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Review Article

# Antibiotic prevention of postcataract endophthalmitis: a systematic review and meta-analysis

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## ABSTRACT.

Endophthalmitis is one of the most feared complications after cataract surgery. The aim of this systematic review was to evaluate the effect of intracameral and topical antibiotics on the prevention of endophthalmitis after cataract surgery. A systematic literature review in the MEDLINE, CINAHL, Cochrane Library and EMBASE databases revealed one randomized trial and 17 observational studies concerning the prophylactic effect of intracameral antibiotic administration on the rate of endophthalmitis after cataract surgery. The effect of topical antibiotics on endophthalmitis rate was reported by one randomized trial and one observational study. The quality and design of the included studies were analysed using the Cochrane risk of bias tool. The quality of the evidence was evaluated using the GRADE approach. We found high-to-moderate quality evidence for a marked reduction in the risk of endophthalmitis with the use of intracameral antibiotic administration of cefazolin, cefuroxime and moxifloxacin, whereas no effect was found with the use of topical antibiotics or intracameral vancomycin. Endophthalmitis occurred on average in one of 2855 surgeries when intracameral antibiotics were used compared to one of 485 surgeries when intracameral antibiotics were not used. The relative risk (95% CI) of endophthalmitis was reduced to 0.12 (0.08; 0.18) when intracameral antibiotics were used. The difference was highly significant ( $p < 0.00001$ ). Intracameral antibiotic therapy is the best choice for preventing endophthalmitis after cataract surgery. We did not find evidence to conclude that topical antibiotic therapy prevents endophthalmitis.

**Key words:** antibiotic therapy – cataract surgery – cefuroxime – endophthalmitis – prevention

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## Introduction

Cataract surgery is the most frequently performed elective surgical procedure in many Westernized countries. Although cataract surgery is generally considered a safe procedure resulting in a favourable visual outcome, surgical complications do occur. The most feared complication is postoperative endophthalmitis which is an infectious condition caused by micro-organisms introduced to the interior of the eye during or after the surgical procedure. The visual outcome after endophthalmitis is often very poor. Seventeen per cent of patients in the European Society of Cataract and Refractive Surgeons (ESCRS) study had a final visual acuity  $\leq 20/200$  and 48.3% had a final visual acuity  $\leq 20/40$  (Barry et al. 2009). Treatment of endophthalmitis often requires further surgery and hospitalization; thus, every case of endophthalmitis puts a heavy burden on the healthcare system (Fongsre et al. 2004; Schmier et al. 2007), not to mention the distress and loss of quality of life experienced by the patient (Clark et al. 2008).

During cataract surgery, an incision is made in the anterior segment of the eye to remove the cataractous lens. Corneal incisions may allow inflow of ocular surface fluid even after hydrosealing (Herretes et al. 2005). The use

of clear corneal incisions has been found to be a risk factor for endophthalmitis (Cao et al. 2013), but the evidence is not conclusive (Lundstrom 2006). Microbiological examinations have shown that the rate of contamination of the surgical fluids is high (up to 50%) in spite of preoperative cleaning of the conjunctiva with povidone-iodine and preoperative use of topical antibiotic (Balestrazzi et al. 2012). The rate of positive samples from the anterior chamber is usually <5% (Parmar et al. 2006; Cornut et al. 2010; Baillif et al. 2012; Kumar et al. 2012) but has been reported to be as high as 14% (Das et al. 2009). The rate of anterior chamber contamination is similar after manual small-incision cataract surgery and phacoemulsification (Kumar et al. 2012). Contaminated surgical equipment (Malathi et al. 2006), IOLs (Ramappa et al. 2012) and viscoelastic material (Voss et al. 2012) may also cause outbreaks of endophthalmitis.

The risk of endophthalmitis is higher in older patients (West et al. 2005; Wejde et al. 2005b; Kamalarajah et al. 2007; Freeman et al. 2010; Cao et al. 2013), in patients with wound dehiscence (Wejde et al. 2005b), after posterior capsule rupture (Wong & Chee 2004a; Wejde et al. 2005b; Kamalarajah et al. 2007), when face masks are not worn in theatre (Kamalarajah et al. 2007) and in patients using immunosuppressants (Kamalarajah et al. 2007). Surgeons and clinics that perform a large number of cataract surgeries annually have a lower rate of endophthalmitis than those who perform fewer surgeries (Fang et al. 2006). The incidence of endophthalmitis has by some been reported to drop with technical advancement from intracapsular cataract extraction (ICCE) over extracapsular cataract extraction (ECCE) to the phacoemulsification technique and the use of small incisions that is possible due to foldable IOLs (Mayer et al. 2003; Wejde et al. 2005b; Freeman et al. 2010), whereas others have found a steady rate of endophthalmitis cases in spite of changing surgical procedures (Semmens et al. 2003).

As endophthalmitis is an infection, it should be preventable by antibiotic treatment. The question is which type of antibiotic treatment provides the best prevention against postcataract endophthalmitis? Prophylactic antibiotic treatment can be given as topical treatment preoperatively to reduce the

bacterial load on the conjunctiva before surgery. It can be given during surgery directly into the anterior chamber or as a subconjunctival injection. Finally, it can be given as topical treatment postoperatively. Globally, we face increasing problems concerning resistance of micro-organisms to antibiotic treatment probably because of a too liberal use. Thus, prophylactic antibiotic treatment should be given wisely to offer the best possible protection against endophthalmitis whilst protecting the patient and the society against selection of multiresistant bacterial strains. The aim of this study was to evaluate the available scientific data on the efficacy of the prophylactic effect of intracameral, peri-operative antibiotic delivery and topical antibiotic treatment as these two regimes are the most widely used. The present work was undertaken after an initiative by the Danish National Health and Medicines Authorities to formulate evidence-based guidelines on surgery for age-related cataract. A 2013 Cochrane review analysed the use of preoperative, intra-operative or postoperative antibiotics of any delivery route, but only randomized trials were included resulting in a conclusion based upon the recent ESCRS study and three older randomized trials using various routes of antibiotic administration (Gower et al. 2013). A great number of non-randomized studies have been published as the ESCRS study reporting endophthalmitis prevalence with and without the use of intracameral antibiotics and we decided to include this information in our analysis.

## Material and Methods

This systematic review and resulting meta-analyses were performed based on the principles described in the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al. 2011f). First, we defined the topic of the systematic review using the Patient, Intervention, Comparison and Outcome (PICO) approach (Guyatt et al. 2011a).

We formulated two PICO questions to examine both the prophylactic efficacy of topical antibiotic treatment and intracameral antibiotic therapy on postoperative endophthalmitis in patients with age-related cataract undergoing phacoemulsification:

- (1) Is the risk of endophthalmitis (O) lower in patients with age-related cataract undergoing phacoemulsification (P) with the use of intracameral antibiotic administration (I) or in patients not receiving intracameral antibiotics (C)?
- (2) Does topical antibiotic treatment (I) or no topical antibiotic treatment (C) result in the lowest number of endophthalmitis cases (O) in patients with age-related cataract undergoing phacoemulsification (P)?

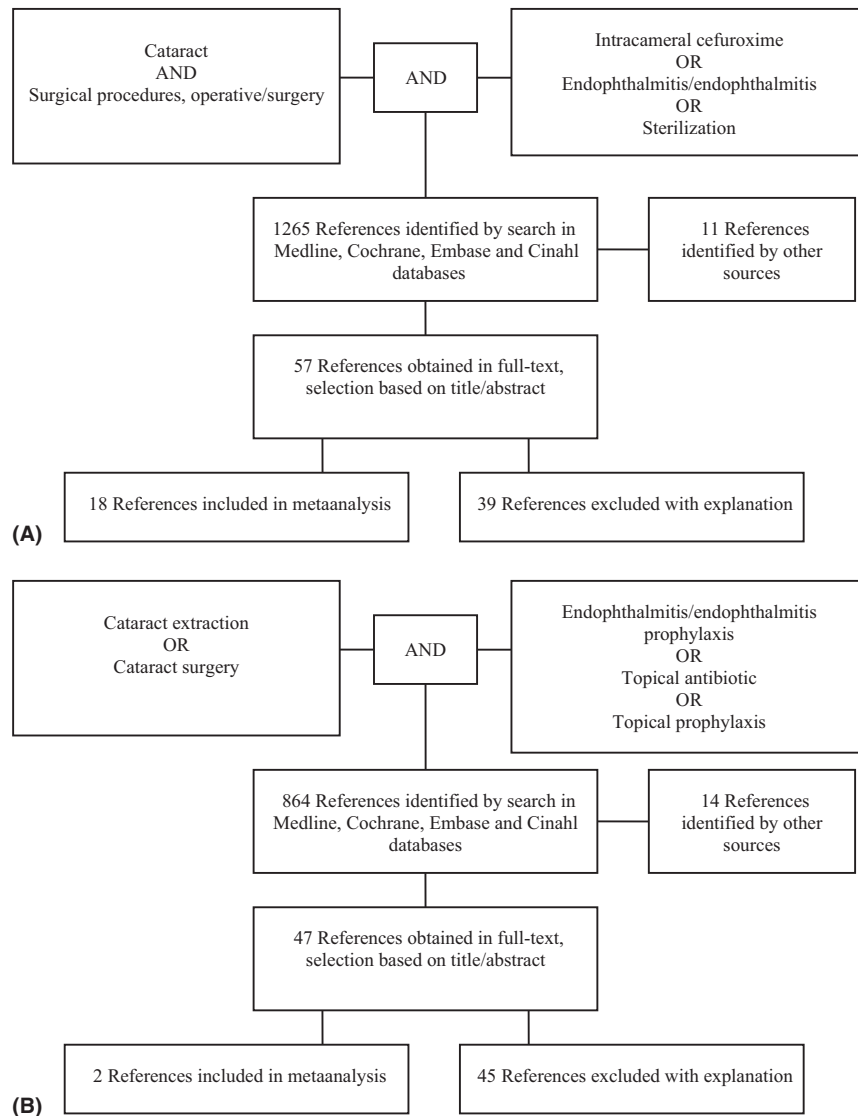
Randomized clinical trials and non-randomized trials were considered for inclusion if they reported on the incidence of postoperative endophthalmitis in patients undergoing surgery for age-related cataract. Furthermore, the study should compare endophthalmitis rates in two comparable populations receiving/not receiving antibiotic therapy, either intracamerally or topically. For a non-randomized trial to be included, the study had to compare endophthalmitis rates in the same institution(s) in two different time periods: one time period using antibiotic prevention of endophthalmitis and one time period not using antibiotic prevention. Studies that only reported cases and not the prevalence of endophthalmitis were excluded.

The outcome measure was endophthalmitis. Endophthalmitis was defined as clinical cases of postoperative endophthalmitis, that is both culture-positive and culture-negative cases.

A systematic literature search was conducted in July 2014 in the EMBASE, MEDLINE, Cochrane Library and CINAHL databases. A schematic presentation of the literature search is provided in Fig. 1A for intracameral antibiotic prophylaxis and in Fig. 1B for topical antibiotic prophylaxis. The search was limited to references published within the last 10 years in the English or Scandinavian languages. The time limit was chosen to ensure that the studies used surgical methods comparable to modern surgical methods, that is phacoemulsification. The search strategy is shown in Fig. 1.

According to Danish law, no institutional review board approval was needed for the study.

All included studies were reviewed by two reviewers independently (LK and PF), and the quality of the studies was evaluated using the Cochrane risk of



**Fig. 1.** Schematic presentation of the literature search (A) literature search profile for intracameral antibiotic prophylaxis of postoperative endophthalmitis (B) literature search profile for topical antibiotic prophylaxis of postoperative endophthalmitis Both search profiles were limited to the publications published in English or the Scandinavian languages published within the last 10 years.

bias tool (Higgins & Green 2011). In short, the Cochrane risk of bias tool assesses the risk of bias associated with the selection of patients (randomization or patient allocation and concealment of allocation), study performance (blinding of patients and personnel), detection of outcomes (blinding of outcome assessment), attrition of data (such as missing patients or drop-outs), reporting of study findings (selective outcome reporting) or other types of bias. Data from each included study were extracted independently by two reviewers (LK and PF). Data were entered into a meta-analysis providing relative risk ratios based on the available scientific data. Disagreement was resolved by discussion and consensus. This part of the

systematic review was carried out using the Review Manager Software [Review Manager (RevMan) 2012].

The quality of the evidence for each prespecified outcome was evaluated across the included studies using the GRADE system by two reviewers independently (LK and PF). Each outcome was analysed for study limitations (risk of bias, e.g. lack of allocation concealment or lack of blinding of patients or outcome assessors, incomplete accounting of patients and outcome, selective outcome reporting or other limitations) (Guyatt et al. 2011g), inconsistency (different results between studies) (Guyatt et al. 2011d), indirectness (was the study population and intervention comparable to the patient

population and intervention that is relevant to the readers of meta-analysis, use of surrogate measures) (Guyatt et al. 2011c), imprecision (large confidence intervals or the lack of statistical strength by included studies to answer the posed question) (Guyatt et al. 2011b) and risk of publication bias (e.g. lack of reporting of negative findings) (Guyatt et al. 2011e). The quality of the evidence for the prespecified outcome (endophthalmitis rate) could be up or downgraded based on the assessment of each of the limitations mentioned above. Finally, tables summarizing the findings and the quality of the evidence were prepared using the Grade Profiler software (GRADE profiler 2011).

Dichotomous outcome data were analysed by calculating risk ratios. The Review Manager 5 Software [Review Manager (RevMan) 2012] was used for the estimation of overall treatment effects. Random-effect models were used to calculate pooled estimates of effects.

## Results

### Endophthalmitis epidemiology

The systematic literature search revealed several studies that reported the rate of endophthalmitis after cataract surgery (Table 1). Reported endophthalmitis rates after cataract surgery vary greatly between different continents, between neighbouring countries and even within the same country. The average rate of endophthalmitis ranges from a high of one case per 315–368 surgeries in Africa and South America, respectively, over one case per ~700 surgeries in Asia, Australia and North America to a low of one case per 1418 surgeries in Europe. Even in Europe, the rate varies greatly from 0.3 per 1000 surgeries in Sweden (Friling et al. 2013) to seven per 1000 surgeries in a French report (Barreau et al. 2012).

We also identified 21 studies reporting the microbiological findings in endophthalmitis cases (Table 2). The reader should note that only studies reporting more than 50 cases of endophthalmitis were included in Table 2 as the finding of uncommon bacteria in small studies could skew the prevalence of causative micro-organisms. In up to half of the clinically diagnosed endophthalmitis cases, no causative micro-organism was found. The predominant causative micro-organism was coagulase-negative staphylococci with *Staphylococcus aureus* ranking second. In Sweden, where the national rate of endophthalmitis is the lowest reported globally possibly due to a nearly universal use of intracameral cefuroxime, the rate of infection caused by enterococci is high (Wejde et al. 2005a; Lundstrom et al. 2007; Friling et al. 2013). Fungi are a rare cause of endophthalmitis after cataract surgery and were only reported in large numbers from India (Gupta et al. 2003).

### Intracameral antibiotic and endophthalmitis risk

A systematic literature search identified one randomized controlled trial

**Table 1.** Overview on the global prevalence of endophthalmitis.

Study	Country	Incidence of endophthalmitis (%)
Africa		26/8190 (0.32%)
van der Merwe et al. (2012)	South Africa	26/8190 (0.32%)
Asia		1108/763 690 (0.15%)
Lin et al. (2011)	China	9/94 650 (0.01%)
Yao et al. (2013)	China	66/201 757 (0.03%)
Lalitha et al. (2005)	India	19/22 294 (0.09%)
Ravindran et al. (2009)	India	38/42 426 (0.09%)
Haripriya et al. (2012)	India	21/79 777 (0.03%)
Matsuura et al. (2013)	Japan	11/34 762 (0.03%)
Nagaki et al. (2003)	Japan	15/11 595 (0.13%)
Al-Mezaine et al. (2009)	Saudi Arabia	20/29 509 (0.07%)
Wong & Chee (2004b)	Singapore	34/44 803 (0.08%)
Tan et al. (2012)	Singapore	21/50 177 (0.04%)
Wu et al. (2006a)	Taiwan	46/21 562 (0.21%)
Wu et al. (2006b)	Taiwan	12/10 614 (0.11%)
Fang et al. (2006)	Taiwan	772/108 705 (0.71%)
Trinavarat et al. (2006)	Thailand	24/11 059 (0.22%)
Australia		723/504 471 (0.14%)
Ellis (2003)	Australia	5/633 (0.79%)
Semmens et al. (2003)	Australia	188/94 653 (0.20%)
Li et al. (2004)	Australia	210/117 083 (0.18%)
Rosha et al. (2006)	Australia	92/162 120 (0.06%)
Clark et al. (2011)	Australia	228/129 982 (0.18%)
Europe		1253/1 777 045 (0.07%)
ESCRS 2007 (ESCRS Endophthalmitis Study Group 2007)	Europe	29/16 603 (0.17%)
Eurequo 2012 (Lundstrom et al. 2012)	Europe	148/406 703 (0.04%)
Haapala et al. (2005)	Finland	47/29 350 (0.16%)
Barreau et al. (2012)	France	36/5115 (0.70%)
Ness et al. (2011)	Germany	16/26 566 (0.06%)
Krikonis et al. (2009)	Greece	7/8393 (0.08%)
Khan et al. (2005)	Ireland	43/8763 (0.49%)
Rahman & Murphy (2014)	Ireland	5/8239 (0.06%)
Kessner et al. (2014)	Israel	40/13 284 (0.30%)
Raen et al. (2013)	Norway	9/15 954 (0.06%)
Beselga et al. (2014)	Portugal	16/15 689 (0.10%)
Garat et al. (2005)	Spain	31/18 579 (0.17%)
Garcia-Saenz et al. (2010)	Spain	42/13 652 (0.31%)
Romero-Aroca et al. (2012)	Spain	83/25 001 (0.33%)
Rodriguez-Caravaca et al. (2013)	Spain	44/19 463 (0.23%)
Montan et al. (2002a)	Sweden	20/32 180 (0.06%)
Wejde et al. (2005a)	Sweden	112/188 151 (0.06%)
Lundstrom et al. (2007)	Sweden	109/225 471 (0.05%)
Friling et al. (2013)	Sweden	135/464 996 (0.03%)
Mayer et al. (2003)	UK	30/18 191 (0.16%)
Patwardhan et al. (2006)	UK	44/12 362 (0.36%)
Kelly et al. (2007)	UK	7/12 831 (0.05%)
Mollan et al. (2007)	UK	101/101 920 (0.10%)
Yu-Wai-Man et al. (2008)	UK	46/38 819 (0.12%)
Carrim et al. (2009)	UK	25/12 500 (0.20%)
Anijee et al. (2010)	UK	14/16 606 (0.08%)
Myneni et al. (2013)	UK	14/21 664 (0.06%)
North America		6935/5 122 623 (0.14%)
Shorstein et al. (2013)	California	19/16 264 (0.12%)
Lloyd & Braga-Mele (2009)	Canada	6/13 931 (0.04%)
Hatch et al. (2009)	Canada	617/422 177 (0.15%)
Freeman et al. (2010)	Canada	754/490 690 (0.15%)
Rudnisky et al. (2014)	Canada	23/75 318 (0.03%)
Miller et al. (2005)	Florida	7/15 920 (0.04%)
Wykoff et al. (2010)	Florida	8/28 568 (0.03%)
Thoms et al. (2007)	Michigan	5/815 (0.61%)
Buzard & Liapis (2004)	Nevada	0/5131 (0%)
Wallin et al. (2005)	Utah	27/15 254 (0.18%)
Jensen et al. (2005)	Utah	26/9079 (0.29%)
Moshirfar et al. (2007)	Utah	14/20 013 (0.07%)



Table 1. (Continued)

Study	Country	Incidence of endophthalmitis (%)
Jensen et al. (2008)	Utah	40/29 276 (0.14%)
West et al. (2005)	USA	1026/477 627 (0.21%)
Stein et al. (2011)	USA	357/221 594 (0.16%)
Keay et al. (2012)	USA	4006/3 280 966 (0.12%)
South America		74/27 264 (0.27%)
Melo et al. (2010)	Brazil	73/24 590 (0.30%)
Galvis et al. (2014)	Colombia	1/2674 (0.04%)

evaluating the effect of intracameral cefuroxime on the prevention of post-phacoemulsification endophthalmitis (Seal et al. 2006; ESCRS Endophthalmitis Study Group 2007). Furthermore, we found 17 observational studies describing the prevalence of endophthalmitis in the same institution(s) before and after introducing intracameral delivery of an antibiotic agent at the conclusion of surgery (Wejde et al. 2005a; ESCRS Endophthalmitis Study Group 2007; Lundstrom et al. 2007; Yu-Wai-Man et al. 2008; Garat et al. 2009; Anijeet et al. 2010; Barreau et al. 2012; van der Merwe et al. 2012; Romero-Aroca et al. 2012; Tan et al. 2012; Beselga et al. 2014; Friling et al. 2013; Matsuura et al. 2013; Myneni et al. 2013; Rodriguez-Caravaca et al. 2013; Shorstein et al. 2013; Galvis et al. 2014; Rudnisky et al. 2014). Of those 17 studies, 10 studies reported the rates of endophthalmitis with and without intracameral cefuroxime (Wejde et al. 2005a; Lundstrom et al. 2007; Yu-Wai-Man et al. 2008; Barreau et al. 2012; van der Merwe et al. 2012; Beselga et al. 2014; Friling et al. 2013; Myneni et al. 2013; Rodriguez-Caravaca et al. 2013; Shorstein et al. 2013; Galvis et al. 2014; Rudnisky et al. 2014; ). Finally, three studies reported the rates of endophthalmitis with and without intracameral vancomycin (Anijeet et al. 2010; Rudnisky et al. 2014; Shorstein et al. 2013).

The characteristics of included studies are provided in Appendix S1. Characteristics of studies excluded from the analysis as well as reason for exclusion are presented in Appendix S2.

The randomized controlled trial was conducted as a European multicenter

trial after an initiative by the European Society of Cataract and Refractive surgeons (Seal et al. 2006; ESCRS Endophthalmitis Study Group 2007). It was planned to include 35 000 participants, but the study was stopped after recruitment of 16 603 patients as the treatment effect was so marked that it was deemed unethical to continue the study. A total of 29 cases of clinically suspected endophthalmitis were detected. The rate of endophthalmitis was 0.6 per 1000 surgeries when intracameral cefuroxime was used at the conclusion of surgery versus 3.0 per 1000 surgeries when intracameral cefuroxime was not used. The difference was highly statistically significant, RR 0.21 (95% CI: 0.08; 0.55) (Fig. 2).

Since the publication of the ESCRS trial, several institutions have adopted the prophylactic intracameral administration of antibiotic. In total, 17 publications describing the rate of endophthalmitis reported by single institutions or countries before and after changing prophylactic regimes were identified. The majority of these studies are from Europe (Wejde et al. 2005a; Lundstrom et al. 2007; Garat et al. 2009; Anijeet et al. 2010; Barreau et al. 2012; van der Merwe et al. 2012; Romero-Aroca et al. 2012; Beselga et al. 2014; Friling et al. 2013; Myneni et al. 2013; Rodriguez-Caravaca et al. 2013), but findings from Asia (Tan et al. 2012; Matsuura et al. 2013), Africa (van der Merwe et al. 2012), North America (Shorstein et al. 2013; Rudnisky et al. 2014) and South America (Galvis et al. 2014) are also included in the analysis.

Based on the non-randomized studies, the risk of endophthalmitis was significantly lower in patients treated with intracameral cefazolin, cefuroxime and moxifloxacin, whereas no significant effect was found for intracameral vancomycin (see Fig. 2). The relative

risk [RR (95% confidence interval)] of endophthalmitis was reduced to 0.10 (0.06; 0.17) in patients receiving cefazolin, 0.09 (0.05; 0.15) in patients receiving cefuroxime, 0.22 (0.10; 0.50) in patients receiving moxifloxacin and 0.30 (0.02; 3.90) in patients receiving vancomycin.

In total, 1 192 330 cataract surgeries and 719 cases of endophthalmitis were included in the analysis. There were 356 cases of endophthalmitis in the 1 016 387 surgeries where intracameral antibiotics were used compared to 363 cases of endophthalmitis in the 175 943 surgeries where intracameral antibiotics were not used. Thus, endophthalmitis occurred in one of 2855 surgeries when intracameral antibiotics was used compared to one of 485 surgeries when no intracameral antibiotic was used. None of the studies included in the meta-analyses above reported adverse events associated with the use of intracameral antibiotic treatment.

The quality of evidence was high for the randomized trial and moderate for the observational studies concerning cefuroxime and cefazolin and low to very low for the observational studies concerning moxifloxacin and vancomycin, respectively (Table 3). The quality of the evidence for the observational studies concerning cefazolin and cefuroxime was upgraded because of the very large effect of intracameral antibiotic treatment.

#### Topical antibiotics and risk of endophthalmitis

After a systematic review of the literature, we found one randomized trial (Seal et al. 2006; ESCRS Endophthalmitis Study Group 2007) and one retrospective study (Råen et al. 2013) evaluating the effect of topical antibiotic treatment on the rate of endophthalmitis. Characteristics of the included studies are presented in Appendix S3, and characteristics of excluded studies are presented in Appendix S4.

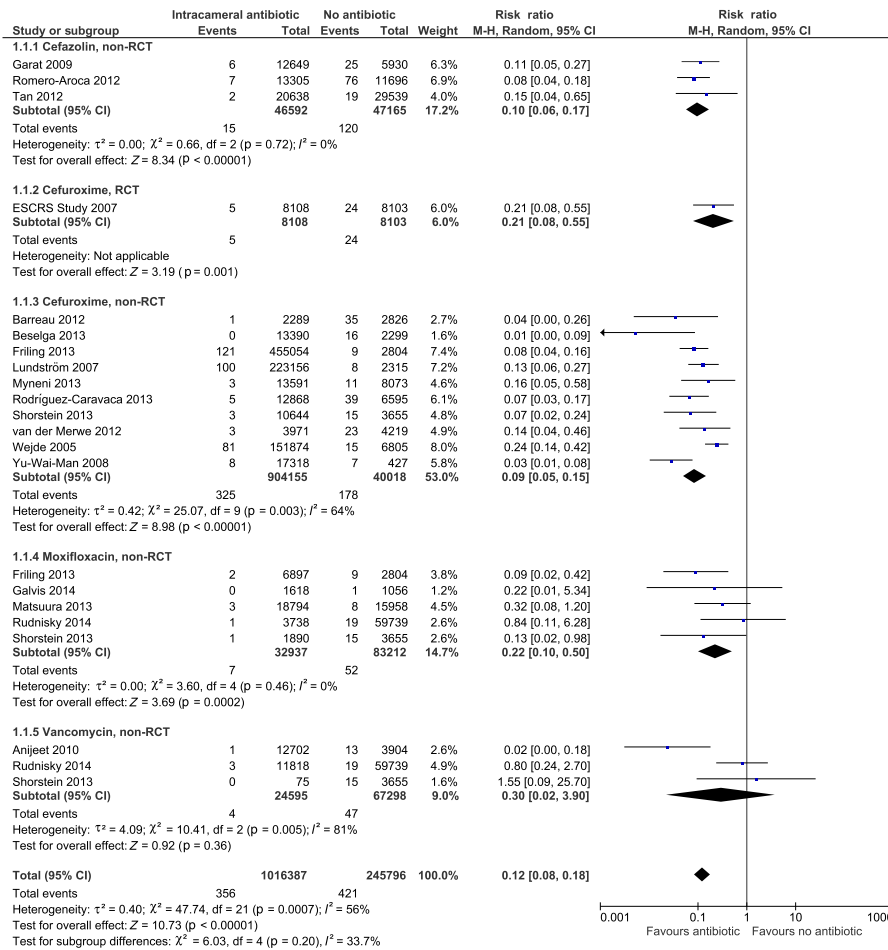
The ESCRS study was designed in a 2 × 2 factorial design, and besides examining the prophylactic effect of intracameral cefuroxime, the study also evaluated the prophylactic effect of 1 hr preoperative topical 0.5% levofloxacin treatment versus placebo (Seal et al. 2006; ESCRS Endophthalmitis Study Group 2007). In addition to the preop-

**Table 2.** Causative micro-organisms in endophthalmitis after cataract surgery.

Study id	Country	Years	No. of cases	Culture negative	Gram +	Coagulase-negative staphylococci	Staphylococcus aureus	Enterococcus	Gram -	Fungi
<b>Asia</b>										
Yao et al. (2013)	China	2006–2011	311	54%	48%	23%	7%	1%	39%	13%
Gupta et al. (2003)	India	1996–2001	64	39	14	8	3	1	11	0
Joseph et al. (2012)	India	2008–2010	124	77	5	0	2	0	7	27
Jindal et al. (2014)	India	2006–2013	64	27	20	14	4	0	17	–
Cheng et al. (2010)	Taiwan	2002–2008	248	–	124	60	9	0	89	20
Ng et al. (2005)	Australia	1980–2000	59	25	15	1	8	4	19	0
Europe			213	46%	86%	47%	18%	0%	12%	2%
Kodjikian et al. (2009)	France	2003–2004	213	99	113	61	24	–	16	2
Cornut et al. (2012)	France	2004–2005	1282	30%	88%	45%	10%	13%	11%	0%
Sandvig & Dannevig (2003)	Norway	1996–1998	95	50	39	26	6	0	3	0
Romero-Aroca et al. (2012)	Spain	1996–2002	100	30	66	33	14	0	4	0
Wejde et al. (2005a)	Sweden	1999–2001	111	23	75	32	7	11	4	1
Lundstrom et al. (2007)	Sweden	2002–2004	83	28	44	37	5	0	6	0
Friling et al. (2013)	Sweden	2005–2010	112	14	77	30	6	23	14	0
Kamalarajah et al. (2004)	UK	1999–2000	109	20	79	34	9	25	9	0
Pijl et al. (2010)	The Netherlands	1996–2006	135	20	94	35	–	42	19	0
Altan et al. (2009)	Turkey	2000–2007	199	88	103	54	10	3	8	0
North America			250	84	152	89	20	3	10	0
Recchia et al. (2005)	USA	1989–2000	88	31	35	18	8	1	22	0
Mollan et al. (2007)	USA	1996–2004	911	25%	92%	64%	12%	3%	6%	1%
Lalwani et al. (2008)	USA	1996–2005	497	175	304	180	43	13	17	7
Shirodkar et al. (2012); Shirodkar et al. (2012)*	USA	2000–2009	103	44	98	38	3	2	2	0
South America			73	7	66	50	5	0	7	0
Melo et al. (2010)	Brazil	2002–2008	92	–	–	57	11	–	–	–
			73	37%	83%	57%	4%	2%	17%	0%
			73	27	38	26	2	1	8	0

Only studies reporting more than 50 cases of endophthalmitis after cataract surgery are included in the table. Bacterial species are expressed as number of a given species demonstrated after culture. For each continent, the total number of endophthalmitis cases and the percentage of culture-negative cases and the percentage of Gram-positive and Gram-negative staphylococci, coagulase-negative staphylococci, staphylococcus aureus and enterococci are reported – not reported.

\* Publication excluded from calculation of percentages of culture-positive species and culture-negative samples because of too few data.



**Fig. 2.** Forest plot showing the effect of peri-operative, prophylactic intracameral antibiotic treatment as reported in the randomized trial and the 17 observational studies reporting endophthalmitis rate in patients receiving intracameral antibiotic prophylaxis (cefazolin, cefuroxime, moxifloxacin or vancomycin) versus no intracameral antibiotic prophylaxis.

erative randomized treatment, all patients received topical 0.5% levofloxacin for 6 days after cataract surgery. The rate of endophthalmitis was 1.5 per 1000 patients in those treated preoperatively with levofloxacin versus 2.1 per 1000 patients in those not treated with topical levofloxacin preoperatively. The difference between the two groups was not statistically significant, RR 0.71 (95% CI: 0.34; 1.48) (Fig. 3).

The effect of postoperative topical chloramphenicol treatment was reported in a retrospective Norwegian study (Råen et al. 2013). In Sweden, topical antibiotic treatment is not used routinely and yet the reported rates of endophthalmitis are among the lowest reported worldwide (see Table 1). This prompted the Department of Ophthalmology at the University Hospital of Oslo in Norway to stop using postoperative antibiotic topical treatment, and they evaluated the rate of endophthalmitis in the years preceding and

following the change in postoperative topical antibiotic treatment. All patients received intracameral cefuroxime unless they had a history of penicillin allergy. The rate of endophthalmitis was 0.7 per 1000 patients in the time period where topical chloramphenicol was used versus 0.5 per 1000 patients in the time period where no topical antibiotic treatment was used postoperatively. The difference between time periods was not significant, RR 1.43 (95% CI: 0.38; 5.31) (Fig. 3).

The summary of findings and the quality of evidence concerning the prophylactic use of topical antibiotic treatment is presented in Table 4. The quality of evidence was high for the randomized trial evaluating the rate of endophthalmitis in patients randomized to preoperative levofloxacin or placebo. The quality of evidence was graded as low according to the GRADE guidelines for the retrospective study (Guyatt et al. 2011g).

## Discussion

Endophthalmitis is the most feared complication after cataract surgery. There are striking global differences in the prevalence of endophthalmitis. The risk of endophthalmitis is more than doubled in the USA compared to Europe even when comparing nationwide data covering the period of time, 0.05% in the years 2002–2004 in Sweden (Lundstrom et al. 2007) versus 0.12% in the years 2003–2004 in the USA (Keay et al. 2012). Although the populations covered by the reports may not be directly comparable, both aforementioned reports are based on a very large number of patients, 225 000 in the Swedish report and 3 280 000 in the US report, and both report from publically funded healthcare systems (the Medicare in the US). A direct comparison between the different reports of endophthalmitis rates is not always possible as important information on major

**Table 3.** Summary of findings and quality of evidence concerning the prophylactic role of intracameral antibiotic administration.

Outcomes: post-phacoemulsification endophthalmitis rates	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk without intracameral antibiotic	Risk difference with intracameral antibiotic (95% CI)
Cefazolin, non-RCT	93 757 (3 studies)	⊕⊕⊕⊕ moderate <sup>†</sup> Due to large effect	RR 01 (006–017)	3 per 1000	2 fewer per 1000 (from 2 fewer to 2 fewer)
Cefuroxime, RCT	16 211 (1 study)	⊕⊕⊕⊕ high	RR 021 (008–055)	3 per 1000	2 fewer per 1000 (from 1 fewer to 3 fewer)
Cefuroxime, non-RCT	944 173 (10 studies)	⊕⊕⊕⊕ moderate <sup>†</sup> Due to large effect	RR 009 (005–015)	4 per 1000	4 fewer per 1000 (from 4 fewer to 4 fewer)
Moxifloxacin, non-RCT	116 149 (5 studies)	⊕⊕⊕⊕ low	RR 022 (01–05)	1 per 1000	0 fewer per 1000 (from 0 fewer to 1 fewer)
Vancomycin, non-RCT	91 893 (3 studies)	⊕⊕⊕⊕ very low <sup>†,‡,§</sup> Due to inconsistency, imprecision	RR 03 (002–39)	1 per 1000	0 fewer per 1000 (from 1 fewer to 2 more)

CI = confidence interval; RR = risk ratio.

GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate.

Randomized trials begin as high-quality evidence and can be upgraded or downgraded Observational studies begin as low quality of evidence and can be upgraded or downgraded. The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>†</sup> Upgraded because of marked effect of intracameral antibiotic.

<sup>‡</sup> Large differences in estimates and confidence intervals between studies.

<sup>§</sup> Too few events (endophthalmitis cases) and included patients for a definite conclusion to be drawn plus confidence interval cross RR 1.0.

risk factors, for example age, gender, capsule rupture or the use of intracameral antibiotics, is not always available. Nevertheless, the data bring us one important message: the rate of endophthalmitis can be reduced if prophylactic actions are taken.

This raises the important question: What is the most effective prophylactic regime? The aim of the present systematic review was to evaluate the effect of antibiotic treatment alone, but the role of cleaning the conjunctiva by povidone-iodine, keeping the eye lashes out of the surgical field and treating blepharitis prior to surgery, is also of importance. It is, however, beyond the scope of the present study to provide evidence-based recommendations for non-antibiotic prophylactic regimes.

We examined the evidence for a prophylactic role of intracameral cefuroxime and found high-quality evidence that it significantly reduces the rate of endophthalmitis (ESCRS Endophthalmitis Study Group 2007; Seal et al. 2006). Two to four cases of endophthalmitis can be avoided per 1000 cataract surgeries performed when intracameral cefuroxime is used. The finding of the randomized trial was confirmed by several retrospective, observational studies (Wejde et al. 2005a; ESCRS Endophthalmitis Study Group 2007; Lundstrom et al. 2007; Yu-Wai-Man et al. 2008; Garat et al. 2009; Anijeet et al. 2010; Barreau et al. 2012; van der Merwe et al. 2012; Romero-Aroca et al. 2012; Tan et al. 2012; Beselga et al. 2014; Friling et al. 2013; Galvis et al. 2014; Matsuura et al. 2013; Myneni et al. 2013; Rodriguez-Caravaca et al. 2013; Shorstein et al. 2013; Rudnisky et al. 2014). The ESCRS study has been criticized for a high rate of endophthalmitis in the non-cefuroxime group, but as the present meta-analysis demonstrates, comparable rates of endophthalmitis in the non-cefuroxime group was found in the ESCRS study and in the observational studies. Furthermore, the rate in the non-cefuroxime group is comparable to that reported in many of the studies summarized in Table 1. Thus, the authors of the present systematic review have found that the ESCRS reports high-quality and reliable data that undisputedly demonstrate a significant prophylactic effect of intracameral cefuroxime. Several studies have shown that intracameral cefuroxime at a dose of 1 mg in 0.1 ml is safe for the human eye (Montan et al.



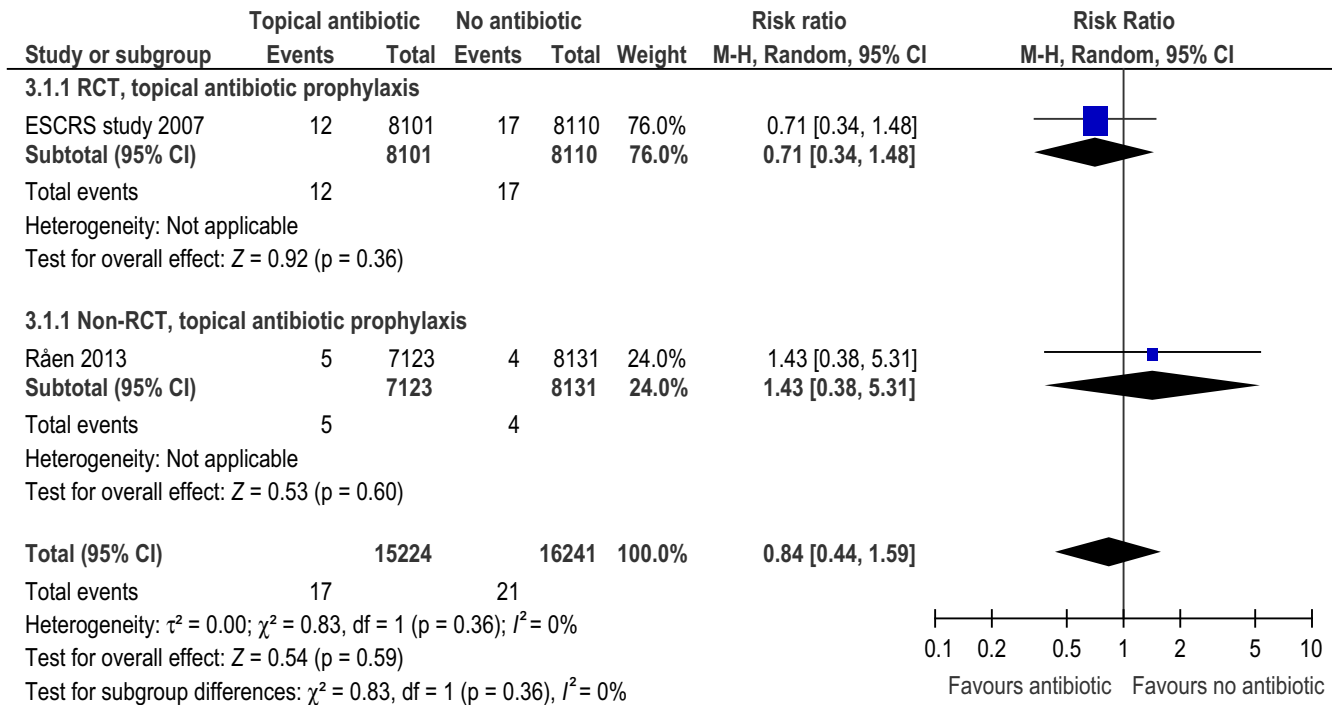


Fig. 3. Forest plot showing the effect of prophylactic topical antibiotic therapy as reported in the randomized trial and in the observational study.

2002b; Gupta et al. 2005; Lam et al. 2010).

Surveys on the use of prophylactic antibiotic regimes published after the publication of the ESCRS trial show that there are large global differences in the use of intracameral antibiotic therapy. In Sweden, nearly all patients receive intracameral antibiotic (99%) (Friling et al. 2013). The ESCRS 2012 survey found that 74% always used intracameral antibiotics (Barry 2014). A Greek study found that 50% of surgeons use intracameral cefuroxime (Mataftsi et al. 2011). In the UK, 40% (Murjaneh et al. 2010) to 54% (Nanavaty & Wearne 2010) of ophthalmology units and 63% of the United Kingdom and Ireland Society of Cataract and Refractive surgeons (Gore et al. 2009) use intracameral antibiotic as standard. The ASCRS survey showed that 30% used intracameral antibiotic; of those who did, half used it as injection and the other half in the irrigation fluid, whereas nearly all surgeons (98%) used topical antibiotic postoperatively (Chang et al. 2007). In Singapore, 30% of surgeons use intracameral antibiotic (Han & Chee 2012). In New Zealand, 24% use intracameral antibiotic and 92% use postoperative topical antibiotic (Pick et al. 2008). The main reason for not

using intracameral antibiotic reported in the above-mentioned studies has been a fear of risks associated with the use and the lack of a commercially available preparation.

Around 5% of patients who are allergic to penicillin may respond with cross-reactivity to cephalosporins. Serious systemic anaphylactic reactions have been reported after the use of intracameral cefuroxime (Villada et al. 2005). However, a study based on 36 patients with penicillin allergy (ranging from rash to loss of consciousness) did not find any adverse effects after subconjunctival cefuroxime injection (Mitra & McElvanney 2006). Each surgeon must make his or her own choice when it comes to the use of intracameral cefuroxime in patients with a history of allergic reaction to penicillin or cephalosporin.

One of the practical problems associated with intracameral cefuroxime has been the lack of a commercially available ready-to-use drug. This has caused fear of dilution errors. Erroneous injection of 3 mg in 0.1 ml in six patients did not result in adverse effects (Sakarya & Sakarya 2010), whereas 62.5 mg resulted in macular infarction (Qureshi & Clark 2011). A larger case series from Finland showed that erroneously high amounts of cefuroxime

(between 10 and 100 mg intracamerally) resulted in severe ocular toxicity with corneal oedema and lowering of visual field sensitivity but that half of the patients ended with a reasonable (>0.5 Snellen) visual acuity (Olavi 2012). In Europe, a ready-to-mix solution of cefuroxime has been approved, thus minimizing the risk of dilution errors. It is hoped that a ready-to-mix cefuroxime formulation will also be available in the rest of the world in the future. Using intracameral cefuroxime is not cost-free, but studies have shown that intracameral cefuroxime is cost-effective, whereas the topical use of ciprofloxacin, ofloxacin, moxifloxacin and gatifloxacin is not (Sharifi et al. 2009).

So far, no international ophthalmological society has advocated strongly for the use of intracameral cefuroxime. A joint European initiative aimed at improving the quality of cataract surgery, the EUREQUO, reports lower incidence of postoperative endophthalmitis after intracameral cefuroxime but does not recommend the use/no use of intracameral antibiotic (Lundstrom et al. 2012). The Canadian Ophthalmological Society has a consensus statement saying that if the surgeon has a higher endophthalmitis rate than published norms, consideration should be

**Table 4.** Summary of findings and quality of evidence for the prophylactic use of topical antibiotic treatment.

Outcomes: endophthalmitis rates after phacoemulsification using topical antibiotics	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk without topical antibiotic	Risk difference with topical antibiotic (95% CI)
Endophthalmitis rate, RCT	16 211 (1 study)	⊕⊕⊕⊕	RR 0.71 (0.34–1.48)	2 per 1000	1 fewer per 1000 (from 1 fewer to 1 more)
Endophthalmitis rate, observational study	15 254 (1 study)	HIGH ⊕⊕⊕⊕ LOW	RR 1.43 (0.38–5.31)	0 per 1000	0 more per 1000 (from 0 fewer to 2 more)

CI = confidence interval; RR = risk ratio.

GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate. The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

given to change to intracameral or subconjunctival antibiotic supplementation (Canadian Ophthalmological Society Cataract Surgery Clinical Practice Guideline Expert Committee 2008). The recommendations from the British Royal College of Ophthalmologists are similar to the Canadian (The Royal College of Ophthalmologists 2010). The American Association of Ophthalmologists recommends ‘It would appear that antibiotic use on the day of surgery is important rather than waiting until the next day. Any additional prophylactic antibiotic strategy in the perioperative period is up to the ophthalmologist to determine’ (American Academy of Ophthalmology 2011). The findings reported in the present study should, however, lead all ophthalmological societies to make a strong recommendation to use intracameral cefuroxime.

The second part of the present systematic review deals with the use of topical antibiotics in the prevention of endophthalmitis. Surveys have shown that nearly all surgeons prescribe topical antibiotics to be administered after cataract surgery (Rosha et al. 2006; Chang et al. 2007; Pick et al. 2008). In theory, topical antibiotics may work by reducing the number of bacteria on the conjunctiva, thus lowering the risk of intraocular contamination either during surgery or through a leaking wound postoperatively. Three days of topical antibiotic treatment reduces the number of positive conjunctival samples by approximately 50% (Inoue et al. 2008; He et al. 2009). In other words, even after several days of antibiotic treatment, a high number of bacteria remain on the conjunctiva lowering the theoretical rationale for topical antibiotic prophylaxis. Topical antibiotic therapy was not found to lower the rate of endophthalmitis in the ESCRS study (ESCRS Endophthalmitis Study Group 2007) nor in a retrospective Norwegian study (Råen et al. 2013). Unnecessary antibiotic therapy carries a risk of selecting drug-resistant bacterial strains. An American study found that five of 31 endophthalmitis cases treated with perioperative gatifloxacin or moxifloxacin were resistant to gatifloxacin and moxifloxacin (Deramo et al. 2006). We did not find a protective effect of topical antibiotics. In addition, we did not find evidence that postoperative use of topical antibiotics increases the risk of endophthalmitis as has been

described after anti-VEGF injections (Cheung et al. 2012; Storey et al. 2014).

## Conclusions and recommendations

In conclusion, we found strong and consistent evidence that intracameral cefuroxime administered at the conclusion of cataract surgery significantly lowers the risk of endophthalmitis. Two to four cases of endophthalmitis per 1000 surgeries can be avoided if surgeons adopt the use of intracameral cefuroxime and the authors of the review strongly recommend its use. We could not find any evidence that topical antibiotic treatment after cataract surgery lowers the risk of endophthalmitis. As there is no documented effect of topical antibiotic treatment and its use may be associated with concern for selection of resistant bacterial strains, we cannot recommend using it.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

- Appendix S1.** Characteristics of included studies, intracameral antibiotic prophylaxis.
- Appendix S2.** Characteristics of excluded studies, intracameral antibiotic prophylaxis.
- Appendix S3.** Characteristics of included studies.
- Appendix S4.** Characteristics of excluded studies.