

REVIEW

## Effect of a booster dose of influenza vaccine in patients with hemodialysis, peritoneal dialysis and renal transplant recipients: A systematic literature review and meta-analysis

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### ABSTRACT

Booster influenza vaccination has been recommended for patients with chronic renal disease in order to enhance the immune response to the influenza vaccine; however, the efficacy of a booster influenza vaccination is a matter of controversy. Therefore, we made a meta-analysis to determine the efficacy in patients with hemodialysis (HD), peritoneal dialysis (PD) and renal transplant recipient (RT). The sero-protection rate was used as a serologic parameter to describe the immune response to the vaccine. Statistical analysis was performed to calculate the pooled rate difference (RD) and 95% confidence interval (CI). The pooled RD for the H1N1, H3N2 and B influenza vaccines was 0.02 (95% CI: -0.02–0.06), 0.05 (95% CI: -0.01–0.11), 0.04 (95% CI: -0.02–0.10), respectively. We concluded that a booster dose of the influenza vaccine did not effectively enhance immunogenicity. Therefore, a booster dose of vaccine is not recommended for patients with hemodialysis, peritoneal dialysis and renal transplant recipients.

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### KEYWORDS

hemodialysis; influenza vaccine; immunogenicity; meta-analysis; peritoneal dialysis; renal transplant recipient

### Introduction

Influenza leads to a substantial increase in morbidity and mortality each year. Worldwide, influenza infection causes 3–5 million severe illnesses and 250,000–500,000 deaths annually.<sup>1</sup> Patients with chronic renal disease have a higher mortality rate than the general population. Compared with the general population, the annual mortality rate for sepsis is 20-fold higher in transplant recipients and 100 to 300-fold higher in dialysis patients.<sup>2</sup> Because chronic renal disease patients have compromised immunity, they are vulnerable to influenza infection.<sup>3,4</sup> Moreover, influenza infection results in severe complications. Influenza infection is a significant threat to this population of patients. For the above reasons, these patients benefit from prevention of influenza infection more so than the general population.

In healthy people the influenza vaccination is safe and effective, but challenges exist when the influenza vaccine is administered to patients with chronic renal disease. Indeed, it has been reported that the influenza vaccine has weakened efficacy in patients with chronic renal disease.<sup>5</sup> Under such circumstances, many strategies have been proposed to strengthen the immunogenicity of the influenza vaccine; a booster vaccination is one compelling example. Although this measure was implemented in 1987 by Versluis et al.,<sup>6</sup> the anticipated effect has not been clearly established in these patients. The booster vaccination means increasing the influenza antigen supply to patients with chronic renal disease,

which would accelerate depletion of the limited global influenza antigen supply.

The benefit of a booster vaccination has been a matter of controversy in patients with HD, PD and RT. Only a few studies have addressed this issue, and the reliability of the studies was limited because of the small number of patients. A meta-analysis is thus a useful tool to collate the scattered evidence.

In the current study we determined the efficacy of a booster influenza vaccination in patients with chronic renal disease, including patients undergoing hemodialysis, peritoneal dialysis, and kidney transplantation, and verified the clinical benefit of a booster influenza vaccination.

### Results

#### Literature review

Three hundred 3 relevant records were retrieved from the China National Knowledge Infrastructure (CNKI), Pubmed, Cochrane Library, Embase, and ScienceDirect databases. Only nine full text articles were eligible after screening. All of the studies were cohort studies. The quality of all studies was >5 stars. The details of the process are shown in Figure 1.

Three records from Germany collected data during the same season and in the same location.<sup>7–9</sup> We had doubts that the data came from one population. Similarly, 2 records from The Netherlands were based on data collection during the same season and in

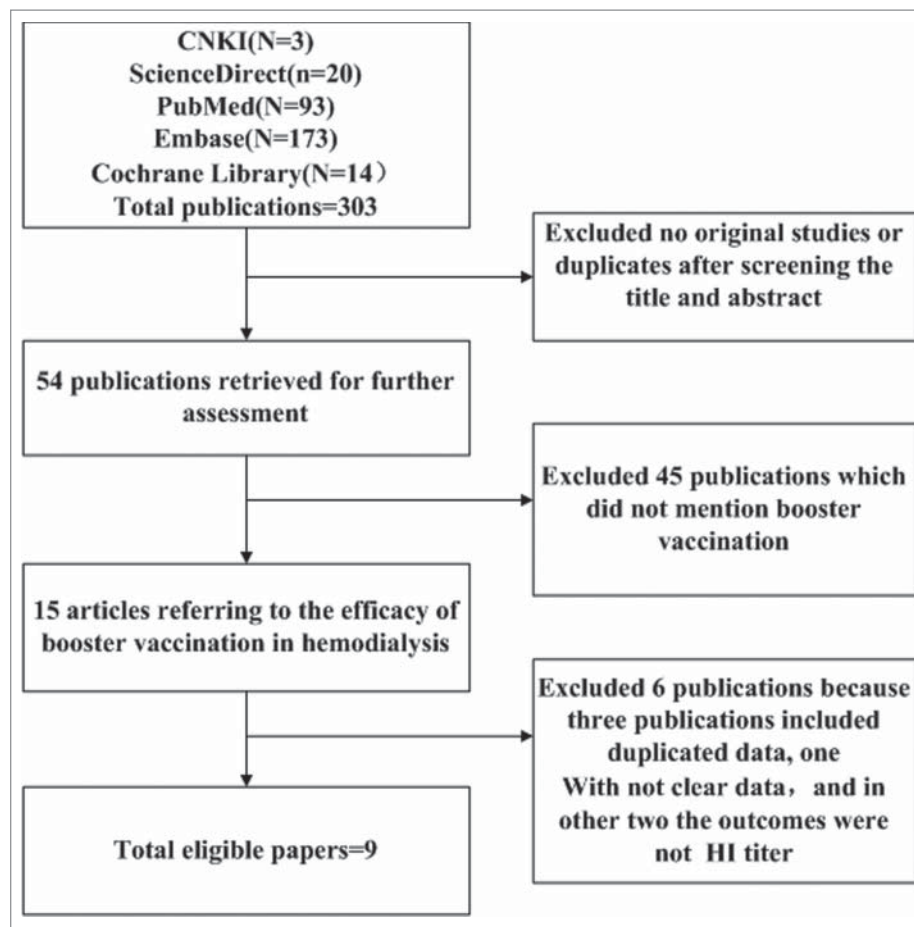


Figure 1. Flow chart of study selection.

the same location.<sup>6,10</sup> Under such conditions, we abstracted information from one study that had the most detailed data to avoid pooling the data from overlapping populations.

### Description of included studies

The eligible publications included 2 from The Netherlands, 2 from Belgium, and one each from Italy, Korea, Spain, Germany,

and France (Table 1). All of the papers were published between 1987 and 2013. Most of the patients who were recruited in the studies were elderly. The exact number of patients could not be derived from the original studies. In only one study was a comparison (first vs. booster vaccination) made between different groups of patients.<sup>11</sup>

The vaccine used in all the studies was monovalent or trivalent, and administered via the intramuscular route

Table 1. Description of characteristics of the included studies.

First Author	year of publication	study year	country	population	Age	F/M	Interval between transplantation and vaccination (years)	Years on dialysis	NOS
Beyer	1987	1985–1986	Netherlands	HD	57(17,76)	55/53	NA	2(0.2,12)	S <sub>2</sub> ;C <sub>2</sub> ;O <sub>3</sub> ;T <sub>7</sub>
Vogtlander	2004	1998–1999	Netherlands	HD	70	22/22	NA	2.7	S <sub>4</sub> ;C <sub>2</sub> ;O <sub>2</sub> ;T <sub>8</sub>
Tanzi	2007	2003–2004	Italy	HD	65.3 ± 13.5	23/35	NA	NA	S <sub>0</sub> ;C <sub>2</sub> ;O <sub>3</sub> ;T <sub>5</sub>
Song	2006	2003–2004	Korea	HD	50.0 ± 6.9	17/23	NA	2.2 ± 1.1	S <sub>4</sub> ;C <sub>1</sub> ;O <sub>2</sub> ;T <sub>7</sub>
				HD_C	48.6 ± 6.7	25/20	NA	1.8 ± 0.8	
Scharpe	2009	2003–2004	Belgium	HD	67 ± 14	79/122	NA	3.83 ± 4.67	S <sub>2</sub> ;C <sub>2</sub> ;O <sub>1</sub> ;T <sub>5</sub>
Scharpe	2008	2003–2004	Belgium	RT	56 ± 13	60/105	6.3(3.1,10.4)	NA	S <sub>3</sub> ;C <sub>2</sub> ;O <sub>3</sub> ;T <sub>8</sub>
Quintana	2013	2009–2010	Spain	HD	59.84 ± 15	24/34	NA	3.83 ± 4.70	S <sub>2</sub> ;C <sub>2</sub> ;O <sub>3</sub> ;T <sub>7</sub>
				PD	55.29 ± 14.72	5/9	NA	2.08 ± 1.1	
				RT	54.04 ± 12.04	26 % 26	6.88 ± 7.28	NA	
Brakemeier	2012	2009–2010	Germany	RT	52.2 ± 15	NA	>=0.5	NA	S <sub>1</sub> ;C <sub>2</sub> ;O <sub>3</sub> ;T <sub>6</sub>
Le Corre	2012	2009–2010	France	RT	50.9(20,64)	32/89	3.4 (0.5,31)	NA	S <sub>2</sub> ;C <sub>2</sub> ;O <sub>3</sub> ;T <sub>7</sub>

Note. HD, hemodialysis; HD\_C, control group who was hemodialysis patient receiving one dose of vaccine;

PD, peritoneal dialysis; RT, renal transplant; F/M, female/male; NA, not available;

NOS, the Newcastle–Ottawa Scale for cohort studies; S<sub>N</sub>, the number of stars for cohort selection section;

C<sub>N</sub>, the number of stars for cohort comparability section; O<sub>N</sub>, the number of stars for cohort outcome section;

T<sub>N</sub>, the total number of stars.

**Table 2.** Information of vaccine used in the eligible studies and the immunogenicity.

First Author	vaccine formation	vaccine strains	dosage (ug)	interval between the first and the boost dose	GMT		
					one dose	booster dose	fold increase in GMT
Beyer	split trivalent vaccine	A/Chile/1/83(H1N1)	15	30 days	NA	NA	NA
		A/Pilippines/2/82(H3N2)	15		NA	NA	NA
		B/USSR/100/83	15		NA	NA	NA
Vogtlander	subunit trivalent vaccine	A/Beijing/262/95(H1N1)	15	56 days	46	53.4	0.16
		A/Sydney/5/97(H3N2)	15		36.4	60.9	0.67
		B/Beijing/184/93	15		46	47.2	0.03
Tanzi	subunit trivalent MF59-adjuvanted vaccine	A/NewCaledonia/20/99 (H1N1)	15	30 days	52	61.5	0.18
		A/Panama/2007/99(H3N2)	15		44	49	0.11
		B/HongKong/330/2001	15		26.3	27.9	0.06
Song	split trivalent vaccine	A/New Caledonia/20/99 (H1N1)	15	28 days	21.54	24.28	0.13
		A/Moscow/10/99 (H3N2)	15		37.13	64.09	0.73
		B/HongKong/330/2001	15		25.62	21.14	0.83
Scharpe (2009)	split trivalent vaccine	A/New Caledonia/20/99 (H1N1)	15	90 days	NA	NA	NA
		A/Panama/2007/99 (H3N2)	15		NA	NA	NA
		B/Shangdong/7/97	15		NA	NA	NA
Scharpe (2008)	split trivalent vaccine	A/New Caledonia/20/99 (H1N1)	15	90 days	NA	NA	NA
		A/Panama/2007/99 (H3N2)	15		NA	NA	NA
		B/Shangdong/7/97	15		NA	NA	NA
Quintana	split monovalent AS03A-adjuvanted vaccine	A%California%7% 2009(H1N1)	3.75	21 days	95.5	124.9	0.31(HD)
					344.5	350.2	0.01(PD)
					31.8	46.5	0.46(RT)
Brakemeier	split monovalent AS03A-adjuvanted vaccine	A%California%7%2009(H1N1)	3.75	21 ± 3.5 days	46.3	67.4	0.46
Le Corre	split monovalent vaccine	A%California%7%2009(H1N1)	15	21 days	47.6	59	0.23

Note. GMT, Geometric Mean Titer; NA, not available.

(Table 2). The formation of influenza vaccine was subunit and split. MF-59 and AS03A adjuvant was applied in 3 studies.<sup>8,12,13</sup> The interval between the first and booster vaccination ranged from 28–90 d. The interval between vaccination and serology was 21–30 d. The dosage of influenza vaccine in 8 eligible studies was 15 µg for each virus strain. In the other 2 studies, the dosage of H1N1 vaccine was 3.75 µg.

### Risk of bias assessment

Several aspects of the study might have caused bias. Booster vaccination might have a distinct influence on patients with different renal conditions. The interval between the first and booster vaccination was different in the eligible studies. Different schedules for booster vaccination may have diverse efficacy. Different formations of the vaccine could produce inconsistent immunogenicity. Age is also a significant factor which affects the immunogenicity of a vaccine. The age of the patients was heterogeneous in different groups. Years on dialysis might have an effect on the immune system. The patients with different years on dialysis might have various humoral responses to the influenza vaccine. Because of possible risk of bias from above sources, subgroup analysis for H1N1 vaccine was performed to determine them. Subgroup analysis showed they did not induce bias (data shown in Table 3).

The efficacy of the booster vaccination could not influence publication because negative and positive results have equal research value. After analysis, all the evidence from funnel plots and the Egger's test showed that there was no publication bias in the meta-analysis (data not shown).

### Efficacy of booster vaccination in patients with HD, PD and RT

Eight hundred eighty-four patients in the current study had detailed information about the immunogenicity of the first dose of the influenza vaccine. For each virus strain of influenza vaccine, a serologic response of approximately 72% of the patients reached sero-protection (HI antibody titer >40). The sero-protection rates in the patients met the Committee for Proprietary Medical Products (CPMP) criteria.<sup>14</sup>

The rate difference (RD) for sero-protection (first vs. booster vaccination) was used to measure the efficacy of an additional dose of the influenza vaccine. The pooled results showed (Fig. 2–4) that the booster vaccination could not significantly increase the sero-protection rate in patients with HD, PD and RT. The pooled RD for the H1N1 vaccine was 0.02 (95% confidence interval (CI): –0.02–0.06). For the H3N2 vaccine, the pooled RD was 0.05 (95% CI: –0.01–0.11). For the B-type influenza vaccine, the pooled RD was 0.04 (95% CI: –0.02–0.10).

In order to better understand the efficacy of booster vaccination in dialysis patients and renal allograft recipients, fold-increase in geometric mean titer (GMT) from pre-booster to post-booster time point was also taken into consideration. The fold-increase in GMT was 0.24(95% CI:0.09–0.39) For the H1N1 vaccine, 0.50(95% CI:0.17–0.84) for the H3N2 vaccine, 0.06(95% CI:–0.07–0.31) for the B-type vaccine.

### Discussion

Our findings showed that a single dose of influenza vaccine induces a sub-optimal immune response, and the effect reaches the CPMP criteria. Thus, a single dose of influenza vaccine is

**Table 3.** Rate difference of Sero-protection (H1N1) by subgroup analysis.

subgroup	number of group	booster dose		one dose		rate difference (95%CI)	Test for subgroup difference (P value)
		events	total	events	total		
overall	12	584	775	652	884	0.02 [-0.02, 0.06]	NA
Renal conditions							
PD	2	30	33	27	33	0.09 [-0.08, 0.26]	0.73
HD	6	290	390	368	497	0.02 [-0.04, 0.07]	
RT	4	264	352	257	354	0.02 [-0.04, 0.08]	
Interval between the first and booster vaccination							
≤30	9	314	464	302	474	0.04 [-0.02, 0.10]	0.27
>30	3	270	311	350	410	0.00 [-0.05, 0.05]	
Formation of vaccine subunit	9	485	628	553	729	0.02 [-0.02, 0.06]	0.67
split	3	99	147	99	155	0.04 [-0.05, 0.14]	
Mean or median age							
≤50	4	148	227	149	234	0.02 [-0.06, 0.10]	0.96
>50	8	436	548	503	650	0.02 [-0.02, 0.07]	
Mean or median years on dialysis							
≤2.5	3	163	204	240	303	0.01 [-0.06, 0.08]	0.66
>2.5	4	143	205	142	213	0.03 [-0.05, 0.12]	

capable of protecting patients with HD, PD and RT from influenza infection. After a booster dose of influenza vaccine was administered to patients, the sero-protection rates increased; however, a booster vaccination did not yield a satisfactory immunopotentiating effect

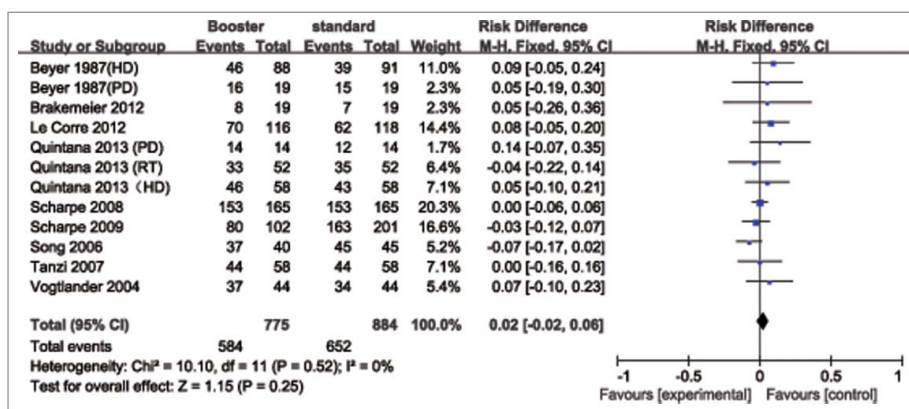
An influenza vaccine is the most cost-effective way to prevent influenza infection. An influenza vaccination can also significantly decrease the number of severe complications and mortality rate. It has been reported that influenza vaccine activity is 70%–90% in healthy populations >65 y of age.<sup>15</sup> Our outcomes showed that influenza vaccine activity was slightly reduced in patients with HD, PD and RT. Therefore, the beneficial effect of influenza vaccine would also be realized in patients with HD, PD and RT.

Booster vaccination has long been recommended to patients with a compromised immune system to improve the level of protection of patients with chronic renal disease; however, our results showed that a booster dose of vaccine was not effective. This finding does not mean that there is no benefit of booster vaccination in other populations. As Gueller et al. reported,<sup>16</sup> after hematopoietic stem cell transplantation, patients benefit from a booster influenza vaccination. The potentiating effect of

a booster dose influenza vaccine was also reported in liver transplant recipients.<sup>17</sup> Additional studies are needed to determine the efficacy of booster vaccination in other populations, such as the very elderly, HIV patients, and patients with autoimmune disease.

The sero-protection rate, mean fold increase in HI antibody titer, and sero-conversion rate are generally used to describe the antibody response to an influenza vaccine. We chose the sero-protection rate as the serologic parameter to measure the immunogenicity of the influenza vaccine because of the public health objectives. HI titer of 40 is generally accepted to represent a 50% protective titer for seasonal influenza A viruses in adult populations. The sero-conversion rate and mean fold increase in HI antibody are only related to the immunologic response and cannot assess the economic effectiveness in a population.

An annual influenza vaccine has been recommended, thus a portion of patients with HD, PD and RT had pre-vaccination antibody to the vaccine antigen. In this study we could not assess the influence of pre-vaccination because of lacking adequate information about the baseline HI titer. One may ponder the effect of the baseline HI titer on assessing the efficacy of a

**Figure 2.** Forest plot of the efficacy of a booster (H1N1) influenza vaccine in patients with HD, PD and RT.



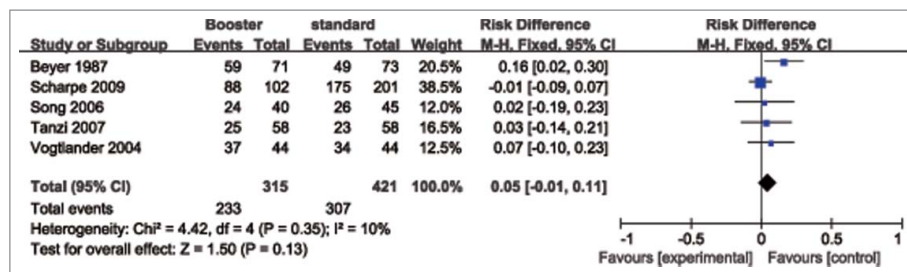


Figure 3. Forest plot of the efficacy of a booster (H3N2) influenza vaccine in patients with HD, PD and RT.

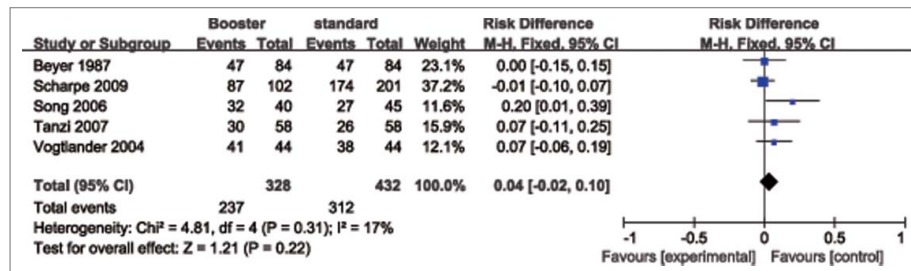


Figure 4. Forest plot of the efficacy of a booster (B-type) influenza vaccine in patients with HD, PD and RT.

booster vaccination; however, the situation that a part of the patients had pre-vaccination was close to an actual real-life situation. One research by Agnieszka Mastalerz-Migas et al. may help us to eliminate above concern.<sup>18</sup> They concluded that although influenza vaccination in previous seasons leads to higher baseline HI titer, it is of little influence on immunoresponse to current influenza immunization in the dialysis patients.

On the basis of our findings, we believe it is not prudent to recommend a booster influenza vaccination in patients with chronic renal disease. A booster dose of influenza vaccine would result in wasting the limited antibody supply. Our findings would reduce an excess dose of influenza vaccine being offered to patients. Although patients with chronic renal disease have impaired immune response to the influenza vaccine, one dose of influenza vaccine is protective. This phenomenon should attract us to further consider whether or not other efforts on improving the immunogenicity of influenza vaccine in patients are cost-effective.

The present meta-analysis had several limitations. Firstly, sero-protection rate did not completely demonstrate the actual effectiveness of booster vaccination. It is a great challenge to directly assess the actual effectiveness because lacking related studies. Sero-protection rate is an indirect parameter to show the actual effectiveness of vaccine, for at least 50% of vaccinees are protected when the HI titer is >40. Second, Subgroup analysis was performed only on the H1N1 vaccine. Without enough information about the other strain vaccine in the included studies, the present data was difficult to be divided into subgroups.

## Conclusion

Although the influenza vaccine had impaired immunogenicity, one dose of influenza vaccine induced an adequate immune response in the patients. A booster dose of the influenza vaccine

did not effectively enhance immunogenicity. Therefore, a booster dose of vaccine is not recommended for in patients with hemodialysis, peritoneal dialysis and renal transplant recipients.

## Methods

### Retrieval strategy and selection criteria

We searched PubMed, Embase, the Cochrane Library, the China National Knowledge Infrastructure, and Science Direct databases for articles published before January 2016. The key words used in the retrieval process were influenza vaccine, influenza vaccination, dialysis, hemodialysis, continuous ambulatory peritoneal dialysis, CAPD, peritoneal dialysis, renal failure, chronic renal failure, chronic kidney disease, chronic renal insufficiency, end stage renal disease, ESRD, and CKD. The articles were independently screened by 2 reviewers (YPL and XJX) in the sequence of title, abstract, and full text. Disagreements were resolved by discussion until consensus was achieved. An eligible study must have met the inclusion criteria, as follows: studies involving patients with chronic renal diseases who received an influenza vaccination; the study outcome was hemagglutination-inhibiting (HI) antibody against influenza virus; a comparison of the immunogenicity of the influenza vaccine was made between the standard and booster vaccination in the same or a different group of patients. The exclusion criteria were as follows: study sample size <5; not clear and original data; and duplicated data.

### Data abstraction and quality assessment

We discussed which data we needed from each article and designed a questionnaire to survey the articles. The extracted information included the following: authors' names; publication year; study design; sample size; age of patients; years on

dialysis; and vaccine type. The outcome that we abstracted from the articles was the sero-protection rate. The sero-protection rate is a percentage of vaccine recipients with a serum HI titer >1:40 after vaccination. A HI titer >1:40 can be viewed as protective in healthy adults.<sup>19</sup> Study quality was assessed using the Newcastle–Ottawa Scale.<sup>20</sup> The full NOS score was 9 stars which consist of 3 stars from section of cohort selection, 4 stars from section of comparability, and 3 stars from section of outcome. At least 2 researchers (XJX, YPL, and ZFL) independently finished extraction and quality assessment after reviewing each article. If there were discrepancies during the abstraction and assessment process between the reviewers, the discrepancies were resolved by discussion.

### Data analysis

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.<sup>21</sup> We pooled the outcomes using the Mantel–Haenszel fixed or random model.<sup>22</sup> Selection of the fixed- or random-effects model depended on the result of the Cochrane's Q test. Heterogeneity was significant when the *p* value of the Cochrane's Q test was >10%.<sup>23</sup> When the heterogeneity was significant, the Mantel–Haenszel random model was used. If not, we preferred the Mantel–Haenszel fixed model. The *I*<sup>2</sup> value indicated the degree of inconsistency among the studies, as follows<sup>24</sup>: <25%, homogeneity; 25%–50%, moderate heterogeneity; 50%–75%, large heterogeneity; and >75%, extreme heterogeneity.<sup>25</sup> Publication bias was assessed through visual inspection of funnel plot asymmetry. Asymmetry was also tested by Egger's linear regression analysis.<sup>26</sup> Statistical analysis was performed using RevMan version 5.2 (provided by the Cochrane Collaboration) and STATA 13 (StataCorp, College Station, TX, USA).

### Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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