Effectiveness of influenza vaccines in asthma: a systematic review and meta-analysis

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Summary: This systematic review of RCTs and robust quasi-experimental and epidemiological studies, suggests likely benefits for people with asthma of vaccination against influenza infection, respiratory illness, asthma attacks and other influenza-related asthma complications including asthma related emergency department visits and hospitalizations.

Keywords: influenza, vaccination, immunization, asthma, laboratory confirmed influenza

Abstract

There is uncertainty about the effectiveness of influenza vaccination in people with asthma and its impact on asthma outcomes, which may contribute to the sub-optimal vaccination rates in people with asthma. This systematic review and meta-analysis involved searching 12 international databases for randomized controlled trials (RCTs) and high quality quasi-experimental and epidemiological studies (1970 to 2016). The risk of bias was low for three included RCTs. The quality of three included observational studies was moderate. The quality of evidence was very low for all study outcomes. Pooled vaccine effectiveness in 1,825 people with asthma from two test-negative design case-control studies was 45% (95% CI 31 to 56) for laboratory-confirmed influenza. Pooled efficacy of live vaccines in reducing influenza was 81% (95% CI 33 to 94). Live vaccine reduced febrile illness by 72% (95% CI 20 to 90). Influenza vaccine prevented 59-78% of asthma attacks leading to emergency visits and/or hospitalizations. For people with asthma influenza vaccination may be effective in both reducing influenza infection and asthma attacks.

Abbreviations

ACIP: Advisory Committee on Immunization Practices; **CI:** Confidence interval; **ED:** Emergency Department; **EPHPP:** Effective Public Health Practice Project; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **ILI:** Influenza-like illness; **LAIV:** Live attenuated influenza vaccine; **OR:** Odds ratio; **PROSPERO:** Prospective register of systematic reviews; **RCT:** Randomized controlled trial; **RR:** Risk ratio; **RT-PCR:** Real time – polymerase chain reaction; **S.D:** Standard deviation; **TND:** Test negative design; **US:** United States; **VE:** Vaccine efficacy or effectiveness; **WHO:** World Health Organization;

Introduction

Influenza is an acute respiratory illness caused by infection with the influenza virus, which can be severe and, particularly in high-risk groups, result in considerable morbidity and, in some cases, death [1]. Worldwide, influenza causes an estimated five million cases of severe illness and half a million deaths each year, costing the United States (US) an estimated US$87 billion per annum [2, 3]. In people with asthma, chronic airway inflammation and type-2 immune responses is thought to impair antiviral immunity in the respiratory tract,[4] resulting in susceptibility to severe influenza illness and associated bacterial infection. Mechanisms of increased susceptibility to influenza in asthma include weaker innate immune and T-helper 1 cell responses and a deficient interferon alpha response of plasmacytoid dendritic cells to influenza [5]. Furthermore, influenza infections can lead to severe asthma attacks often requiring hospitalization [6].

Annual immunization with influenza vaccine is currently recommended by the World Health Organization (WHO) and national immunization technical advisory groups in the US and a number of European and other high-income countries [3, 7]. The uptake in people with at-risk conditions – including asthma – is however well below the target of 75% (e.g. 40% in the US 2015-16) [8-10]. The reasons for this lack of coverage are complex and multifactorial, but include a lack of confidence in patients and health care providers in the effectiveness and safety of vaccines [11]. Important in this respect is the hypothesis that the defective mucosal and systemic immunity in asthma may reduce protection provided by influenza vaccines [12, 13]. There may be some grounds to this concern in the context of asthma as a recent Cochrane systematic review [14] investigating the effectiveness of influenza vaccination in those with asthma was inconclusive regarding the efficacy of influenza vaccines. Also of concern is that the safety of live influenza vaccines in infants with wheezing disorders/asthma

has not yet been conclusively established [14]. Given that placebo randomized controlled trials (RCT)s of influenza vaccination are no longer undertaken in people with asthma (the last placebo RCT was carried out in 2001 with none planned),[15] there is the need, in addition to RCTs, to also consider evidence from other study designs [16]. We therefore carried out a systematic review and meta-analysis of RCTs and robust quasi-experimental and epidemiological studies to evaluate the efficacy, effectiveness and safety of influenza vaccination in people with asthma.

Methods

Selection criteria and search strategy

Our methods have been described in detail in our published protocol [17] (PROSPERO registration: CRD42016037219). We searched the published literature (January 1970 to January 2016) for studies investigating the effectiveness of influenza vaccination in people with asthma. Our start date was chosen as the evidence on this subject began to accrue following publication of the paper by Bell et al. in [18] 1978 [19, 20]. See **Supplementary Appendix I** for search strategies.

Risk of bias assessment in individual studies

Two reviewers (EV and KF) independently assessed the risk of bias, and disagreements were resolved through discussion or by the involvement of a third reviewer (CS). The risk of bias of experimental studies was based on the suggested algorithm in the Cochrane Collaboration's tool [21]. Overall low risk of bias was assigned to a study with low risk of bias for all six domains, overall unclear risk was assigned to a study with unclear risk of bias for one or more domains, and overall high risk of bias was assigned to a study with high risk of bias for one or more domains.

The Quality Assessment Tool for Quantitative Studies Dictionary developed by the Effective Public Health Practice Project (EPHPP) was used for the evaluation of observational studies and non-randomized controlled studies [22]. The overall quality was rated as strong in the absence of weak ratings in each of the six components, moderate overall rating in the presence of one weak rating, and weak overall rating in the presence of two or more weak ratings.

Data analysis

Separate meta-analyses were performed for clinically and methodologically comparable experimental and observational studies in order to estimate the incidence or frequency of influenza infection (laboratory confirmed) and febrile illness. Random-effects models were used to summarize the findings depending on the degree of clinical heterogeneity of the studies. For dichotomous outcomes, the treatment effect was estimated using a risk ratio (RR) with 95% confidence intervals (CI) or odds ratio (OR) with 95% CIs. Vaccine efficacy/effectiveness (VE) is usually reported as a percentage e.g. (1-OR)*100. Safety data from cross-over trials could not be pooled together due to lack of adequate data regarding the two cross-over periods. Statistical heterogeneity was assessed using the standard χ^2 test and I^2 statistic, which describes the proportion of dispersion across studies due to true heterogeneity rather than to a sampling error (0-100% heterogeneity). We contacted authors of included studies that had missing data. All statistical analyses were undertaken using RStudio version 0.99.893 [23].

'Confidence intervals (for figures 1-5 in Supplementary Appendix II) were produced using the generic inverse variance method for meta-analysis. We provided pooled estimates for

each VE outcome combining all study designs (regardless of their clinical or methodological heterogeneity). Due to studies' asymmetric 95% CIs, pooled treatment effects and their 95% CIs were provided using the log relative estimates and standard errors as input.'

Results

Selection of studies and study characteristics

Our initial research identified 20,396 unduplicated records. After screening titles and abstracts, 318 potentially eligible studies were selected for full review. Thirty-two studies eligible for inclusion were identified through database searches and a further three studies through reference screening. We therefore included 35 studies enrolling 142,519 patients with asthma in the qualitative synthesis and four studies in the meta-analyses (**Figure 1**). A brief summary of vaccine types per each endpoint is provided in Table 1. Full citations for these 35 articles [A1–A35] are provided in **Supplementary Appendix II**, along with detailed study characteristics and methodological critiques (**Tables S1-8**).

Risk of bias assessment in individual studies

The overall risk of bias was high in five RCTs, unclear in 12 RCTs and low in three RCTs (**Figure 2**). The overall quality of 12 studies (six non-RCTs and six cohort studies) was rated as "weak". In two case-control studies and in one cohort study, the overall quality was rated as "moderate" (**Figure 3**) (**Tables S2-5**).

Overall quality of evidence

The body of evidence regarding influenza VE and safety regarding primary and secondary outcomes was rated using the GRADE approach as being of very low quality due to inconsistency, indirectness, and imprecision across studies. In addition, the strength of

evidence for the protective effects of vaccination against pulmonary function and school or work absenteeism was rated as very low since the evidence was based on single studies. Thus, the consistency, directness, and precision of the pooled overall estimation could not be assessed. Similarly, the evidence of safety of influenza vaccination against influenza infection and respiratory tract illness was assigned as very low as it was provided by single studies (**Table S6**).

Vaccine efficacy and effectiveness against influenza infection

Nosocomial outbreaks of A (H1N1) and B subtypes were observed during two consecutive years (1988-89 and 1989-90) among 84 children with asthma [A12, A20]. Protection provided by LAIV in these children against laboratory confirmed influenza was found in two small RCTs (pooled VE 81%; 95% CI: 33 to 94; **Figure 4**). A large multicenter RCT evaluated the efficacy of the live vaccine compared to the inactivated vaccine against community-acquired culture-confirmed influenza illness in children (aged 6-17 years) [A6]. LAIV efficacy was significantly higher than the inactivated influenza vaccine. LAIV efficacy against influenza subtypes antigenically similar to those included in the vaccine was 35% (95% CI: 4 to 56).

A meta-analysis was undertaken of two TND studies performed in the US during the seasons 2011-13 [A31, A32]. In 2011/12, the influenza vaccine in the US was well matched and influenza A H3N2 predominated with A H1N1 and both influenza B (Victoria and Yamagata) also circulating [24]. In 2012/13, H3N2 again predominated with a late season predominance of influenza B [25]. The influenza VE for people with asthma ranged was 38% (95% CI: 0 to 63·0) in 2011/12 and 46% (95% CI: 32 to 58) in 2012/13. Once these results were pooled, we found an overall VE of 45% (95% CI: 31 to 56; **Figure 5**) in preventing RT-

PCR laboratory confirmed influenza in 1,825 individuals with asthma (aged ≥6 months) [A31, A32].

One prospective cohort study assessed the effectiveness of the influenza vaccine in preventing influenza in 338 children (2005/6 season). There were no laboratory confirmed influenza infection cases in the vaccinated group, while eight (4·4%) unvaccinated children had an infection [A33]. In a non-RCT, efficacy of inactivated vaccine was 42% (95% CI: 21 to 57) against influenza infection (diagnosed by virus isolation or HI antibody titre increase) in 137 children (aged 2-14 years) [A26].

Vaccine efficacy and effectiveness against asthma attacks and other clinical outcomes

Protective effects of vaccination against asthma exacerbation were also observed in four studies [A7, A28, A29, A35]. One RCT [A7] found that influenza vaccine protected against the incidence, frequency and duration of asthma attacks in 201 children (aged 1-15 years). Acute asthma attacks were lower in the vaccinated group (39/79) compared to the unvaccinated group (82/122) (RR 0.73; 95% CI: 0.57 to 0.95).

VE against asthma attacks was also studied in three observational cohort studies [A28, A29, A35]. In the first study, inactivated influenza vaccine provided higher protection against asthma attacks (defined as wheezing episodes) (mean ± S.D.: 1·6 ± 1.6) compared to the unimmunized group (mean ± S.D.: 6·2 ± 3.9) ($p<0.001$) [A28]. The second study found a reduction in attacks after controlling for asthma severity and other confounders. Protective incidence rate ratios were observed for the 1994/5 season (0·59; 95% CI: 0·43 to 0·81), and the 1995/6 season (0·65; 95% CI: 0·52 to 0·80), but not for the 1993-4 season (0·78; 95% CI: 0·55 to 1·10) [A29]. In the third study, the rate of asthma attacks was significantly ($p=0.037$)

lower in the vaccine group (mean ± S.D.: 0·14 ± 0·4) compared to control group (mean ± S.D.: 0·35 ± 0·61) during the 2002/3 season, but not in the 2001/2 season [A35].

Six studies assessed VE in preventing hospitalizations from asthma attacks or respiratory infections [A2, A7, A21, A26-A28]. A RCT assessed the duration of hospitalization for influenza-like-illness (ILI) accompanied by asthma, ILI and asthma alone in 93 children (aged 6-16). The length of hospitalization for ILI alone ($p<0·01$) and ILI accompanied by asthma ($p<0·05$) was significantly lower in the bivalent inactivated vaccine group compared to the unvaccinated group [A2]. In a cohort study, the number of hospitalizations was 0·2 ± 0·6 (mean ± S.D.) among the inactivated vaccine recipients and 1·3 ± 1·5 (mean ± S.D.) among controls ($p<0.001$) [A28].

Two studies [A6, A27] assessed the protective effects of vaccination against asthma or respiratory illness consultations. A retrospective cohort study reported higher visits to a pediatric clinic among vaccine recipients (2.14) than in the unvaccinated ones (0.71; OR: 2·9; 95% CI: 2·0 to 4·1) [A27].

VE against respiratory illness was found in four studies [A26, A28, A33, A34]. Pooled estimates regarding live attenuated VE against febrile illness were estimated from two RCTs [A12, A20]. Pooled VE of 72% (95% CI: 20 to 90; **Figure 6**) was observed against febrile illness during two nosocomial outbreaks with A (H1N1) and B subtypes [A12, A20]. In another trial, clinical efficacy of inactivated subunit vaccine against febrile influenza illness was 49% (95% CI: 24 to 66) in 137 children (aged 2-14 years) ($p<0.01$). A higher vaccine efficacy (74%) was observed in children ≤ seven years old ($p<0.01$) [A26]. Three cohort studies reported protective effects of vaccination against respiratory illness. In the first study,

the number of respiratory tract illnesses were significantly lower (mean ± S.D.: 2·2 ± 2·1) in the inactivated vaccine recipients compared to the unvaccinated group (mean ± S.D.: 6·9 ± 3·9) ($p<0.001$) [A28]. The second study found that 0·6% of vaccine recipients had a respiratory syncytial virus infection compared to 2·5% of controls. In addition, protective effects of the vaccine were also observed against other respiratory infections (RR: 0·61; 95% CI: 0·29 to 0·95) and bronchiolitis (RR: 0·47; 95% CI: 0·26 to 0·84) [A33]. In the last study, the effectiveness of the inactivated subunit vaccine was 56% (95% CI: 18 to 76) against acute respiratory disease (defined as ILI, bronchitis, bronchiolitis, asthma exacerbation or otitis media) during the 1996-7 season. In particular, higher VE of 77% (95% CI: 35 to 92) was found in younger children < six years old [A34].

The VE in preventing asthma-related emergency department (ED) visits was evaluated in three studies [A7, A27, A28]. A cohort study observed lower ED visits for asthma exacerbations among inactivated vaccine recipients (mean ± S.D.: 0·4 ± 0·9) than the unvaccinated group (mean ± S.D.: 2·2 ± 2·6) ($p<0.001$) [A28]. In contrast, another cohort study of vaccinated children had more ED visits for asthma or pneumonia (OR 2·0; 95% CI: 1·2 to 3·1) [A27].

The protective effects against increased use of asthma medication were also reported in two studies [A7, A28]. In a RCT, the frequency of bronchodilator use was lower in the vaccinated group (35/79) compared to unvaccinated group (77/122; VE: 50%; 95% CI: 0.34 to 0.64) [A7]. A cohort study reported significantly ($p<0.001$) higher number of bronchodilator administrations in the unvaccinated group (mean ± S.D.: 6·2 ± 3·9) than the inactivated vaccine group (mean ± S.D.: 1·6 ± 1·6). Similarly, prednisolone administrations were significantly ($p<0.001$) higher in the unvaccinated group (mean ± S.D.: 1·1 + 1·2) compared

to vaccinated group (mean ± S.D.: 0·1 ± 0·3) [A28]. No improvements in pulmonary function and reduction in work/school absenteeism were found from influenza vaccine [A6, A21].

Safety

There was no increased risk of serious local or systemic adverse reactions, or vaccine-related asthma exacerbations or symptoms (e.g. wheeze) or respiratory illnesses [A1, A4-20, A22, A22-25, A30]. One trial comparing live to inactivated vaccine found a significant increase in wheezing symptoms in the inactivated group [A6]. In two [A2, A15] of 16 studies pulmonary function deterioration was found following vaccination, although these were not accompanied by asthma symptoms, increased medication or health-care utilization. We found four non-RCTs [A22-A25] and one observational study [A30] (not included in the Cates review [14]). These found that influenza vaccine led to no increase in post-vaccine asthma attack or symptoms when compared to placebo (for non-RCT studies) or no vaccine (observational studies) (**Table S7**).

Discussion

Our findings indicate that influenza vaccination prevents influenza and other clinically important health outcomes in people with asthma. Pooled estimates from observational TND studies suggest that influenza vaccination is beneficial against laboratory-confirmed influenza (VEs ranging from 38-46%, with a pooled estimate of 45%) [A31, A32]. Influenza vaccination reduced asthma exacerbations, healthcare use, respiratory illness and medications for asthma [A2, A7, A12, A20, A26, A28, A29, A33, A35]. However, much of this evidence comes from observational studies and therefore bias and residual confounding are alternative possible explanations. For each outcome also, the quality of the body of evidence (across all included studies using GRADE) was very low.

There are several reasons why there is a need to consider evidence from robust quasi-experimental and observational studies. A Cochrane review of RCTs on this subject, which found inconclusive evidence to support influenza vaccination in those with asthma,[14] whilst well conducted, was however of limited value to decision makers, clinicians or patients. This is because there have been no relevant placebo RCTs over the last 15 years and none are in progress or planned as it has been considered unethical to withhold vaccination, particularly from those most at risk of severe influenza illness. Furthermore, observational TND studies are used to help inform national advisory bodies on their influenza vaccination programs. For instance, the US Advisory Committee on Immunization Practices (ACIP) did not recommend the use of LAIV for the 2016/17 season due to evidence of no effectiveness (3%) of LAIV from US based TND studies [7]. Amongst children with a history of asthma or wheezing however superior efficacy of LAIV was found compared to trivalent inactivated influenza vaccine [26]. Therefore, further research to establish the effectiveness of LAIV amongst children with asthma using observational study data is required [27].

Strengths and limitations

Most studies differed by recruitment methods, vaccine ascertainment methods, type of vaccines and outcome definitions (in some cases outcomes were not described). Particularly, the definition and evaluation of asthma exacerbations is an important point of variability across studies. An additional file shows further characteristics of included studies (**Table S8)**. Most studies (experimental and observational) also recruited children or adults less than 65 years old. Thus, only a few studies have assessed influenza vaccination in older people with asthma.

In three RCTs, the low sensitivity of viral culture tests to confirm influenza infection may have affected the accuracy of the results [A12, A20, A26]. Furthermore in three studies, residual immunity from previous vaccination or influenza exposure from previous seasons may have affected VE estimates [A31, A32, A34].

With the small number of studies included in each meta-analysis, publication bias could not be adequately assessed. Planned subgroup and sensitivity analysis (e.g. VE against influenza B and influenza A sub-types) could not be carried out due to lack of data from the included studies [17]. Also, more in-depth analyses, which include the number, nature and antigenic distance specified by virus mutations across sequential circulating variants and vaccine components and the role of prior vaccination are required [28]. This will require larger TND studies with pooling of data across regions and countries. We did not found new substantive evidence for LAIV safety, beyond those studies included in the Cates' review [14].

Conclusions

Public health initiatives are required to improve the current low vaccine uptake in people with asthma [10]. Evidence from clinical trials and observational studies suggests that the influenza vaccine is safe and that it likely benefits people with asthma against influenza infection, respiratory illness, asthma attacks and other influenza-related asthma complications including asthma related ED visits and hospitalizations.

NOTES:

Authorship

EV wrote this review. AS and CS contributed to conceiving this review, and commented critically on several drafts of the review. CB contributed to defining the study question and planning the review, and commented critically on several drafts of the review. KF screened studies, extracted data, and appraised the quality of the studies. BvW, JM and LR contributed on a draft of this review with critical comments. JS, NP and SJ contributed to the writing of the review. LT contributed in the creation of the early drafts of this review.

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Conflict of Interest

We declare no competing interests.

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Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram.

Figure 2: Risk of bias summary: review authors' judgments about each risk of bias item for each RCT. *this rating was based on the Cochrane guideline

Figure 3: Quality assessment of the non-RCTs and observational studies using the EPHPP quality assessment tool.

Figure 4: Live attenuated influenza vaccine versus no vaccine against influenza infection (RCTs)

Figure 5: Seasonal influenza vaccine versus no vaccine against laboratory confirmed (RT-PCR) influenza infection (test-negative design studies)

Figure 6: Live attenuated influenza vaccine versus no vaccine against febrile illness (RCTs)

Table 1. Summary of publications reporting the effectiveness and safety of influenza vaccines

	Publications (No.) per vaccine type[a]			
Publications (No.) per outcome[a]	Inactivated	Live	Both	Not specified
***Influenza**	**1**	**2**	**1**	**3**
(7 publications)	Sugaya 1994 [A26]	Miyazaki 1993 [A12] Tanaka 1993 [A20]	Fleming 2006 [A6]	McLean 2015 [A31] Ohmit 2014 [A32] Otero 2009 [A33]
***Asthma exacerbation**	**4**			**3**
(7 publications)	Bueving 2004 [A3] Abadoglu 2004 [A21] Sugaya 1994 [A26] Jaiwong 2015 [A28]			Gharagozlou 2006 [A7] Kramarz 2001 [A29] Watanabe 2005 [A35]
Hospitalization	**4**			**2**
(6 publications)	Bell 1978 [A2] Abadoglu 2004 [A21] Sugaya 1994 [A26] Jaiwong 2015 [A28]			Gharagozlou 2006 [A7] Christy 2004 [A27]
Consultations			**1**	**1**
(2 publications)			Fleming 2006 [A6]	Christy 2004 [27]
Emergency visits	**1**			**2**
(3 publications)	Jaiwong 2015 [A28]			Gharagozlou 2006 [A7] Christy 2004 [A27]
Respiratory illness	**5**	**2**		**1**
(8 publications)	Bueving 2004 [A3] Abadoglu 2004 [A21] Sugaya 1994 [A26] Jaiwong 2015 [A28] Smits 2002 [A34]	Miyazaki 1993 [A12] Tanaka 1993 [A20]		Jaiwong 2015 [A28]
Asthma medication	**1**			**1**
(2 publications)	Jaiwong 2015 [A28]			Gharagozlou 2006 [A7]
Pulmonary function	**1**			
(1 publication)	Abadoglu 2004 [A21]			
School/work absence			**1**	
(1 publication)			Fleming 2006 [A6]	
Safety	**17**	**4**	**1**	**2**
(24 publications)	Bell 1978 [A2] Bueving 2004 [A4] Castro 2001 [A5] Govaert 1993 [A8] Hahn 1980 [A9] Kmiecik 2007 [A10] Miller 2003 [A11] Nicholson 1998 [A13] Ortwein 1987 [A14] Pedroza 2009 [A15] Reid 1998 [A17] Sener 1999 [A18] Stenius 1986 [A19] Campbell 1984 [A22] Chiu 2003 [A23] Kava 1987 [A24] Kim 2003[A25]	Atmar 1990 [A1] Miyazaki 1993 [A12] Redding 2002 [A16] Tanaka 1993 [A20]	Fleming 2006 [A6]	Gharagoszlou 2006 [A7] Kramarz 2000 [A30]

[a] See Supplementary Appendix II for details
*Primary outcomes

Figure 1

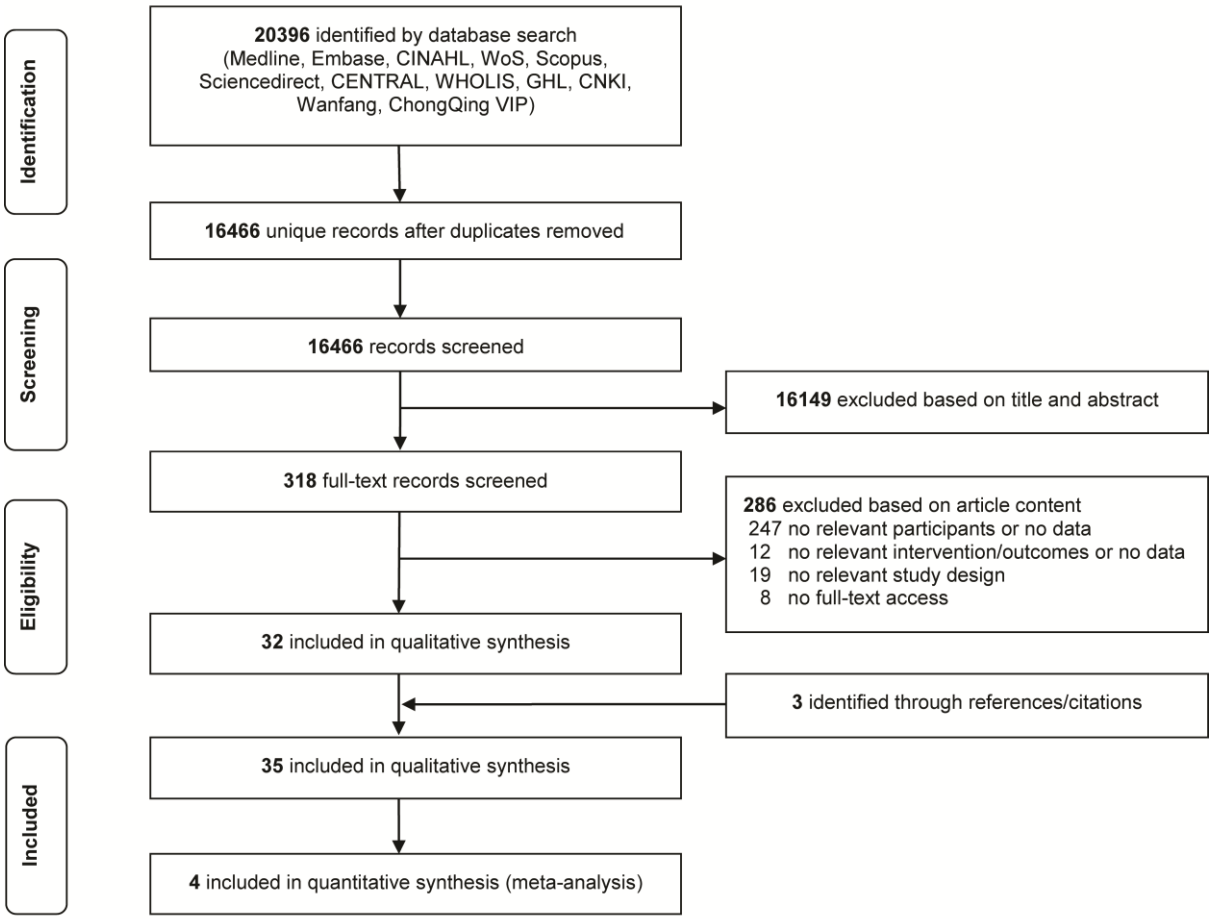

Identification
Screening
Eligibility
Included
20396 identified by database search (Medline, Embase, CINAHL, WoS, Scopus, Sciencedirect, CENTRAL, WHOLIS, GHL, CNKI, Wanfang, ChongQing VIP)
16466 unique records after duplicates removed
16466 records screened
16149 excluded based on title and abstract
318 full-text records screened
286 excluded based on article content
247 no relevant participants or no data
12 no relevant intervention/outcomes or no data
19 no relevant study design
8 no full-text access
32 included in qualitative synthesis
3 identified through references/citations
35 included in qualitative synthesis
4 included in quantitative synthesis (meta-analysis)

Figure 2

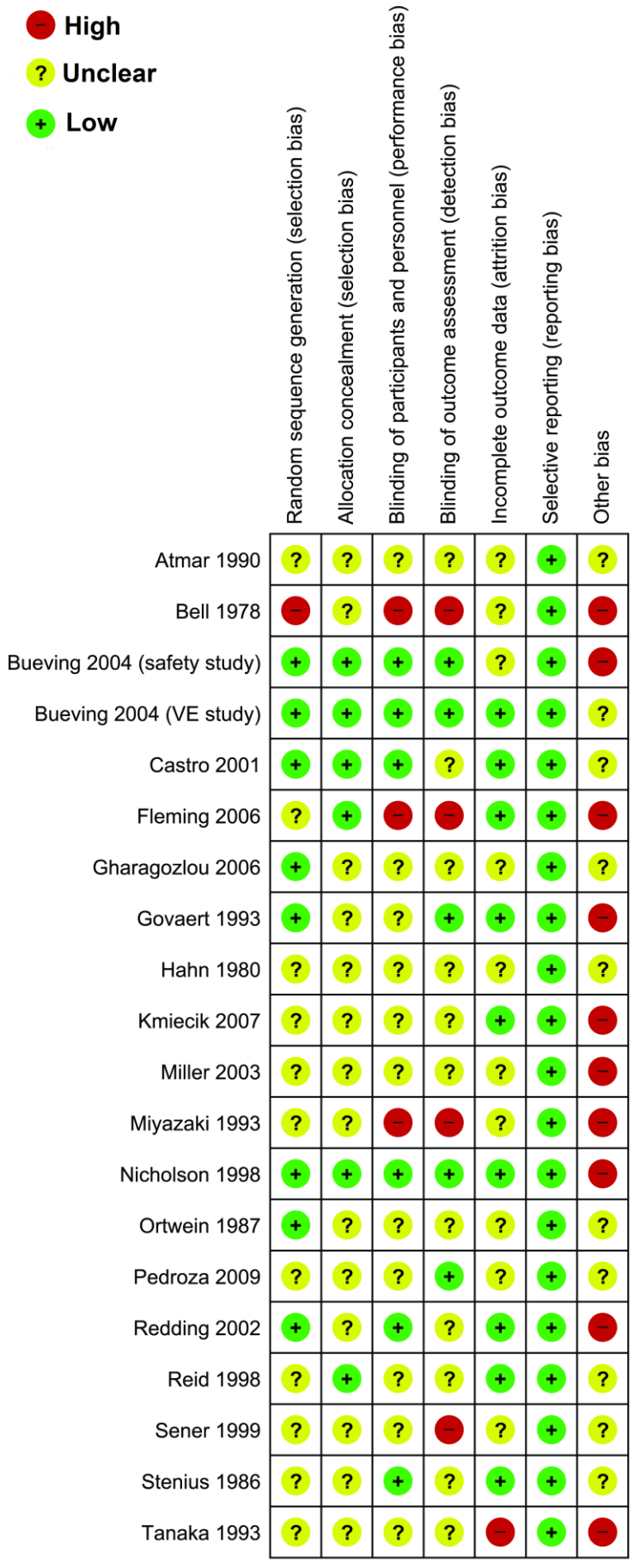

High
Unclear
Low
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Atmar 1990
Bell 1978
Bueving 2004 (safety study)
Bueving 2004 (VE study)
Castro 2001
Fleming 2006
Gharagozlou 2006
Govaert 1993
Hahn 1980
Kmiecik 2007
Miller 2003
Miyazaki 1993
Nicholson 1998
Ortwein 1987
Pedroza 2009
Redding 2002
Reid 1998
Sener 1999
Stenius 1986
Tanaka 1993

Figure 3

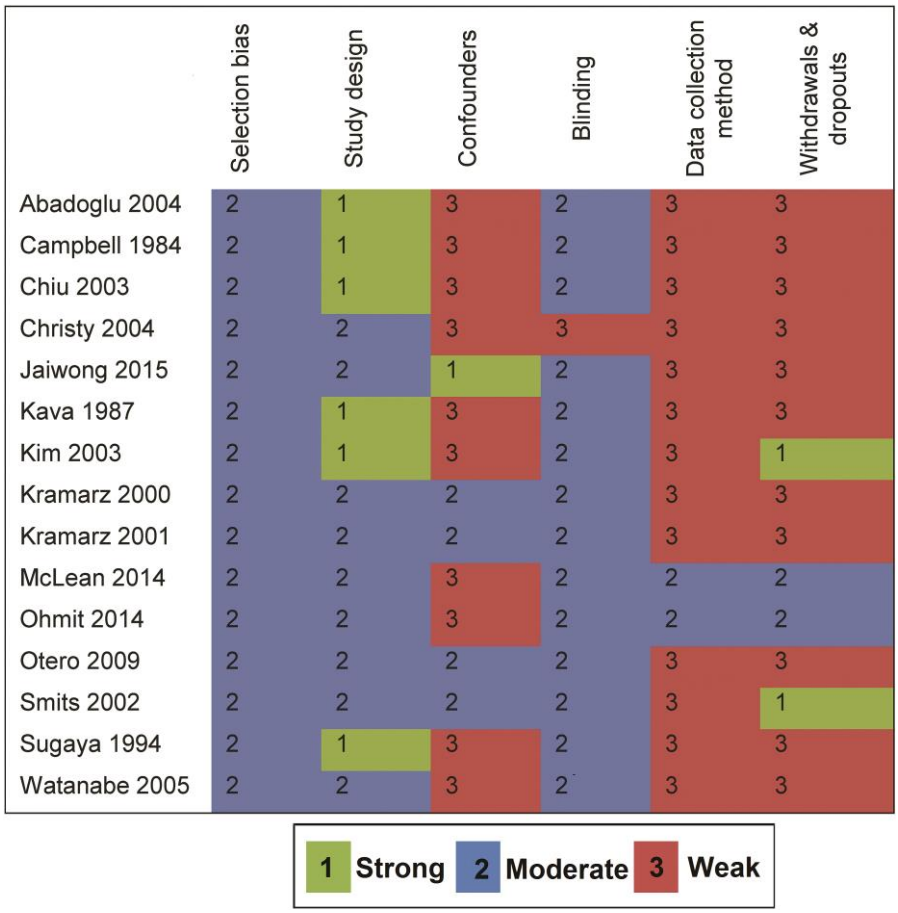

Selection bias
Study design
Confounders
Blinding
Data collection method
Withdrawals & dropouts
Abadoglu 2004 2 1 3 2 3 3
Campbell 1984 2 1 3 2 3 3
Chiu 2003 2 1 3 2 3 3
Christy 2004 2 2 3 3 3 3
Jaiwong 2015 2 2 1 2 3 3
Kava 1987 2 1 3 2 3 3
Kim 2003 2 1 3 2 3 1
Kramarz 2000 2 2 2 2 3 3
Kramarz 2001 2 2 2 2 3 3
McLean 2014 2 2 3 2 2 2
Ohmit 2014 2 2 3 2 2 2
Otero 2009 2 2 2 2 3 3
Smits 2002 2 2 2 2 3 1
Sugaya 1994 2 1 3 2 3 3
Watanabe 2005 2 2 3 2 3 3
1 Strong
2 Moderate
3 Weak

Figure 4

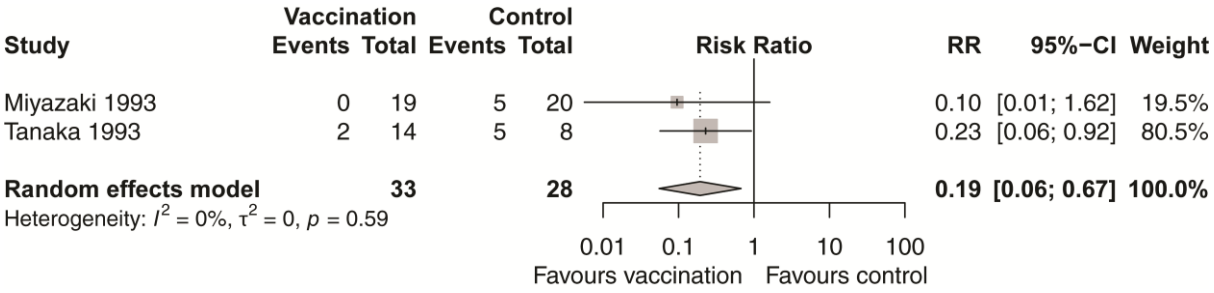

Study
Vaccination Events Total
Control Events Total
Risk Ratio
RR 95%−CI Weight
Miyazaki 1993 0 19 5 20 0.10 [0.01; 1.62] 19.5%
Tanaka 1993 2 14 5 8 0.23 [0.06; 0.92] 80.5%
Random effects model 33 28 0.19 [0.06; 0.67] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.59
0.01 0.1 1 10 100
Favours vaccination
Favours control

Figure 5

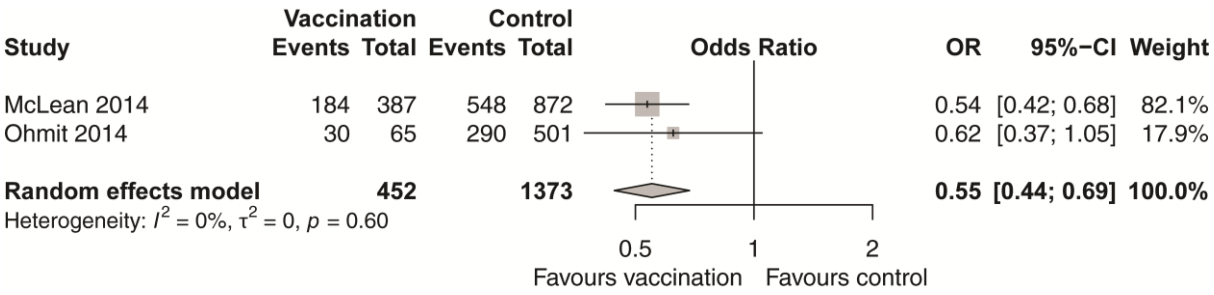
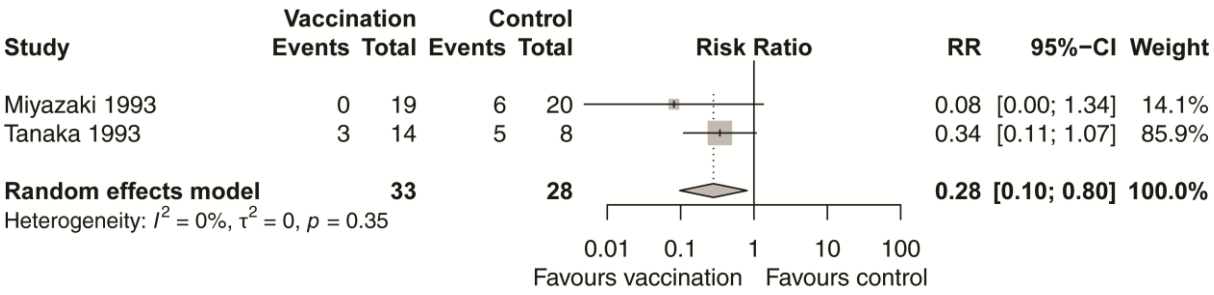

Study
Vaccination Events Total
Control Events Total
Odds Ratio
OR 95%−CI Weight
McLean 2014 184 387 548 872 0.54 [0.42; 0.68] 82.1%
Ohmit 2014 30 65 290 501 0.62 [0.37; 1.05] 17.9%
Random effects model 452 1373 0.55 [0.44; 0.69] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.60
0.5
1
2
Favours vaccination
Favours control

Figure 6


Study
Vaccination Events Total
Control Events Total
Risk Ratio
RR 95%−CI Weight
Miyazaki 1993 0 19 6 20 0.08 [0.00; 1.34] 14.1%
Tanaka 1993 3 14 5 8 0.34 [0.11; 1.07] 85.9%
Random effects model 33 28 0.28 [0.10; 0.80] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.35
0.01 0.1 1 10 100
Favours vaccination
Favours control