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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

comparison of the three strains included in both vaccines and the efficacy for an additional strain not included in the TIV vaccine. The studies included either one TIV vaccine arm only or would include two different TIV vaccine arms containing each B lineage separately. Therefore QIV was compared to two types of TIV vaccine (either B/Victoria or B/Yamagata) with studies contributing either one or both comparisons. We report comparisons of seroprotection and seroconversion for QIV versus TIV in the meta-analysis. For immunogenicity outcome, if the required study data were not provided for the whole study, then the data were extracted only from the sub-groups available in the study.

2.2.2. Adverse events

The number or percentage of subjects who experienced vaccine adverse events within 7 days post-vaccination was extracted from the studies. The proportion of adverse events were analysed by local and systemic events. For comparison with QIV, adverse events from TIV-B/Victoria and TIV-B/Yamagata groups were combined as pooled TIV by adding together the number of adverse events and the total number of participants. This was required as one of the studies reported adverse events pooled across the two TIV arms so analysis by the two TIV types was not possible. Local reactions were pain, redness and swelling, and systemic events were fatigue, headache, myalgia and fever. The most frequently reported local or systemic events in QIV and TIV were also assessed. Serious adverse events (SAEs) and deaths related to vaccines and adverse events of special interest such as Guillain–Barré syndrome, Bell's palsy, optic neuritis and encephalitis were reviewed in the study.

2.3. Statistical analysis

Study specific risk ratios (RR) and their 95% confidence intervals (CI) were estimated and plotted in forest plots for seroprotection, seroconversion and adverse events. These risk ratios compared proportions of subjects receiving QIV versus those who received TIV for each of the outcomes above. Estimates were pooled using inverse variance weighting and random effects to allow for between study heterogeneity. The I^2 statistic, which estimates the percentage of total variation across studies due to heterogeneity, was used to assess the level of heterogeneity [25]. All analyses were conducted in Review Manager (version 5.3) [26]. P-values < 0.05 were considered to be statistically significant in the meta-analysis.

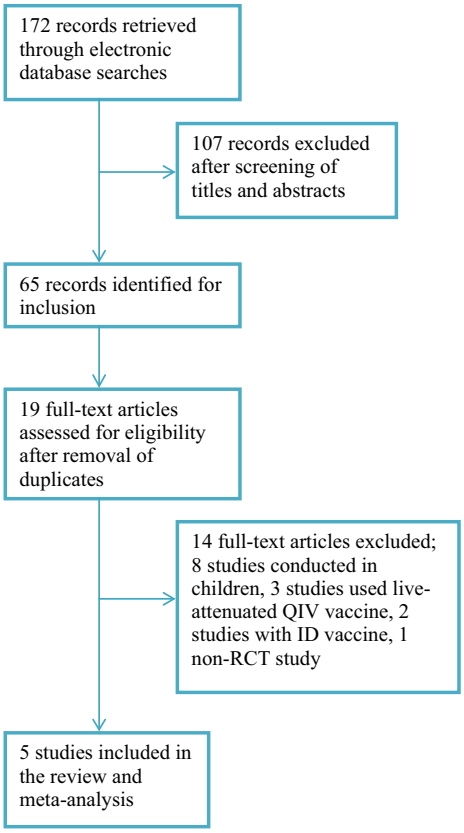

Fig. 1. Flow diagram for study selection. QIV: quadrivalent influenza vaccine, ID: intradermal, RCT: randomised controlled trial.

2.4. Sensitivity analysis

A sensitivity analysis was conducted to investigate the influence of length of follow-up for reporting adverse events. We excluded a study that reported adverse events up to 3 days post-vaccination [16], as all other studies reported adverse events up to 7 days after vaccination. We then reported the overall pooled estimate RR for the adverse events after removal of the study to see if the results changed substantially.

2.5. Quality of included studies

The quality of studies was investigated independently by two authors (AMM and AAC) using the Cochrane's risk of bias assessment [27]. Studies were assessed for potential sources of bias according to key domains such as selection bias, performance bias, detection bias, attrition bias, and reporting and other bias. Each trial was reviewed for presence of random sequence generation; allocation concealment; blinding of participants, investigators and outcome assessors; and method of reporting in the trial, and described as low, unclear or high risk of bias appropriately. We used PRISMA checklist items in accordance with the PRISMA statement, to report the study's findings in the meta-analysis [28].

3. Results

In all, 172 articles were retrieved from the initial search. After review of titles and abstracts, and removal of duplicates, 19 articles remained for full review. The flow diagram of study selection is shown in Fig. 1. Five RCTs met the inclusion criteria and were included in the final review and meta-analysis. A minimum of 4623 and 4342 participants were included in the meta-analyses for QIV versus TIV including B/Victoria (TIV-B/Victoria) and QIV versus TIV including B/Yamagata (TIV-B/Yamagata) for the immunogenicity outcome analyses [15,16,18,24,29]. The characteristics of the included RCTs are described in Table 1.

Amongst the included studies, one was double blind [18], three [15,24,29] were partially blinded and one was an open-label trial [16]. In general, studies showed low risk of bias. Most studies used 'intention-to-treat' (ITT) for the adverse events outcome analysis; however, studies used 'per-protocol analysis set' for the immunogenicity outcome. Attrition bias was rated as high risk due to incomplete outcome assessment in the meta-analysis, as immunogenicity was assessed using 'per-protocol analysis' in the included RCTs. Studies showed approximately less than 3% of withdrawals and lost to follow-up, and only one study had approximately 15% drop-outs in the TIV group only. Studies reported adequately for participants' selection and performance method, and outcomes were assessed appropriately, therefore there were low risks for selection bias, performance and detection bias. The quality of included studies is summarised in the appendix Fig. A1.

3.1. Immunogenicity

A total of five studies were included for the immunogenicity outcome in the meta-analysis. No significant differences were

Table 1
Study characteristics of included studies.

Study (year), Ref.	Country	Type of study	Study period	Age (year); Mean age, QIV vs TIV	Total number of subjects randomized/ vaccinated (N)	Intervention vaccine (QIV)	Vaccine strains in QIV	Vaccine strains in TIV	Vaccine manufacturer
Beran et al. [24]	Czech Republic	Phase I/II, single-blind	July 2008–January 2009	18–60; 38.6 y vs 37.4 y	420	QIV (inactivated split-virion) or (non-adjuvanted or low-dose adjuvanted [LD QIV-AS])	A/Solomon Islands/03/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/ 2004 (B/Vic), B/Jiangsu/10/ 2003 strain (B/Yam)	2007–2008 TIV or LD TIV-AS (low-dose adjuvated TIV); H1N1, H3N2, B/Malaysia/ 2506/2004 (B/Vic)	GlaxoSmithKline (GSK)
Greenberg et al. [16]	USA	Phase II, open-label	October–December 2009	18 and over; 56.7 y vs 55 y	590	QIV (Inactivated)	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), B/Brisbane/60/2008 (B/Vic), B/Florida/04/2006 (B/Yam)	2009–2010 TIV: H1N1, H3N2, B/Brisbane/60/2008 (B/Vic); 2008–2009 TIV: H1N1, H3N2, B/Florida/04/2006 (B/Yam)	Sanofi Pasteur, Swiftwater, PA, USA
Kieninger et al. [15]	Germany, Romania, Spain, Korea, Taiwan, USA	Phase III, partially-blind	October 2010–June 2011	18 and over; 57.9 y vs 58.1 y	4656	QIV (inactivated split-virion)	A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (B/Vic), B/Brisbane/3/2007 (B/Yam)	TIV-Vic: H1N1, H3N2, B/ Brisbane/60/2008 (B/Vic); TIV-Yam: H1N1, H3N2, B/ Brisbane/3/2007 (B/Yam)	GlaxoSmithKline (GSK), Dresden, Germany
Pepin et al. [29]	France, Germany	Phase III, double-blind	October 2011–June 2012	18 and over; 55.1 y vs 55.1–56 y	1565	QIV (inactivated)	A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (B/Vic), B/Florida/04/2006 (B/Yam)	2010–2011 TIV (licensed): A/ H1N1, A/H3N2, B/Brisbane/ 60/2008 (B/Vic); investigational TIV: A/H1N1, A/H3N2, B/Florida/04/2006 (B/Yam)	Sanofi Pasteur
Tinoco et al. [18]	Canada, Mexico, USA	Phase III, double-blind	2010–2011	18 and over; 50 y vs ~50 y	1703	QIV (inactivated quadrivalent split-virion)	A/H1N1 (A/California/7/ 2009), A/H3N2 (A/Victoria/ 210/2009), B/Brisbane/60/ 2008 (B/Vic), B/Florida/4/ 2006 (B/Yam)	2010–2011 TIV (Inactivated): A/H1N1 (A/California/7/ 2009), A/H3N2 (A/Victoria/ 210/2009), B/Brisbane/60/ 2008 (B/Vic) or B/Florida/4/ 2006 (B/Yam)	FluLaval™ GlaxoSmithKline, Quebec, Canada

QIV: quadrivalent influenza vaccine; TIV: trivalent influenza vaccine; vs: versus; H1N1 or A/H1N1: influenza A subtype; H3N2 or A/H3N2: influenza A subtype; B/Vic: B/Victoria lineage; B/Yam: B/Yamagata lineage.

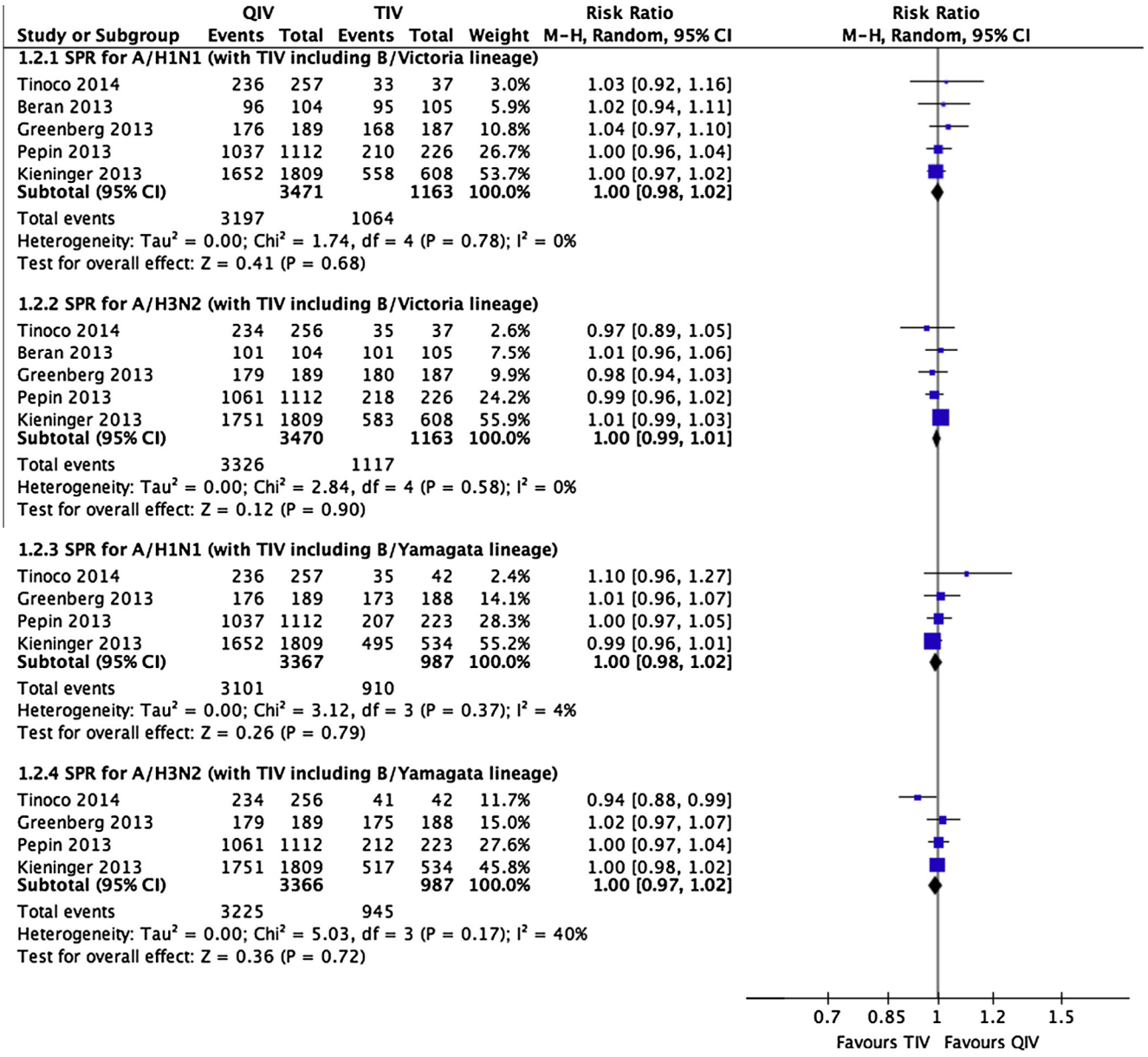

Fig. 2a. Seroprotection rate (SPR) at day 21 post-vaccination, QIV versus TIV in adults (A strains). (SPR is defined as the percentage of participants with a HAI titres ⩾40).

observed for three common strains (2As and 1B of TIV vaccine lineage) between QIV and TIV. Significant heterogeneity was observed for immunogenicity outcomes in the meta-analysis.

Figs. 2a and 2b show forest plots of the risk ratios for the seroprotection rate for each A and B strain, comparing QIV with either TIV-B/Victoria or TIV-B/Yamagata, respectively. The pooled seroprotection RRs for A/H1N1, and A/H3N2 were 1.0 (95%CI: 0.98–1.02), and 1.0 (95%CI: 0.99–1.01) for TIV-B/Victoria, and 1.0 (95%CI: 0.98–1.02) and 1.0 (95%CI: 0.97–1.02) for TIV-B/Yamagata (Fig. 2a).

When comparing QIV for the B lineage in the TIV, the pooled seroprotection RRs were 1.0 (95%CI: 0.99–1.01, $p = 0.43$) for B/Victoria and 1.0 (95%CI: 0.99–1.0, $p = 0.52$) for B/Yamagata lineage. QIV showed superior seroprotection for the B lineage not included in the TIV, with SPR RRs of 1.14 (95%CI: 1.03–1.25, $p = 0.008$) for B/Victoria and 1.12 (95%CI: 1.02–1.22, $p = 0.01$) for B/Yamagata as shown in Fig. 2b.

Similarly, seroconversion rates are described in Figs. 3a and 3b. Pooled SCR RRs were 1.01 (95%CI: 0.97–1.06) for A/H1N1 and 0.98 (95%CI: 0.89–1.08) for A/H3N2 for TIV-B/Victoria. For the comparison of QIV with TIV-B/Yamagata, RRs were 1.00 (95%CI: 0.93–1.07) and 0.99 (95%CI: 0.93–1.04) for A/H1N1 and A/H3N2, respectively (Fig. 3a).

When comparing QIV for the B lineage in the TIV, the pooled seroconversion RRs were 1.05 (95%CI: 0.99–1.12, $p = 0.11$) for B/Victoria and 1.08 (95%CI: 0.99–1.18, $p = 0.10$) for B/Yamagata. QIV showed superior seroconversion for the B lineage not included in the TIV, with SCR RRs of 1.78 (95%CI: 1.24–2.55, $p = 0.002$) for B/Victoria and 2.11 (95%CI: 1.51–2.95, $p < 0.001$) for B/Yamagata (Fig. 3b).

3.2. Immunogenicity in persons aged > 60 years

Data for this age group were available from 2 studies [16,29], and thus analysed separately in the meta-analysis. For A strains, QIV had similar immune responses to TIV (data not shown). QIV induced superior immunogenicity to the B lineage not included in the TIV, with SPR RR of 1.16 (95%CI: 1.0–1.34, $p = 0.05$), for B/Yamagata, and RR of 1.19 (95%CI: 0.88–1.61, $p = 0.27$) for

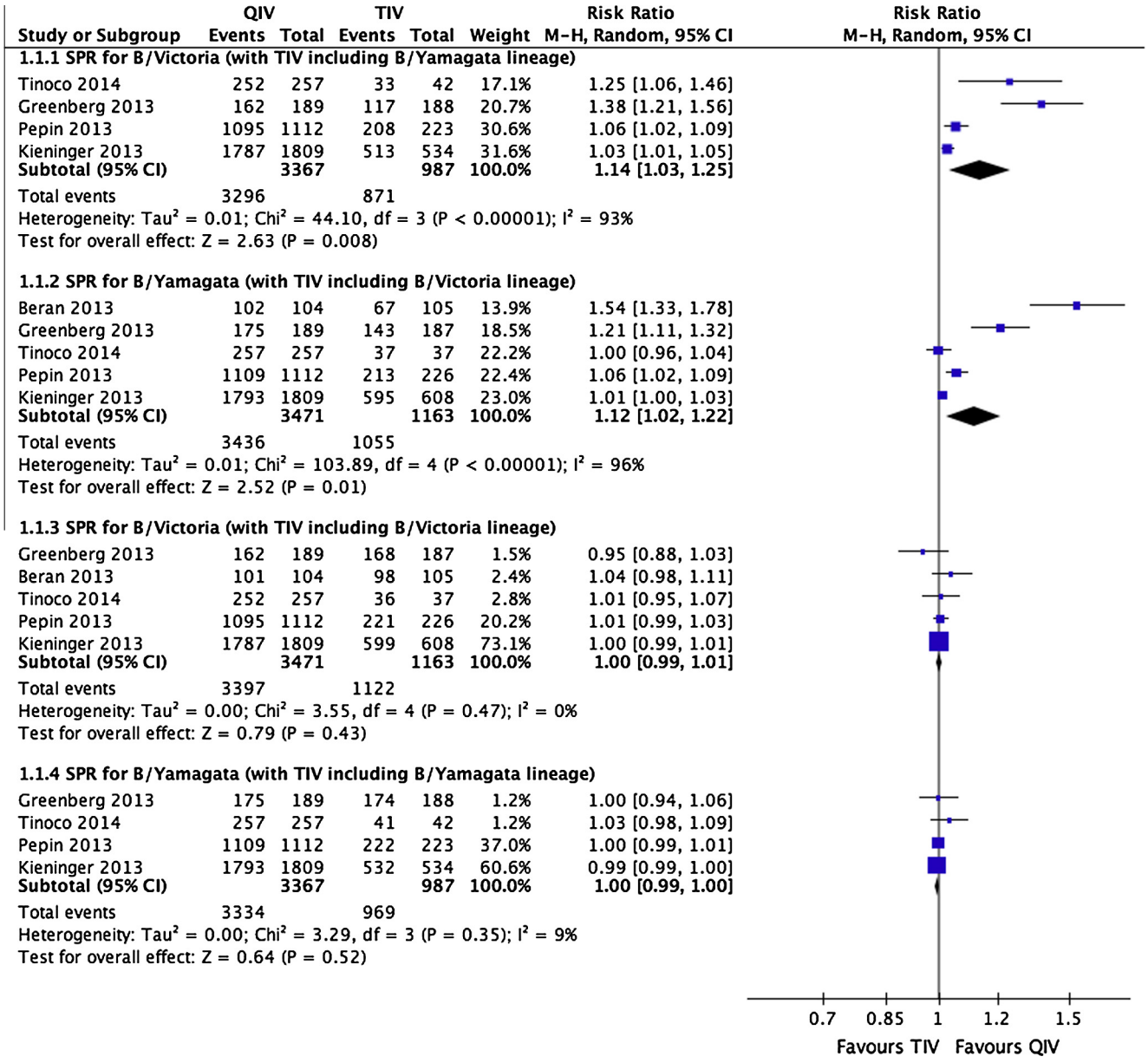

Fig. 2b. Seroprotection rate (SPR) at day 21 post-vaccination, QIV versus TIV in adults (B lineages).

B/Victoria, respectively. Similarly, seroconversion RRs were higher for the B lineage not included in the TIV. SCR RR were 2.70 (95%CI: 1.12–6.51, $p = 0.03$) and 2.78 (95%CI: 2.11–3.66, $p < 0.001$) for B/Victoria and B/Yamagata, respectively. For RRs of seroprotection and seroconversion rate, no significant differences were found between QIV and the B lineage in the TIV (data not shown).

3.3. Adverse events

Three studies [16,24,29] reported the total number of subjects with one or more local and the number with one or more systemic adverse event within 7 days post-vaccination, and pooled RRs were determined for the two vaccine groups. One study reported adverse events within 3 days post-vaccination [16]. The largest, multicentre trial was not included in this analysis because adverse events were not categorised into local or systemic events [15].

There were no significant differences in the occurrence of any local or systemic events, with pooled RRs of 1.16 (95%CI: 0.96–1.40, $p = 0.12$) and 1.07 (95%CI: 0.95–1.20, $p = 0.25$), respectively, comparing QIV with combined TIV containing either or both B lineages (Fig. 4). Evidence of heterogeneity was seen for local reactions. Injection-site pain was the most frequently reported solicited local event, and fatigue, headache and myalgia were commonly reported solicited systemic events among the studies. From the available study data, pooled RRs for each of pain, headache, fatigue, and myalgia were estimated. There was a higher incidence of injection-site pain with QIV, with a pooled RR of 1.18 (95%CI: 1.03–1.35, $p = 0.02$) (Appendix, Fig. A2). There were low occurrence of redness and swelling in both vaccine groups and were reported less than 6–8% across the studies.

QIV did not show any significant differences in frequently reported systemic adverse events such as headache, fatigue and myalgia when compared to TIV (data not shown). Studies reported the number of participants experiencing fever. Fever had very low incidence in both QIV and TIV groups, ranging from 0.0% to 1.0% in QIV and 0.0% to 1.1% in TIV, respectively. One study reported one immediate (within 30 min) unsolicited adverse event with QIV of grade 2-nausea, and which was considered as treatment-related by the investigators [29]. Studies also reported that both solicited local and systemic adverse events were transient in nature, and they

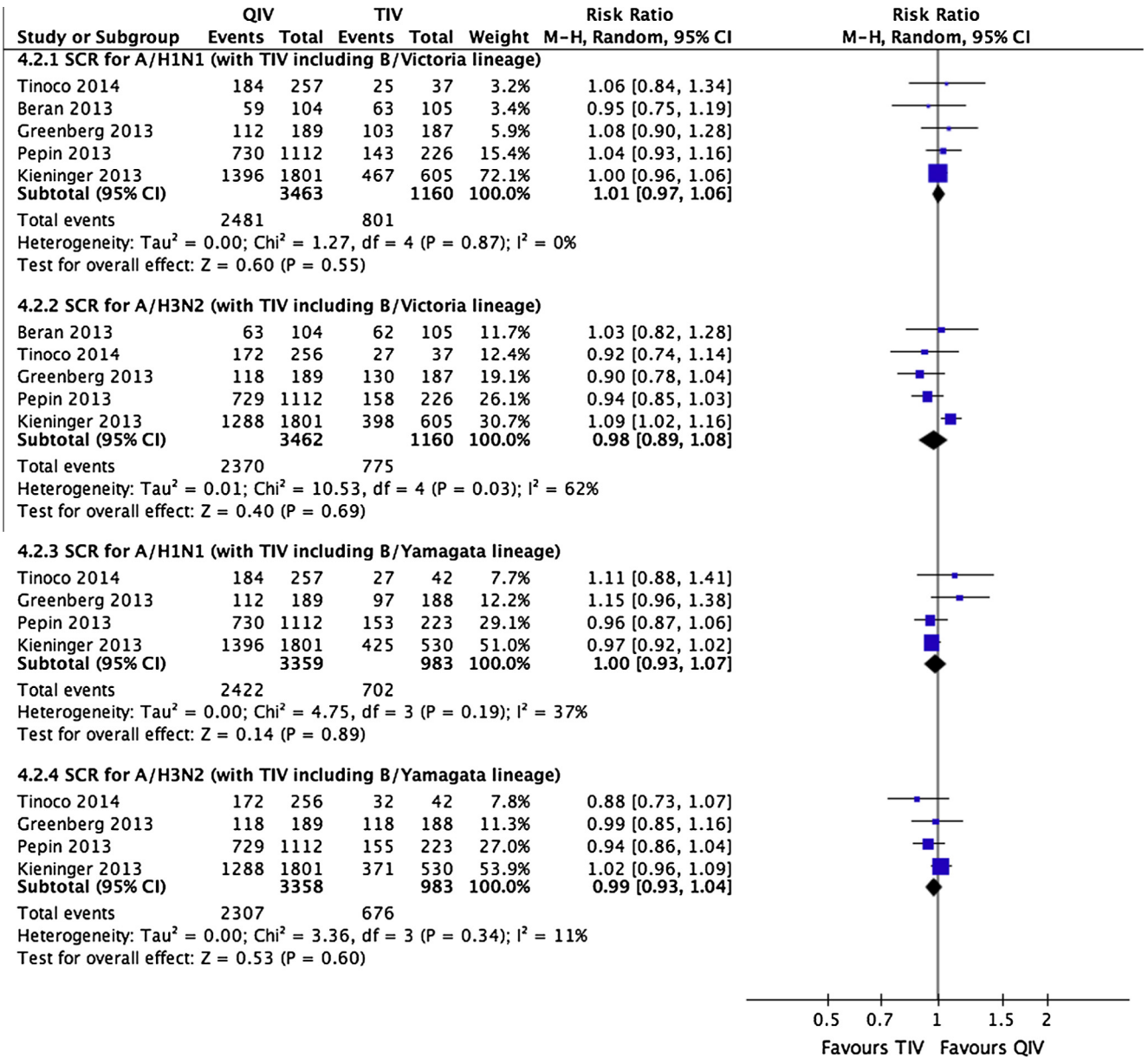

Fig. 3a. Seroconversion rate (SCR) at day 21 post-vaccination, QIV versus TIV in adults (A strains). (SCR is defined as the percentage of participants with either a pre-vaccination HAI titre <10 and a post-vaccination HAI titre ⩾40 or a pre-vaccination HI titre ⩾10 and a ⩾4-fold increase in HI titre after vaccination).

were mild or grade 1 or 2 in general. Studies found that solicited and unsolicited adverse events were comparable between QIV and TIV. Unsolicited adverse events and serious adverse events (SAEs) were followed up at 21 days or 6 months after vaccination. During 21 days post vaccination, frequently reported unsolicited adverse events were nasopharyngitis, cough, and oropharyngeal pain among QIV and TIV groups [15,16,18]. SAEs were comparable between QIV and TIV; ranged from 0.5% to 2.8% in QIV and 0.6% to 2.6% in TIV group [15,18,29]. However, none of these SAEs were reported as vaccine-related events by the investigators. There were no reports of vaccine-related deaths or adverse events of special interest.

While we could not include the study by Kieninger et al. [15] in the meta-analysis of one or more local or systemic adverse events, the number of subjects enrolled in that study was larger than the combined number of subjects in our meta-analysis of the remaining studies. The Kieninger et al. study did not find any significant difference in any single adverse event, including injection-site pain [15].

3.4. Sensitivity analysis

We performed a sensitivity analysis for the adverse events outcome, to determine the impact on the duration of follow-up for adverse events, as one study [16] reported the local and systemic adverse events at day 3 post-vaccination rather than 7 days. The pooled RRs for adverse events were similar after removal of the particular study (data not shown).

4. Discussion

To our knowledge, this is the first meta-analysis comparing immunogenicity and safety of inactivated QIV against TIV in the adult population. The meta-analysis confirms that, in adults, the inactivated QIV used in the studies had equivalent efficacy against the shared three strains between the two vaccines and statistically significant superior efficacy against B lineage not included in the TIV. QIV provided a 14% (95%CI: 3–25) and 78% (95%CI: 24–155)

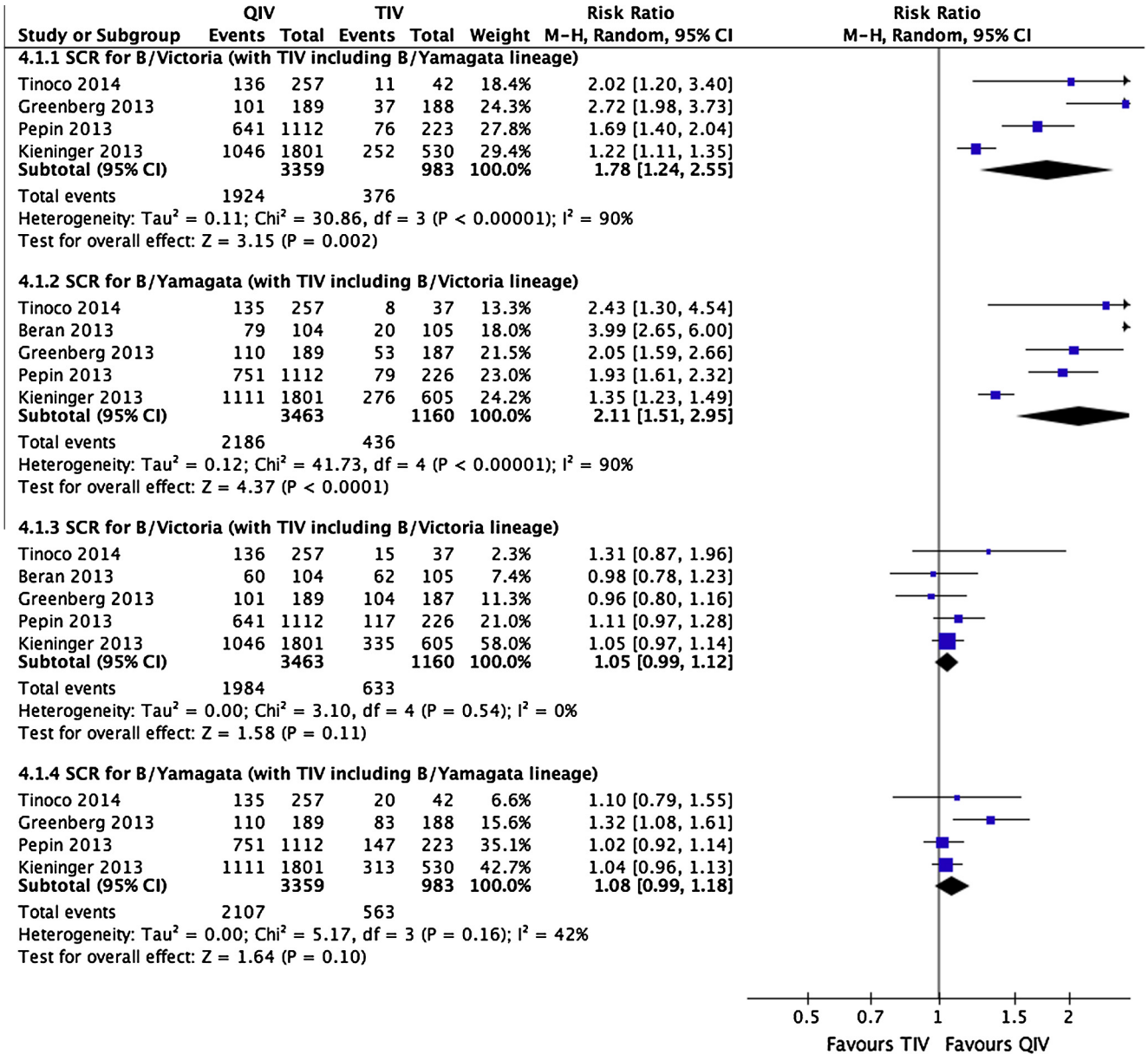

Fig. 3b. Seroconversion rate (SCR) at day 21 post-vaccination, QIV versus TIV in adults (B lineages).

higher seroprotection and seroconversion rate respectively, when compared to TIV for B/Victoria, and a 12% (95%CI: 2–22) and 111% (95%CI: 51–195) higher seroprotection and seroconversion rate for B/Yamagata, respectively. The immunogenicity of the three strains common to both vaccines was not compromised. In addition, QIV induced statistically significant higher seroconversion rates for older adults (>60 years) against the non-TIV B lineage. Overall QIV would deliver improved protection and reduce the burden of influenza B infections in the population when there is a mismatch between the circulating and TIV B lineage.

Our meta-analysis showed a comparable safety profile between QIV and TIV. However, QIV had slightly increased frequency of injection-site pain compared to TIV. While there was no statistically significant difference in overall rate of adverse events, a non-randomised observational post-marketing surveillance study conducted during the 2015 influenza season in Western Australia showed a small difference in the low rate of local reactions (injection- site pain or swelling) following QIV (6.9%) compared with TIV (4.2%) among healthcare professionals [30]. Differences in adverse events rates may be due to differences in vaccine formulation by different vaccine manufactures, and the addition of an extra antigen in QIV [30]. QIV contains an additional 15 μg of influenza antigens compared to TIV, giving a total 60 μg. However, our meta-analysis did not find any significant differences in the systemic events, headache and myalgia between the two vaccines. Fever was reported in studies but occurred at very low rates. Trials reported that the rate of both local and systemic adverse events were transient and short-lived, and resolved within 1–3 days in both vaccine groups. No vaccine-related SAEs or deaths were associated with the vaccines. Although QIV had a slight increase in local reaction (injection-site pain) compared to TIV, the potential benefit of QIV is considered to be greater with regards to improved protection from the infection in the population.

We included only randomised controlled trials in the meta-analysis, thus limiting sources of potential bias in the study. Despite using "per-protocol analysis" for the immunogenicity outcome, all studies appropriately reported the number of participant withdrawals and loss to follow-up, and withdrawal rates were

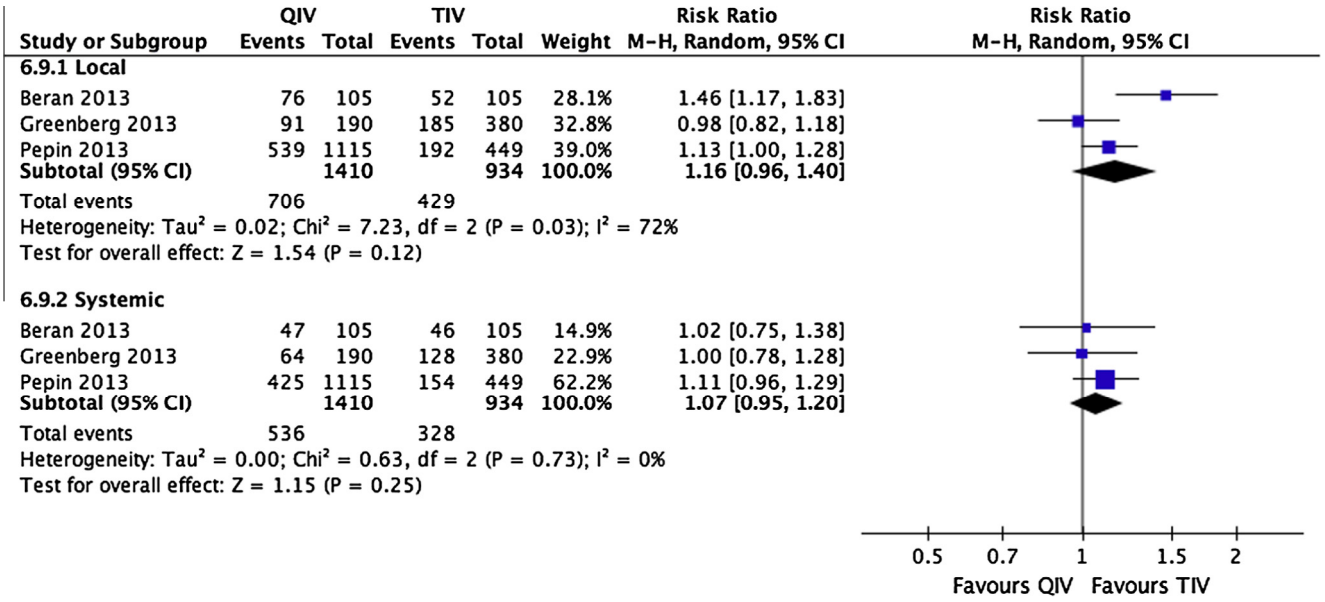

Fig. 4. Adverse events during 0–7 days post vaccination, QIV versus pooled TIV (TIV groups combined (TIV-B/Victoria & TIV-B/Yamagata); local- number of subjects with local adverse events; systemic-number of subjects with systemic adverse events).

small and comparable among the vaccine groups. Thus, attrition bias is unlikely to be important. In the meta-analysis, there was evidence of significant heterogeneity among the studies. We applied a random effects model to allow for this. Heterogeneity in study findings may have been due to variation in age of study subjects, being conducted in different countries with varied influenza seasons, using different vaccine manufacturers, and variation in HI responses of subjects due to different historical exposures to natural infection or vaccination. A small but statistically significant difference in local reaction between the two vaccines that the meta-analysis revealed highlights the limited statistical power of individual RCTs, which individually reported a similar reactogenicity profile. Our meta-analysis provides greater statistical power, due to the larger sample size, to detect smaller difference in adverse and rarer event rates compared to individual RCTs.

Does the immunogenicity reported in these studies translate into efficacy or clinical protection against infection? The included studies reported HI antibody titre responses by means of seroprotection and seroconversion rates. The relationship between HI antibody titre and clinical protection is well established, and is frequently used for assessment of vaccine efficacy. A HI titre of $\geqslant$40 has been reported as providing 50% protection against infection by influenza [31]. This association is also supported by a modelling study, finding that, regardless of vaccination status of individual and the viral strains (either A or B), a positive and statistically significant relationship exists between HI antibody titre and clinical protection against influenza infection [32]. RCTs included in our meta-analysis [15,16,18,24,29] reported that QIV demonstrated at least comparable or a higher level of seroprotection and seroconversion rates than TIV, and also met the criteria outlined by the Center for Biologics Evaluation and Research (CBER), and Committee for Human Medicinal Products (CHMP) for the licensure of influenza vaccine from US and Europe [33,34].

Historically, it is reported that there was little or no cross-protection for infection by one B lineage against the other in immunologically naïve animals (ferrets) and in human studies [35–37]. In contrast, significant cross-reactivity between the two B lineages was reported in a study of middle-aged and elderly adults by the trivalent vaccine [38]. Other studies also reported an evidence of cross-reactive responses following influenza vaccination with alternate B lineages [39,40]. A meta-analysis of RCTs of TIV by Tricco et al. [41] showed vaccine efficacy of 52% and 77% for mismatched and matched B lineages in adults, respectively, providing that there is a cross-reactivity of 67.5% by TIV between the two B lineages. Variations in cross-reactivity among individuals or in the population can be explained by antigenic variability of influenza strains as well as previous exposure of influenza infection or vaccination [38,40].

To date, few modelling studies reported the cost-effectiveness of QIV over TIV [22,42–46]. A study by Clements et al. [46] reported that

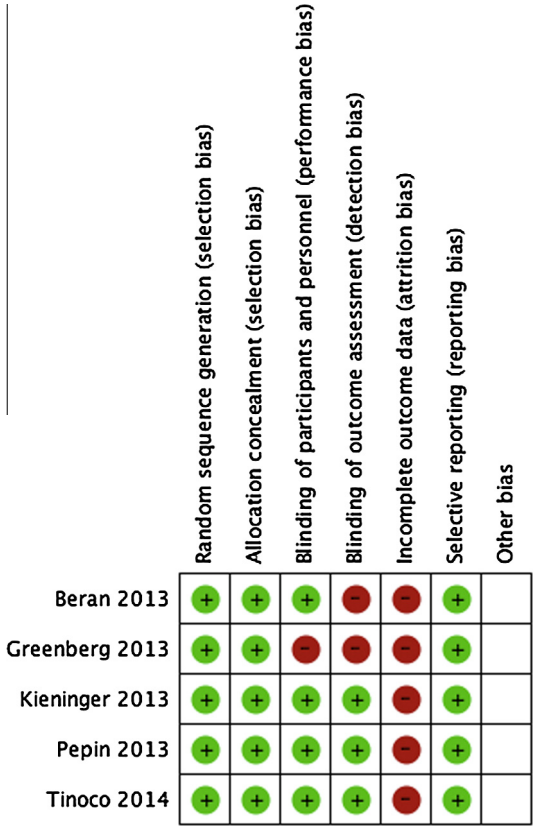

Fig. A1. Risk of bias summary for each included study.

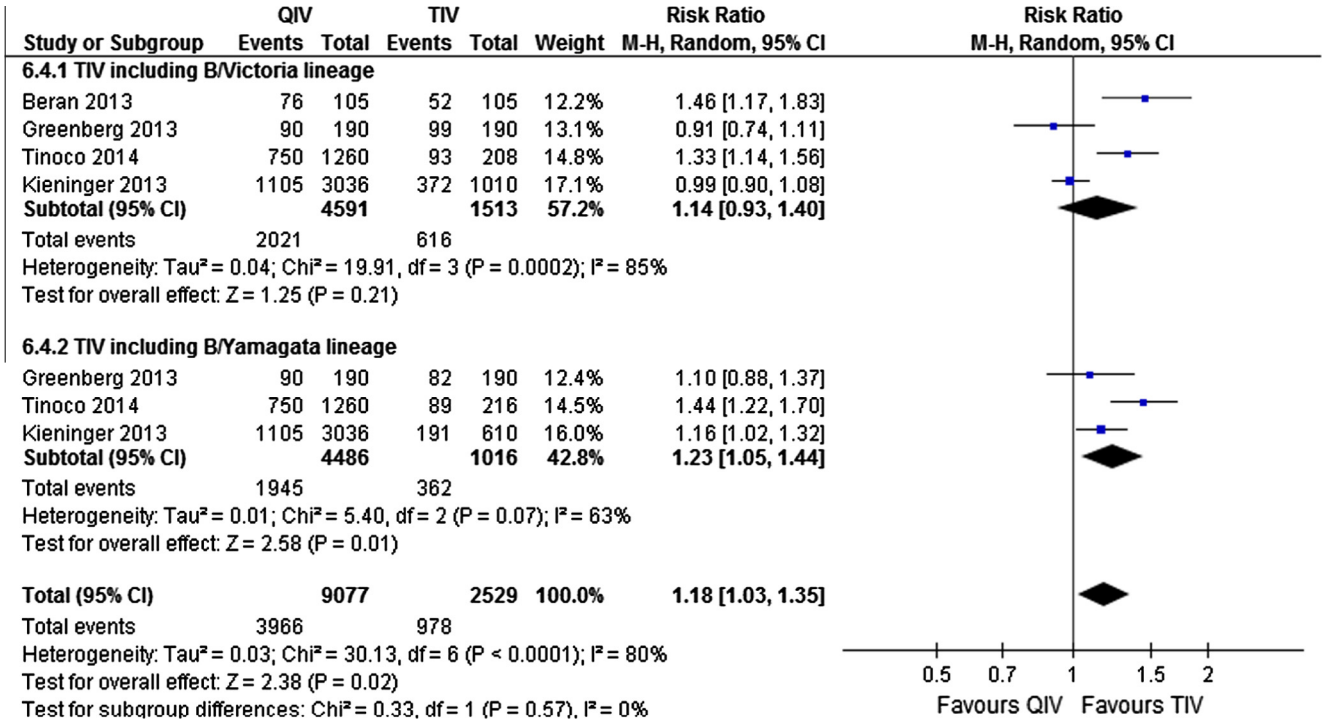

Fig. A2. Adverse event analysis for injection-site pain during 0–7 days post vaccination, QIV versus TIV. (*Greenberg, 2013 – adverse events were followed up within 3 days after vaccination*).

on average per influenza season in the United States, the overall costs of direct medical and indirect costs saved were about by US$111.6 million and US$218.7 million, respectively, with QIV compared to TIV using a base-case model. In general, QIV offers improved protection from the unmatched influenza B infections; however switching of QIV into routine immunisation programs, would require proper cost-effectiveness analyses studies comparing incremental cost-effectiveness of QIV over TIV. Costs associated with influenza infections are substantial and both direct and indirect costs are to be considered in the economic burden of the disease. The importance of appropriate modelling studies in estimating the costs and benefits of using QIV over TIV, and by per country-level consideration, when switching between two vaccination programs in the population has been pointed out [47]. Other factors such as productivity and cost of vaccine should also be considered for utilisation of QIV extensively.

There are limitations in the current study. Our meta-analysis is limited to non-adjuvant formulation and inactivated vaccines only and thus our results may not apply for other vaccine formulations. We only studied RCTs in the adult population and our findings cannot be generalised to children. In elderly people, immune responses to vaccination are complex and sophisticated due to immunosenescence, and had less antibody responses compared to adults [48]. Our findings in older adults may be limited as there were only two RCTs of older adults where data were applicable in the meta-analysis [16,29]. In general, HI antibody responses were assessed at 21 days post-vaccination. One trial described the antibody responses at 6 months, and found that HI titres were lower at 6 months than at 21 days and remained higher than baseline levels. Immunogenicity for B lineages was higher than A strains at 6 months [18]. Persistent of long-term vaccine efficacy should also be explored further for QIV in particular with B lineages. Another limitation in our meta-analysis is that surrogate outcomes (laboratory values) were assessed for the efficacy of vaccine, and thus these findings may not reflect actual clinical efficacy or effectiveness at a population level. Last, our study may have been subject to language, publication or database bias. We did not assess for publication bias due to limited number of studies included in the meta-analysis. Nonetheless, we believed that the meta-analysis provided a larger sample size in the summary estimates, thus it's unlikely to alter our results.

5. Conclusion

In adults, inactivated QIV induced comparable immune responses to TIV for A strains and the B lineage common to both QIV and TIV, and showed statistically significant higher immunogenicity for the B lineage not included in the comparison TIV. This meta-analysis demonstrates that QIV compared to TIV, was tolerable and immunogenic to all four strains. The use of QIV would reduce undesirable mismatched B infections and offer potential advantages over TIV by reducing influenza-related morbidity and mortality in the adult population. Few studies examined older adults specifically and thus more research is needed in this age group. In addition, future studies of vaccine safety and cost-effectiveness of QIV might be useful.

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Author's contribution

AMM: Contributed to conceptual design of the study, selected the studies, and collected and extracted the data, analysed the data and wrote the first draft of the manuscript.

AAC: Contributed to study selection and collected and extracted the data.

DJM: Contributed to statistical advice and edited the manuscript.

RMT: Contributed to statistical advice and edited the manuscript.

CRM: Conceived and contributed to design of the study, contributed to statistical advice, and editing of manuscript.

All authors: Interpreted the results and reviewed the manuscript.

Conflicts of interest

AMM: None to declare.
AAC: Nothing to declare.
DJM: Nothing to declare.
RMT: Nothing to declare.
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Appendix A

See Figs. A1 and A2.

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