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Reappraisal of previously reported meta-analyses on antibiotic prophylaxis in laparoscopic cholecystectomy. A systematic review

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ABSTRACT

Objectives: Many researchers have addressed overdosage and inappropriate antibiotic administration. To reduce unnecessary antibiotic use, many meta-analyses concerning antibiotic prophylaxis for low-risk laparoscopic cholecystectomy have been performed. All of these meta-analyses concluded that prophylactic antibiotics are not required for low-risk laparoscopic cholecystectomies. However, most trials in these meta-analyses had a small sample size and were considered as statistically underpowered for the rare event of postoperative infections in low-risk cholecystectomies. This study aimed to verify this conclusion by a systematic review of these meta-analyses.

Methods: A systematic review was undertaken. Searches were limited to meta-analyses and systematic reviews. Electronic databases were searched from inception until March 2016. The search was performed on PubMed and Cochrane Library databases using the following keyword combinations: “antibiotic prophylaxis”, “laparoscopic cholecystectomy”, “systematic review or meta-analysis”. Two independent reviewers selected meta-analyses or systematic reviews evaluating prophylactic antibiotics for laparoscopic cholecystectomy. All of the randomized controlled trials (RCTs) analyzed in these meta-analyses were also reviewed.

Results: Seven meta-analyses regarding prophylactic antibiotics for low-risk laparoscopic cholecystectomy that included a total of 28 RCTs were included. After reviewing these meta-analyses, 48 miscounts of the number of outcomes were found. Twenty-three of the 48 miscounts were disadvantageous and eight

were advantageous regarding antibiotics, and the remaining 17 showed similar results for antibiotics and controls. Six RCTs were inappropriate for the meta-analyses. One trial targeted patients with acute cholecystitis. Another trial measured insufficient outcomes. The original source of a third trial was not found. The study protocol of the remaining three was not appropriate for the meta-analyses. After correcting the above miscounts and excluding the six inappropriate RCTs, pooled risk ratios were recalculated. Subsequently, we showed the different result that antibiotics significantly reduced the risk of postoperative infections.

Conclusions: Prophylactic antibiotics are effective for elective laparoscopic cholecystectomy to prevent postoperative infectious diseases.

Strengths and limitations of this study

- This is the first study to systematically review and reappraise previously reported meta-analyses.
- Many randomized, controlled trials (RCTs) and meta-analyses concerning prophylactic antibiotic administration have been performed to reduce unnecessary antibiotic use. We reassessed all of these meta-analyses and their related RCTs, and found some issues. After correcting these issues and recalculating the pooled relative risks, we found different results from the original conclusions of these meta-analyses.

- The RCTs that were included in these meta-analyses were performed in many countries, which have different life environments and a different health care system. Therefore, making definitive conclusions for the effects of antibiotic prophylaxis at this time is difficult.

Key words

prophylactic antibiotics, laparoscopic cholecystectomy, randomized controlled trial, meta-analysis, surgical site infection.

INTRODUCTION

Many clinical researchers have addressed the issue of overdosage of antibiotics and inappropriate administration because antibiotic resistance is one of the biggest current threats to global health. Moreover, advanced nations face an increasing healthcare burden with a growing number of the aging population. Under these situations, many randomized, controlled trials (RCTs) concerning prophylactic antibiotic administration for low-risk laparoscopic cholecystectomy have been performed to reduce unnecessary antibiotics use. Additionally, many meta-analyses,[1-7] were performed that analyzed a large number of RCTs,[8-35] and evaluated the role of prophylactic antibiotics for low-risk laparoscopic cholecystectomy. All of these meta-analyses showed no significant difference in the occurrence of postoperative infectious complications, including surgical site infections (SSIs), between the prophylactic antibiotics group and the non-prophylaxis group. Therefore, the conclusion was reached that prophylactic antibiotics are not required for low-risk laparoscopic cholecystectomy. However, most trials in these meta-analyses had a relatively small sample size and were considered as statistically underpowered for the rare event of postoperative infections in low-risk cholecystectomies. Meta-analyses that reviewed RCTs with a small sample size are problematic in that the true occurrence of postoperative infections might be underestimated,[36]. To reassess the results of these meta-analyses, we performed a systematic review of meta-analyses on antibiotic prophylaxis for low-risk laparoscopic cholecystectomy, and also reviewed all of their related RCTs.

METHODS

To reappraise previous published meta-analyses or systematic reviews, searches were performed in PubMed and Cochrane Library databases in March 2016. We used the following keyword combinations: “antibiotic prophylaxis”, “laparoscopic cholecystectomy”, and “systematic review or meta-analysis”. The current systematic review for meta-analyses and systematic reviews was performed following the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines,[37]. The literature search for the meta-analyses and systematic reviews was restricted to articles that were published in the English language. Additionally, all of the RCTs that were analyzed in these meta-analyses were collected and reviewed. The outcomes described in each meta-analysis were compared with the results shown in their original RCTs. Two investigators extracted and reviewed the data independently. Disagreements were resolved by interaction, discussion, and consensus.

The definition of prophylactic antibiotics for our review was antibiotics that were only provided preoperatively, or preoperatively and postoperatively, for prevention of postoperative infectious complications. A low risk of developing postoperative complications was defined as patients undergoing elective laparoscopic cholecystectomy for benign gallbladder diseases, but not for urgent surgery. Meta-analyses and systematic reviews for RCTs comparing antibiotic treatment *versus* placebo or no treatment in patients with a benign gallbladder disease undergoing laparoscopic cholecystectomy were included. Outcomes

that were assessed were occurrence rates of SSI, distant infection, and overall infection.

SSIs were defined as superficial or deep incisional infections or organ/space infections according to the Guideline for Prevention of Surgical Site Infection, 1999,[38]. Distant infections were defined as infections occurring at sites other than the surgical site. Overall infections were defined as the sum of SSIs and distant infections. Some of the meta-analyses did not use the SSI classification defined by the guidelines mentioned above. They classified “wound infections” and “major infections” instead of the SSI classification. In these cases, we rearranged the outcomes according to the SSI classification. Organ/space infections that were included as “major infections” were treated as SSIs and recalculated. Similarly, distant infections that were included as “major infections” were treated as distant infections.

The following data regarding eligible meta-analyses were retrieved: eligibility criteria, information sources, search methods, study selection, data collection process, synthesis of results, number of RCTs included, total number of patients, heterogeneity results, analysis methods used, pooled SSIs, pooled distant infections, pooled overall infections, and conclusions. All of the literatures of RCTs that were analyzed in each meta-analysis was then collected. The following data were retrieved when reported: demographics, study design, eligibility criteria, antibiotic treatment schedule, number of randomized patients,

SSIs, distant infections, and overall infections. The outcomes demonstrated in each meta-analysis were meticulously compared with all of their original RCTs.

Statistical analysis

Standard meta-analysis methods were applied according to the Cochrane Handbook for Systematic Reviews of Interventions,[39] to evaluate the effect of antibiotics on the occurrence of SSIs, distant infections, and overall infections. Data were analyzed on an intention-to-treat basis. When this information was not available, per-protocol data were used. Outcome measures were risk ratios (RRs) with 95% confidence intervals (CIs), weighted by the inverse of their variances. Antibiotic treatment was considered the experimental treatment, and thus RRs are reported as antibiotic/no antibiotic ratios. Consistency of results (effect sizes) among studies was assessed using two standard heterogeneity tests, the chi square test-based Cochran Q test and the I^2 statistic. Inconsistency across studies was considered as low, moderate, and high for I^2 values below 40%, between 30 and 60%, and greater than 50%, respectively, according to the Cochrane Handbook,[39]. Heterogeneity was considered significant when the I^2 value was greater than 50%, the Cochran *Q* test *P* value was less than 0.1, or both. The fixed-effects model and the random-effects model were used to calculate the overall effect. The fixed-effects model was calculated using the Mantel–Haenszel method, and the random-effects model was calculated using the DerSimonian–Laird method. R statistical software (Version 3.1.1) was used for all of the calculations.

RESULTS

The search yielded 18 articles. After exclusions, seven meta-analyses,[1-7] in English regarding prophylactic antibiotics for low-risk laparoscopic cholecystectomy remained (Fig. 1). These meta-analyses were published between January 2003 and January 2016. Table 1 shows the sample sizes, outcomes, and conclusions of the meta-analyses. Of these seven meta-analyses, two studies,[1, 5] did not estimate overall infections. For analysis methods, the fixed-effects model was used in two studies,[4, 5], and the random-effects model in two studies,[2, 7]. The remaining three studies did not mention which model was applied for the final evaluation,[1, 3, 6]. No heterogeneity was found in any of the meta-analyses, except for the overall infections in the most recent meta-analysis,[7]. Of these seven meta-analyses, four studies,[1, 3, 4, 6] did not use the SSI classification. In these cases, the outcomes were rearranged according to the SSI classification as described in the Methods section.

Table 1 Previous meta-analyses regarding prophylactic antibiotics for laparoscopic cholecystectomy.

Published date (No of RCTs included)	Group	Analysis model	Heterogeneity	No. of postoperative infections (%)			OR (95%CI) of the overall infections	Conclusions
				SSIs	Distant infections	Overall infections		
2003[1] (5)	Antibiotics Control	not stated	not significant	9/528 (1.7) 9/371 (2.4)	4/528 (0.8) 6/371 (1.6)	— —	—	Do not support the use of prophylactic antibiotics.
2004[2] (6)	Antibiotics Control	Random effects	not significant	12/567 (2.1) 12/407 (2.9)	4/567 (0.7) 6/407 (1.5)	16/567 (2.8) 18/407 (4.4)	0.69 (0.34 to 1.43)	No need to administer routine antibiotics.
2008[3] (9)	Antibiotics Control	not stated	not significant	15/797 (1.9) 17/640 (2.7)	4/499 (0.8) 6/297 (2.0)	19/797 (2.4) 23/640 (3.6)	0.66 (0.35 to 1.24)	Antibiotics do not prevent infections.
2009[4] (15)	Antibiotics Control	Fixed effects	not significant	25/1465 (1.7) 27/1443 (1.9)	6/613 (1.0) 9/452 (2.0)	31/1465 (2.1) 36/1443 (2.5)	0.77 (0.47 to 1.27)	Antibiotics are unnecessary.
2010[5] (11)	Antibiotics Control	Fixed effects	not significant	24/900 (2.7) 25/764 (3.3)	7/657 (1.1) 10/531 (1.9)	— —	—	No evidence to support or refute antibiotics.
2011[6] (12)	Antibiotics Control	not stated	not significant	25/991 (2.5) 21/946 (2.2)	11/786 (1.4) 11/736 (1.5)	36/991 (3.6) 32/946 (3.4)	1.11 (0.68 to 1.82)	Antibiotics are not necessary.
2016[7] (19)	Antibiotics Control	Random effects	not significant except for overall infections	65/2709 (2.4) 82/2550 (3.2)	28/1488 (1.9) 51/1338 (3.8)	62/1488 (4.2) 96/1338 (7.2)	0.64 (0.36 to 1.14)	Antibiotics should not be administered.

RCT, randomized controlled trial; SSI, surgical site infection; OR, odds ratio; CI, confidence interval; —, not estimated.

Superscript numbers indicate reference numbers.

These seven meta-analyses included a total of 28 RCTs and 7065 patients, and these RCTs were published between 1995 and 2014,[8-35]. The relationship between the RCTs and the meta-analyses is shown in Fig. 2. Of these 28 RCTs, one report of a trial was in Spanish [8] and eight were in Chinese,[14, 15, 17, 18, 20, 23, 24, 27]. All of the trials estimated SSIs, while 12 trials evaluated not only SSIs, but also distant and overall postoperative infections,[9, 10, 13, 15, 21, 24, 26, 27, 29, 32-34]. After reviewing these meta-analyses and all of their related RCTs, the following issues were found.

First, the number of postoperative infections, including SSIs, distant infections, and overall infections, described in each meta-analysis were meticulously compared with the original RCTs. Subsequently, we found a total of 48 simple miscounts of the number of outcomes in six,[2-7] of seven meta-analyses related to 15 RCTs,[9-11, 13, 16, 18-22, 25, 28, 29, 32, 34]. An example of this miscount in outcome is that organ/space infections were not taken account as SSIs in one RCT,[34] in a meta-analysis,[7]. Of these 48 miscounts, 23 were disadvantageous and eight were advantageous regarding antibiotics. The remaining 17 miscounts showed similar results for antibiotics and controls. Details of these miscounts and the relationship between the miscounts and the meta-analyses or the RCTs are shown in supplementary appendix S1.

Second, of the 28 RCTs, six trials were inappropriate for selection in the meta-analyses,[18, 20, 23, 27, 28, 34]. One of the trials targeted patients with

acute cholecystitis instead of low-risk cholecystectomies,[34]. Additionally, all of the patients in both arms in this RCT were administered prophylactic antibiotics. The authors estimated the efficacy of additional postoperative oral antibiotics after prophylactic administration of antibiotics. They did not compare prophylactic antibiotic treatment versus no antibiotic treatment. This RCT had a different study aim and target compared with the other RCTs. A second trial had insufficient endpoints,[28]. This trial did not estimate incisional infections and only estimated organ/space infections. Therefore, this trial could not properly estimate the occurrence of SSIs. In a third trial, its original source was not found, even by an inquiry of the library of the authors' institution for information,[18]. The study protocol of the remaining three trials was different from the other trials,[20, 23, 27]. One of their arms included only postoperative administration of antibiotics. The study arms did not appear to be suitable for prophylaxis. These six RCTs were thought to be inappropriate for these meta-analyses, and were excluded from the current analysis.

After correcting the above-mentioned miscounts and excluding the inappropriate six trials, the pooled RRs and the 95% CIs were recalculated for a total of 5168 patients in 22 RCTs using the fixed-effects and random-effects models. We found that the results were different from the conclusions of previous meta-analyses (Table 2). When using the fixed-effects model, antibiotics significantly reduced all of the risks of postoperative SSIs, distant infections, and overall infections. The forest plot of SSI is shown in Fig. 3. A significant reduction

in distant infections was found with the random-effects model. No heterogeneity was found in SSIs, distant infections, and overall infections. Details of the results of the current meta-analysis are shown in supplementary appendix S2.

Table 2 Reappraisal results of pooled risk ratios of postoperative infections for low risk laparoscopic cholecystectomy.

Postoperative infections	Total No of patients	Fixed-effects model			Random-effects model		
	(No of RCTs)	RR	95%CI	P	RR	95%CI	P
Surgical site infections	5168 (22)	0.71	0.51 to 0.99	0.045	0.75	0.53 to 1.07	0.117
Distant infections	3170 (10)	0.37	0.19 to 0.73	0.004	0.45	0.22 to 0.92	0.028
Overall infections	3170 (10)	0.50	0.34 to 0.75	0.0006	0.63	0.36 to 1.09	0.1

RCT, randomized controlled trial; RR, risk ratio; CI, confidence interval.

DISCUSSION

Currently, administration of prophylactic antibiotics in patients undergoing cholecystectomy for the low-risk group is not recommended. This is because of the modest risk of developing an SSI and costs to the healthcare system. Additionally, there is a global campaign that aims to reduce inappropriate antibiotic administration to tackle the issue of emerging microbial resistance and increasing healthcare costs due to the era of an aging population. However, to date, there is little evidence regarding a reduction in medical costs and microbial resistance after eliminating antibiotic prophylaxis. Although omitting prophylactic antibiotics is thought to lower medical costs, only one RCT has shown medical costs of prophylactic antibiotic administration for low-risk cholecystectomies,[33]. This trial demonstrated that a reduction in cost was unexpectedly achieved by using prophylactic antibiotics, not by sparing antibiotics.

Generally, wide use of prophylactic antibiotics is thought to cause microbial resistance. However, evidence on this issue is not available. Microbial resistance might arise by a long duration of a large amount of therapeutic antibiotic administration rather than by a short course and small amount of prophylactic antibiotic use. When postoperative infection occurs, it requires therapeutic use of antibiotics, which may finally cause microbial resistance. If prophylactic antibiotics can prevent postoperative infections, prophylaxis may reduce microbial resistance by decreasing therapeutic antibiotic administration. Because a prolonged period of antimicrobial therapy contributes to a higher

prevalence of resistance, the optimal antibiotic choice for prophylaxis is required to prevent microbial resistance. There might be bias against “prophylactic” antibiotics because of previous overdosage of “therapeutic” antibiotic agents that have caused microbial resistance.

There are some problems of meta-analyses,[39]. When the results from a meta-analysis have low heterogeneity, the fixed-effects model tends to be used for analysis, while the random-effects model tends to be applied when relatively higher heterogeneity is found. However, knowing in advance whether heterogeneity is low or high is difficult for clinical researchers before beginning the meta-analysis. Therefore, researchers can choose the random-effects model or the fixed-effects model in accordance with their wishes after obtaining the results of their meta-analysis. The random-effects model tends to show no statistical difference between two groups, whereas the fixed-effects model tends to show a statistical difference. If researchers wish to indicate no difference from their meta-analysis, they would choose the random-effects model. However, if they wish to indicate a difference, they would choose the fixed-effects model. In these situations, the researchers’ bias can possibly affect the outcomes of the meta-analysis.

The current reappraisal results showed no heterogeneity and the fixed-effects model showed that prophylactic antibiotics significantly reduced the occurrence of postoperative SSIs, distant infections, and overall infections. Moreover, even

when the random-effects model was used, distant infections were significantly reduced by prophylaxis. Considering these results, we are unable to conclude that prophylactic antibiotics are unnecessary.

In conclusion, although all of the previous meta-analyses concluded that prophylactic antibiotics were unnecessary, no definitive conclusions for the effects of antibiotic prophylaxis on postoperative infections can be made at this time. The effects of antibiotic prophylaxis on medical costs and microbial resistance are also unclear at present. Large-scale, well-conducted RCTs, rather than meta-analyses, regarding prophylactic antibiotics of which outcomes include not only postoperative infections, but also microbial resistance and medical costs, are required in the future. The outcomes of these RCTs should be evaluated without bias.

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Competing interests None declared.

Data sharing statement No additional data are available.

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Figure legends

Fig. 1 Flow diagram of articles included in the systematic review.

Fig. 2 Relationship between randomized controlled trials and meta-analyses.

Fig. 3 Forest plot comparing surgical site infection in patients who underwent elective laparoscopic cholecystectomy with or without antibiotics. The fixed-effects model was calculated using the Mantel–Haenszel method for meta-analysis. Risk ratios are shown with 95% confidence intervals. Superscript numbers indicate reference numbers.

Supplementary appendix

S1 Meta-analyses and their related randomized controlled trials.

S2 Reassessment of data from meta-analyses.

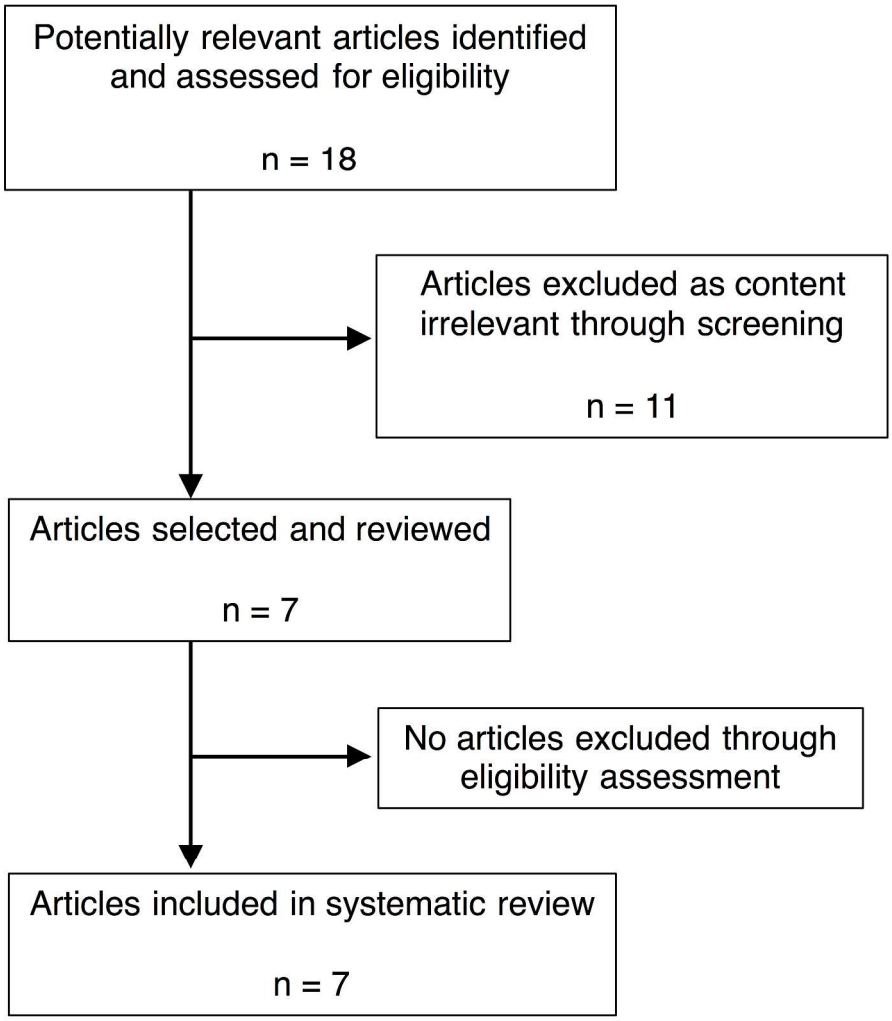

Fig. 1 Flow diagram of articles included in the systematic review.

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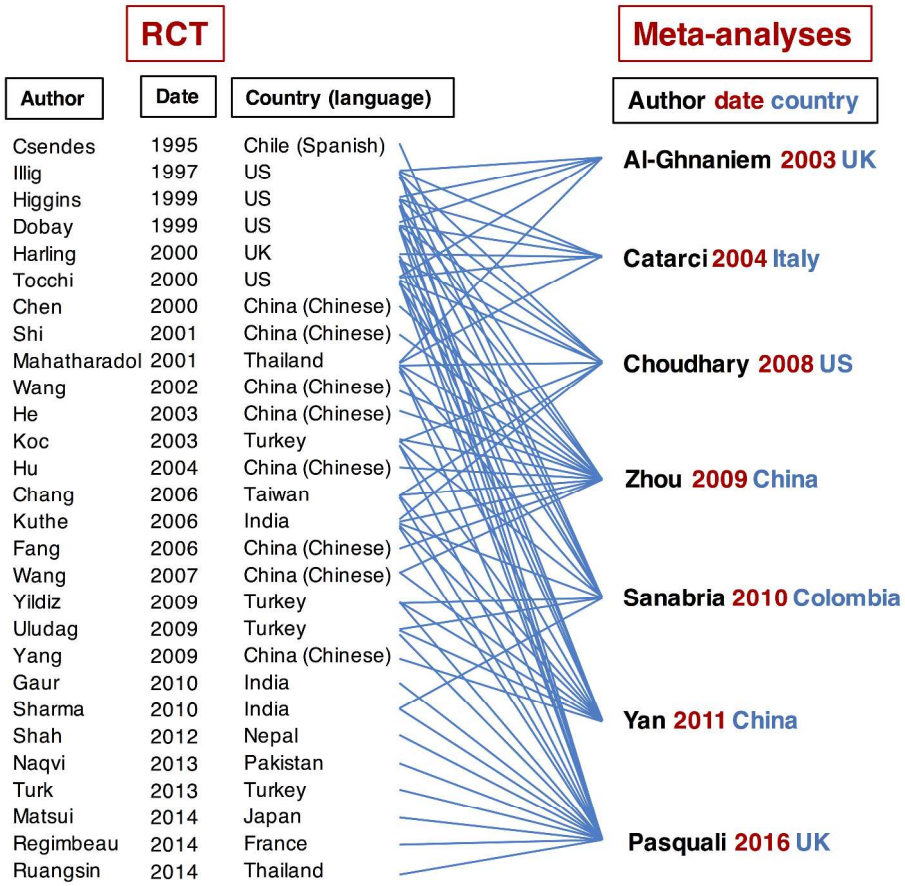

Fig. 2 Relationship between randomized controlled trials and meta-analyses.

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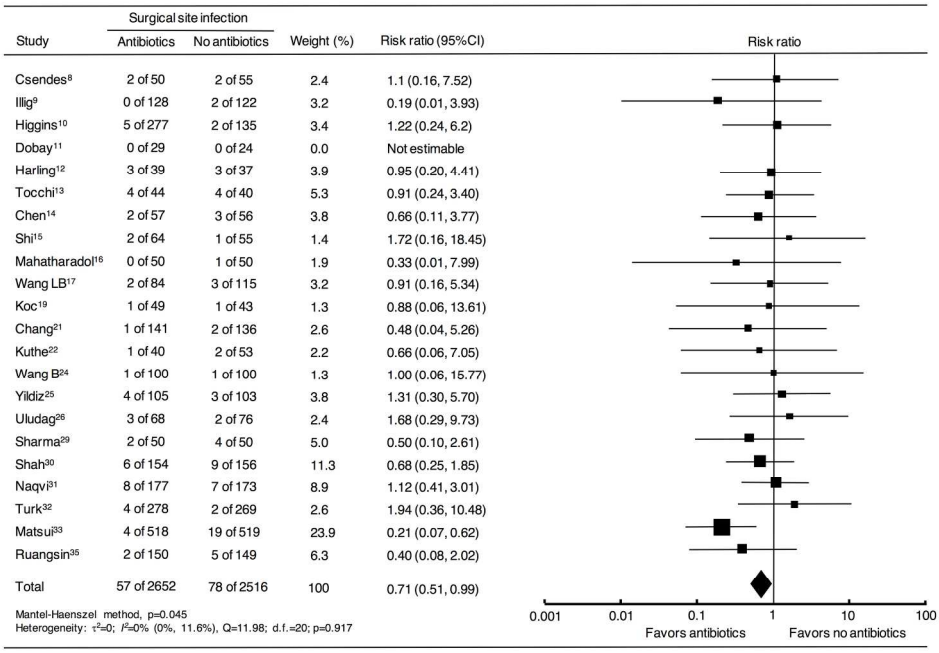

Fig. 3 Forest plot comparing surgical site infection in patients who underwent elective laparoscopic cholecystectomy with or without antibiotics. The fixed-effects model was calculated using the Mantel–Haenszel method for meta-analysis. Risk ratios are shown with 95% confidence intervals. Superscript numbers indicate reference numbers.

209x148mm (300 x 300 DPI)

S1 Appendix. Meta-analyses and their related randomized, controlled trials.

	Meta-analyses				Al-Ghnaniem[1] *Brit J Surg* (2003) UK						Catarci[2] *Surg Endosc* (2004) Italy						Choudhary[3] *J Gastrointest Surg* (2008) US						Zhou[4] *Ailment Pharmacol Ther* (2009) China						Sanabria[5] *Cochrane* (2010) Colombia						Yan[6] *J Laparoendosc Adv Surg Tec* (2011) China						Pasquali[7] *Brit J Surg* (2016) UK						Outcomes after Reappraisal					
	RCTs				SSI		Distant infection		Overall infection		SSI		Distant infection		Overall infection		SSI		Distant infection		Overall infection		SSI		Distant infection		Overall infection		SSI		Distant infection		Overall infection		SSI		Distant infection		Overall infection		SSI		Distant infection		Overall infection		SSI		Distant infection		Overall infection	
	First author	Date	Country	language	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control	Antibiotics	Control
1	Csendes[8]	1995	Chile	Spanish																									2/50	2/55											2/50	2/55						
2	Illig[9]	1997	US	English	0/128	2/122	1/128	2/122			0/128	2/120	1/128	2/120	1/128	4/120							0/128	2/122	1/128	2/122	1/128	4/122	0/128	1/122	1/128	2/122							0/128	1/122	1/128	2/122	1/128	4/122	0/128	2/122	1/128	2/122	1/128	4/122
3	Higgins[10]	1999	US	English	5/277	2/135	2/277	1/135			5/276	2/135	2/276	1/135	7/276	3/135							5/277	2/135	2/277	1/135	7/277	3/135	5/277	2/135	1/277	0/135					Forest plot miscount		5/277	2/135	2/277	1/135	7/277	3/135	5/277	2/135	2/277	1/135	7/277	3/135
4	Dobay[11]	1999	US	English	0/29	0/24					0/29	0/24																													0/24	0/29					0/29	0/24		
5	Harling[12]	2000	UK	English							3/39	3/37																	3/39	3/37											3/39	3/37					3/39	3/37		
6	Tocchi[13]	2000	US	English	4/44	4/40	1/44	3/40			4/44	4/40	1/44	3/40	5/44	7/40							4/44	4/40	1/44	3/40	5/44	7/40	4/44	4/40	1/44	3/40							4/44	4/40	1/44	3/40	5/44	7/40	4/44	4/40	1/44	3/40	5/44	7/40
7	Chen[14]	2000	China	Chinese																			2/57	3/56																			2/57	3/56						
8	Shi[15]	2001	China	Chinese																			2/64	1/55	1/64	2/55	3/64	3/55															2/64	1/55	1/64	2/55	3/64	3/55
9	Mahatharadol[16]	2001	Thailand	English	0/50	1/50					0/51	1/51											0/50	1/50					0/25	1/50	0/50	1/50							0/50	1/50					0/50	1/50				
10	Wang LB[17]	2002	China	Chinese																			2/84	3/115																			2/84	3/115						
#	11 He[18]	2003	China	Chinese																			3/70	2/68																			Original source was not found							
	12 Koc[19]	2003	Turkey	English																			1/49	1/43					1/49	1/43	1/49	1/43									1/49	1/43						
§	13 Hu[20]	2004	China	Chinese																			1/98	1/98																			1/99	1/100						
	14 Chang[21]	2006	Taiwan	English																			1/141	2/136	0/141	0/136	1/141	2/136											Forest plot miscount		1/141	2/136	0/141	0/136	1/141	2/136	1/141	2/136	0/141	0/136	1/141	2/136
	15 Kuthe[22]	2006	India	English													Forest plot miscount						1/40	2/53					1/40	2/53											1/40	2/53						
§	16 Fang[23]	2006	China	Chinese																			2/263	2/372																			2/263	2/372						
	17 Wang B[24]	2007	China	Chinese																			1/100	1/100	1/100	1/100	2/100	2/100															1/100	1/100	1/100	1/100	2/100	2/100		
	18 Yildiz[25]	2009	Turkey	English																									4/105	3/103											4/105	3/103						
	19 Uludag[26]	2009	Turkey	English																									3/68	2/76	4/68	5/76									3/68	2/76	4/68	5/76	7/68	7/76	3/68	2/76	4/68	5/76	7/68	7/76
§	20 Yang[27]	2009	China	Chinese																																							1/49	1/49	3/49	1/49	4/49	2/49		
¶	21 Gaur[28]	2010	India	English																																					5/210	4/203					Number of infections were unclear					
	22 Sharma[29]	2010	India	English																									2/50	4/50	0/50	0/50									2/50	4/50	0/50	0/50	2/50	4/50	2/50	4/50	0/50	0/50	2/50	4/50
	23 Shah[30]	2012	Nepal	English																									2/50	4/50	RCT not estimate		RCT not estimate								6/154	9/156						
	24 Naqvi[31]	2013	Pakistan	English																									6/154	9/156											8/177	7/173						
	25 Turk[32]	2013	Turkey	English																									8/177	7/173											4/278	2/269	RCT not estimate		RCT not estimate		4/278	2/269	0/278	0/269	4/278	2/269
	26 Matsui[33]	2014	Japan	English																									4/278	2/269	RCT not estimate		RCT not estimate								4/518	19/519	2/518	16/519	6/518	35/519	4/518	19/519	2/518	16/519	6/518	35/519
‡	27 Regimbeau[34]	2014	France	English																									4/518	19/519	2/518	16/519	6/518	35/519							13/207	11/207	18/207	24/207	31/207	35/207	21/207	22/207	17/207	23/207	31/207	35/207
	28 Ruangsin[35]	2014	Thailand	English																									13/207	11/207	18/207	24/207	31/207	35/207							2/150	5/149					2/150	5/149		
																	No discription of the number of outcomes. Forest plot only																		No discription of the number of outcomes. Forest plot only													

Superscript numbers indicate reference numbers.

Red numbers indicate that the number of outcomes differed from the number in each original RCT.

Grey cells indicate when each RCT and meta-analysis estimated outcomes.

Yellow cells indicate the miscounts by each meta-analysis that were disadvantageous for antibiotics; **23.**

Blue cells indicate the miscounts by each meta-analysis that were advantageous for antibiotics; **8.**

Green cells indicate the miscounts by each meta-analysis that showed similar results for antibiotics and controls; **17.**

Light blue cells indicate the RCTs that were excluded.

\# Excluded because no original source found.

§ Excluded because of an inappropriate study design.

¶ Excluded because of innappropriate outcomes measures.

‡ Excluded because of a different study aim and target.

S2 Appendix Reassessment of data from meta-analyses.

SSI each study

Studies	RR	95%CI	%W(fixed)	%W(random)
Csendes	1.1000	[0.1609; 7.5194]	2.4%	3.4%
Illig	0.1907	[0.0092; 3.9314]	3.2%	1.4%
Higgins	1.2184	[0.2395; 6.1992]	3.4%	4.7%
Dobay	NA		0.0%	0.0%
Harling	0.9487	[0.2042; 4.4068]	3.9%	5.3%
Tocchi	0.9091	[0.2433; 3.3966]	5.3%	7.2%
Chen	0.6550	[0.1137; 3.7720]	3.8%	4.1%
Shi	1.7188	[0.1601; 18.4460]	1.4%	2.2%
Mahatharadol	0.3333	[0.0139; 7.9896]	1.9%	1.2%
Wang LB	0.9127	[0.1559; 5.3420]	3.2%	4.0%
Koc	0.8776	[0.0566; 13.6094]	1.3%	1.7%
Chang	0.4823	[0.0442; 5.2573]	2.6%	2.2%
Kuthe	0.6625	[0.0622; 7.0523]	2.2%	2.2%
Wang B	1.0000	[0.0634; 15.7669]	1.3%	1.6%
Yildiz	1.3079	[0.3001; 5.7003]	3.8%	5.7%
Uludag	1.6765	[0.2887; 9.7349]	2.4%	4.0%
Sharma	0.5000	[0.0959; 2.6074]	5.0%	4.6%
Shah	0.6753	[0.2463; 1.8518]	11.27	12.21
Naqvi	1.1170	[0.4140; 3.0137]	8.92	12.61
Turk	1.9353	[0.3574; 10.4784]	2.56	4.35
Matsui	0.2109	[0.0723; 0.6158]	23.92	10.82
Ruangsin	0.3973	[0.0783; 2.0160]	6.32	4.71

SSI results

model	RR	95%CI	z	p-value	method
Fixed effect model	0.7095	[0.5070; 0.9927]	-2.0024	0.0452	Mantel-Haenszel
Random effect model	0.7545	[0.5304; 1.0733]	-1.5666	0.1172	DerSimonian-Laird

Quantifying heterogeneity:
tau^2 = 0; H = 1 [1; 1.06]; I^2 = 0% [0%; 11.6%]

Test of heterogeneity:

Q	d.f.	p.value
11.98	20	0.9167

Distant infections each study

Studies	RR	95%CI	%W(fixed)	%W(random)
Illig	0.4766	[0.0438; 5.1886]	6.7%	9.0%
Higgins	0.9747	[0.0892; 10.6550]	4.4%	9.0%
Tocchi	0.3030	[0.0328; 2.7965]	10.3%	10.4%
Shi	0.4297	[0.0400; 4.6115]	7.1%	9.1%
Chang	NA		0.0%	0.0%
Wang B	1.0000	[0.0634; 15.7669]	3.3%	6.8%
Uludag	0.8941	[0.2502; 3.1948]	15.5%	31.7%
Sharma	NA		0.0%	0.0%
Turk	NA		0.0%	0.0%
Matsui	0.1252	[0.0289; 0.5419]	52.6%	24.0%

Distant infections results

model	RR	95%CI	z	p-value	method
Fixed effect model	0.3747	[0.1914; 0.7333]	-2.8654	0.0042	Mantel-Haenszel
Random effect model	0.4475	[0.2185; 0.9168]	-2.1974	0.0280	DerSimonian-Laird

Quantifying heterogeneity:
tau^2 = 0; H = 1 [1; 1.71]; I^2 = 0% [0%; 65.9%]

Test of heterogeneity:

Q	d.f.	p.value
5.13	6	0.5274

Overall infections each study

Studies	RR	95%CI	%W(fixed)	%W(random)
Illig	0.2383	[0.0270; 2.1021]	5.8%	5.4%
Higgins	1.1372	[0.2987; 4.3289]	5.7%	11.0%
Tocchi	0.6494	[0.2239; 1.8832]	10.4%	14.3%
Shi	0.8594	[0.1807; 4.0863]	4.6%	9.0%
Chang	0.4823	[0.0442; 5.2573]	2.9%	4.6%
Wang B	1.0000	[0.1437; 6.9606]	2.8%	6.5%
Uludag	1.1176	[0.4131; 3.0237]	9.4%	15.3%
Sharma	0.5000	[0.0959; 2.6074]	5.7%	8.3%
Turk	1.9353	[0.3574; 10.4784]	2.9%	8.0%
Matsui	0.1718	[0.0729; 0.4049]	49.7%	17.5%

Overall infections results

model	RR	95%CI	z	p-value	method
Fixed effect model	0.5034	[0.3394; 0.7468]	-3.4114	0.0006	Mantel-Haenszel
Random effect model	0.6257	[0.3580; 1.0937]	-1.6455	0.0999	DerSimonian-Laird

Quantifying heterogeneity:
tau^2 = 0.2714; H = 1.25 [1; 1.81]; I^2 = 35.6% [0%; 69.3%]

Test of heterogeneity:

Q	d.f.	p.value
13.98	9	0.1229

209x297mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9-11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, 7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	-
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Reappraisal of previously reported meta-analyses on antibiotic prophylaxis for low-risk laparoscopic cholecystectomy: An overview of systematic reviews

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Primary Subject Heading:	Gastroenterology and hepatology
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Reappraisal of previously reported meta-analyses on antibiotic prophylaxis for low-risk laparoscopic cholecystectomy: An overview of systematic reviews

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ABSTRACT

Introduction: Many researchers have addressed over-dosage and inappropriate use of antibiotics. Many meta-analyses have investigated antibiotic prophylaxis for low-risk laparoscopic cholecystectomy with the aim of reducing unnecessary antibiotic use. Most of these meta-analyses have concluded that prophylactic antibiotics are not required for low-risk laparoscopic cholecystectomies. This study aimed to assess the validity of this conclusion by systematically reviewing these meta-analyses.

Methods: A systematic review was undertaken. Searches were limited to meta-analyses and systematic reviews. PubMed and Cochrane Library electronic databases were searched from inception until March 2016 using the following keyword combinations: “antibiotic prophylaxis”, “laparoscopic cholecystectomy”, and “systematic review or meta-analysis”. Two independent reviewers selected meta-analyses or systematic reviews evaluating prophylactic antibiotics for laparoscopic cholecystectomy. All of the randomized controlled trials (RCTs) analyzed in these meta-analyses were also reviewed.

Results: Seven meta-analyses regarding prophylactic antibiotics for low-risk laparoscopic cholecystectomy that had examined a total of 28 RCTs were included. Reviewing of these meta-analyses revealed 48 miscounts of the number of outcomes. Six RCTs were inappropriate for the meta-analyses; one targeted patients with acute cholecystitis, another measured inappropriate outcomes, the original source of a third was not found, and the study protocols of the remaining three were not appropriate for the meta-analyses. After correcting

the above miscounts and excluding the six inappropriate RCTs, pooled risk ratios were recalculated. These showed that, contrary to what had previously been concluded, antibiotics significantly reduced the risk of postoperative infections. The rates of surgical site, distant, and overall infections were all significantly reduced by antibiotic administration (risk ratio [95% confidence interval]; 0.71 [0.51–0.99], 0.37 [0.19–0.73], 0.50 [0.34–0.75], respectively).

Conclusions: Prophylactic antibiotics reduce the incidence of postoperative infections after elective laparoscopic cholecystectomy.

Strengths and limitations of this study

- This is the first study to systematically review and reappraise previously reported meta-analyses.
- Many randomized, controlled trials (RCTs) and meta-analyses concerning prophylactic antibiotic administration have been performed to reduce unnecessary antibiotic use. We reassessed all of these meta-analyses and their related RCTs.
- We found 48 miscounts of the number of outcomes as well as six RCTs that were inappropriate for selection in the meta-analyses.
- Because the RCTs that were included in these meta-analyses were performed in many countries with different life environments and health care systems, drawing definitive conclusions about the effects of antibiotic prophylaxis is problematic.

Key words

laparoscopic cholecystectomy, meta-analysis, prophylactic antibiotics, randomized controlled trial, surgical site infection, systematic review

INTRODUCTION

Many clinical researchers have addressed the issue of over-dosage of antibiotics and inappropriate administration because antibiotic resistance is one of the biggest current threats to global health. Moreover, developed nations are facing increasing medical costs associated with the aging of the population. Accordingly, many randomized controlled trials (RCTs) concerning prophylactic antibiotic administration for low-risk laparoscopic cholecystectomy have been performed with the aim of reducing unnecessary antibiotic use and thus minimizing antibiotic resistance and controlling increasing medical costs. Additionally, many meta-analyses [1-7] have analyzed a large number of RCTs [8-35] to evaluate the role of prophylactic antibiotics for low-risk laparoscopic cholecystectomy. All of these meta-analyses have found no significant difference in the rate of postoperative infectious complications, including surgical site infections (SSIs), between patients receiving versus not receiving prophylactic antibiotics. It has therefore been concluded that prophylactic antibiotics are not required for low-risk laparoscopic cholecystectomy. However, most trials in these meta-analyses had such small samples that they were considered statistically underpowered for the rare event of postoperative infections after low-risk cholecystectomies. Meta-analyses that reviewed small RCTs are problematic in that the true rates of postoperative infections may have been underestimated [36]. In addition, the most recently published meta-analysis regarding this clinical issue [37] reached a conclusion that was contrary to those of all of the previously published meta-analyses. We therefore performed a systematic review of

meta-analyses on antibiotic prophylaxis for low-risk laparoscopic cholecystectomy to reassess the results of the previously published meta-analyses that concluded no need for antibiotics and to review all of the RCTs examined by them.

METHODS

To reappraise previously published meta-analyses or systematic reviews, PubMed and Cochrane Library databases were searched in March 2016 using the following keyword combinations: “antibiotic prophylaxis”, “laparoscopic cholecystectomy”, and “systematic review or meta-analysis”. The current systematic review for meta-analyses and systematic reviews was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [38]. Only meta-analyses and systematic reviews that were in English were searched. Additionally, all of the RCTs that were analyzed in these meta-analyses were collected and reviewed and the outcomes described in each meta-analysis compared with those reported in their original RCTs. Two investigators extracted and reviewed the data independently. Disagreements were resolved by interaction, discussion, and consensus.

For the present review, prophylactic antibiotics were defined as antibiotics that were provided preoperatively, or preoperatively and postoperatively, for preventing postoperative infectious complications. Patients at low risk of developing postoperative complications were defined as those undergoing

elective laparoscopic cholecystectomy for benign gallbladder diseases and did not include those undergoing urgent surgery. Meta-analyses and systematic reviews of RCTs comparing antibiotic treatment with placebo or no treatment in patients with benign gallbladder diseases undergoing laparoscopic cholecystectomy were included. The outcomes of rates of SSI, distant infection, and overall infection were assessed.

SSIs were defined as superficial or deep incisional infections or organ/space infections according to the Guideline for Prevention of Surgical Site Infection 1999 [39]. Distant infections were defined as infections occurring at sites other than the surgical site. Overall infections were defined as the sum of SSIs and distant infections. Some of the meta-analyses did not use the SSI classification specified in this guidelines but classified infections as “wound infections” or “major infections”. In the present study, these infections were reclassified according to the SSI classification. Organ/space infections that had been reported as “major infections” were treated as SSIs and recalculated. Similarly, distant infections that were reported as “major infections” were treated as distant infections.

The following data regarding eligible meta-analyses were retrieved: eligibility criteria, information sources, search methods, study selection, data collection process, synthesis of results, number of RCTs examined, total number of patients, heterogeneity results, analysis methods used, pooled SSIs, pooled

distant infections, pooled overall infections, and conclusions. All of the original reports of RCTs that were analyzed in each meta-analysis were then collected and the following data retrieved from then when reported: patient characteristics, study design, eligibility criteria, antibiotic treatment schedule, number of randomized patients, SSIs, distant infections, and overall infections. The outcomes used in each meta-analysis were meticulously compared with those reported for their original RCTs.

Statistical analysis

Standard meta-analysis methods were applied according to the Cochrane Handbook for Systematic Reviews of Interventions [40] to evaluate the effect of antibiotics on the incidence of SSIs, distant infections, and overall infections. Data were analyzed on an intention-to-treat basis. When this information was not available, per-protocol data were used. Outcome measures were risk ratios (RRs) with 95% confidence intervals (CIs) weighted by the inverse of their variances. Antibiotic treatment was considered the experimental treatment; thus RRs are reported as antibiotic/no antibiotic ratios. Consistency of results (effect sizes) among studies was assessed using two standard heterogeneity tests, the χ^2 test-based Cochran Q test and the I^2 statistic. Inconsistency across studies was considered as low, moderate and high for I^2 values below 40%, between 30% and 60%, and greater than 50%, respectively, according to the Cochrane Handbook [39]. Heterogeneity was considered significant when the I^2 value was greater than 50%, the Cochran *Q* test *P* value was less than 0.1, or both.

Fixed-effects and random-effects models were used to calculate the overall effect. The fixed-effects model was calculated using the Mantel–Haenszel method and the random-effects model using the DerSimonian–Laird method. R statistical software (Version 3.1.1) was used for all calculations.

RESULTS

The search yielded 18 articles of which 11 were excluded for following reasons; eight had irrelevant contents, two were not in English, and the remaining one was not a meta-analysis or systematic review. Whereas there were no discrepancies between the two observers regarding decisions to include/exclude each meta-analysis, there were two discrepancies regarding decisions to include/exclude each RCT. The reasons for these discrepancies were as follows; One observer had overlooked an inappropriate study design for Reference 23 and inappropriate outcome measures for Reference 28. These discrepancies were resolved by discussion between the two observers. Results of the full search strategy and Kappa statistics are shown in Supplementary Appendixes S1 and S2, respectively.

After exclusions, seven meta-analyses [1-7] in English regarding prophylactic antibiotics for low-risk laparoscopic cholecystectomy remained (Fig. 1), all of which were published between January 2003 and January 2016. Table 1 shows the sample sizes, outcomes and conclusions of these meta-analyses. Two [1, 5] of these seven meta-analyses did not calculate overall incidence of infections.

As to analysis methods, the fixed-effects model was used in two studies [4, 5] and the random-effects model in two studies [2, 7]. The remaining three studies did not mention which model was used for the final evaluation [1, 3, 6]. No heterogeneity was found in any of the meta-analyses except for overall rate of infection in the most recent meta-analysis [7]. Four [1, 3, 4, 6] of these seven meta-analyses did not use the SSI classification. As described in the Methods section, the outcomes in these studies were reclassified according to the SSI classification for the present study.

Table 1. Previous meta-analyses regarding prophylactic antibiotics for laparoscopic cholecystectomy.

Published date (No of RCTs included)	Group	Analysis model	Heterogeneity	No. of postoperative infections (%)			OR (95%CI) of the overall infections	Conclusions
				SSIs	Distant infections	Overall infections		
2003[1] (5)	Antibiotics Control	not stated	not significant	9/528 (1.7) 9/371 (2.4)	4/528 (0.8) 6/371 (1.6)	— —	—	Do not support the use of prophylactic antibiotics.
2004[2] (6)	Antibiotics Control	Random effects	not significant	12/567 (2.1) 12/407 (2.9)	4/567 (0.7) 6/407 (1.5)	16/567 (2.8) 18/407 (4.4)	0.69 (0.34 to 1.43)	No need to administer routine antibiotics.
2008[3] (9)	Antibiotics Control	not stated	not significant	15/797 (1.9) 17/640 (2.7)	4/499 (0.8) 6/297 (2.0)	19/797 (2.4) 23/640 (3.6)	0.66 (0.35 to 1.24)	Antibiotics do not prevent infections.
2009[4] (15)	Antibiotics Control	Fixed effects	not significant	25/1465 (1.7) 27/1443 (1.9)	6/613 (1.0) 9/452 (2.0)	31/1465 (2.1) 36/1443 (2.5)	0.77 (0.47 to 1.27)	Antibiotics are unnecessary.
2010[5] (11)	Antibiotics Control	Fixed effects	not significant	24/900 (2.7) 25/764 (3.3)	7/657 (1.1) 10/531 (1.9)	— —	—	No evidence to support or refute antibiotics.
2011[6] (12)	Antibiotics Control	not stated	not significant	25/991 (2.5) 21/946 (2.2)	11/786 (1.4) 11/736 (1.5)	36/991 (3.6) 32/946 (3.4)	1.11 (0.68 to 1.82)	Antibiotics are not necessary.
2016[7] (19)	Antibiotics Control	Random effects	not significant except for overall infections	65/2709 (2.4) 82/2550 (3.2)	28/1488 (1.9) 51/1338 (3.8)	62/1488 (4.2) 96/1338 (7.2)	0.64 (0.36 to 1.14)	Antibiotics should not be administered.

RCT, randomized controlled trial; SSI, surgical site infection; OR, odds ratio; CI, confidence interval; —, not estimated.

Superscript numbers indicate reference numbers.

These seven meta-analyses included a total of 28 RCTs and 7065 patients; these RCTs were published between 1995 and 2014 [8-35]. The relationships between the RCTs and meta-analyses are shown in Fig. 2. Of these 28 RCTs, one was reported in Spanish [8] and eight in Chinese [14, 15, 17, 18, 20, 23, 24, 27]. All of these trials estimated SSIs and 12 of them also evaluated distant and overall postoperative infections [9, 10, 13, 15, 21, 24, 26, 27, 29, 32-34]. Review of these meta-analyses and all of their related RCTs revealed the following issues.

First, the number of postoperative infections, including SSIs, distant infections and overall infections, reported in each meta-analysis were meticulously compared with those cited in the original RCTs. This comparison revealed 48 simple miscounts of the number of outcomes in six [2-7] of seven meta-analyses that had examined 15 RCTs [9-11, 13, 16, 18-22, 25, 28, 29, 32, 34]. An example of such a miscount in outcome is that organ/space infections were not included as SSIs in one RCT [34] in a meta-analysis [7]. Of these 48 miscounts, 23 were disadvantageous and eight were advantageous regarding antibiotics. The remaining 17 miscounts showed similar results for antibiotics and controls. Details of these miscounts and the relationships between them and the meta-analyses or RCTs are shown in supplementary appendix S3.

Second, six of the 28 RCTs were inappropriate for inclusion in the meta-analyses [18, 20, 23, 27, 28, 34]. One of these six trials targeted patients with acute

cholecystitis rather than low-risk cholecystectomies [34]. Additionally, all of the patients in both arms in this RCT had received prophylactic antibiotics. The authors had investigated the efficacy of additional postoperative oral antibiotics after prophylactic administration of antibiotics rather than comparing prophylactic antibiotic treatment with no antibiotic treatment. This RCT had a different study aim and target than the other RCTs. A second trial had insufficient endpoints [28], having failed to include incisional infections but examined only organ/space infections. The incidence of SSIs could therefore not be accurately extracted from this report. The original source of a third trial was not found, even after requesting information from the library of the authors' institution [18]. The study protocols of the remaining three trials were different from those of the other trials [20, 23, 27]. One of their arms was only postoperative administration of antibiotics; thus, the study arms did not appear to be suitable for prophylaxis. These six RCTs were considered inappropriate for these meta-analyses, which were therefore excluded from the current analysis.

After correcting the above-mentioned miscounts and excluding the six inaccurate trials, the pooled RRs and 95% CIs were recalculated for a total of 5168 patients in 22 RCTs using fixed-effects and random-effects models, yielding results that differed from the conclusions of the original previous meta-analyses (Table 2). According to the fixed-effects model, antibiotics significantly reduced the risks of all three categories of postoperative infection: SSIs, distant infections, and overall infections. A forest plot of for SSI is shown in

Fig. 3. A significant reduction in distant infections was found with the random-effects model. No heterogeneity was found in SSIs, distant infections, or overall infections. Details of the results of the current meta-analysis are shown in supplementary appendix S4.

A funnel plot of the available studies is presented in Fig. 4. Egger's test yielded a p-value of 0.745, indicating there was likely no publication bias. However, the plot did not scatter completely symmetrically, particularly in the lower-right aspect, possibly indicating that small studies reporting negative results have not been published. Results of meta-regression analyses showed no significant differences regarding publication year, publication language, and event rates of antibiotic (SA ratio) and control groups (SC ratio) (supplementary appendix S5). Sensitivity and trial-sequential analyses were not performed because the results of meta-regression analyses indicated no statistical differences in these analyses. Additionally, no correlation analyses were performed because several of the RCTs included had not reported conflicts of interest or funding sources.

Table 2. Results of reappraisal of pooled risk ratios for postoperative infections after low risk laparoscopic cholecystectomy.

Postoperative infections	Total No of patients (No of RCTs)	Fixed-effects model			Random-effects model		
		RR	95%CI	P	RR	95%CI	P
Surgical site infections	5168 (22)	0.71	0.51 to 0.99	0.045	0.75	0.53 to 1.07	0.117
Distant infections	3170 (10)	0.37	0.19 to 0.73	0.004	0.45	0.22 to 0.92	0.028
Overall infections	3170 (10)	0.50	0.34 to 0.75	0.0006	0.63	0.36 to 1.09	0.1

RCT, randomized controlled trial; RR, risk ratio; CI, confidence interval.

DISCUSSION

Currently, administration of prophylactic antibiotics to patients undergoing low-risk cholecystectomy is not recommended because of the modest risk of developing an SSI and healthcare costs. Additionally, there is a global campaign to reduce inappropriate antibiotic administration with the aims of minimizing further development of microbial resistance and the increasing healthcare costs associated with aging of the population. However, to date, there is little evidence regarding reducing medical costs and microbial resistance by eliminating antibiotic prophylaxis. Although omitting prophylactic antibiotics is thought to lower medical costs, only one RCT has reported the medical costs of prophylactic antibiotic administration for low-risk cholecystectomies [33]. This trial unexpectedly demonstrated that reduction in cost was associated with using prophylactic antibiotics rather than withholding them.

Widespread use of prophylactic antibiotics is generally thought to cause microbial resistance. However, there is little evidence to support this. Microbial resistance may be caused by administering large amounts of therapeutic antibiotic for long periods rather than by short courses of small amounts of prophylactic antibiotics. When postoperative infection does occur, it requires therapeutic use of antibiotics, which may result in microbial resistance. If prophylactic antibiotics can prevent postoperative infections, prophylaxis may reduce microbial resistance by reducing administration of antibiotics therapeutically. Because prolonged antimicrobial therapy is associated with a

higher prevalence of resistance, optimal prophylactic antibiotics are required to prevent microbial resistance. Some of the bias against “prophylactic” antibiotics may be attributable to previous over-dosage of “therapeutic” antibiotic agents having resulted in microbial resistance.

There are two possible reasons for our results being contrary to those of past meta-analyses. The first is the correction of 48 miscounts of the number of events in 15 RCTs to strictly accord with the definition of SSIs. The second reason is the exclusion of six inappropriate RCTs. The exclusion of one [34] of these six trials may have greatly influenced the reversal of previous findings because it was relatively large trial and the greatest number of miscounts of this trial were found in the most recent meta-analysis [7] by the current review.

The fixed-effects model is most appropriate when results of a meta-analysis have low heterogeneity, whereas the random-effects model is indicated when there is relatively high heterogeneity [40]. The results of the current reappraisal showed no heterogeneity and the fixed-effects model showed that prophylactic antibiotics significantly reduce the incidence of postoperative SSIs, distant infections, and overall infections. Moreover, even when the random-effects model was used, the incidence of distant infections was found to have been significantly reduced by prophylaxis. Considering these results, we cannot validly conclude that prophylactic antibiotics are unnecessary.

Most of the previous meta-analyses concluded prophylactic antibiotics were unnecessary because there was no significant difference between the two arms. However, the absence of a statistically significant difference does not validly lead to the conclusion that antibiotics are unnecessary, the only valid conclusion is that there is insufficient evidence to support or refute the efficacy of prophylactic antibiotics. Nevertheless, six of seven meta-analyses rejected prophylactic antibiotics, which in turn introduced a bias into the meta-analyses. Rather than meta-analyses, a large-scale, well-conducted RCT regarding the effect of prophylactic antibiotics on incidence of postoperative infections is needed to reach a definitive conclusion. Such an RCT would require a sample size of around 4500 cases with alfa error of 0.5 and power of 0.8, based on an incidence of SSIs of 2.1% (57/2652) in the Antibiotics group versus 3.1% (78/2516), in the Control group, as determined by the current study.

One limitation of this study is such 'super-analysis of analyses' is also open to bias and error because, even in a 'super-analysis', it is impossible to completely remove all bias inherent in the assessed meta-analyses and in their original RCTs. We tried our best to avoid measurement bias by integrating the criteria of the events and precisely recounting the number of events in the meta-analyses and all of the RCTs. In addition, the RCTs that were included in these meta-analyses were performed in many countries with their differing life environments and health care systems. Therefore, drawing definitive conclusions about the effects of antibiotic prophylaxis is problematic.

In conclusion, although all the previous meta-analyses except for the most recent one [37] concluded that prophylactic antibiotics are unnecessary, no definitive conclusions concerning the effects of antibiotic prophylaxis on postoperative infections can validly be drawn as yet. The effects of antibiotic prophylaxis on medical costs and microbial resistance also remain unclear. Large-scale RCTs regarding prophylactic antibiotics that address the outcomes of microbial resistance and medical costs as well as postoperative infections are required in the future. All possible sources of bias should be eliminated in these RCTs.

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Author contributions All authors made substantial contributions to this work. YM, SS, SH and HK all contributed to the conception and design of the review and YM drafted the paper. YM and SS read and screened all retained manuscripts independently. YM, SH, TK and TK rated the quality of the papers. All authors read and approved the final manuscript.

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Competing interests None declared.

Data sharing statement No additional data are available.

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Figure legends

Fig. 1. Flow diagram of articles included in the systematic review.

Fig. 2. Relationships between randomized controlled trials and meta-analyses.

Fig. 3. Forest plot comparing surgical site infection in patients who underwent elective laparoscopic cholecystectomy with or without antibiotics. The fixed-effects model was calculated using the Mantel–Haenszel method for meta-analysis. Risk ratios are shown with 95% confidence intervals. Superscript numbers indicate reference numbers.

Fig. 4. Funnel plot for determination of publication bias.

Supplementary appendix

S1 Results of full search strategy

S2 Kappa statistics

S3 Meta-analyses and their related randomized controlled trials

S4 Reassessment of data from meta-analyses

S5 Results of meta-regression analyses

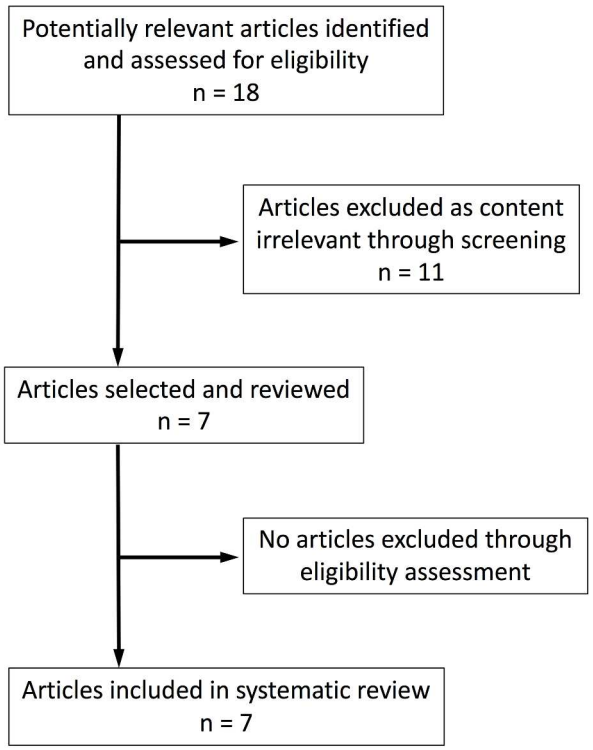

Fig. 1. Flow diagram of articles included in the systematic review.

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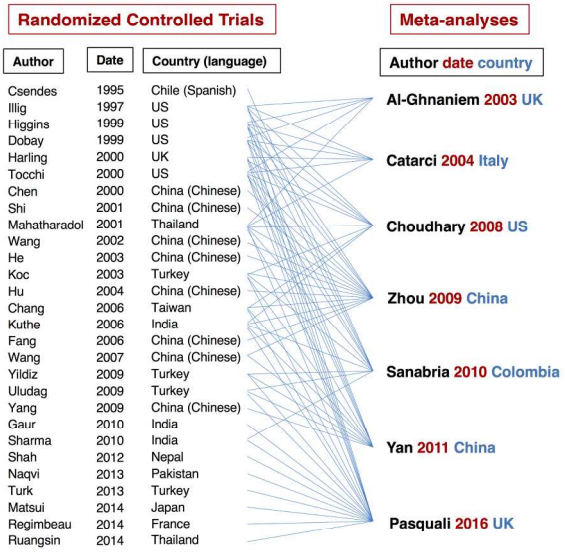

Fig. 2. Relationships between randomized controlled trials and meta-analyses.

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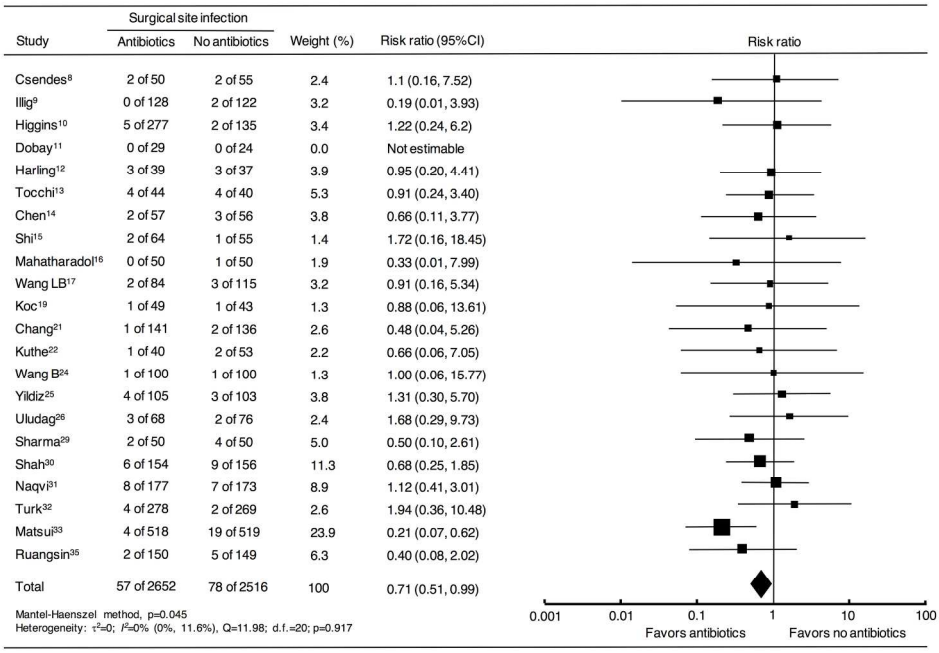

Fig. 3. Forest plot comparing surgical site infection in patients who underwent elective laparoscopic cholecystectomy with or without antibiotics. The fixed-effects model was calculated using the Mantel–Haenszel method for meta-analysis. Risk ratios are shown with 95% confidence intervals. Superscript numbers indicate reference numbers.

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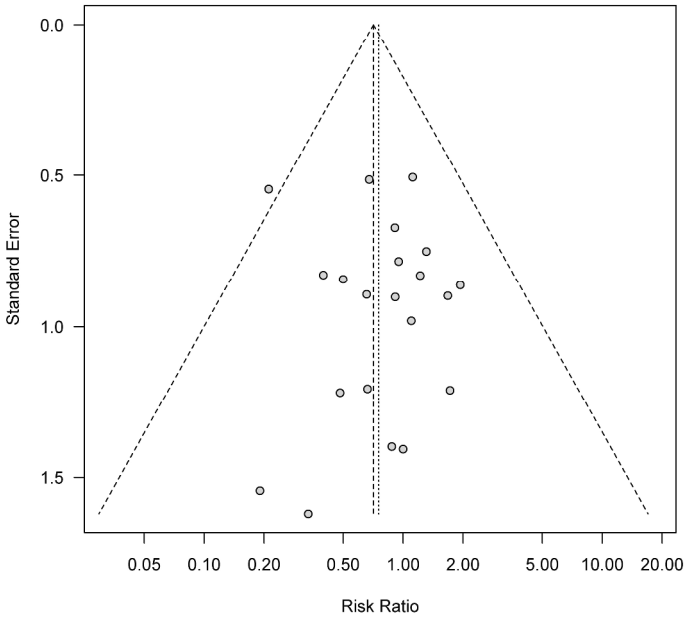

Fig. 4. Funnel plot for determination of publication bias.

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Results of full search strategy

PubMed and Cochrane Library databases were searched in March 2016 using the following keyword combinations: “antibiotic prophylaxis”, “laparoscopic cholecystectomy”, and “systematic review or meta-analysis”. This search yielded the 18 articles listed below.

1. Anthuber M, Schrempf M. Meta-analysis for perioperative antibiotics during laparoscopic cholecystectomy. *Chirurgy* 2016;87:251.
2. Pasquali S, Boal M, Griffiths EA, et al. Meta-analysis of perioperative antibiotics in patients undergoing laparoscopic cholecystectomy. *Brit J Surg* 2016;103:27–34.
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The 11 articles in blue font (1, 3, 8–10, 13–18) were excluded after screening because of inappropriate content.

Reasons for exclusion

Article 1: Not in English
Articles 3, 8–10, 13: Irrelevant content
Article 14: Not a meta-analysis or systematic review
Articles 15, 16: Irrelevant content
Article 17: Not in English
Article 18: Irrelevant content

	Meta-analyses First author	Observer 1	Observer 2
1	Anthuber	exclude	exclude
2	Pasquali	include	include
3	Cochrane	exclude	exclude
4	Yan	include	include
5	Sanabria	include	include
6	Zhou	include	include
7	Choudhary	include	include
8	Gurusamy	exclude	exclude
9	Alexakis	exclude	exclude
10	Goldfaden	exclude	exclude
11	Catarci	include	include
12	Al-Ghnaniem	include	include
13	Shah	exclude	exclude
14	Colizza	exclude	exclude
15	Mandato	exclude	exclude
16	Raraty	exclude	exclude
17	Gondret	exclude	exclude
18	Gouma	exclude	exclude

		Observer 1	
		Agree	Disagree
Observer 2	Agree	7	0
	Disagree	0	11

	RCTs First author	Observer 1	Observer 2
1	Csendes[8]	include	include
2	Illig[9]	include	include
3	Higgins[10]	include	include
4	Dobay[11]	include	include
5	Harling[12]	include	include
6	Tocchi[13]	include	include
7	Chen[14]	include	include
8	Shi[15]	include	include
9	Mahatharadol[16]	include	include
10	Wang LB[17]	include	include
11	He[18]	exclude	exclude
12	Koc[19]	include	include
13	Hu[20]	exclude	include
14	Chang[21]	include	include
15	Kuthe[22]	include	include
16	Fang[23]	exclude	exclude
17	Wang B[24]	include	include
18	Yildiz[25]	include	include
19	Uludag[26]	include	include
20	Yang[27]	exclude	exclude
21	Gaur[28]	exclude	exclude
22	Sharma[29]	include	include
23	Shah[30]	include	include
24	Naqvi[31]	include	include
25	Turk[32]	include	include
26	Matsui[33]	include	include
27	Regimbeau[34]	exclude	include
28	Ruangsin[35]	include	include

Superscript numbers indicate reference numbers.

		Observer 1	
		Agree	Disagree
Observer 2	Agree	22	6
	Disagree	24	4

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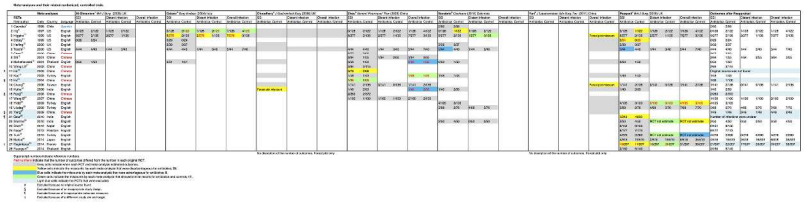


296x209mm (300 x 300 DPI)

Reassessment of data from meta-analyses.

SSI each study

Studies	RR	95%CI	%W(fixed)	%W(random)
Csendes	1.1000	[0.1609; 7.5194]	2.4%	3.4%
Illig	0.1907	[0.0092; 3.9314]	3.2%	1.4%
Higgins	1.2184	[0.2395; 6.1992]	3.4%	4.7%
Dobay	NA		0.0%	0.0%
Harling	0.9487	[0.2042; 4.4068]	3.9%	5.3%
Tocchi	0.9091	[0.2433; 3.3966]	5.3%	7.2%
Chen	0.6550	[0.1137; 3.7720]	3.8%	4.1%
Shi	1.7188	[0.1601; 18.4460]	1.4%	2.2%
Mahatharadol	0.3333	[0.0139; 7.9896]	1.9%	1.2%
Wang LB	0.9127	[0.1559; 5.3420]	3.2%	4.0%
Koc	0.8776	[0.0566; 13.6094]	1.3%	1.7%
Chang	0.4823	[0.0442; 5.2573]	2.6%	2.2%
Kuthe	0.6625	[0.0622; 7.0523]	2.2%	2.2%
Wang B	1.0000	[0.0634; 15.7669]	1.3%	1.6%
Yildiz	1.3079	[0.3001; 5.7003]	3.8%	5.7%
Uludag	1.6765	[0.2887; 9.7349]	2.4%	4.0%
Sharma	0.5000	[0.0959; 2.6074]	5.0%	4.6%
Shah	0.6753	[0.2463; 1.8518]	11.27	12.21
Naqvi	1.1170	[0.4140; 3.0137]	8.92	12.61
Turk	1.9353	[0.3574; 10.4784]	2.56	4.35
Matsui	0.2109	[0.0723; 0.6158]	23.92	10.82
Ruangsin	0.3973	[0.0783; 2.0160]	6.32	4.71

SSI results

model	RR	95%CI	z	p-value	method
Fixed effect model	0.7095	[0.5070; 0.9927]	-2.0024	0.0452	Mantel-Haenszel
Random effect model	0.7545	[0.5304; 1.0733]	-1.5666	0.1172	DerSimonian-Laird

Quantifying heterogeneity:
tau^2 = 0; H = 1 [1; 1.06]; I^2 = 0% [0%; 11.6%]

Test of heterogeneity:

Q	d.f.	p.value
11.98	20	0.9167

Distant infections each study

Studies	RR	95%CI	%W(fixed)	%W(random)
Illig	0.4766	[0.0438; 5.1886]	6.7%	9.0%
Higgins	0.9747	[0.0892; 10.6550]	4.4%	9.0%
Tocchi	0.3030	[0.0328; 2.7965]	10.3%	10.4%
Shi	0.4297	[0.0400; 4.6115]	7.1%	9.1%
Chang	NA		0.0%	0.0%
Wang B	1.0000	[0.0634; 15.7669]	3.3%	6.8%
Uludag	0.8941	[0.2502; 3.1948]	15.5%	31.7%
Sharma	NA		0.0%	0.0%
Turk	NA		0.0%	0.0%
Matsui	0.1252	[0.0289; 0.5419]	52.6%	24.0%

Distant infections results

model	RR	95%CI	z	p-value	method
Fixed effect model	0.3747	[0.1914; 0.7333]	-2.8654	0.0042	Mantel-Haenszel
Random effect model	0.4475	[0.2185; 0.9168]	-2.1974	0.0280	DerSimonian-Laird

Quantifying heterogeneity:
tau^2 = 0; H = 1 [1; 1.71]; I^2 = 0% [0%; 65.9%]

Test of heterogeneity:

Q	d.f.	p.value
5.13	6	0.5274

Overall infections each study

Studies	RR	95%CI	%W(fixed)	%W(random)
Illig	0.2383	[0.0270; 2.1021]	5.8%	5.4%
Higgins	1.1372	[0.2987; 4.3289]	5.7%	11.0%
Tocchi	0.6494	[0.2239; 1.8832]	10.4%	14.3%
Shi	0.8594	[0.1807; 4.0863]	4.6%	9.0%
Chang	0.4823	[0.0442; 5.2573]	2.9%	4.6%
Wang B	1.0000	[0.1437; 6.9606]	2.8%	6.5%
Uludag	1.1176	[0.4131; 3.0237]	9.4%	15.3%
Sharma	0.5000	[0.0959; 2.6074]	5.7%	8.3%
Turk	1.9353	[0.3574; 10.4784]	2.9%	8.0%
Matsui	0.1718	[0.0729; 0.4049]	49.7%	17.5%

Overall infections results

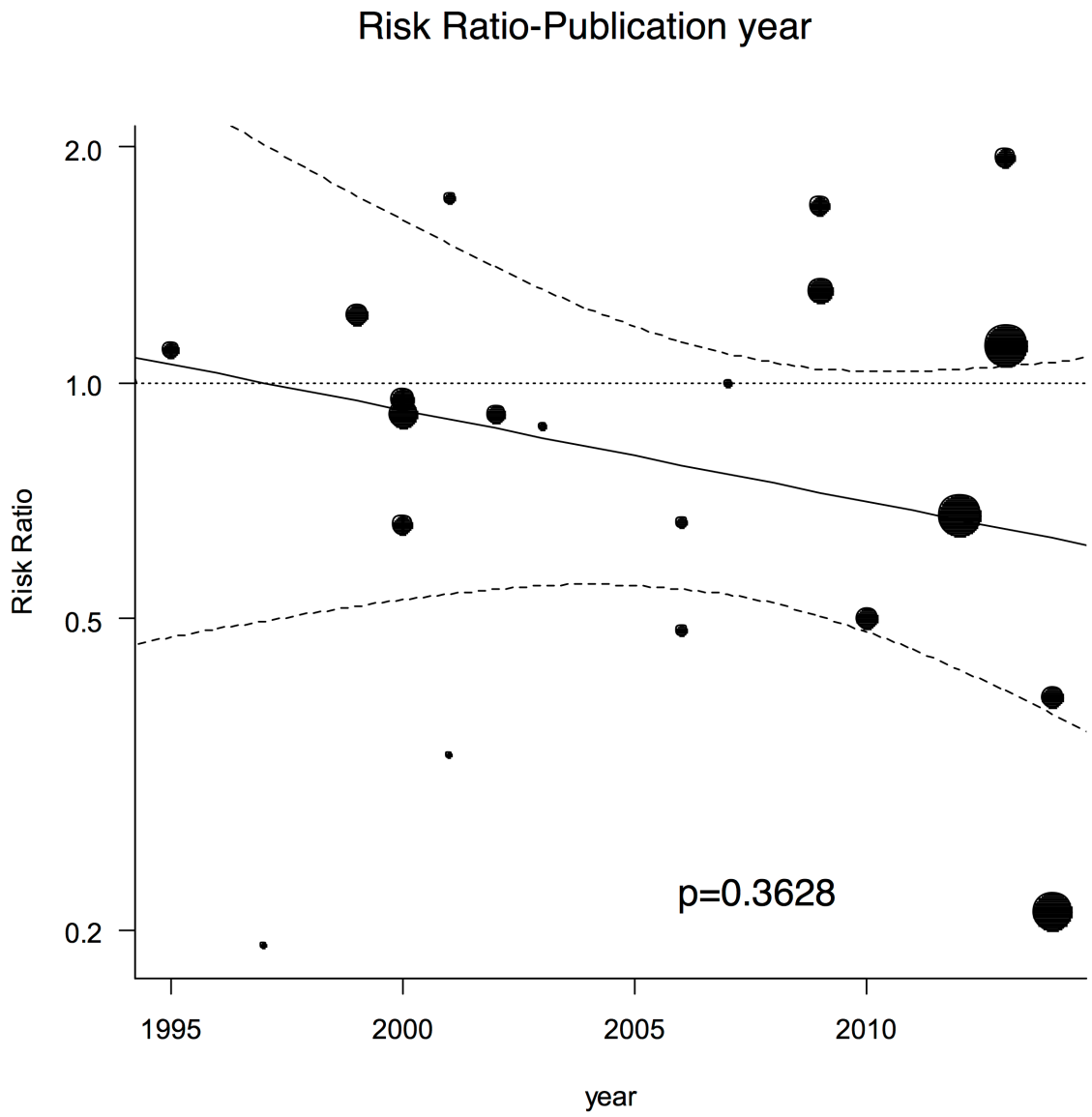
model	RR	95%CI	z	p-value	method
Fixed effect model	0.5034	[0.3394; 0.7468]	-3.4114	0.0006	Mantel-Haenszel
Random effect model	0.6257	[0.3580; 1.0937]	-1.6455	0.0999	DerSimonian-Laird

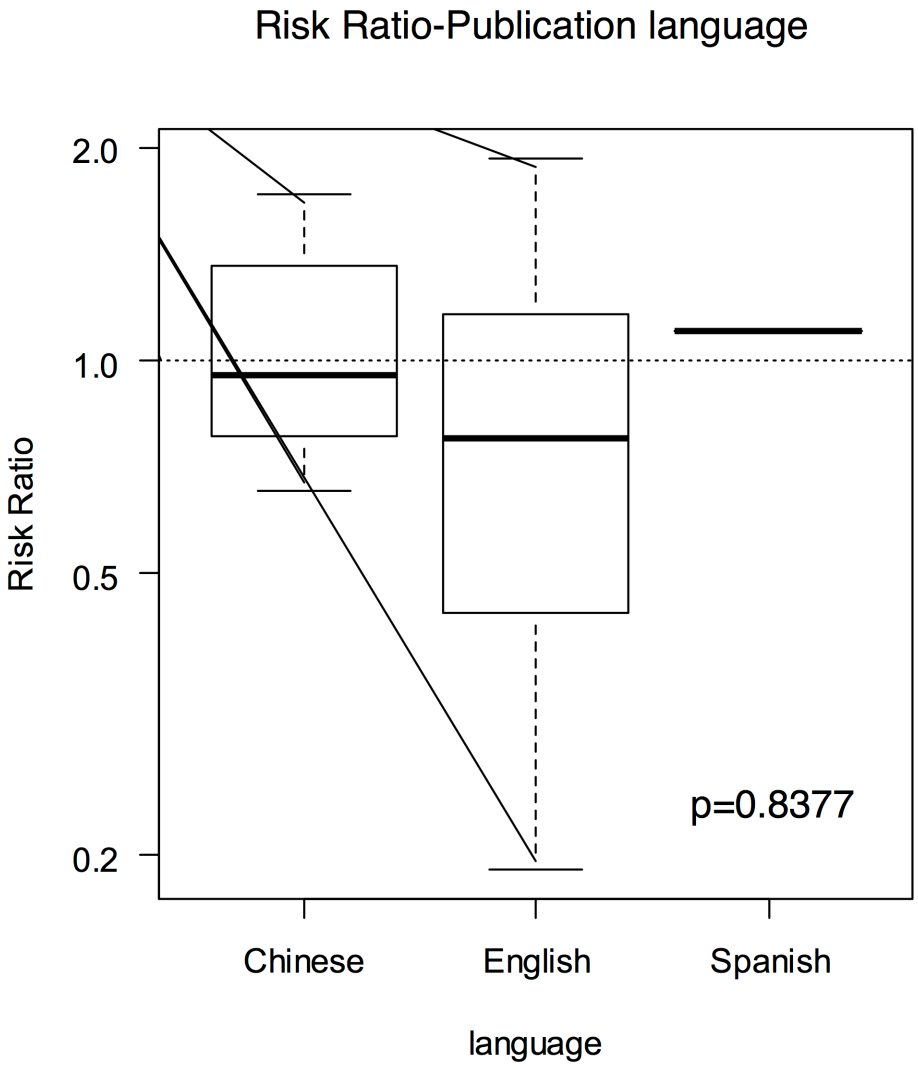
Quantifying heterogeneity:
tau^2 = 0.2714; H = 1.25 [1; 1.81]; I^2 = 35.6% [0%; 69.3%]

Test of heterogeneity:

Q	d.f.	p.value
13.98	9	0.1229

296x420mm (300 x 300 DPI)


Risk Ratio-Publication year
Risk Ratio
2.0
1.0
0.5
0.2
p=0.3628
1995
2000
2005
2010
year


Risk Ratio-Publication language
2.0
1.0
0.5
0.2
Risk Ratio
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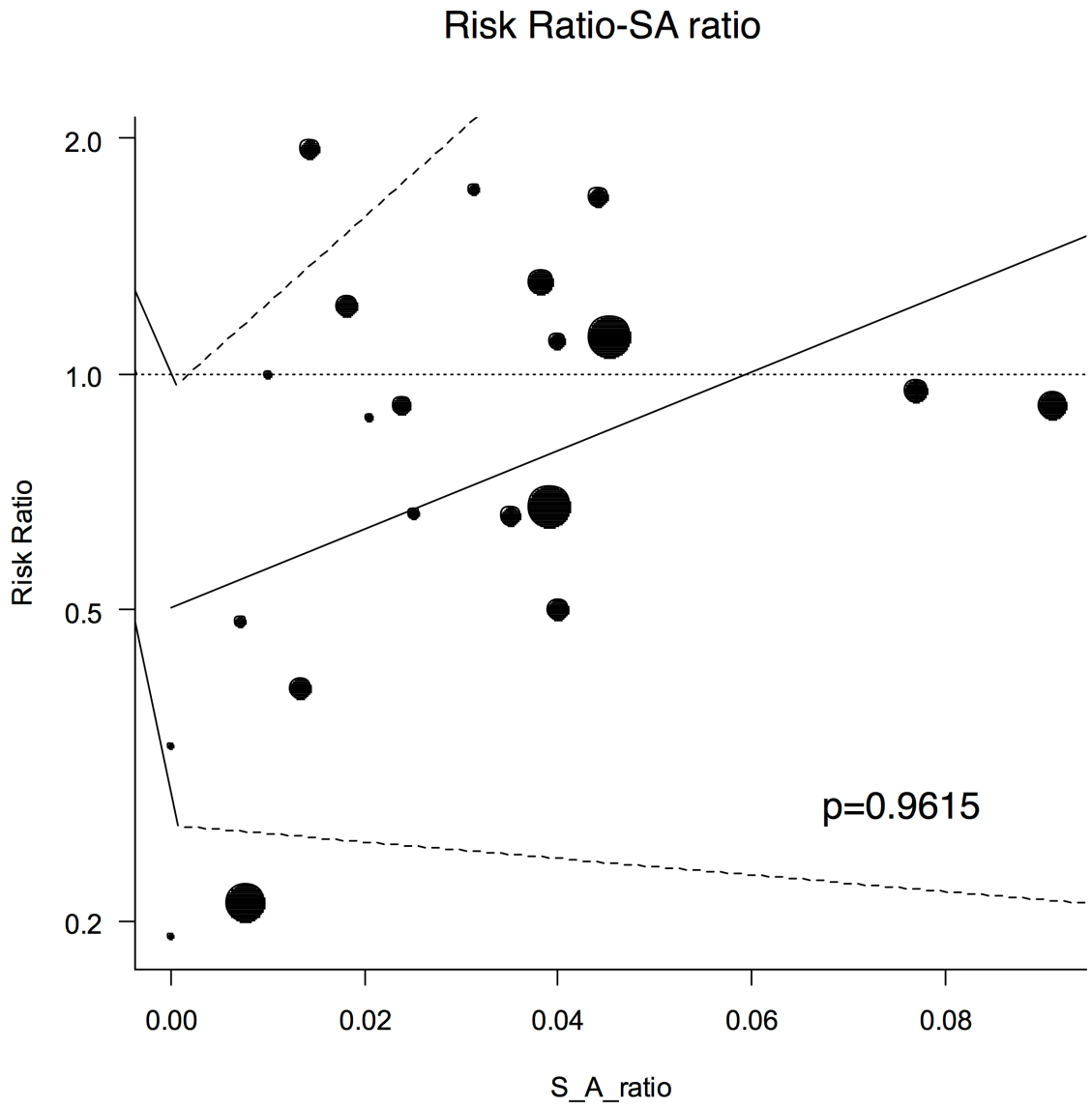
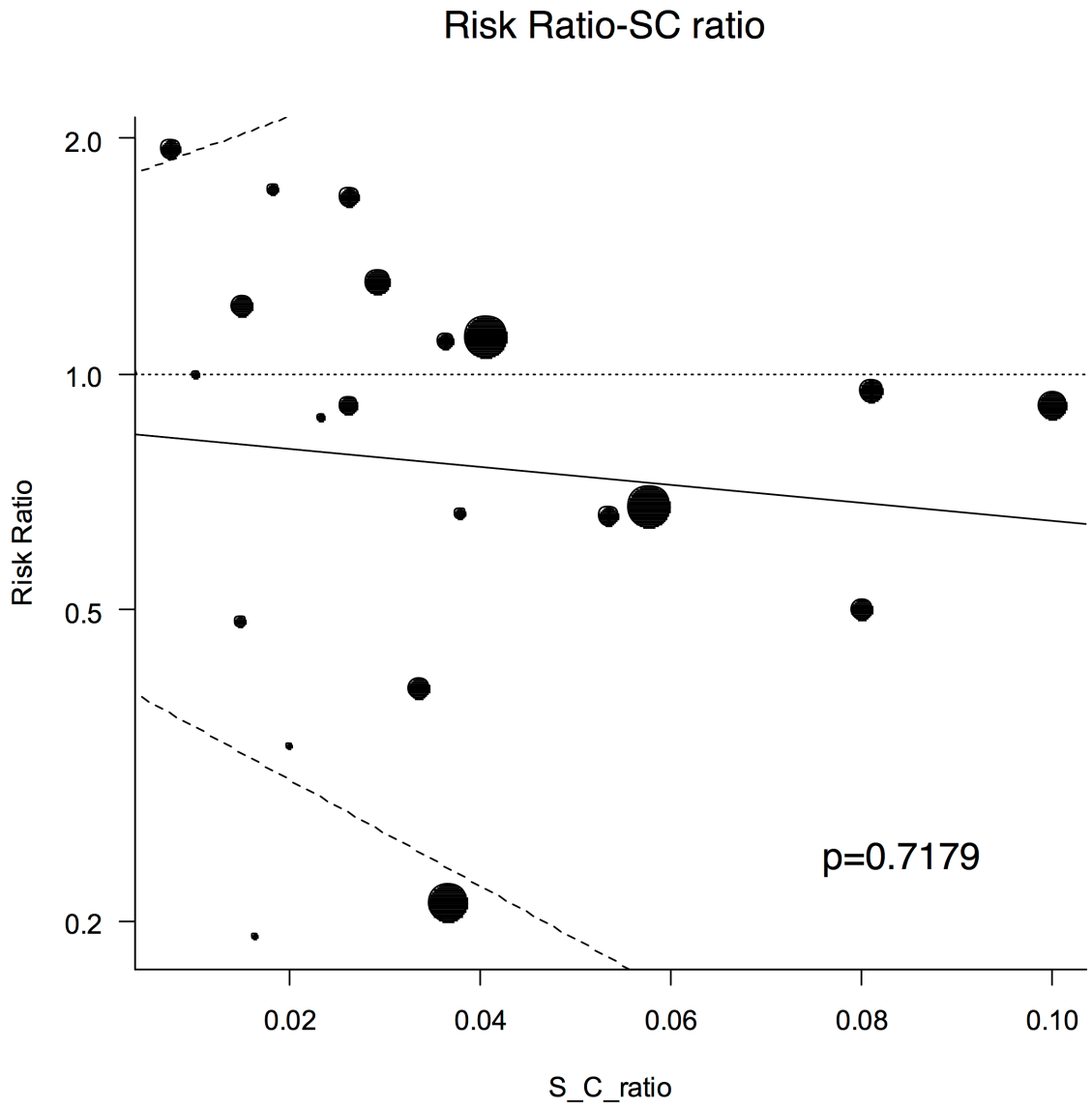
Chinese
English
Spanish
language


Risk Ratio-SA ratio
2.0
1.0
0.5
0.2
Risk Ratio
0.00
0.02
0.04
0.06
0.08
S_A_ratio
p=0.9615


Risk Ratio-SC ratio
Risk Ratio
2.0
1.0
0.5
0.2
0.02
0.04
0.06
0.08
0.10
S_C_ratio
p=0.7179

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5,6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5,6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6, S1, S2, S3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6-8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, S1, S2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, S1, S2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8,9, S5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8,9, S5

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8,9, S4

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8,9, S5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	S5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Fig1, S1, S2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-11, S3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14, S5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-14, Fig4, S5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14, S5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-15, S3, S4, S5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18,19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18,19
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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