pooling was on the basis of the log odds ratio and variance, with the exponential of the pooled result re-expressed as VE.

2.7 | Assessment of heterogeneity

Potential statistical heterogeneity was assessed on the basis of the I^2 statistic in line with the Cochrane methodology.[17] The I^2 value was interpreted based on the magnitude and direction of effects, and on the strength of evidence for heterogeneity based on the chi-squared statistic. Where multiple studies were available for a given outcome and there was evidence of heterogeneity, consideration was given to subgroup analysis and meta-regression to identify potential sources of heterogeneity. Subgroup analysis was considered where studies could be meaningfully grouped based on consistently provided data. Meta-regression was only considered if there were 10 or more studies available reporting a given outcome.

2.8 | Grading of recommendations assessment, development and evaluation and 'summary of findings' table

The certainty of evidence for each outcome was assessed using the Grading of recommendations assessment, development and evaluation (GRADE) methodology.[23] The five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) were interpreted by two reviewers to assess the quality of the body of evidence for each outcome of interest (as defined in the PICOs). New guidance regarding the assessment of NRSIs was incorporated, whereby these types of studies are not penalised for their design and begin the assessment as a high certainty of evidence like their RCT counterparts.[24] As a broad range of safety outcomes were assessed by the included studies, a number were chosen which were thought to best reflect this outcome as a whole and which were relatively consistent across the vaccines of interest within this review: combined local reactions, pain, combined systemic reactions, and fever. Summary of findings tables were generated using the GRADEpro® software.

3 | RESULTS

The collective search strategy for this series of systematic reviews resulted in 26,844 records, with 2 further records being identified from additional sources (Figure 1). After removal of duplicates, 19,822 records were screened for relevance. Of 868 records subject to full-text review, 758 were subsequently excluded based on the predefined eligibility criteria. Thirty–six studies included studies presented results concerning high-dose influenza vaccines.[25-60] Of these studies, 2 related to efficacy[25,60] (with 2 additional analysis papers of DiazGranados et al. contributing to overall results),[26,27] 9 related to effectiveness[28-36,61] and 23 related to safety (with additional safety data from the efficacy study by DiazGranados et al.).[25,37-59] Where issues with missing data were encountered, the study authors were contacted. No imputation of missing data was used. Given the small numbers of studies available for most comparisons, there was limited power to explore sources of heterogeneity and a risk of identifying spurious associations. The characteristics of studies relating to efficacy or effectiveness, vaccine and circulating strains' characteristics, characteristics of studies relating to the safety and GRADE assessments are provided in Supplementary Appendices 1.3 to 1.7.

3.1 | Efficacy

Two RCTs were identified that met the inclusion criteria for this systematic review. The first RCT investigated the relative efficacy of HD-IIV3 compared with trivalent standard-dose inactivated influenza vaccine (SD-IIV3) in older adults (aged ≥ 65 years) for laboratory-confirmed influenza (primary outcome), culture-confirmed influenza, and respiratory illness across protocol-defined influenza-like illness and modified CDC-defined influenza-like illness for all strains and vaccine specific strains.[25] This trial was associated with two additional analyses papers.[26,27] The authors reported vaccine efficacy against influenza-like illness and respiratory illness based on both laboratory- and culture-confirmed diagnosis. The high-dose vaccine had higher efficacy relative to standard-dose vaccine for laboratory-confirmed protocol-defined influenza-like illness (VE = 24.2%, 95% CI 9.7–36.5, moderate-certainty evidence, supplementary appendix 6), but not for a modified CDC-defined influenza-like illness (VE = 20.6%, 95% CI −4.6 to 39.9). The high-dose vaccine had higher efficacy against respiratory illness (VE = 18.3%, 95% CI 5.0–29.8). High-dose vaccination was further associated with reduced all-cause hospitalisation (VE = 6.9%, 95% CI 0.5–12.8), serious cardio–respiratory events (VE = 17.7%, 95% CI 6.6–27.4), and pneumonia events (VE = 39.8%, 95% CI 19.3–55.1).

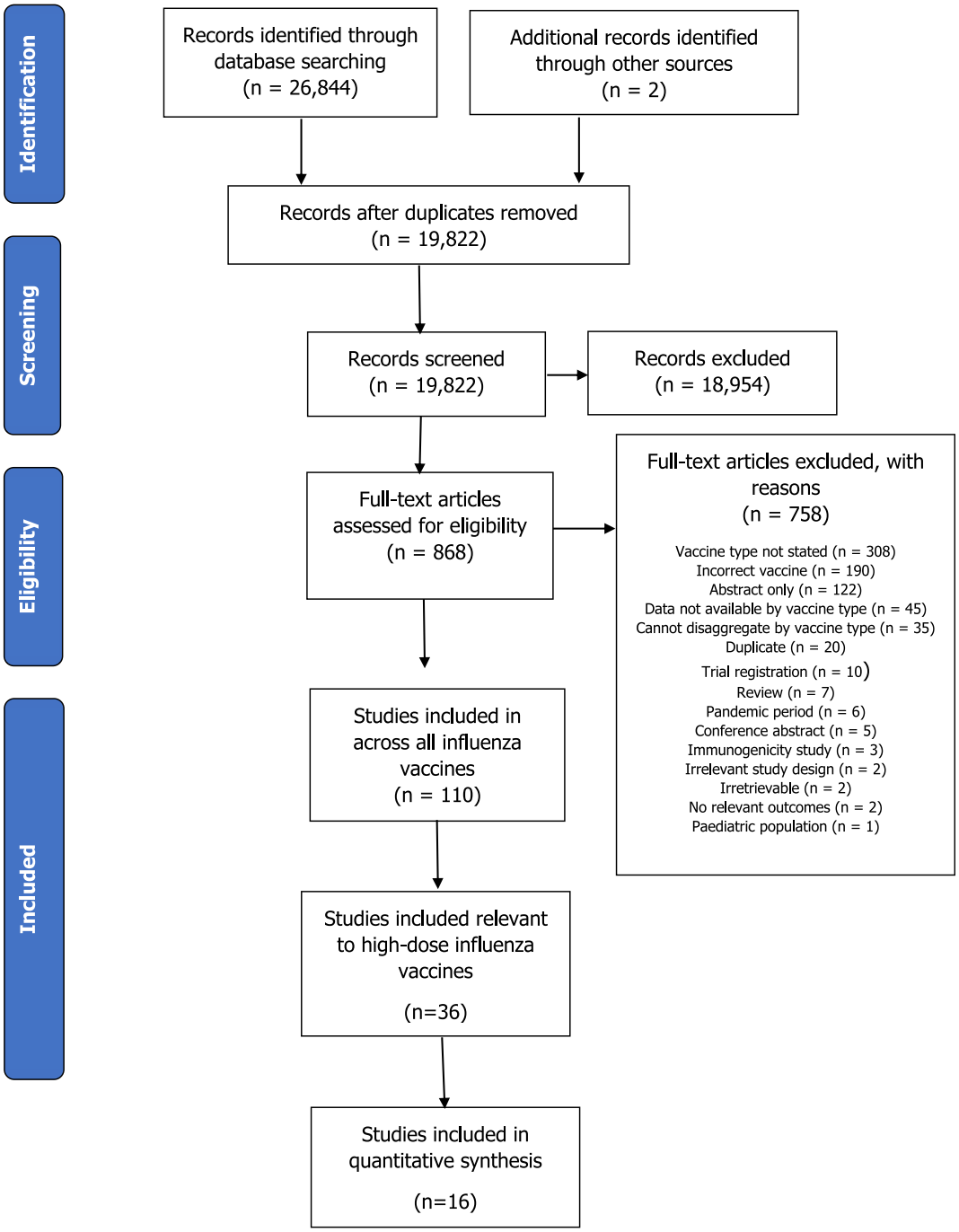

FIGURE 1 PRISMA flow diagram

There was no statistically significant effect on asthma/COPD/bronchial events, influenza events, or other respiratory events. There was limited evidence regarding efficacy in relation to influenza type/subtypes due to the small number of cases other than influenza A (H3N2) (VE = 23.3%, 95% CI 6.0–37.5).

The second efficacy study identified reported data for an additional outcome (not laboratory-confirmed).[60] The study investigated the relative efficacy of HD-IIV3 compared with SD-IIV3 in older adults (aged ≥ 65 years) for the prevention of respiratory-related hospital admissions. The primary outcome was hospital admissions related to pulmonary and influenza-like conditions on the basis of ICD-9 coded Medicare claims. The authors reported higher vaccine efficacy for HD-IIV3 against respiratory-related hospital admissions (VE = 12.7%, 95% CI 1.8%–22.4%) and pneumonia-related hospital admissions (VE = 20.9%, 95% CI 4.7%–73.3%), based on a sample of 38,225 nursing home residents who had 'fee-for-service' Medicare data available. In intention-to-treat analyses (that included nursing home residents without 'fee-for-service' data), a reduction in all-cause hospitalisations was reported (VE = 6.7%, 95% CI 1.5%–11.6%).

3.2 | Effectiveness

Nine studies contained results relevant to the effectiveness of high-dose influenza vaccines.[28-36] Of these, one was a test-negative case-control study[28] and eight were cohort studies.[29-36]

Only one study presented data relevant to the prevention of laboratory-confirmed influenza for high-dose influenza vaccines.[28] This study compared HD-IIV3 with no vaccination in older adults for the 2014–2015 season and reported a VE of 22% (95% CI −82 to 66) and 89% (95% CI 47–100) for influenza A(H3N2) and influenza B, respectively. The authors note a probable mismatch with the influenza A(H3N2) strain in circulation.

3.3 | Additional outcomes

Eight studies presented data related to additional outcomes relevant to this review: influenza-related hospitalisation, influenza- or pneumonia-related hospitalisation, influenza hospital encounters, influenza office visits and influenza-like illness (Table 1).[29,30,32-36,62] All of these studies were cohort design and compared HD-IIV3 with SD-IIV3 in older adult populations.

3.3.1 | Influenza-related hospitalisations

Two studies presented data for the prevention of influenza-related hospitalisations across six influenza seasons.[30,32] As shown in Figure 2 there was a significant difference in effect in favour of HD-IIV3 for this outcome across all influenza seasons (VE = 11.8%, 95% CI 6.4–17.0, REM, I^2 = 81.3%, low-certainty evidence).

3.3.2 | Influenza- or pneumonia-related hospitalisations

Four studies presented data regarding influenza- or pneumonia-related hospitalisations across six influenza seasons,[29,33,35,36] three of which were included in pooled analyses. As shown in Figure 3, relative to SD-IIV3, there was a significant difference in effect in favour of HD-IIV3 across all influenza seasons (VE = 13.7%, 95% CI 9.5–17.7, REM, I^2 = 15.0%, low-certainty evidence). One study was excluded from pooled analyses as it was conducted in older adults undergoing maintenance haemodialysis; the authors noted no significant difference between the vaccines.[29]

3.3.3 | Influenza-related hospital encounters

Five studies presented data regarding influenza-related hospital encounters across six influenza seasons.[30,32,34,35,62] As shown in Figure 4, relative to SD-IIV3 there was a significant difference in effect in favour of HD-IIV3 across all influenza seasons (VE = 13.1%, 95% CI 8.4–17.7, REM, I^2 = 89%, low-certainty evidence).

3.3.4 | Influenza-related office visits

As shown in Figure 5, two studies possessed data relating to influenza-related office visits across three influenza seasons.[30,34] There was a significant difference in favour of HD-IIV3 for this outcome (VE = 3.5%, 95% CI 1.5–5.5, FEM, I^2 = 94.5%, low-certainty evidence).

3.3.5 | Influenza-like illness

As shown in Table 1, one study presented data regarding influenza-like illness with a pooled estimate of VE across five influenza seasons for older adults undergoing maintenance haemodialysis.[29] No significant difference in VE between HD-IIV3 and SD-IIV3 was noted.

3.4 | Safety

Twenty–four studies included in this systematic review concerned the safety of high-dose influenza vaccines.[25,37-59] Of these, 19 were RCTs[25,37-54] and five were non-randomised studies.[55-59]

3.4.1 | Serious adverse events

Four studies reported serious adverse events (SAEs) which were deemed to be potentially related to receipt of a high-dose influenza vaccine.[37,42,43] Chang et al.[37] reported small-fibre neuropathy in a subject 42 days after vaccination with HD-IIV3. DiazGranados et al.[42] reported one case of cranial-nerve VI palsy, one case of hypovolaemic shock associated with diarrhoea and one case of acute disseminated encephalomyelitis. During the 6 month follow-up period in the study conducted by Falsey et al.[43] one diagnosis of Crohn's disease and one of Myasthenia Gravis were noted. An active surveillance study for Guillain-Barré syndrome conducted by Arya et al.[55] noted no excess risk after high-dose vaccination in the primary analysis. However, an elevated risk of Guillain-Barré syndrome was reported in the secondary analysis timeframe (8–21 days).

3.4.2 | Local reactions

Seven studies possessed sufficiently comparable data to enable quantitative synthesis regarding local reactions for high-dose influenza vaccines.[39,42,43,47,51,52,54] All compared HD-IIV3 with SD-IIV3 or quadrivalent standard dose inactivated influenza vaccine (SD-IIV4) for outcomes including combined local reactions, pain,

TABLE 1 Effectiveness of high-dose influenza vaccines for additional outcomes

Author	Season	Comparator	Vaccine effectiveness (1- risk ratio)	95%CI (lower)	95%CI (upper)	Strain mismatch
Influenza-related hospitalisation						
Lu 2019[32]	2012–2013	SD-IIV3	0.27	0.20	0.34	Well-matched
Lu 2019[32]	2013–2014	SD-IIV3	0.10	–0.01	0.19	Well-matched
Lu 2019[32]	2014–2015	SD-IIV3	0.10	0.05	0.14	Mismatch
Lu 2019[32]	2015–2016	SD-IIV3	0.06	–0.06	0.17	Well-matched
Lu 2019[32]	2016–2017	SD-IIV3	0.11	0.02	0.19	Well-matched
Izurieta 2019[30]	2017–2018	SD-IIV3	0.10	0.08	0.12	Not reported
Lu 2019[32]	2017–2018	SD-IIV3	0.08	0.00	0.16	Well-matched
Influenza- or pneumonia-related hospitalisation						
Butler 2019[a,29]	2010–2015	SD-IIV3	–0.02	–0.10	0.08	Variable
Richardson 2015[33]	2010–2011	SD-IIV3	0.02	–0.40	0.32	Well-matched
Young-Xu 2019[36]	2010–2011	SD-IIV3	0.11	–0.02	0.22	Not reported
Young-Xu 2019[36]	2011–2012	SD-IIV3	0.16	–0.05	0.33	Not reported
Young-Xu 2019[36]	2012–2013	SD-IIV3	0.10	–0.03	0.21	Not reported
Young-Xu 2019[36]	2013–2014	SD-IIV3	0.14	–0.13	0.34	Not reported
Young-Xu 2019[36]	2014–2015	SD-IIV3	0.18	0.04	0.30	Not reported
Young-Xu 2018[35]	2015–2016	SD-IIV3	0.25	0.02	0.43	Well-matched
Influenza-related hospital encounters						
Izurieta 2015[31]	2012–2013	SD-IIV3	0.21	0.15	0.25	Not reported
Lu 2019[32]	2012–2013	SD-IIV3	0.23	0.18	0.28	Well-matched
Shay 2017[34]	2012–2013	SD-IIV3	0.36	0.09	0.56	Well-matched
Lu 2019[32]	2013–2014	SD-IIV3	0.15	0.08	0.22	Well-matched
Shay 2017[34]	2013–2014	SD-IIV3	0.03	–0.47	0.35	Mismatch
Lu 2019[32]	2014–2015	SD-IIV3	0.09	0.06	0.12	Mismatch
Lu 2019[32]	2015–2016	SD-IIV3	0.05	–0.04	0.14	Well-matched
Young-Xu 2018[35]	2015–2016	SD-IIV3	0.14	–0.08	0.32	Well-matched
Lu 2019[32]	2016–2017	SD-IIV3	0.13	0.06	0.18	Well-matched
Izurieta 2019[30]	2017–2018	SD-IIV3	0.09	0.07	0.11	Not reported
Lu 2019[32]	2017–2018	SD-IIV3	0.05	–0.02	0.11	Well-matched
Influenza-related office visits						
Shay 2017[34]	2012–2013	SD-IIV3	0.22	0.17	0.27	Well-matched
Shay 2017[34]	2013–2014	SD-IIV3	0.13	0.05	0.20	Mismatch
Izurieta 2019[30]	2017–2018	SD-IIV3	0.01	–0.02	0.03	Not reported
Influenza-like illness						
Butler 2019[a,29]	2009–2015	SD-IIV3	0.00	–0.04	0.05	Variable

Note: Interpreted from narrative provided by included studies.

[a]Older adult population undergoing maintenance haemodialysis.

redness, swelling, induration and ecchymosis. The pooled estimates are displayed in Supplementary Appendix 1.8. As shown, high-dose inactivated influenza vaccines (HD-IIV) were associated with a significantly higher frequency of combined local reactions (RR = 1.40, 95% 1.20–1.64, three RCTs, FEM, I^2 = 25%, low-certainty evidence), pain (RR = 1.56, 95% CI 1.26–1.93, seven RCTs, REM, I^2 = 57%, moderate-certainty evidence), swelling (RR = 2.20, 95% CI 1.12–4.32, I^2 = 46%, six RCTs, low-certainty

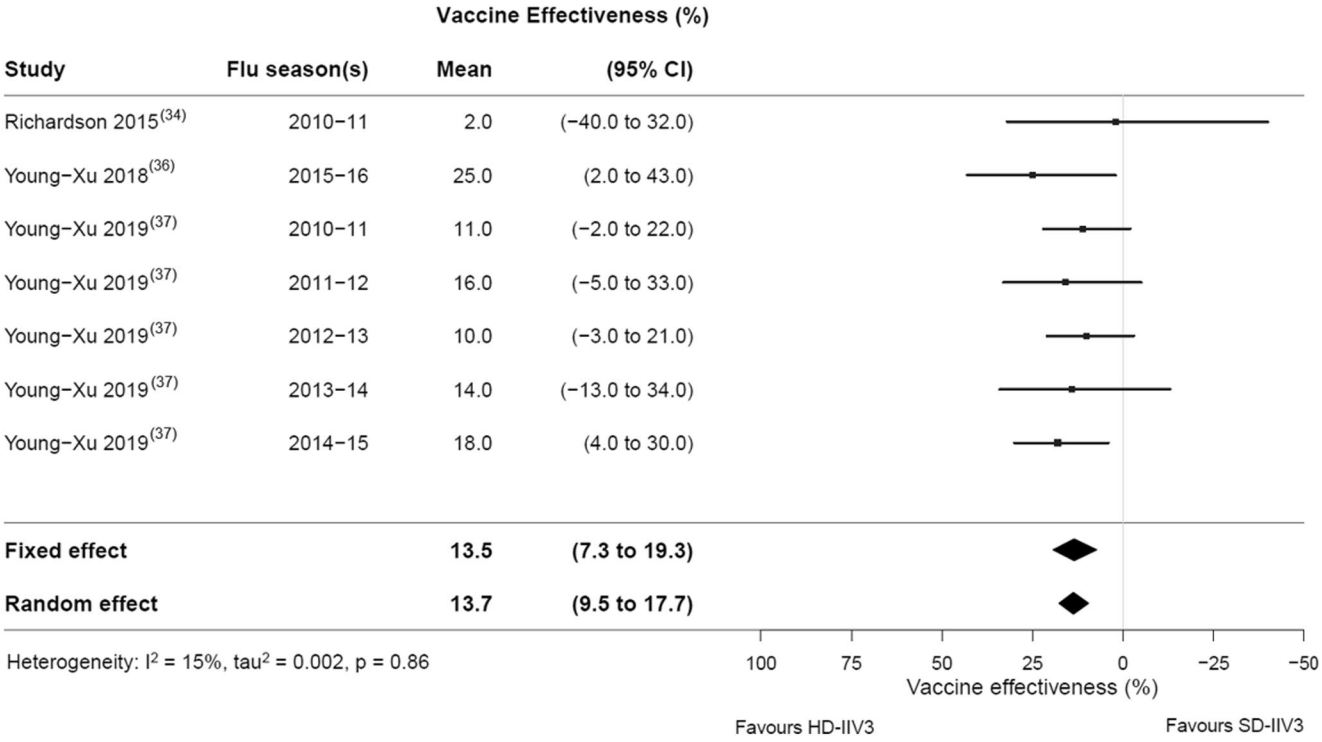

FIGURE 2 Vaccine effectiveness of high-dose inactivated influenza vaccines (HD-IIV3) versus standard-dose influenza vaccines (SD-IIV3) against any influenza-related hospitalisation

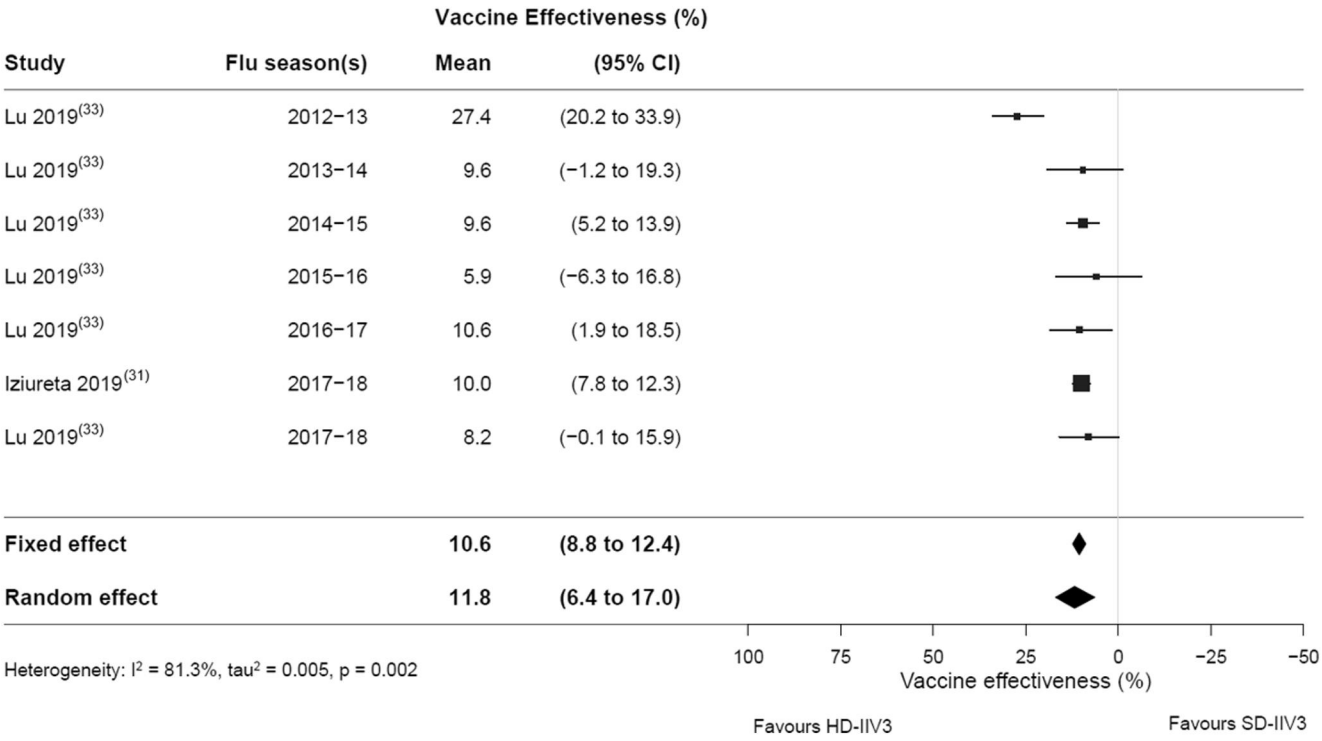

FIGURE 3 Vaccine effectiveness of high-dose inactivated influenza vaccines (HD-IIV3) versus standard-dose influenza vaccines (SD-IIV3) against any influenza- or pneumonia-related hospitalisation

evidence) and induration (RR = 1.63 95% CI 1.10–2.39, FEM, I^2 = 68%, two RCTS, low-certainty evidence). There was no significant difference between vaccines for the remaining outcomes (low-moderate certainty evidence). As shown in Supplementary Appendix 1.9, similar results were displayed for older adults (≥65 years) within sub-group analyses.

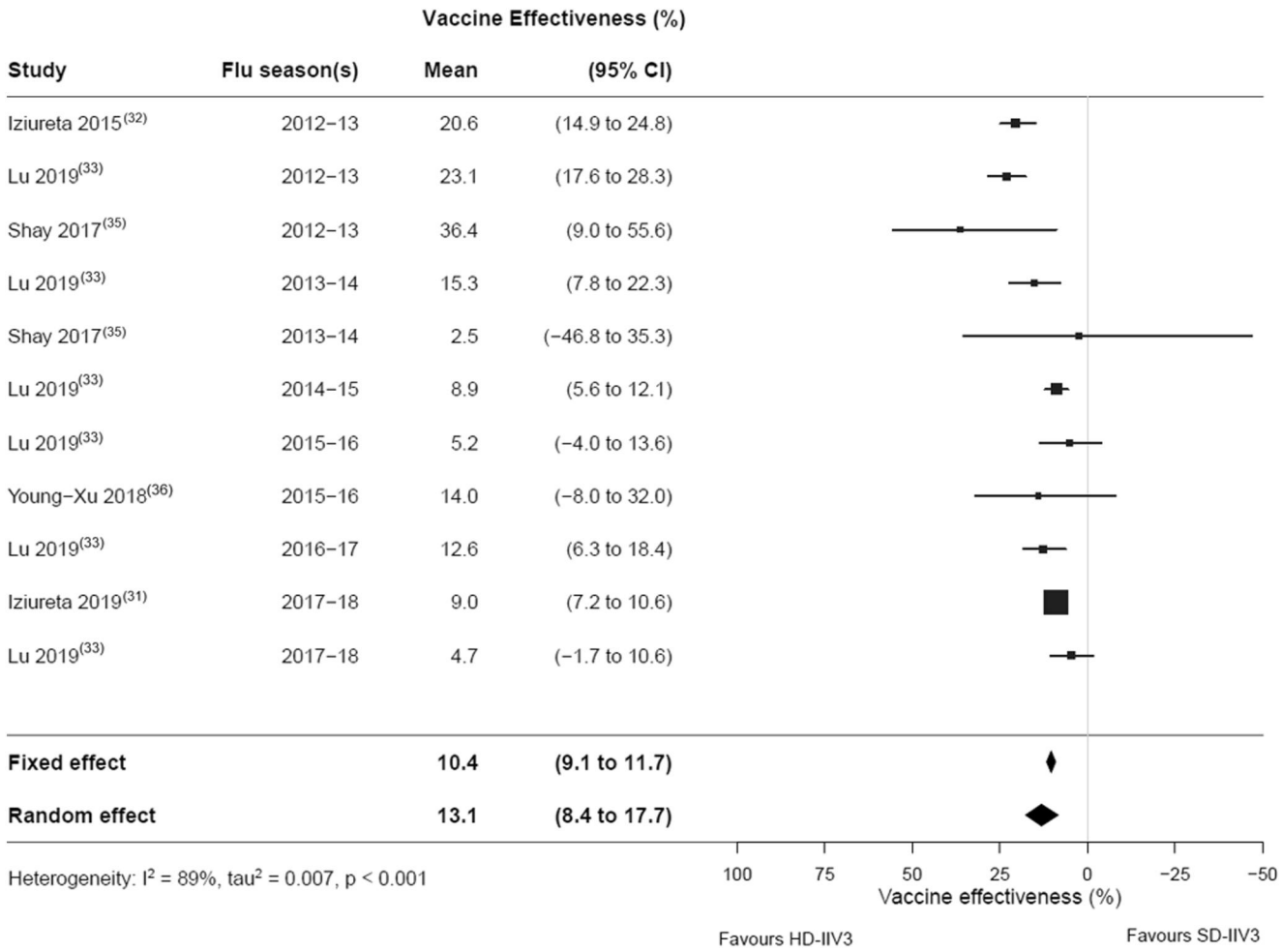

FIGURE 4 Vaccine effectiveness of high-dose inactivated influenza vaccines (HD-IIV3) versus standard-dose influenza vaccines (SD-IIV3) against any influenza-related hospital encounters

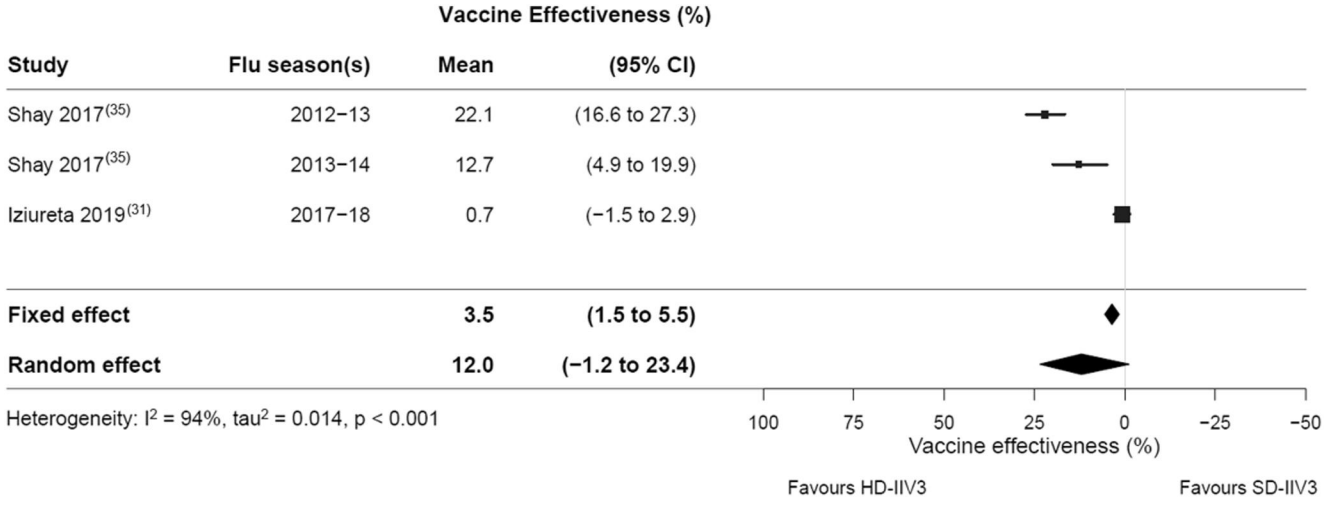

FIGURE 5 Vaccine effectiveness of high-dose inactivated influenza vaccines (HD-IIV3) versus standard-dose influenza vaccines (SD-IIV3) against any influenza-related office visits

Among studies which were excluded from pooled analyses, Cowling et al.[40] reported a statistically higher frequency of tenderness and swelling in those who received HD-IIV3 compared with SD-IIV4. Similarly Kaka et al.[58] reported a significantly higher frequency of local reactions in HD-IIV3 versus SD-IIV3, with the difference largely related to injection site pain. Sanchez et al.[53] compared

intramuscular HD-IIV4, subcutaneous HD-IIV4 and subcutaneous SD-IIV4; intramuscular administration was associated with lower reactogenicity than subcutaneous administrations. Chang et al.[37] noted comparable rates of adverse reactions when a HD-IIV4 was compared with a HD-IIV3.

3.4.3 | Systemic reactions

Seven studies had sufficiently comparable data to enable quantitative synthesis regarding systemic reactions to high-dose influenza vaccines.[39,42,43,47,51,52,54] All compared HD-IIV3 or HD-IIV4 with SD-IIV3 or SD-IIV4 for the following outcomes: combined systemic reactions, fever, headache, malaise, myalgia, chills, diarrhoea and fatigue. The pooled estimates are displayed in Supplementary Appendix 1.8. As shown, HD-IIV were associated with a significantly higher frequency of headache (RR = 1.35, 95% CI 1.02–1.77, REM, I^2 = 0%, seven RCTs, moderate-certainty evidence), chills (RR = 1.73, 95% CI 1.07–2.81, REM, I^2 = 0%, four RCTs, low-certainty evidence), and malaise (RR = 1.28, 95% CI 1.08–1.51, REM, I^2 = 0%, seven RCTs, moderate-certainty evidence). No significant difference between vaccine groups was noted for the remaining outcomes (very-low to moderate certainty evidence). As shown in Supplementary Appendix 1.9, similar results were displayed for older adults within sub-group analyses.

Sanchez et al.[53] compared intramuscular HD-IIV4, subcutaneous HD-IIV4 and subcutaneous SD-IIV4; intramuscular administration was associated with a lower overall frequency of systemic reactions. Chang et al.[37] noted comparable rates of adverse reactions when a HD-IIV4 was compared with a HD-IIV3.

3.4.4 | Safety of high-dose influenza vaccines in at-risk populations

Eight studies included within this review were categorised as investigating the safety profile of high-dose influenza vaccines in at-risk groups, namely: individuals with malignancy,[56,57,59] rheumatoid arthritis,[38] haematopoietic stem cell transplant (HSCT) recipients,[44] transplant recipients[50] and those undergoing oncological interventions.[45]

With regards to individuals with malignancy or undergoing oncological treatment, Chong et al.[57] reported no significant difference in the incidence of new onset immune-related adverse events following vaccination with HD-IIV3 compared with SD-IIV3 or SD-IIV4. Strowd et al.[59] and Branagan et al.[56] noted that high-dose vaccination was well-tolerated in their respective single-arm trials, and Jamshed et al.[45] noted that high dose vaccination was generally well-tolerated compared with SD-IIV.

In patients with rheumatoid arthritis who received HD-IIV3 or SD-IIV4, Colmegna et al.[38] reported similar frequencies of local and systemic reactions in both groups. Similarly, no significant differences in local or systemic reactions were noted between HD-IIV3 and SD-IIV3 in solid-organ transplant recipients.[50] In HSCT recipients, Halasa et al.[44] noted a significantly higher frequency of combined local reactions in those receiving HD-IIV3 compared with SD-IIV3, with no difference noted between the groups in terms of systemic reactions. In individuals with HIV, McKittrick et al.[48] noted no significant difference in local or systemic reactions between recipients of HD-IIV3 compared with SD-IIV3.

3.5 | Risk of bias

The risk of bias for efficacy and safety RCTs investigating high-dose influenza vaccines is summarised in Figure 6 (summary graph in Supplementary Appendix 1.10). The two efficacy RCTs were deemed to be at an unclear risk of bias due to lack of clarity in one key domain. Of the 19 RCTs assessing a safety outcome of high-dose influenza vaccines, 1 (5%) was judged to be at a low risk of bias, 16 (84%) were deemed to be at an unclear risk of bias and 2 (11%) were deemed to be at a high risk of bias. Of note, the influence of industry funding as captured under the domain of other bias, resulted in the majority of studies being deemed to be at an unclear risk of bias overall.

The risk of bias of NRSIs providing data on the effectiveness and safety of high-dose influenza vaccines is summarised in Supplementary Appendix 1.11. One test-negative design case-control study, which investigated the prevention of influenza, was deemed to be at a low risk of bias. One (12.5%) NRSI investigating additional outcomes was deemed to be at a low risk of bias, four (50.0%) at a moderate risk, and three (37.5%) at a serious risk. Areas of poor reporting included confounding variables, selection bias and missing data. Three studies presented data relating to safety with all deemed to be at a serious risk of bias.

4 | DISCUSSION

This systematic review aimed to synthesise the existing evidence base for the efficacy, effectiveness and safety of high-dose influenza vaccines. This review included 36 studies, of which 2 related to efficacy[25] (with 2 additional analyses papers contributing to overall results),[26,27] 9 related to effectiveness[28-36,61] and 23 related to safety (with one efficacy study also presenting safety data).[25,37-59]

One RCT was identified for inclusion in this review which investigated a high-dose influenza vaccine compared with a standard-dose equivalent in older adults for the primary outcome of laboratory-confirmed influenza. The results highlighted better protection against laboratory-confirmed influenza with the use of the high-dose vaccine. Data were limited in relation to the efficacy of this form of vaccine against influenza type/subtypes due to low case numbers. One test negative case-control study was identified that compared the effectiveness of a high-dose influenza vaccine with no vaccination for the primary outcome of laboratory-confirmed influenza in older adults. While the high-dose vaccine was associated with

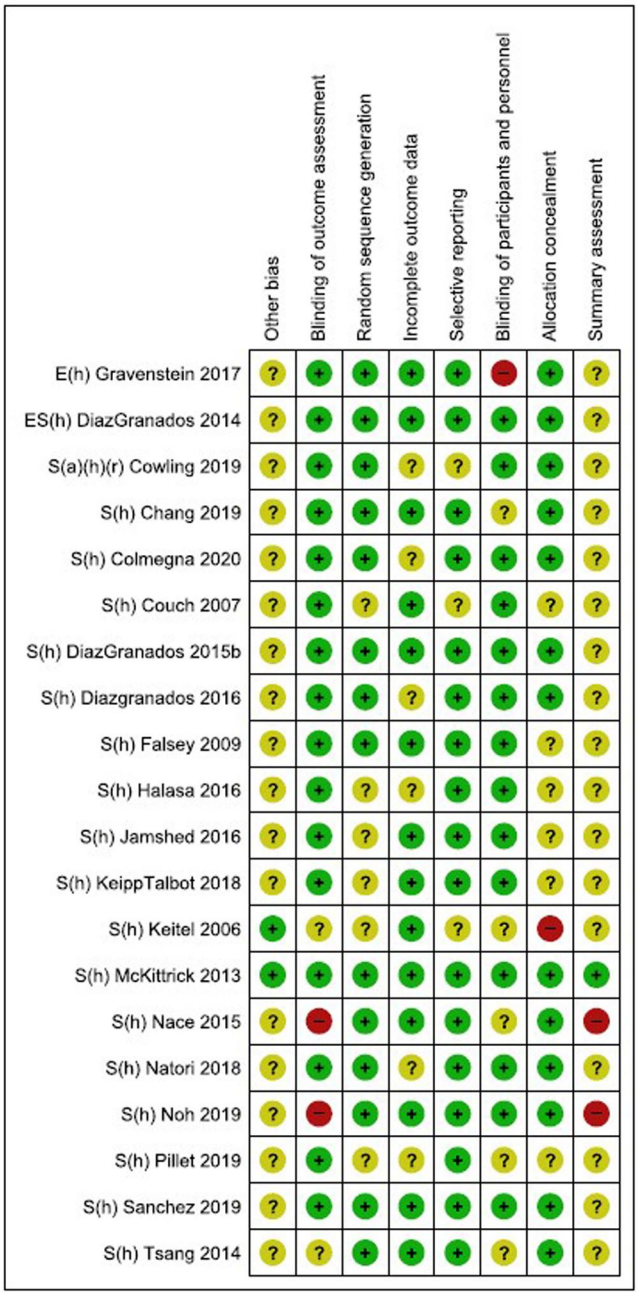

FIGURE 6 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

a significant reduction in laboratory-confirmed influenza B, no significant effect was seen for influenza A(H3N2), with a likely mismatch of the latter to circulating strains. In terms of additional outcomes of interest to this review, the included studies highlight a larger effect with high-dose influenza vaccines compared with standard-dose equivalents for influenza-related hospitalisation, influenza- or pneumonia-related hospitalisation, influenza-related hospital encounters, influenza-related office visits and respiratory-related hospital admissions. Significant caution should be used when interpreting these results in the context of the primary research question given that these studies were typically cohort design and the proxy outcomes are non-specific due to the absence of gold standard laboratory- or culture-confirmation.[63] A reasonable evidence base was presented for the safety of trivalent and quadrivalent high-dose influenza vaccines compared with their standard-dose counterparts. The findings of this review highlight that high-dose vaccines are likely associated with a higher frequency of local and systemic reactions.

The results of this systematic review are in line with previous reviews of efficacy and effectiveness of high-dose influenza vaccinations compared with standard dose equivalents,[11,64] with the limited evidence-base available suggesting that greater protection is provided with these enhanced vaccines. However, the results presented by the observational studies included within this present review highlight that irrespective of the vaccine type, the requirement for accurate strain matching appears to be an important cornerstone in the overall effectiveness of vaccination.[65,66] Although the increased dosage of HA per strain with these vaccines aims to enhance overall response and immunogenicity, their vulnerability to mismatch may be similar to traditional influenza vaccines. In terms of the overall safety of high-dose influenza vaccines compared with standard-dose, the findings of this review of an increase in reactions is unsurprising and likely attributed to the composition of these vaccines, which contain a fourfold increase in the antigens included compared to standard.[10,11] These symptoms are typically reported as mild and transient in nature.[9] Of note, the incidence of SAEs directly linked to high-dose vaccination appears to be low, as further emphasised by a previous review in this research area,[11] and reflected in the continued licencing of these vaccines for use in older adult populations in light of ongoing pharmacovigilence monitoring.[9]

4.1 | Clinical and research implications

The collective data for efficacy and effectiveness, albeit limited, appear to suggest that high-dose influenza vaccines provide greater protection than standard dose or no vaccination in older adults; a population who are likely to experience poorer outcomes from influenza infection compared with their younger counterparts. Limited data exists for the assessment of efficacy and effectiveness against disaggregated influenza type/subtypes. While the inclusion criteria for this review considered evidence in those aged 18 years and older, all data identified for efficacy and effectiveness from studies within this review were noted to exclusively reflect those aged 65 years or older. In terms of safety data, a number of studies included participants aged 18 years or older. As shown in Supplementary Appendix 1.9, within subgroup analyses the safety outcomes for older adults (aged 65 years or older) were similar to those for adults of all ages. Safety analyses indicate that although high-dose vaccination is associated with greater local and systemic reactions compared with standard-dose equivalents in adults aged 18 years or older; the benefit of potentially greater protection for influenza related outcomes is likely balanced against these undesirable, but largely minor, risks.

Although a large body of RCT evidence was presented for safety of high-dose influenza vaccines which is likely reflective of regulatory requirements, the body of evidence for efficacy and effectiveness was

limited particularly for the most impactful outcome of laboratory-confirmed influenza. There is a need for more high-quality, robust trials in the future particularly to address the uncertainty with regard to protection in light of matched and mismatched vaccine strain seasons, and a consistency needed in terms of outcomes reported. Of note, the data coverage within this review was limited by the individual reporting within included studies with resultant restrictions encountered in terms of data extraction and data analyses. Recommendations to improve the reporting of these studies in the future have been proposed which are anticipated to greatly facilitate the synthesis of evidence in this research area in the future.[67]

Since completion of the search for this systematic review a number of potentially relevant studies have been identified which largely report data relating to the secondary outcomes outlined. One RCT compared the efficacy of HD-IIV3 to SD-IIV4 for the prevention of all-cause mortality or hospitalisations for cardiac or pulmonary causes in individuals with high-risk cardiovascular disease, with no significant differences noted between the treatment groups.[68] Four NRSIs were identified which compared high-dose with standard-dose vaccination; in line with the main findings of this review, high-dose vaccination was generally reported to provide greater protection across the outcomes investigated.[69-72] In terms of relative effectiveness compared with other newer or enhanced influenza vaccinations, six NRSIs were identified which included comparisons between high-dose and MF-59 adjuvanted vaccines,[70,73-77] with one also including comparisons to cell-based vaccines;[77] variation was noted in terms of the significance of effect estimates reported across the studies.

4.2 | Strengths and limitations

The findings of this systematic review should be interpreted with consideration of its strengths and limitations overall. A robust approach to the review process was employed with the publication of a defined protocol and adherence to guidelines to standardise conduct and reporting.

This review was unable to answer a proposed research question regarding within-season protection duration associated with high-dose influenza vaccines due to a lack of data overall. This outcome consists of a complex interaction between a large number of factors including, age, previous vaccination history, previous infection history, circulating strain clade and research design.[78] However, it is anticipated that with the increased use of these enhanced influenza vaccines, a larger data coverage will emerge. This should facilitate answers regarding this outcome, in particular with comprehensive datasets such as those collected by the I-MOVE initiative in Europe.[79] Immunogenicity measures were outside the scope of this systematic review, however inclusion of such factors may provide more insight to the potential benefits of high-dose influenza vaccines in future reviews. Comparative studies of high-dose influenza vaccines with other newer and enhanced vaccines, such as MF-59® adjuvanted, would further facilitate decision- and policy-making.

A further limitation of the study designs included in this systematic review is that many of the studies may have been opportunistic and not based on a formal power calculation to determine sample size. Additionally, data were often extracted from larger studies examining a range of vaccine types and therefore the ability to detect effects, particularly for specific influenza types/subtypes, may be limited. Given the nature of this research area, there are likely to be ongoing issues in relation to study design investigating the benefits of using high-dose influenza vaccines relative to other vaccine types, underscoring the importance of the systematic review approach to gather and synthesise all relevant evidence.

A final important consideration is the potential risk of bias of industry funding and industry affiliation. The potential for this form of bias resulted in a large number of studies in this review being deemed to be at an unclear risk overall. Such factors have been documented as potentially influencing the likelihood of publication of favourable results when considering influenza vaccines.[80] The conduct of sufficiently powered and publicly-funded trials to assess these vaccines in an effort to reduce the uncertainty regarding industry bias has been suggested as crucial for future research.[81]

5 | CONCLUSION

Overall, high-dose influenza vaccines may provide better protection against laboratory-confirmed influenza and proxy outcome measures compared with SD-IIV3 in older adults. However, the evidence base is limited and largely restricted to cohort studies, so caution should be used when interpreting these results. A large body of evidence indicates that high-dose vaccines elicit more reactions overall compared with standard-dose equivalents, which is not surprizing given dosage differences, however these seem relatively minor in the context.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest declared by any member of the evaluation team.

ETHICS STATEMENT

Ethics approval was not necessary.

AUTHOR CONTRIBUTIONS

Laura Comber: Formal analysis, investigation, project administration, writing – original draft, writing – reviewing and editing. Eamon O

Murchu: Methodology, formal analysis, investigation, project administration, writing – original draft, writing – reviewing and editing. Conor Teljeur: Methodology, formal analysis, investigation, project administration, writing – original draft, writing – reviewing and editing. Karen Jordan: Formal analysis, investigation, project administration, writing – original draft, writing – reviewing and editing. Michelle O'Neill: Methodology, writing – reviewing and editing. Liam Marshall: Formal analysis, investigation, writing – reviewing and editing. Sarah Hawkshaw: Formal analysis, investigation, writing – reviewing and editing. Patricia Harrington: Methodology, formal analysis, investigation, project administration, writing – original draft, writing – reviewing and editing. Máirín Ryan: Methodology, formal analysis, investigation, project administration, writing – original draft, writing – reviewing and editing. Pasi Penttinen: Conceptualization, methodology, project administration, writing – reviewing and editing. Kari Johansen: Conceptualization, methodology, project administration, writing – reviewing and editing. Nathalie Nicolay: Conceptualization, methodology, project administration, writing – reviewing and editing. Anna-Sara Carnahan: Conceptualization, methodology, writing – reviewing and editing. Jaime Jesús Pérez Martín: Conceptualization, methodology, writing – reviewing and editing. Anna Hayman Robertson: Conceptualization, methodology, writing – reviewing and editing. Jorgen de Jonge: Conceptualization, methodology, writing – reviewing and editing. Tyra Krause: Conceptualization, methodology, writing – reviewing and editing. Hanna Nohynek: Conceptualization, methodology, writing – reviewing and editing. Ioanna Pavlopoulou: Conceptualization, methodology, writing – reviewing and editing. Richard Pebody: Conceptualization, methodology, writing – reviewing and editing. Marta Soler–Soneira: Conceptualization, methodology, writing – reviewing and editing. Ole Wichmann: Conceptualization, methodology, writing – reviewing and editing. All authors attest they meet the ICMJE criteria for authorship

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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