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Vaccine Efficacy of Seasonal Inactivated Influenza Vaccine Using in Chinese Children and Adolescent Under 18 Years of Age: A Meta-Analysis

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Abstract

Objective: To evaluate vaccine effectiveness (VE) of seasonal inactivated influenza vaccine (SIIV) in Chinese children and adolescent under18 years of age.

Methods: We searched China National Knowledge Internet (CNKI), Wan Fang Database (WF), PubMed, EMBASE and the Cochrane Library for Chinese and English language articles describing VE of SIIV in Chinese children and adolescent under 18 years of age. Meta-analysis, sensitivity analysis, subgroup analysis and publication bias test were performed using Rev Man software, version 5.1 and STATA statistical software, version 11.0.

Results: A total of 19 studies in 17 papers were included. The overall VE of SIIV for influenza like illness (ILI) was 68% (95%CI: 56-76%) in RCTs while that was 59% (95%CI: 46-68%) in cohort studies. The pooled VE of SIIV for ILI varied by age of subjects (VE=61% in subjects aged ≤ 6 years versus 57% in subjects aged 7-18 years) in cohort studies. The pooled VE of SIIV for ILI varied by vaccine types both in RCTs (VE=71% for domestic vaccine versus 49% for imported vaccine) and cohort studies (VE=53% for domestic vaccine versus 60% for imported vaccine).

Conclusions: SIIV provided good protection from ILI in Chinese children and adolescents aged 0-18 years. More studies of VE on SIIV with larger samples are needed for supporting the subgroup analysis in future.

Keywords: Vaccine efficacy; Seasonal inactivated influenza vaccine; Meta analysis; Children; Adolescents

Introduction

Influenza A and B viruses can cause seasonal influenza through droplets and aerosols originating from the respiratory secretions of patients or infected people. Although the number of influenza associated deaths declines substantially, it has been estimated that the annual incidence rates are 5%-10% in adults and 20%-30% in children worldwide [1]. Children under 5 years of age, and especially those under 2 years of age, have a higher burden of seasonal influenza than other population. A review estimated that there were 90 million new seasonal influenza cases in 2008 (including 28000-111500 deaths) and majority of deaths from influenza occurred in developing countries [2].

Epidemiologic observation has suggested that children have the highest attack rates of influenza. In two studies from the United States [3,4], a substantial excess of hospital admission rates was observed in healthy children. A substantial burden of morbidity and hospital admission for influenza among children below 15 years has been reported in Honk Hong [5]. In Chinese mainland, there was no accurate data on morbidity and mortality on confirmed seasonal influenza, but the incidence of influenza like illness (ILI) was 13.1%-13.7% from 2001 to 2003 [6].

Seasonal Inactivated Influenza Vaccine (SIIV) consists of three strains representing influenza A (H3N2), A (H1N1), and B viruses and it is generally acknowledged that SIIV is one of the most effective ways to prevent seasonal influenza epidemics [7]. Recommendations on SIIV vary in different countries. SIIV is recommended to the people aged ≥ 50 years, healthy children aged 6-23 months, and other high risk groups in United States, while in most other countries SIIV is generally recommended to the people ≥ 65 years or other high risk groups, but not in children1. In China, SIIV is a Category II (parent-pay) vaccine and is currently recommended to the children aged from 6 months to 5 years, elder population over 60 years of age, persons with specific chronic diseases, health-care workers and pregnant women [8].

There were three published reviews on assessing the vaccine efficacy (VE) in health children [9-11]. These quantitative estimates were relatively similar, but their conclusions were inconsistent. One review expressed a skeptical attitude on universal childhood SIIV vaccination, while the other two reviews considered that SIIV vaccination was a possible option for preventing seasonal influenza among healthy children. However, there were relatively few SIIV VE data from China in the international literature.

To provide a comprehensive overview on this issue, a meta-analysis was conducted to assess the VE of SIIV in Chinese children/adolescents less than 18 years of age, and to provide evidence-based data for improving the SIIV immunization strategy.

Methods

Literature search

In order to include all literatures evaluated the VE of SIIV in Chinese children/adolescents under 18 years of age for this study, we searched China National Knowledge Internet (CNKI) (through January, 2015), Wan Fang Database (WF) (from 1980 through January 2015), PubMed (through January 2015), EMBASE (through January 2015) and the Cochrane Library according to the following strategy: (influenza OR flu) AND vaccine* AND (child* OR adolescent* OR young) as key words in the title/abstract. We reviewed reference lists of each article and implemented manual searches in some relevant journals, such as the Chinese Journal of Vaccines and Immunization [in Chinese], Vaccine and Human Vaccines and Immunotherapeutics. We also contacted the corresponding authors for more details if necessary. Studies published only in English or Chinese were included.

Inclusion and exclusion criteria

We included published studies on evaluating the VE of SIIV in healthy Chinese children/adolescents under 18 years of age, and we ignored the type of vaccine (domestic/imported), number of doses, sample size. Prospective studies such as randomized controlled trials (RCT), cohort studies, and other observational studies were included. The exclusion criteria of this analysis included studies of methodology, molecular biology, vaccine development, animal studies, popular science lectures, news articles, and reviews. The studies on the live attenuated influenza vaccine were also excluded. When more than one article was based on a same trail data, only the most recent published report was included. Included studies must have a control group that received a placebo or got vaccination other than SIIV, and it should provide sufficient data to calculate the incidence of ILI or common cold (CC), coverage rate, or relative risks/odds ratios (RR/OR) with 95% confidence interval (CI), respectively.

Data extraction and quality assessment

Every included studies was evaluated separately by two researchers who were blind to resources and authors. The information of the included studies towards authors, year of publication, journal, study design, age of subjects, number of vaccine doses, type of vaccine, number of ILI/CC cases in both vaccination and control group were extracted and entered into a prepared table. The Jadad scale [12], which consists 3 items on randomization, masking and withdrawals/dropouts, was adapted to assessing the methodological quality of RCTs. The range of the Jadad scale is from 0 to 5. RCTs with scores of 0-3 and 4-5 were defined as low and high quality in this analysis, respectively. The Newcastle-Ottawa Scale (NOS) [13], which consists 9 items on sample selection, comparability and outcome, was adopted to assessing the methodological quality of non-randomized studies. The NOS assigns a maximum of nine points to each study. Non-randomized studies with scores of 1-3, 4-6, and 7-9 were defined as low, median, and high quality in this analysis, respectively.

Statistical analysis

The units of this analysis were single comparisons of one treatment versus control group in a influenza season after SIIV vaccination, hence, when more than one treatment was found in a study, every treatment was compared with the relevant control group and included as a separate unit in the meta-analysis. This meta-analysis was also conducted for ILI and CC separately. The $\chi 2$ test was used to evaluate heterogeneity among included studies and we considered a P value <0.10 as being significant. We calculated RR for RCTs and cohort studies while OR for case control studies. Pooled estimates of RR/OR with 95% CI were calculated using random effects models if there was significant heterogeneity among included studies. On the contrary, fixed effects models were adopted. VE was defined as (1-RR) ×100%, and similarly for the OR. Since studies with different design had different strength of evidence, pooled estimates were presented separately. Studies with lower quality were included in the sensitivity analysis. We implemented subgroup analysis using the random effect model to explore reasons of heterogeneity according to the following two factors:

(1) Age of subjects- Persons aged 0-6 years were categorized as group 1 while persons aged 7-18 was categorized as group 2.

(2) Type of vaccine (domestic/imported)- Begg's test and Egger's test was used to evaluate the publication bias.

Meta-analysis, sensitivity analysis, and subgroups analysis were performed by RevMan software, version 5.1. Publication bias evaluations were performed by STATA statistical software, version 11.0.

Results

Literature search results and the characteristics of included studies

A total of 3409 articles were identified from the literature search process. After screening the titles and abstracts, we excluded 3357 articles as they were duplicate or irrelevant. 35 articles were also excluded as they did not provide insufficient data. Finally, 17 articles [14-30], involving 19 studies, were included in this meta-analysis (one article contained three different studies). All the included studies were published in Chinese. All the 19 studies referred to one dose. Of the 19 studies, 3 were RCTs and 16 were cohort studies. Two of the three RCTs included children aged 7 years and the other included adolescents aged 7-12 years. One RCT used domestic SIIV and the others used imported SIIV. Six cohort studies included children aged 0-6 years and the others included adolescents aged 7-18 years. Ten cohort studies used domestic SIIV and the others used imported SIIV (Table 1). All the included RCTs articles were of high quality. Among articles of cohort studies, seven were high quality, six studies were median quality and one study was low quality (Table 2). All studies used only one vaccine type and the following up period lasted for at least one year.

Meta-analysis of VE of SIIV

Among RCTs for ILI, pooled estimates of RR was 0.32(95%CI: 0.24-0.44) and the pooled estimates of VE was 68% (95%CI: 56-76%) (Figure 1). Among cohort studies for ILI, pooled estimates of RR was 0.41 (95%CI: 0.32-0.54) and the pooled estimates of VE was 59% (95%CI: 46-68%) (Figure 2). Among cohort studies for CC, pooled estimates of RR was 0.76 (95%CI: 0.56-1.03) (Figure 3).

Sensitivity analysis

Sensitivity analysis was conducted according to the total NOS score. Through deleted the study with total score of 3, the pooled RR for ILI among the remaining thirteen cohort studies was 0.4 (95% CI: 0.31-0.55) and Z statistic was 6.09 (P<0.00001). The pooled RR for CC among the remaining six cohort studies was 0.79 (95% CI: 0.57-1.10) and Z statistic was 1.38 (P=0.17). The relevant pooled estimates were not substantially different.

Subgroup analysis

In cohort studies, the pooled estimate of RR for ILI was 0.39(95% CI: 0.24-0.64) among persons aged ≤ 6 years and 0.43(95% CI: 0.30-0.61) among persons aged 7-18 years. The pooled estimate of RR for CC was 0.55(95% CI: 0.49-0.62) among persons aged ≤ 6 years and 0.86(95% CI: 0.57-1.29, P=0.47) among persons aged 7-18 years. We did not conduct the subgroup analysis in RCTs as all these studies were implemented among persons aged >6years (Table 3).

In RCTs, the pooled estimate of RR for ILI was 0.29(95% CI: 0.17-0.48) for domestic vaccine while 0.51 (95% CI: 0.40-0.64) for imported vaccine. In the cohort studies, the pooled estimate of RR for ILI was 0.47 (95%

Ref No.	Study No.	First author [Published year]	Journal	Design	Age of subjects	Domestic/ imported	Incidence rate of ILI		Incidence rate of CC	
							Vaccination group	Control group	Vaccination group	Control group
14	1	Jianping Han [2000]	Chinese Journal of Vaccine and Immunization	Cohort study	5 years	Imported	9/662	43/532	236/662	342/532
15	2	Jun Wang [2001]	Chinese Journal of Epidemiology	RCT	7-12 years	Imported	19/200	51/200		
16	3	Xiaohua Xie [2001]	Disease Surveillance	Cohort study	8-13 years	Imported	32/406	53/351	125/406	123/351
17	4	Zhaohu Yuan [2002]	Jiangsu prevention medicine	Cohort study	8 years	Imported	25/2102	93/1820	599/2102	991/1820
18	5	Yan Lin [2003]	Chinese Journal of Urban and Rural Enterprise Hygiene	Cohort study	8-13 years	Imported	79/1054	142/1057	317/1054	330/1057
19	6	Mingxin Guo [2004]	Chinese Journal School Doctor	Cohort study	15 years	Domestic			83/95	64/95
20	7	Ming Liu [2005]	Chinese General Practice	Cohort study	7 years	Domestic	13/308	19/307		
21	8	Ling Liu [2005]	Journal of Nursing Science	RCT	7 years	Imported	9/100	29/100		
22	9	Siyu Chen [2008]	Journal of Medical Theory and Practice	Cohort study	<6 years	Domestic	12/197	19/200		
23	10	Guolin Bian [2010]	Zhejiang prevention medicine	Cohort study	9 years	Imported	10/253	14/308		
24	11	Hua Zhang [2011]	Practical Journal of Cardiac and Vascular Disease	Cohort study	8-13 years	Imported			26/198	16/99
25	12	Xuefeng Liu [2011]	Neimongol Journal of Traditional Chinese Medicine	RCT	7 years	Domestic	16/180	56/180		
26*	13	Yuyan Fan [2012]	Shanxi Medical Journal	Cohort study	< 6 years	Domestic	Mar-54	26/76		
	14	Yuyan Fan [2012]	Shanxi Medical Journal	Cohort study	7-12 years	Domestic	11/121	21/58		
	15	Yuyan Fan [2012]	Shanxi Medical Journal	Cohort study	13-18 years	Domestic	7/112	24/73		
27	16	Tiantian Diao [2012]	Journal of Harbing medical university	Cohort study	< 3 years	Domestic	11/118	23/120	16/118	30/120
28	17	Dong Sun [2013]	Chinese Community Doctor	Cohort study	4 years	Domestic	23/500	63/500		
29	18	Shanshan Zeng [2014]	Chinese Primary Health Care	Cohort study	< 5 years	Domestic	15/273	207/2846		
30	19	Xiaoding He [2014]	Chinese Journal of School Health	Cohort study	14-16 years	Domestic	23/698	9/157		

Table 1: Basic information of studies included in this meta-analysis
*: The article contains more than one study

CI: 0.38-0.58) for domestic vaccine while 0.40 (95% CI: 0.24-0.65) for imported vaccine; the pooled estimate of RR for CC was 0.86 (95% CI: 0.32-2.32, P=0.77) for domestic vaccine while 0.71 (95% CI: 0.53-0.95) for imported vaccine.

Publication bias

Potential publication bias for both two outcomes (ILI and CC) was evaluated by Begg's funnel plot. The Begg' s test results showed no significant publication bias as the P values were 0.174 for ILI and 0.368 for CC, respectively. Similarly, Egger's test results showed no evidence for significant publication bias as the P value was 0.105 for ILI and 0.294 for CC, respectively (Figure 4).

Discussion

The VE is one of most necessary and valuable evidence for formulating the vaccination strategies. As the VE of SIIV varied across different population and areas, implementation of systematic, standard meta-analysis can provide scientific evidence for developing immunization strategy. This meat-analysis involving over 16000 participants aged 0-18 years provided definitive quantitative evidence of SIIV in children and adolescents in China.

Study or Subgroup	Vaccination Events	Vaccination Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jun Wang 2001	19	200	51	200	37.5%	0.37 [0.23, 0.61]
Ling Liu 2005	9	100	29	100	21.3%	0.31 [0.15, 0.62]
Xuefeng Liu 2011	16	180	56	180	41.2%	0.29 [0.17, 0.48]
Total (95% CI)		**480**		**480**	**100.0%**	**0.32 [0.24, 0.44]**
Total events	44		136			

Heterogeneity: Chi² = 0.56, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 7.01 (P < 0.00001)

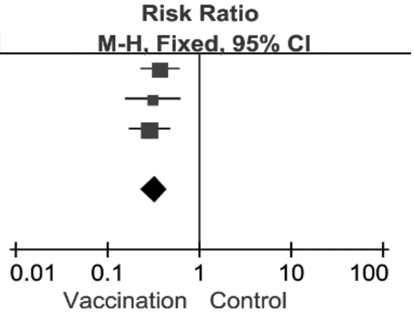

Figure 1: Comparison of VE of SIIV for RCT studies (Outcome: ILI)

Study or Subgroup	Vaccination Events	Vaccination Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Dong Sun 2013	23	500	63	500	8.7%	0.37 [0.23, 0.58]
Guolin Bian 2010	10	253	14	308	5.8%	0.87 [0.39, 1.92]
Jianping Han 2000	9	662	43	532	6.4%	0.17 [0.08, 0.34]
Ming Liu 2005	13	308	19	307	6.6%	0.68 [0.34, 1.36]
Shanshan Zeng 2014	15	273	207	2846	8.2%	0.76 [0.45, 1.26]
Siyu Chen 2008	12	197	19	200	6.5%	0.64 [0.32, 1.29]
Xiaoding He 2014	23	698	9	157	6.1%	0.57 [0.27, 1.22]
Xiaohua Xie 2001	32	406	53	351	9.1%	0.52 [0.34, 0.79]
Yan Lin 2003	79	1054	142	1057	10.5%	0.56 [0.43, 0.72]
Yuyan Fan(1) 2012	3	54	26	76	3.8%	0.16 [0.05, 0.51]
Yuyan Fan(2) 2012	11	121	21	58	6.9%	0.25 [0.13, 0.49]
Yuyan Fan(3) 2012	7	112	24	73	5.8%	0.19 [0.09, 0.42]
Zhaohu Yuan 2002	25	2102	93	1820	8.9%	0.23 [0.15, 0.36]
Tiantian Diao 2012	11	118	23	120	6.7%	0.49 [0.25, 0.95]
Total (95% CI)		**6858**		**8405**	**100.0%**	**0.41 [0.32, 0.54]**
Total events	273		756			

Heterogeneity: Tau² = 0.16; Chi² = 40.38, df = 13 (P = 0.0001); I² = 68%
Test for overall effect: Z = 6.40 (P < 0.00001)

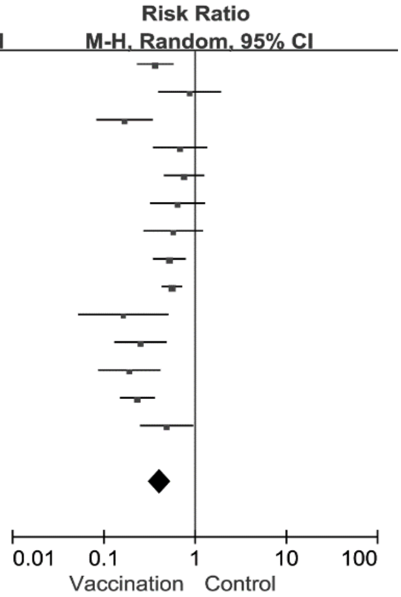

Figure 2: Comparison of VE of SIIV in cohort studies (Outcome: ILI)

Study or Subgroup	Vaccination Events	Vaccination Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hua Zhang 2011	26	198	16	99	10.4%	0.81 [0.46, 1.44]
Jianping Han 2000	236	662	342	532	16.0%	0.55 [0.49, 0.63]
Mingxin Guo 2004	83	95	64	95	15.7%	1.30 [1.11, 1.52]
Tiantian Diao 2012	16	118	30	120	10.7%	0.54 [0.31, 0.94]
Xiaohua Xie 2001	125	406	123	351	15.3%	0.88 [0.72, 1.08]
Yan Lin 2003	317	1054	330	1057	15.9%	0.96 [0.85, 1.10]
Zhaohu Yuan 2002	599	2102	991	1820	16.2%	0.52 [0.48, 0.57]
Total (95% CI)		**4635**		**4074**	**100.0%**	**0.76 [0.56, 1.03]**
Total events	1402		1896			

Heterogeneity: Tau² = 0.15; Chi² = 152.31, df = 6 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.74 (P = 0.08)

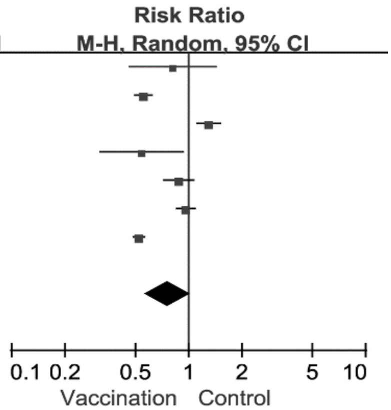

Figure 3: Comparison of VE of SIIVin cohort studies (Outcome: CC)

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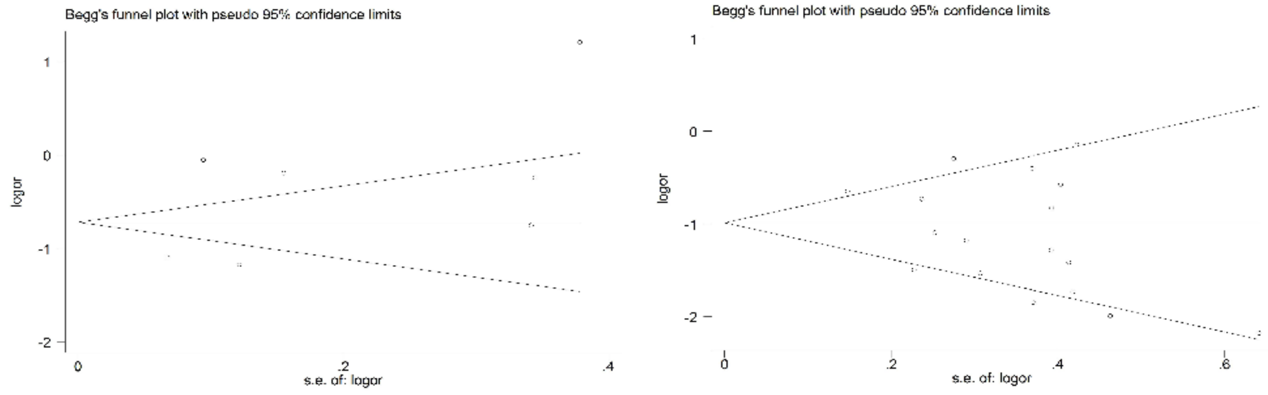

Figure 4: Begg's Funnel plot of included studies of SIIV (outcome: ILI for left figure and CC for right figure)

Study design	Ref No.	First author[Published year]	Randomization	Masking	withdrawals/dropouts	Total score
RCT	2	Jun Wang [2001]	2	2	1	5
	8	Ling Liu [2005]	2	2	1	5
	12	Xuefeng Liu [2011]	2	2	1	5
Study design	**Ref No.**	**First author[Published year]**	**Selection**	**Comparability**	**Outcome/exposure**	**Total score**
Cohort study	1	Jianping Han [2000]	3	2	1	6
	3	Xiaohua Xie [2001]	3	2	2	7
	4	Zhaohu Yuan [2002]	3	2	1	6
	5	Yan Lin [2003]	3	2	3	8
	6	Mingxin Guo [2004]	3	2	2	7
	7	Ming Liu [2005]	3	2	2	7
	9	Siyu Chen [2008]	3	1	2	6
	10	Guolin Bian [2010]	3	2	2	7
	11	Hua Zhang [2011]	2	2	2	6
	13	Yuyan Fan [2012]	3	2	2	7
	14	Tiantian Diao [2012]	2	0	1	3
	15	Dong Sun [2013]	3	1	2	6
	16	Shanshan Zeng [2014]	3	1	2	7
	17	Xiaoding He [2014]	3	1	2	6

Table 2: Results of the quality assessment using the Newcastle-Ottawa Scale (NOS)

Notes: The quality of RCTs was assessed by Jadad scale (the maximum points forrandomization is 2, for masking is 2, for withdrawals/dropouts is 1 and for total score is 9); the quality of cohort studies was assessed by NOS scale (the maximum points for selection is 4, for comparability is 2, for outcome is 3 and for total score is 9).

The VE of SIIV among healthy children had been evaluated by three meta-analysis and the estimates of VE against ILI ranged from 28%-45% [9-11]. Although the estimates of VE of SIIV for ILI were substantially concordant, the authors gave contrasting interpretations due to the relevant methodological issues (outcome definition, criteria of study inclusion or exclusion). The overall estimates of the VE of SIIV in this study were 59% for ILI among RCTs and 68% for ILI among cohort study. The possible reason for difference of VE compared with previous reports was that the pooled estimates were from more trails and subjects than previous reviews. Compared with high VE of other vaccines such as varicella vaccine or measles containing vaccine, the lower VE of SIIV for ILI may be attributed to the fact that many pathogens other than influenza virus may confuse the clinical diagnosis and some of the clinically confirmed cases could not be prevented even by a SIIV even with totally efficacious [31]. Unfortunately, we could not estimate the VE of SIIV for laboratory confirmed cases because these data were not available yet.

Given the wide disparities caused by potential impact factors like study design, settings, age of subjects and other potential impact factors

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Variables	Design	Level	ILI			CC#		
			RR(95% *CI*)	VE(95% *CI*)	Model	RR(95% *CI*)	VE(95% *CI*)	Model
Age of subjects	Cohort study	≤ 6years	0.39(0.24-0.64)	61% (36-76%)	Random	0.55(0.49-0.62)	45% (38-51%)	Fixed
	Cohort study	7-18 years	0.43(0.30-0.61)	57% (39-70%)	Random	0.86(0.57-1.29)	-	Random
Vaccine type	RCT	Domestic*	0.29(0.17-0.48)	71% (52-83%)	-	-		
	RCT	Imported	0.51(0.40-0.64)	49% (36-60%)	Fixed	-		
	Cohort study	Domestic	0.47(0.38-0.58)	53% (42-62%)	Fixed	0.86(0.32-2.32)	-	Random
	Cohort study	Imported	0.40(0.24-0.65)	60% (35-76%)	Random	0.71(0.53-0.95)	29% (5-47%)	Random

Table 3: Results of subgroup analysis on VE of SIIV

#: There was no included RCT study using CC as the outcome; *: Only one study included.

not included in this analysis such as disease causing viral strains or matching of the vaccine to the circulating strains, it would be reasonable that there was a significant heterogeneity among included studies. As the heterogeneity indicated, we carried out the subgroup analysis to explore sources of variation. For example, differences were seen by age of subjects and imported/domestic vaccine. The estimate of pooled VE for persons aged ≤ 6 years was relatively higher than that for persons aged 7-18 years while it had been indicated that the VE was greater in elders than in younger ones [32]. The main reasons for our opposite results may include the waning of immunity, the matching of the vaccine to the circulating strains, and the elder ones vaccinated ≤ 6 years of age without any boost in recent years.

Besides the potential source of heterogeneity like age of population, we conducted additional stratified analysis to assess the type of vaccine on VE estimates of SIIV. The estimate of VE for imported SIIV was lower than that for domestic SIIV in RCTs while the estimate of VE for imported SIIV was higher than that for domestic SIIV in cohort studies. These differences might be due to the differences in study design, production of the vaccines. The results from RCTs would be more stable and reliable that cohort studies in general, but there was only three RCTs included in this analysis, especially only one RCT for domestic vaccine and it was too scanty to allow a meaningful analysis. These findings must be interpreted cautious lyas the included articles in this subgroup was limited. Additional VE study on SIIV using RCT design is needed to make that determination. The above impact factors in our subgroup analysis would have valuable implications in practice and the field work as they were key elements in developing or improving the SIIV vaccination strategy.

There were some limitations in this study. First, the number of articles that fit for the inclusion criteria was limited. Secondly, important information such as laboratory confirmed cases of influenza, the level of matching between the vaccine used and circulating strains could not obtain from the original articles, which would potentially impact the pooled estimates. Finally, most of the included studies in this analysis were cohort studies. Since the evidence level from RCT was stronger than that from cohort study, there was some potential bias as the majority of the included articles were cohort design.

In conclusion, this study indicated that SIIV provided good protection from ILI among Chinese children and adolescents aged less than 18 years. More researches of VE on SIIV with larger samples are needed for supporting the subgroup analysis in future.

Conflict of Interests

The authors declare that they have no competing interests.

Author Contributions

Conceived and designed the study: QL, YH. Literature search: YH, BZ. Data extraction and quality assessment: BZ, YC. Meta-analysis: YH, QL. Wrote the manuscript: QL, YH.

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