Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Efficacy and safety of high-dose influenza vaccine in elderly adults: A systematic review and meta-analysis

Krista Wilkinson [a,b,*], Yichun Wei [b], Andrea Szwajcer [c], Rasheda Rabbani [a,d], Ryan Zarychanski [a,d,e,f], Ahmed M. Abou-Setta [a,d], Salaheddin M. Mahmud [a,d]

[a] Department of Community Health Sciences, College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
[b] Public Health Branch, Manitoba Health, Healthy Living and Seniors, Winnipeg, Manitoba, Canada
[c] University of Manitoba Libraries, Winnipeg, Manitoba, Canada
[d] George & Fay Yee Center for Healthcare Innovation, University of Manitoba/Winnipeg Regional Health Authority, Winnipeg, Manitoba, Canada
[e] Department of Internal Medicine, Section of Critical Care, University of Manitoba, Winnipeg, Manitoba, Canada
[f] Department of Haematology and Medical Oncology, CancerCare Manitoba, Winnipeg, Manitoba, Canada

ARTICLE INFO

Article history:
Received 19 August 2016
Received in revised form 8 March 2017
Accepted 31 March 2017
Available online xxxx

Keywords:
Influenza
Influenza vaccines
High-dose
Randomized control trial
Systematic review
Meta-analysis

ABSTRACT

Introduction: Older adults are prioritized for influenza vaccination but also have lowered antibody responses to the vaccine. Higher-doses of influenza antigen may increase immune response and thus be more effective. Our objectives were to compare the efficacy and safety of the high-dose influenza vaccine to the standard-dose influenza vaccine in the elderly (age > 65).

Methods: Data sources: Randomized trials (RCTs) from Medline (Ovid), EMBASE (Ovid), Cochrane Library (Wiley), ClinicalTrials.gov, reference lists of relevant articles, and gray literature.

Study selection: Two reviewers independently identified RCTs comparing high-dose influenza vaccine (60 μg of hemagglutinin per strain) to standard-dose influenza vaccine (15 μg of hemagglutinin per strain) in adults over the age of 65 years.

Data extraction: Two reviewers independently extracted trial-level data including population characteristics, interventions, outcomes, and funding sources. Risk of bias was assessed using the Cochrane Risk of Bias tool.

Results: We included seven eligible trials; all were categorized as having a low ($n = 3$) or unclear ($n = 4$) risk of bias. Patients receiving the high-dose vaccine had significantly less risk of developing laboratory-confirmed influenza infections (Relative Risk 0.76, 95%CI 0.65 to 0.90; I^2 0%, 2 trials, 41,141 patients). Post-vaccination geometric mean titres and seroprotection rates were also higher in high-dose vaccine recipients. There were no protocol-defined serious adverse events in the included trials in either group.

Conclusions: In elderly adults, the high-dose influenza vaccine was well-tolerated, more immunogenic, and more efficacious in preventing influenza infections than the standard-dose vaccine. Further pragmatic trials are needed to determine if the higher efficacy translates into higher vaccine effectiveness in adults over the age of 65.

Contents

* Corresponding author at: Department of Community Health Sciences, S113 Medical Services Building - 750 Bannatyne Ave, University of Manitoba, Winnipeg MB R3E 0W3, Canada.
E-mail address: wilkinsk@myumanitoba.ca (K. Wilkinson).

http://dx.doi.org/10.1016/j.vaccine.2017.03.092
0264-410X/

1. Background

Influenza has a high morbidity and mortality; it has been estimated that in Canada, there are an average of 4000 deaths and 12,200 hospital admissions associated with influenza on an annual basis[1,2]. The risk of a severe outcome associated with seasonal influenza infection increases with age and adults over the age of 65 years account for the majority of influenza-associated hospitalizations and deaths in Canada [3].

Vaccination against influenza is recommended annually as a key prevention strategy with older adults targeted as a high-risk population. There is evidence that seasonal influenza vaccine effectiveness (VE) is lower in adults over the age of 65 than in healthy adults 18–64 years old; recent meta-analysis estimated VE against influenza in older adults at about 49% (95% CI 33,62) while effectiveness was closer to 59% (95% CI 51, 67) for healthy younger adults [4,5]. This reduction in influenza VE may be partially explained by a reduction in immune response to influenza immunization as adults age [6].

Influenza vaccines must be updated and administered annually as the effectiveness of the seasonal vaccine depends on the match between the circulating virus strains and the antigens included in the vaccine. Effectiveness is also dependent on the immune response of the vaccine recipient and several methods have been proposed to improve the efficacy of the conventional influenza vaccines; adding adjuvants, administering vaccine through routes other than the intramuscular standard, or using live-attenuated influenza vaccine instead of the inactivated form [7].

Another strategy to enhance antibody response in the elderly has been the use of high-dose antigen influenza vaccines. These vaccines deliver higher doses of influenza virus antigen than the standard-dose vaccine (typically 60 μg of hemagglutinin per strain compared to 15 μg in standard dose vaccines) to induce a stronger immune response. The increase in antibody in serum is expected to be correlated with an increase in vaccine effectiveness [8].

There have been no previous systematic reviews conducted comparing the vaccine effectiveness of the high-dose influenza vaccine to the standard-dose vaccine in older adults.

The purpose of this systematic review was to identify, critically appraise, and meta-analyze data from prospective randomized controlled trials comparing high-dose trivalent inactivated influenza vaccine to standard-dose trivalent influenza vaccine in adults over the age of 65.

2. Methods

We conducted our systematic review using methodological approaches outlined in the Cochrane Handbook for Systematic Reviewers [9] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [10]. The study protocol was registered in PROSPERO – International prospective register of systematic reviews (CRD42016039387).

2.1. Populations, interventions, comparators, outcome measures, settings, and study designs

We included only randomized, controlled trials of adults over the age of 65 years old. The primary research question was, "In elderly adults (over the age of 65) is the high-dose influenza vaccine, compared to the standard-dose vaccine, associated with prevention of laboratory-confirmed influenza infections, influenza-associated hospitalizations, influenza-associated deaths and serious adverse events?"

The main outcome measure was laboratory-confirmed influenza infection. Secondary outcomes were influenza-associated hospitalizations and deaths, and immune response (immunogenicity and seroprotection). Serious adverse events following immunization were included as safety outcomes.

2.2. Search strategy for identification of studies

We searched Medline (Ovid), EMBASE (Ovid), and Cochrane Library (Wiley) from inception to present using individualized search strategies prepared for each database with the Cochrane Highly Sensitive Search Strategy as a model [9]. The search strategy for Medline and EMBASE is presented in Appendix 4. We searched the World Health Organization's International Clinical Trials Registry Platform and ClinicalTrials.gov and hand-searched relevant conference proceedings for the preceding 5 years to identify planned, ongoing, or recently completed but unpublished trials of high-dose influenza vaccine. The reference lists of included trials were hand-searched for relevant citations. No language, publication date, or publication status restrictions were imposed. We performed reference management in EndNote (version X7.2.1, Thomson Reuters).

2.3. Study selection

We used a 2-stage process for study screening and selection using standardized and piloted screening forms. Two reviewers independently screened the titles and abstracts of search results to determine whether a citation met the inclusion criteria (Appendix 1). The full text of citations classified as *include* or *unclear* were reviewed independently with reference to the predetermined inclusion and exclusion criteria. Discrepancies between the two

Please cite this article in press as: Wilkinson K et al. Efficacy and safety of high-dose influenza vaccine in elderly adults: A systematic review and meta-analysis. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.03.092