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Review

# Immunogenicity and safety of inactivated quadrivalent influenza vaccine in adults: A systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

*Background:* A quadrivalent influenza vaccine (QIV) includes two A strains (A/H1N1, A/H3N2) and two B lineages (B/Victoria, B/Yamagata). The presence of both B lineages eliminate potential B lineage mismatch of trivalent influenza vaccine (TIV) with the circulating strain.
*Methods:* Electronic database searches of Medline, Embase, Cochrane Central Register of Controlled Trials (CCRCT), Scopus and Web of Science were conducted for articles published until June 30, 2015 inclusive. Articles were limited to randomised controlled trials (RCTs) in adults using inactivated intramuscular vaccine and published in English language only. Summary estimates of immunogenicity (by seroprotection and seroconversion rates) and adverse events outcomes were compared between QIV and TIV, using a risk ratio (RR). Studies were pooled using inverse variance weights with a random effect model and the $I^2$ statistic was used to estimate heterogeneity.
*Results:* A total of five RCTs were included in the meta-analysis. For immunogenicity outcomes, QIV had similar efficacy for the three common strains; A/H1N1, A/H3N2 and the B lineage included in the TIV. QIV also showed superior efficacy for the B lineage not included in the TIV; pooled seroprotection RR of 1.14 (95%CI: 1.03–1.25, $p = 0.008$) and seroconversion RR of 1.78 (95%CI: 1.24–2.55, $p = 0.002$) for B/Victoria, and pooled seroprotection RR of 1.12 (95%CI: 1.02–1.22, $p = 0.01$) and seroconversion RR of 2.11 (95%CI: 1.51–2.95, $p < 0.001$) for B/Yamagata, respectively. No significant differences were found between QIV and TIV for aggregated local and systemic adverse events within 7 days post-vaccination. There were no vaccine-related serious adverse events reported for either QIV or TIV. Compared to TIV, injection-site pain was more common for QIV, with a pooled RR of 1.18 (95%CI: 1.03–1.35, $p = 0.02$).
*Conclusion:* In adults, inactivated QIV was as immunogenic as seasonal TIV, with equivalent efficacy against the shared three strains included in TIV, and a superior immunogenicity against the non-TIV B lineage.


**Contents**



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## 1. Introduction

Influenza is a major cause of disease burden globally. Vaccination is the most effective intervention available to prevent influenza infection [1]. Both seasonal and pandemic influenza infections affect all ages; however, children and the older people have the highest incidence, morbidity and mortality from the infection [2,3].

A bivalent inactivated influenza vaccine was widely used from 1944 until the trivalent vaccine (containing A/H1N1, A/H3N2 and one B lineage) was introduced in 1978 [4]. Since then, trivalent influenza vaccine (TIV), either inactivated or live-attenuated, has been the leading prevention strategy against influenza. Current seasonal influenza strains in circulation include two influenza A subtypes (A/H1N1 and A/H3N2), and two antigenically and genetically distinct B lineages (B/Victoria and B/Yamagata). Both influenza A subtypes and both B lineages co-circulate, with relative incidence of each subtype and lineage varying widely by season and geographic region [5,6]. Every year, inclusion of three influenza strains is carefully selected for TIV by the World Health Organisation (WHO) for the upcoming influenza season and recommended for use for northern and southern hemisphere influenza vaccines [7]. TIV includes both A strains and one lineage of B (either B/Victoria or B/Yamagata), and thus mismatch of the vaccine B lineage included in the seasonal TIV has occurred in 25% of seasons across global regions, on average [8].

A meta-analysis of TIVs found protective efficacy of 59% for inactivated TIV in adults and 83% for live-attenuated vaccine in children (6 months to 7 years) [9]. However, efficacy of vaccine varies by age, individual immune response and the degree of cross-protection of the vaccine B lineage against the alternate lineage [10–13].

In 2012, a newly available quadrivalent influenza vaccine (QIV) that includes both B lineages was recommended for use by the WHO to improve protection against influenza B. Randomised controlled trials (RCTs) comparing the QIV with TIV showed that QIV was immunogenic for both A strains and B lineages in adults and children [14–18].

Studies have documented that the use of QIV could result in lower population incidence of influenza infection and its complications [19–21]. A United States (US) study of the 2001/2002–2011/2012 influenza seasons estimated that on average at least 30,000 cases, 3500 hospitalisations and 700 deaths could have been prevented in their population through use of QIV over TIV [22]. Another modelling study from Germany concluded that QIV could have prevented 11.2% of influenza B infections (~395,000 infections per annum in the population) caused by vaccine B lineage mismatch [23].

RCTs of QIV have shown promising results against influenza B [16,18,24]. To our knowledge, no meta-analysis of RCTs in adults has yet been published. Thus, we performed a systematic review and meta-analysis of RCTs to determine the immunogenicity and safety of inactivated QIV compared to TIV in healthy adults.

## 2. Methods

Electronic database searches of Medline, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CCRCT) were conducted for published articles from the earliest available dates reported in the databases to June 30, 2015 inclusive. The search was limited to human studies and randomised controlled trials (RCTs), and studies published in English language only. The inclusion criteria for study selection were studies with immunogenicity and safety outcomes of intramuscular administration of inactivated QIV compared to inactivated TIV in adults aged 18 years and over. We excluded animal studies, experimental and observational epidemiologic studies. Studies that compared quadrivalent vaccine to placebo or any vaccines other than TIV, studies conducted in children and immunocompromised people, studies with live-attenuated or adjuvant quadrivalent vaccines, and RCTs comparing QIV and TIV using other routes of vaccine administration were also excluded in our meta-analysis. Both QIV and TIV vaccines used 15 μg haemagglutinins per strain, and were given as 0.5 mL dose intramuscularly.

### 2.1. Data extraction

Two independent reviewers (AMM and AAC) selected and reviewed the articles and extracted the data by the selection criteria. If the data were not available, we calculated the required data from the percentages reported in the study accordingly. Disagreements between the reviewers were resolved by consensus. One study also examined low-dose adjuvant QIV and TIV vaccines in comparison to standard 15 μg inactivated vaccines [24]. However, for data consistency amongst studies, we did not include data from the low-dose adjuvant vaccines in the meta-analysis.

### 2.2. Outcome measures

Immunogenicity was the primary outcome and the secondary outcome was the number of adverse events, compared between QIV and TIV. Serological outcome assessments were determined by haemagglutination inhibition (HI) assay and immune responses were measured at 21 day post-vaccination. Studies were also analysed for older adults (aged > 60 years) if data were available. All studies were considered for the pooled estimates if relevant results were available.

#### 2.2.1. Immunogenicity

Immunogenicity was measured by means of seroprotection rate (SPR) and seroconversion rate (SCR), and was assessed for each of four strains: A/H1N1, A/H3N2, B/Victoria and B/Yamagata, both in the QIV and TIV groups. The seroprotection rate was defined as the percentage of participants with a HI titre $\geqslant$40, and the seroconversion rate was defined as the percentage of participants with either a pre-vaccination HI titre <10 and a post-vaccination HI titre $\geqslant$40 or a pre-vaccination HI titre $\geqslant$10 and a $\geqslant$4-fold increase in HI titre after vaccination. The efficacy of QIV compared to TIV is a