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Prophylactic antibiotics for postcataract surgery endophthalmitis: a systematic review and network meta-analysis of 6.8 million eyes

Ai Kato[1,2], Nobuyuki Horita[3], Ho Namkoong[4], Eiichi Nomura[1], Nami Masuhara[2], Takeshi Kaneko[5], Nobuhisa Mizuki[1] & Masaki Takeuchi[1]✉

To reveal optimal antibiotic prophylactic regimen for postoperative endophthalmitis (POE), we conducted systematic review and network meta-analysis. A total of 51 eligible original articles, including two randomized controlled trials, were identified. In total, 4502 POE cases occurred in 6,809,732 eyes (0.066%). Intracameral injection of vancomycin had the best preventive effect (odds ratio [OR] 0.03, 99.6% confidence interval [CI] 0.00–0.53, corrected P-value = 0.006, P-score = 0.945) followed by intracameral injection of cefazoline (OR 0.09, 99.6% CI 0.02–0.42, corrected P-value < 0.001, P-score = 0.821), cefuroxime (OR 0.18, 99.6% CI 0.09–0.35, corrected P-value < 0.001, P-score = 0.660), and moxifloxacin (OR 0.36, 99.6% CI 0.16–0.79, corrected P-value = 0.003, P-score = 0.455). While one randomized controlled trial supported each of intracameral cefuroxime and moxifloxacin, no randomized controlled trial evaluated vancomycin and cefazoline. Sensitivity analysis focusing on the administration route revealed that only intracameral injection (OR 0.19, 99.4% CI 0.12–0.30, corrected P-value < 0.001, P-score = 0.726) significantly decreased the risk of postoperative endophthalmitis. In conclusion, intracameral injection of either vancomycin, cefazoline, cefuroxime, or moxifloxacin prevented POE.

Cataract surgery is the most commonly performed ophthalmologic procedure in many industrialized countries, and its frequency continues to increase. An aging society and improved technologies are key factors augmenting the number of cataract surgeries[1]. Endophthalmitis is a sight-threatening disorder caused by intraocular infection through endogenous or exogenous routes. Postoperative endophthalmitis (POE) is a possible complication of intraocular surgeries, particularly cataract surgery, and it can lead to loss of vision. The most common cause of POE is bacteria from the eyelid flora[2,3]. Therefore, the use of perioperative antibiotics is a reasonable strategy for reducing the occurrence of POE. In daily practice, various antibiotics have been used to prevent endophthalmitis, and various routes of antibiotic administration have been proposed accordingly. However, the benefit of antibiotic use has not been sufficiently clear until recently. Because the incidence of postcataract surgery endophthalmitis is less than 0.1%, and it is difficult to design a randomized controlled trial (RCT) for such a rare complication. Therefore, our practice has relied largely on evidence from observational studies. A meta-analysis is also helpful in overcoming disease rarity[4]. Published pairwise meta-analyses revealed that perioperative intracameral vancomycin and moxifloxacin[5], anterior chamber injection of moxifloxacin after cataract surgery[6], and intracameral cefuroxime and moxifloxacin after cataract surgery[7] reduced the risk of endophthalmitis compared with no antibiotic prophylaxis. However, each of these head-to-head meta-analyses evaluated limited treatment options only. Therefore, the optimal antibiotic type and administration route for endophthalmitis prevention are still not evident.

[1]Department of Ophthalmology and Visual Science, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. [2]Department of Ophthalmology, Chigasaki Municipal Hospital, Chigasaki, Kanagawa, Japan. [3]Chemotherapy Center, Yokohama City University Hospital, Yokohama, Kanagawa, Japan. [4]Department of Infectious Diseases, Keio University School of Medicine, Shinjuku, Tokyo, Japan. [5]Department of Pulmonology, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan. ✉email: takeuchi@yokohama-cu.ac.jp

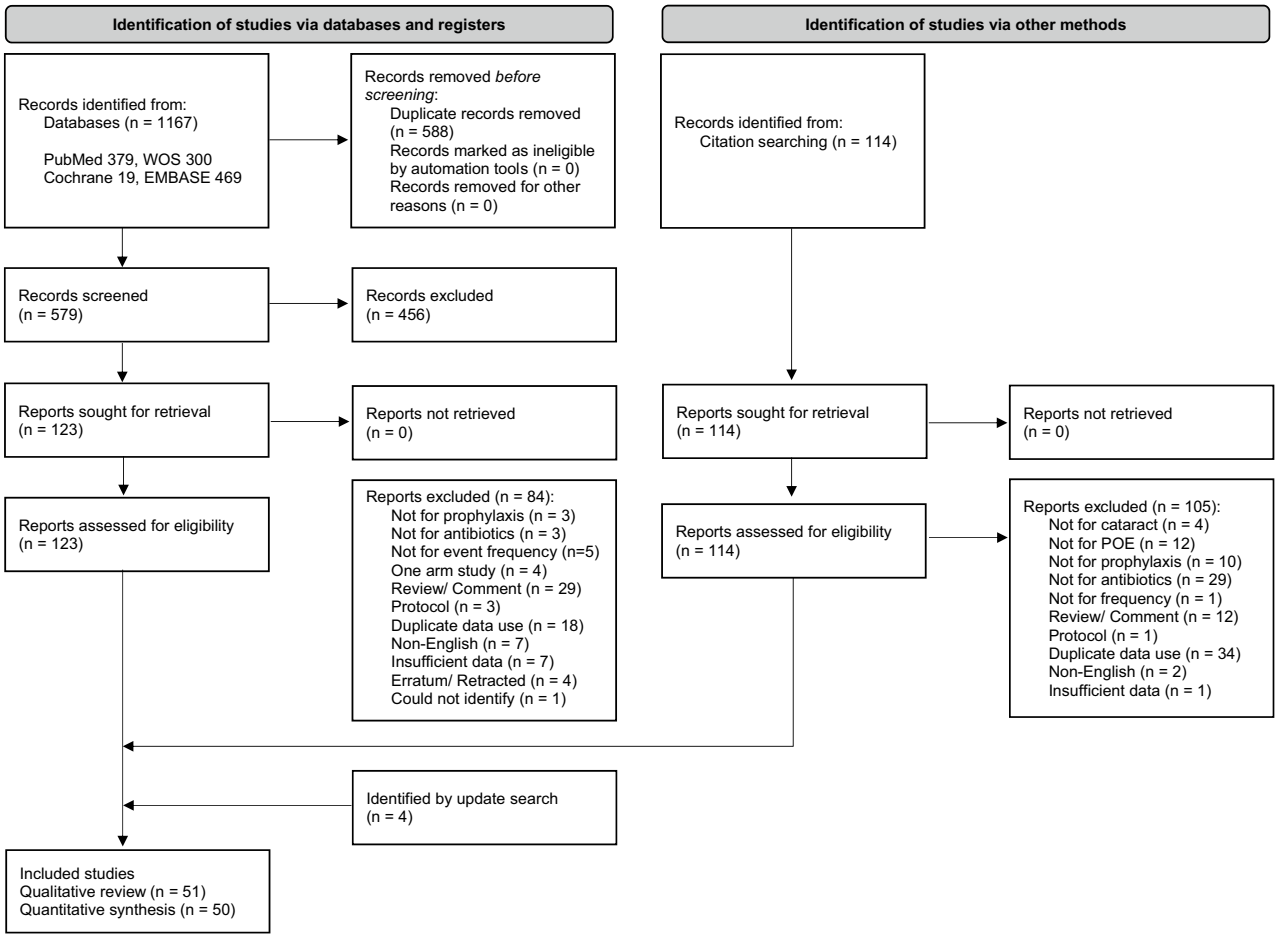

Figure 1. Preferred reporting items for systematic reviews and meta-analyses 2020 flow diagram. *POE* postoperative endophthalmitis.

The current systematic review and network meta-analysis revealed the optimal antibiotic for preventing POE using data from both randomized controlled trials and observational studies.

Results

Study selection and characteristics. We found a total of 1167 and 114 articles by database search and manual search, respectively (Fig. 1). After screening and full-text reading, 47 articles were found to be eligible for our analysis. Approximately 1 year later, the updated database search detected four additional studies. (Fig. 1, Supplementary Reference 1 and Supplementary Table 1).

Among the 51 studies, 43 studies were retrospective observational studies, 6 were prospective observational studies, and only 2 were RCTs (Table 1). The United States had the largest number of reports (N = 10), followed by Spain (N = 7), India (N = 6), Brazil (N = 3), China (N = 3), and Sweden (N = 3). While 45 studies provided data for head-to-head comparison in our study, 6 studies provided data for three or more treatment arms. Thirty-eight reports (75%) designed an arm without prophylactic antibiotics. Single-drug intracameral cefuroxime (N = 15) and single-drug intracameral moxifloxacin (N = 12) were the most widely used antibiotic regimens. The network plot also revealed that the comparison between no prophylactic antibiotic and these two regimens was evaluated most frequently (Fig. 2A).

The median number of eyes in a report was 25,001; however, the sample sizes varied greatly, ranging from 200 to 2,434,008. The total number of analyzed cases was 6,809,732, with 4502 endophthalmitis cases therein. Therefore, the raw event frequency was 0.066%.

Study quality was evaluated using the Newcastle–Ottawa Scale ranging from 7 to 9 (Table 1). The Cochrane Risk of Bias Summary was also presented for two RCTs as Supplementary Fig. 1. Although the straightforward clinical question of the current analysis made it easy to attain a high score on the scale, all observational studies provided only unadjusted raw numbers of patients with and without endophthalmitis.

A study by Asencio[11] was not used for quantitative synthesis because of the use of unspecified aminoglycoside class agent and because it constituted an independent loop in the route model.

Main analysis. Four eligible studies were excluded from the main analysis because they composited independent loops: Tuñí-P[54], azithromycin eye drop versus moxifloxacin eye drop; Jensen[28], gatifloxacin eye drop

Study	Country	Design	Eyes	NOS	Arm 1	Arm 2	Arm 3–8
Akkach (2019) [8]	Australia	Retro	5900	7	NONE	CP(ed)	
Allen (1974) [9]	USA	Retro	36,000	7	NONE	NEOM 0.5% (ped)	CP 0.4%(ped)
Anijeet (2010) [10]	UK	Retro	16,606	7	NONE	VCM 1 mg/0.1 mL(ic)	
Asencio (2014) [11]	Spain	Retro	14,285	7	GM 40 mg/0.5 mL(sc) + AG(ed)	GM 0.08% (irg) + VCM 0.1%(irg) + AG(ed)	
Barreau (2012) [12]	France	Pro	5115	7	NONE	CXM(ic)	
Barry (2007) [13]	Ireland	RCT	16,211	9	NONE	CXM(ic)	LVFX(ed) CXM(ic) + LVFX(ed)
Bhatta (2021)[14]	Nepal	Retro	111,983	7	MFLX 0.5 mg/0.1 mL(ic) + GM 20 mg/0.5 mL(sc)	GM 20 mg/0.5 mL(sc)	
Bohigian (2007) [15]	USA	Retro	5268	7	NONE	CPFX(pldg)	
Cheng (2014) [16]	Australia	Retro	99,448	7	NONE	CEZ(ic)	
Colleaux (2000) [17]	Canada	Retro	13,886	7	NONE	ANY(sc)	
Daien (2016) [18]	France	Retro	2,434,008	7	None	MFLX 0.5 mg/0.1 mL(ic)	
Dave (2021) [19]	India	Retro	66,967	7	NONE	CXM(ic)	
Ferlini (2013) [20]	Argentina	Retro	6001	7	NONE	MFLX 0.5 mg/0.1 mL(ic)	
Friling (2019) [21]	Sweden	Retro	109,534	7	NONE	CXM 1 mg/mL(ic)	
Galvis (2014) [22]	Colombia	Retro	2674	7	NONE	MFLX 0.25 mg/0.05 mL(ic)	
Garat (2009) [23]	Spain	Retro	18,579	7	NONE	CEZ 2.5 mg/0.1 mL(ic)	
Garcia-S (2010) [24]	Spain	Retro	13,652	7	NONE	CXM 1 mg/0.1 mL(ic)	
Guo (2021) [25]	Australia	Retro	42,877	7	CP(ed)	NONE	
Haripriya (2019) [26]	India	Retro	2,062,643	7	NONE	MFLX 0.5 mg/0.1 mL(ic)	
Hollander (2004) [27]	USA	Retro	2718	7	NONE	ANY(oint)	
Jensen (2008) [28]	USA	Retro	29,276	7	ANY(ed)	GFLX 0.3%(ed)	MFLX 0.5%(ed)
Katz (2015) [29]	Israel	Retro	56,094	7	NONE	CXM(ic)	
Kingrey (2019) [30]	USA	Retro	30,649	7	ANY(top)	ANY(top) + VCM(ic)	
Li (2018) [31]	China	Retro	4210	7	NONE	CXM(ic)	
Li (2019) [32]	USA	Retro	32,526	7	ANY(top)	ANY(ic)	
Lundström (2007) [33]	Sweden	Pro	225,471	7	NONE	CXM(ic)	
Ma (2020) [34]	China	Retro	61,299	7	NONE	CXM 0.03% (irg)	
Matsuura (2013) [35]	Japan	Retro	34,752	7	NONE	MFLX 0.05–0.5 mg/mL(ic)	
Melega (2019) [36]	Brazil	RCT	3640	9	NONE	MFLX 0.15 mg/0.03 mL (ic)	
Moser (2019) [37]	Spain	Retro	55,984	7	OFLX 0.3%(top)	CEZ 2.4 mg/0.3 mL(ic) + OFLX 0.3%(top)	CEZ 2.4 mg/0.3 mL(ic) + MFLX(top)
Moshirfar (2007) [38]	USA	Retro	20,013	7	GFLX(top)	MFLX(top)	
Paiva (2016) [39]	Brazil	Retro	200	7	NONE	MFLX 150-µg/0.03 mL (ic)	
Porwal (2021) [40]	India	Retro	19,853	7	NONE	CP 5 mg/mL(ed)	
Råen (2013) [41]	Norway	Retro	15,254	7	NONE	MFLX(ic)	
Rahman (2015) [42]	Ireland	Retro	16,975	7	NONE	CXM(ic)	
Rathi (2020) [43]	India	Pro	42,466	7	CXM 1 mg/0.1 mL(ic)	CXM1mg/0.1 mL(ic) + CPFX(top)	CXM1mg/0.1 mL(ic) + OFLX(top) CXM1mg/0.1 mL(ic) + MFLX(top) MFLX 0.5 mg/0.1 mL(ic) MFLX 0.5 mg/0.1L(ic) + CPFX(top) MFLX 0.5 mg/0.1 mL(ic) + OFLX(top) MFLX 0.5 mg/0.1 mL(ic) + MFLX(top)
Rodriguez-C (2013) [44]	Spain	Retro	19,463	7	NONE	CXM 1 mg/0.1 mL(ic)	
Romero-A (2012) [45]	Spain	Pro	25,001	7	NONE	CEZ 1 mg/0.1 mL(ic)	
Rudnisky (2014) [46]	Canada	Retro	75,295	7	NONE	MFLX(ic)	
Rush (2015) [47]	USA	Retro	20,719	7	NONE	VCM 1 mg/0.1 mL(ic)	
Sharma (2015) [48]	India	Pro	15,122	7	NONE	CXM 1 mg/0.1 mL(ic)	
Shenoy (2021) [49]	India	Retro	214,782	7	NONE	MFLX 0.5 mg/0.1 mL(ic)	
Shorstein (2013) [50]	USA	Retro	4916	7	NONE	CXM or MFLX 0.5 mg/0.1 mL, 2.5 mg/0.5 mL, 5 mg/mL(ic)	
Shorstein (2021) [51]	USA	Retro	204,655	7	CXM 1 mg/0.1 mL(ic)	MFLX 0.1%(ic)	
Sobaci G (2009) [52]	Turkey	Retro	6099	7	NONE	CXM(ic)	
Tan (2012) [53]	Singapore	Retro	50,177	7	CEZ 1 mg/0.1 mL(sc) + GM 8 mg/0.2 mL(sc)	CEZ 1 mg/0.1 mL(ic)	
Tuñí-P (2018) [54]	Spain	Retro	15,146	7	AZM(ed) 15 mg/g	CPFX(ed) 3 mg/ml	
Continued							

Study	Country	Design	Eyes	NOS	Arm 1	Arm 2	Arm 3–8
Vieira (2017) [55]	Brazil	Retro	7195	7	ANY(ed)	ANY(ed) + MFLX(ic) 0.27 mg/0.05 mL	
Wejde (2005) [56]	Sweden	Pro	158,679	7	NONE	ANY(ic)	
Yao (2013) [57]	China	Retro	201,757	7	VCM 1 mg/0.1 mL(ic), 1%(irg) + TB(sc/top)	TB (irg/sc/top)	
Yu-W-M (2008) [58]	UK	Retro	37,170	7	NONE	CXM 1 mg/0.1 mL(ic)	CXM 50 mg/0.5 mL(sc)

Table 1. Characteristics of included studies. RCT, randomized controlled trial; Pro, prospective observational study; Retro, retrospective observational study. NOS, The Newcastle–Ottawa Scale. NONE, no prophylactic antibiotics; CEZ, cefazoline; CXM, cefuroxime; CAZ, ceftazidime; MFLX, moxifloxacin; CPFX, ciprofloxacin; OFLX, ofloxacin; GFLX, gatifloxacin; LVFX, levofloxacin; VCM, vancomycin; NEOM, neomycin; AG, aminoglycoside; GM, gentamycin; TB, tobramycin; AZM, azithromycin; CP, Chloramphenicol. (ic), intracameral; (ed), eye drop; (ped), pre-operative eye drop; (irg), irrigation; (oint), ointment; (sc), subconjunctival injection; (pldg), pledget; (top), topical.

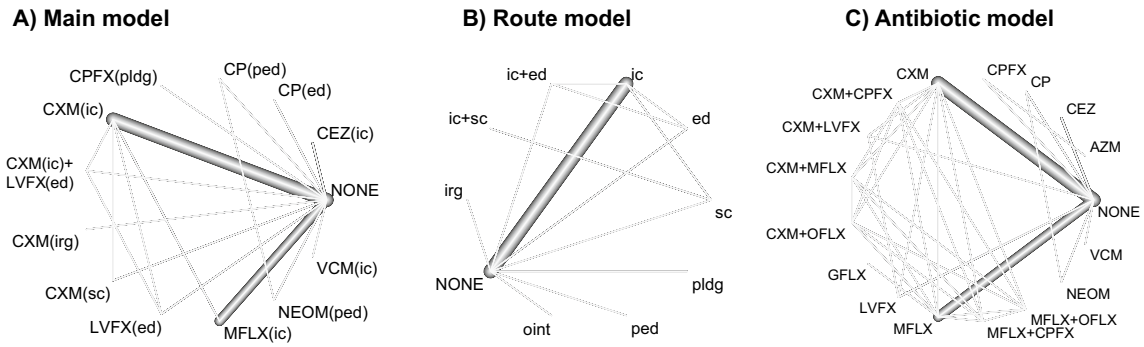

Figure 2. Network graphs. *NONE* no prophylactic antibiotics, *CEZ* cefazoline, *CXM* cefuroxime, *CAZ* ceftazidime, *MFLX* moxifloxacin, *CPFX* ciprofloxacin, *OFLX* ofloxacin, *GFLX* gatifloxacin, *LVFX* levofloxacin, *VCM* vancomycin, *NEOM* neomycin, *GM* gentamycin, *TB* tobramycin, *AZM* azithromycin, *CP* chloramphenicol, *VCM* vancomycin. *ic* intracameral, *ed* eye drop, *ped* pre-operative eye drop, *irg* irrigation, *sc* subconjunctival injection, *pldg* pledget.

versus moxifloxacin eye drop; Asencio[11], "aminoglycoside eyedrop plus subconjunctival gentamycin" versus "aminoglycoside eyedrop plus irrigation with vancomycin plus gentamycin"; Bhatta[14], "moxifloxacin intracameral injection plus subconjunctival gentamycin" versus "subconjunctival gentamycin."

The network plot is shown in Fig. 2A. Overall, a moderate inconsistency was observed ($I^2 = 82\%$). The total number of evaluated eyes was 6,141,523.

A random-model network meta-analysis comprising of 36 reports revealed that intracameral vancomycin had the best preventive effect for endophthalmitis with an OR of 0.03 (99.6% CI 0.00–0.53, Pc = 0.006, Fig. 3A). This treatment also had the highest P-score (0.945) among the 12 treatment options (Supplementary Table 2). Other antibiotics prevented POE were cefazoline intracameral injection (OR 0.09, 99.6% CI 0.02–0.42, Pc < 0.001, P-score = 0.821), cefuroxime intracameral injection (OR 0.18, 99.6% CI 0.09–0.35, Pc < 0.001, P-score = 0.660), and intracameral moxifloxacin (OR 0.36, 99.6% CI 0.16–0.79, Pc = 0.003, P-score = 0.455) (Fig. 3A, Supplementary Table 2). Although some other regimens had lower OR values, these regimens did not have a significant prophylactic effect.

Sensitivity analysis focusing on administration route. Data from 42 articles with 6,239,835 post-surgical eyes were analyzed for this route-comparison analysis. Intracameral injection was compared with no antibiotics in 31 studies, and this comparison involved the largest number of cases (Fig. 2B). According to this network meta-analysis, two intracameral injection-related regimens (intracameral + subconjunctival injection, OR 0.05, 99.4% CI 0.00–0.61, Pc = 0.010, P-score = 0.901; intracameral injection, OR 0.19, 99.4% CI 0.12–0.30, Pc < 0.001, P-score = 0.637) significantly decreased POE risk (Fig. 3B, Supplementary Table 3). Of note, the route with the lowest POE incidence and the highest P-score was intracameral + subconjunctival injection; however, Bhatta[14] was the only study who evaluated this route. The intra-cameral antibiotic doses used in the various published literature were summarized in Table 1. The scatter plot for 31 studies that compared intracameral injection and no antibiotic arms suggests marginal possibility of weak publication bias (Kendall test tau = 0.22, P = 0.092 < 0.1, Supplementary Fig. 2). The use of ointment (OR 0.10, 99.4% CI 0.00–8.77, P-score = 0.720) and irrigation (OR 0.160, 99.4% CI 0.02–1.65, P-score = 0.668) resulted in lower OR values than intracameral injection; however, data for these administration routes are scarce (Fig. 3B).

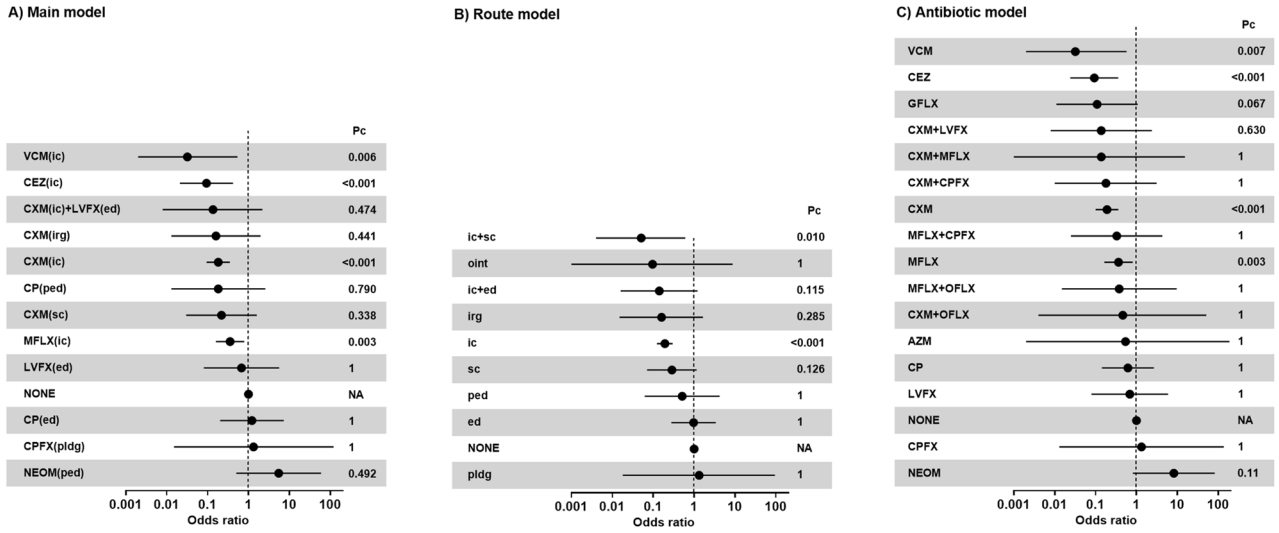

Figure 3. Forest plots. Common comparator was no antibiotic prophylaxis (NONE). Please note that 99.6% confidence interval (CI) for the main model, 99.4% CI for the route model, and 99.7% CI for the antibiotic model were used. Please see Supplementary Table 7 for more detail. Pc, Bonferroni-corrected P value. Please see Supplementary Table 7 for more detail. *NONE* no prophylactic antibiotics, *CEZ* cefazoline, *CXM* cefuroxime, *CAZ* ceftazidime, *MFLX* moxifloxacin, *CPFX* ciprofloxacin, *OFLX* ofloxacin, *GFLX* gatifloxacin, *LVFX* levofloxacin, *VCM* vancomycin, *NEOM* neomycin, *GM* gentamycin, *TB* tobramycin, *AZM* azithromycin, *CP* chloramphenicol, *VCM* vancomycin. *ic* intracameral, *ed* eye drop, *ped* pre-operative eye drop, *irg* irrigation, *sc* subconjunctival injection, *pldg* pledget.

Antibiotic	Studies (RCTs)	Eyes	Pooled frequency (%)	95% CI (%)
VCM(ic)	2 (0)	22,088	0.004	0.000–0.024
CEZ(ic)	4 (0)	70,249	0.011	0.000–0.022
MFLX(ic)	12 (1)	1,573,724	0.019	0.017–0.021
CP(ed)	4 (0)	55,498	0.027	0.011–0.043
CXM(ic)	15 (1)	1,450,272	0.045	0.041–0.048
NONE	39 (2)	2,987,583	0.082	0.079–0.085

Table 2. Pooled arm-level postoperative endophthalmitis frequency. Frequency was pooled using generic inverse variance method. 95% CI: 95% confidence interval. About two or more articles were presented for preventive option evaluation. NONE, no prophylactic antibiotics; CEZ, cefazoline; CXM, cefuroxime; MFLX, moxifloxacin; VCM, vancomycin; CP, Chloramphenicol. (ic), intracameral; (ed), eye drop.

Sensitivity analysis focusing antibiotic type. An additional network meta-analysis was conducted to compare the antibiotic types as a sensitivity analysis. Two studies that made separate small loops were excluded from the analysis: Yao[57] compared vancomycin plus tobramycin and tobramycin; Moser[37] comparing three arms; ofloxacin, cefazoline plus ofloxacin, and cefazoline plus moxifloxacin. A random-model network meta-analysis incorporating 6,396,287 cases from 40 studies revealed that vancomycin was associated with the lowest ophthalmitis risk (OR 0.03, 99.7% CI 0.00–0.57, Pc = 0.007) and the highest P-score of 0.930 (Figs. 2C, 3C, Supplementary Table 4). Cefazoline (OR 0.09, 99.7% CI 0.02–0.36, Pc < 0.001), cefuroxime (OR 0.19, 99.7% CI 0.10–0.36, Pc < 0.001), and moxifloxacin (OR 0.36, 99.7% CI 0.16–0.81, Pc < 0.001) also prevented postsurgical endophthalmitis (Fig. 3C). No combination treatment decreased the risk of endophthalmitis in this model (Fig. 3C).

Sensitivity analyses at single-arm-level incidence. The pooled arm-level endophthalmitis incidence among eyes without antibiotics was 0.082% (95% CI 0.079–0.085, Table 2). Intracameral injection of vancomycin (0.004%, 95%CI 0–0.024), cefazoline (0.011%, 95%CI 0.001–0.022), moxifloxacin (OR 0.019, 95% CI 0.017–0.021), and cefuroxime (OR 0.045, 95% CI 0.041–0.048) lowered the risk of endophthalmitis in patients compared with those who did not use prophylactic antibiotics.

Discussion

We conducted the first network meta-analysis to comprehensively evaluate the efficacy of antibiotics administered for the prevention of POE in a population of 6.8 million eyes. This study highlighted the efficacy of intracameral injection of cefuroxime and moxifloxacin in the prevention of POE in cataract surgery. Network meta-analysis is an analytical method developed as an extension of pairwise meta-analysis and is useful when

multiple interventions are present in a single subject[59]. Network meta-analysis allows us to estimate the relative effects of all interventions by comparing direct and indirect evidence.

Among a wide variety of techniques, intracameral administration is currently the most reliable prophylaxis procedure with accumulated evidence (Fig. 3A,B). Intracameral vancomycin and cefazoline injections led to the best OR and P-scores in the main model (Fig. 3A, Supplementary Table 2). Cefuroxime and moxifloxacin via intracameral injection with the next best OR were supported by more robust evidence from numerous studies including one RCT for each drug (Table 1, Fig. 3A). These findings were validated by sensitivity analysis (Fig. 3C). To date, intracameral cefuroxime and moxifloxacin have been frequently evaluated on this topic; however, vancomycin and cefazoline may work as superior preventive medications. Efficacy of antibiotics through other routes such as ointment, irrigation, and subconjunctival injection were unclear. Furthermore, combination regimen advantage could not be confirmed.

We detected only two RCTs on this topic during our search. The European Society of Cataract and Refractive Surgeons multicenter study published in 2007 applied a 2 by 2 factorial design for 16,603 patients[13]. The use of intracameral cefuroxime injection soon after surgery lowered the risk of POE, whereas topical perioperative levofloxacin did not[13]. In 2019, Melega et al. reported another RCT that recruited 3640 patients. Intracameral moxifloxacin injection reduced the occurrence of postcataract endophthalmitis. Two ultra-large-scale retrospective cohort studies also confirmed the effectiveness of prophylactic intracameral antibiotic administration. Daien et al. investigated data from more than 2 million subjects and concluded that intracameral cefuroxime injection reduced the frequency of POE[18]. According to a recent Indian observational study with 2 million postsurgical eyes, intracameral moxifloxacin lowered the incidence[26]. Based on these RCTs and large cohort studies, intracameral cefuroxime and moxifloxacin were used as first-choice prophylaxis for POE after cataract surgery.

On the other hand, according to our network meta-analysis, vancomycin and cefazoline inoculated into the anterior chamber might be a better choice. We would like to discuss the merit of vancomycin and cefazoline in terms of antibacterial spectrum. Lalwani et al. reported that coagulase-negative staphylococcus accounted for 50 of 73 (68.4%) eyes as causative microbe of endophthalmitis after cataract surgery[60]. Fisch et al. described that POE was most frequently caused by *Staphylococcus epidermidis* and that gram-negative organisms were rarely isolated from this population[61]. Cataracts are an age-related condition, and elderly patients with a history of hospitalization or previous antimicrobial therapy are likely to carry methicillin-resistant *S. aureus* or methicillin-resistant *S. epidermidis*. From the perspective of antimicrobial spectrum, it is easy to explain why vancomycin, which is effective for methicillin-resistant microbes, was highly effective in preventing endophthalmitis. Cefazoline is a narrow-spectrum first-generation cephalosporin. That is especially effective against gram-positive bacteria, and it may be an optimal agent to cover POE-causing microbes. Cefazoline is widely used to prevent wound infection in various surgeries involving skin incisions[62]. Moxifloxacin is a broad-spectrum antibiotic that covers gram-positive, gram-negative, and anaerobic bacteria[63]. However, moxifloxacin is usually not prescribed for the treatment of gram-positive coccus infections because more potent antibiotics with narrower coverage are preferred in terms of bacterial resistance[64]. In fact, recent studies reported that the frequency of coagulase-negative staphylococcus-resistant against moxifloxacin has increased to more than 50%[65,66]. Antibiotic agent for prevention of postcataract surgery should be carefully considered. Regarding the results of the network meta-analysis and the antimicrobial spectrum, vancomycin and cefazolin provided into the anterior chamber are attractive options. Nevertheless, vancomycin and cefazoline have been evaluated in a small number of observational studies and in far fewer patients than cefuroxime and moxifloxacin (Tables 1, 2). We hope that more research will evaluate intracameral vancomycin and cefazoline in the future.

Limitations of this study should be mentioned. First, a majority of the articles used for quantitative synthesis were observational studies without confounding factor adjustment (Table 1). The frequency of POE of 0.066% makes it very difficult to conduct high-quality RCTs and prospective studies. We also mentioned in the "limitation" that the study year might influence the antibiotic efficacy results. In addition to the prophylactic administration of antimicrobial agents, the development of postoperative endophthalmitis is also associated with underlying diseases, therapeutic agents, incision type, disinfection, and intraoperative complications. However, these factors were not considered in this study. Moreover, the registered protocol's insufficient description, lack of inquiry for the missing data, inclusion of conference abstract, possibility of clustered endophthalmitis, and inconsistent results among pooled studies may be limitations of our study. Despite this limitation, our research integrated the currently available data using a solid methodology. Our data would help clinicians and researchers select prophylactic antimicrobial administration after cataract surgery.

In conclusion, we performed the first network meta-analyses using data of more than 6.8 million eyes to identify efficacious antibiotic regimens to prevent POE. Multiple analyses confirmed the advantages of single-agent intracameral antibiotic administration. Cumulative evidence suggests that intracameral injection of cefuroxime and moxifloxacin decreased endophthalmitis. Vancomycin and cefazoline injected into the anterior chamber may be a better option. Single-agent intracameral injection of either vancomycin, cefazoline, cefuroxime, or moxifloxacin prevented POE, and we hope that in future, more research will evaluate intracameral vancomycin and cefazoline in detail.

Methods

Overview. The protocol for this systematic review, which complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Table 5) has been registered on the website of the University Hospitals Information Network (UMIN) Center (ID: UMIN000044376)[67] [UMIN Center. UMIN Clinical Trials Registry. Available at https://www.umin.ac.jp/ctr/index.htm. Accessed on November 25, 2021].

No industry sponsor had any role in our study.

Study search. The electronic database search formulas for PubMed, Web of Science Core Collection, Cochrane Advanced Search, and Embase were composited by well-experienced investigators and are listed in Supplementary Table 6. These databases were searched on May 28, 2021 without time period limitation. An explosion was used for the Embase. Additional manual searches were performed independently by two review authors (AK and MT). References in the review articles (Supplementary Reference 2) and eligible original articles (Table 1) were checked for this step. An updated database search on PubMed was conducted on July 22, 2022.

A review author (NH) provided the EndNote file of candidate articles from database for two review authors after duplication removal using EndNote function. At this step, an additional Excel file of the same list was made. The two review authors independently screened all studies in the file and marked potentially included articles on the Excel sheet. The two review authors read the full text of articles that were marked by at least one review author to eventually select eligible articles. When two authors could not resolve a disagreement, a third author participated in the discussion accordingly (NH).

Publication type and trial design. Both published randomized controlled trials and observational studies were included as long as they were written in English language and if they provided sufficient data. A conference abstract was also permitted as part of the search outcome in this study.

Patients. Patients who underwent cataract surgery were included in this study. Cataract surgery included phacoemulsification and aspiration, as well as intracapsular and extracapsular cataract extraction. The degree of cataract hardness, length and location of the incision wound, concurrent intraocular lens insertion, and intraoperative complications were not considered.

No exclusion criteria were set for age and comorbidities, such as diabetes and immune-compromised status.

Treatments. Perioperative antibiotics that were administered to patients via any route were accepted. Prophylactic antibiotics were categorized with a combination of antibiotic type and administration route for the main analysis. Antibiotics type was grouped by generic names regardless of brand names. Administration routes were categorized into followings: intracameral injection, eye drop, pre-operative eye drop, irrigation, subconjunctival injection, ointment, and pledget. A combined regimen of two or more antibiotics was also allowed.

Quality assessment. The Newcastle–Ottawa Quality Assessment Scale for cohort studies was used for quality assessment. This scale was originally designed for non-RCT studies. However, we used this scale for both RCT and observational studies because each item of the scale is applicable even for an RCT. The Cochrane Risk of Bias Tool was used to additionally evaluate the two RCTs.

Data extraction. The two review authors (AK and MT) extracted the study characteristics, such as author name, year of publication, country of origin, study title, type of antibiotic, route of administration, and number of endophthalmitis events input into Excel sheet. The two review authors checked the original research papers together to solve this once there was a disagreement. When this process did not work well, a third review author (NH) made the decision.

Primary outcome from the main analysis. In the main analysis, the frequencies of postcataract surgery endophthalmitis were compared in terms of odds ratio (OR) as the primary endpoint using a random-model network meta-analysis. Treatment arms were determined by the combination of antibiotic type and administration route, e.g., "intracameral cefuroxime injection". Non-specific categories were not included in the analysis. For example, "intracameral injection of any antibiotic" and "topical administration of vancomycin or moxifloxacin" were excluded. "Topical" administration was not allowed as a category since it was too vague.

Secondary outcomes from the sensitivity analysis. The secondary outcomes were also the frequencies of postcataract surgery endophthalmitis compared and measured using OR. In the first sensitivity network meta-analysis, treatments were categorized by administration route regardless of antibiotic type (route model). The second sensitivity network meta-analysis compared antibiotics ignoring administration maneuvers (antibiotic model).

Treatment-level endophthalmitis frequencies were calculated using a generic variance meta-analysis. The Agresti and Coullb method was applied to estimate standard error[68].

Statistics. The proportion of eyes with endophthalmitis were compared between the two treatment groups using ORs. When one or more cells were null in a two-by-two contingency table, 0.5 was added to all cells as continuity correction. The logarithm of the ORs and their standard errors were pooled using frequentist weighted least squares approach random-model network meta-analysis by the "netmeta" package in R (Gerta Rucker, Freiburg, Germany)[69,70]. A no prophylactic antibiotic (NONE) arm was used as the common comparator, and each prophylactic arm was tested for comparison with the NONE arm. P-values in the network meta-analysis were Bonferroni-corrected to prevent an increase in alpha error due to multiple comparisons (corrected P value, Pc). Similarly, the alpha values for each analysis were reduced, and the confidence intervals were adjusted accordingly (Supplementary Table 7). Overall heterogeneity was assessed by the package. The P-score, which makes ranking order on a 0–1 scale, a frequentist analog to the surface under the cumulative ranking curve, was provided for each network meta-analysis model[71].

I^2 statistics used for heterogeneity evaluation was interpreted as: $I^2 = 0\%$, no heterogeneity; $I^2 > 0\%$ and $< 30\%$, minimal heterogeneity; $I^2 \geq 30\%$ and $< 60\%$, mild heterogeneity; $I^2 \geq 60\%$ and $< 85\%$, moderate heterogeneity; and $I^2 \geq 85\%$, considerable heterogeneity.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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References

1. Haddad, N. M., Sun, J. K., Abujaber, S., Schlossman, D. K. & Silva, P. S. Cataract surgery and its complications in diabetic patients. *Semin. Ophthalmol.* **29**, 329–337 (2014).
2. Chan, E., Mahroo, O. A. & Spalton, D. J. Complications of cataract surgery. *Clin. Exp. Optom.* **93**, 379–389 (2010).
3. Taban, M. *et al.* Acute endophthalmitis following cataract surgery: A systematic review of the literature. *Arch. Ophthalmol. (Chicago, Ill).* **123**, 613–620 (2005).
4. McCarty, C. Endophthalmitis following cataract extraction: The need for a systematic review of the literature. *Br. J. Ophthalmol.* **81**, 97–98 (1997).
5. Huang, J. *et al.* Perioperative antibiotics to prevent acute endophthalmitis after ophthalmic surgery: A systematic review and meta-analysis. *PLoS ONE* **11**, e0166141 (2016).
6. Wang, X. L., Huang, X. Y., Wang, Z. & Sun, W. The anterior chamber injection of moxifloxacin injection to prevent endophthalmitis after cataract surgery: A meta-analysis. *J. Ophthalmol.* **2020**, 7242969 (2020).
7. Linertova, R. *et al.* Intracameral cefuroxime and moxifloxacin used as endophthalmitis prophylaxis after cataract surgery: Systematic review of effectiveness and cost-effectiveness. *Clin. Ophthalmol.* **8**, 1515–1522 (2014).
8. Akkach, S., Kam, J. & Meusemann, R. Post-cataract surgery endophthalmitis: The role of prophylactic antibiotic eye drops. *Clin. Exp. Ophthalmol.* **47**, 555–556 (2019).
9. Allen, H. F. & Mangiaracine, A. B. Bacterial endophthalmitis after cataract extraction. II. Incidence in 36,000 consecutive operations with special reference to preoperative topical antibiotics. *Arch. Ophthalmol. (Chicago, Ill).* **91**, 3–7 (1974).
10. Anijeet, D. R., Palimar, P. & Peckar, C. O. Intracameral vancomycin following cataract surgery: An eleven-year study. *Clin. Ophthalmol.* **4**, 321–326 (2010).
11. Asencio, M. A. *et al.* Impact of changes in antibiotic prophylaxis on postoperative endophthalmitis in a Spanish hospital. *Ophthalmic Epidemiol.* **21**, 45–50 (2014).
12. Barreau, G., Mounier, M., Marin, B., Adenis, J. P. & Robert, P. Y. Intracameral cefuroxime injection at the end of cataract surgery to reduce the incidence of endophthalmitis: French study. *J. Cataract. Refract. Surg.* **38**, 1370–1375 (2012).
13. Prophylaxis of postoperative endophthalmitis following cataract surgery: Results of the ESCRS multicenter study and identification of risk factors. *J. Cataract Refract. Surg.* **33**, 978-988 (2007)
14. Bhatta, S., Pant, N. & Poudel, M. Postoperative endophthalmitis with and without intracameral moxifloxacin prophylaxis in a high volume surgery setting. *BMJ Open Ophthalmol.* **6**, e000609 (2021).
15. Bohigian, G. M. A retrospective study of the incidence of culture-positive endophthalmitis after cataract surgery and the use of preoperative antibiotics. *Ophthalmic Surg. Lasers Imaging.* **38**, 103–106 (2007).
16. Cheng, N., Kam, J., Dawkins, R., Sandhu, S. & Allen, P. Post-cataract surgery endophthalmitis in the modern era: Can we do better?. *Clin. Experiment. Ophthalmol.* **42**, 33 (2014).
17. Colleaux, K. M. & Hamilton, W. K. Effect of prophylactic antibiotics and incision type on the incidence of endophthalmitis after cataract surgery. *Can. J. Ophthalmol.* **35**, 373–378 (2000).
18. Daien, V. *et al.* Effectiveness and safety of an intracameral injection of cefuroxime for the prevention of endophthalmitis after cataract surgery with or without perioperative capsular rupture. *JAMA Ophthalmol.* **134**, 810–816 (2016).
19. Dave, V. P. *et al.* Clinical features and microbiology of post-cataract surgery endophthalmitis with and without intracameral moxifloxacin prophylaxis: Endophthalmitis prophylaxis study report 3. *Indian J. Ophthalmol.* **70**, 158–163 (2022).
20. Ferlini, L. *et al.* Intracameral moxifloxacin for prophylaxis of endophthalmitis after cataract surgery: A case Series. *Investig. Ophthalmol. Visual Sci.* **54** (2013).
21. Friling, E. & Montan, P. Bacteriology and cefuroxime resistance in endophthalmitis following cataract surgery before and after the introduction of prophylactic intracameral cefuroxime: A retrospective single-centre study. *J. Hosp. Infect.* **101**, 88–92 (2019).
22. Galvis, V., Tello, A., Sánchez, M. A. & Camacho, P. A. Cohort study of intracameral moxifloxacin in postoperative endophthalmitis prophylaxis. *Ophthalmol. Eye Dis.* **6**, 1–4 (2014).
23. Garat, M., Moser, C. L., Martin-Baranera, M., Alonso-Tarres, C. & Alvarez-Rubio, L. Prophylactic intracameral cefazolin after cataract surgery: Endophthalmitis risk reduction and safety results in a 6-year study. *J. Cataract Refract Surg.* **35**, 637–642 (2009).
24. García-Sáenz, M. C., Arias-Puente, A., Rodríguez-Caravaca, G. & Bañuelos, J. B. Effectiveness of intracameral cefuroxime in preventing endophthalmitis after cataract surgery Ten-year comparative study. *J. Cataract Refract Surg.* **36**, 203–207 (2010).
25. Guo, B., Au, B., Allen, P. & Van Heerden, A. Role of chloramphenicol eye drops for endophthalmitis prophylaxis following cataract surgery: Outcomes of institutional cessation. *Clin. Exp. Ophthalmol.* **49**, 1116–1118 (2021).
26. Haripriya, A., Chang, D. F. & Ravindran, R. D. Endophthalmitis reduction with intracameral moxifloxacin in eyes with and without surgical complications: Results from 2 million consecutive cataract surgeries. *J. Cataract. Refract. Surg.* **45**, 1226–1233 (2019).
27. Hollander, D. A., Stewart, J. M. & Seiff, S. R. The role of pre-operative topical antibiotics in the prophylaxis of bacterial endophthalmitis post cataract surgery. *Invest. Ophthalmol. Vis. Sci.* **45**, U159–U159 (2004).
28. Jensen, M. K., Fiscella, R. G., Moshirfar, M. & Mooney, B. Third- and fourth-generation fluoroquinolones: Retrospective comparison of endophthalmitis after cataract surgery performed over 10 years. *J. Cataract Refract Surg.* **34**, 1460–1467 (2008).
29. Katz, G. *et al.* Intracameral cefuroxime and the incidence of post-cataract endophthalmitis: An Israeli experience. *Graefes Arch. Clin. Exp. Ophthalmol.* **253**, 1729–1733 (2015).
30. Kingrey, B. & Kingrey, D. Incidence of endophthalmitis in cataract surgery with and without intracameral vancomycin, a clinical review of 30,649 cases of a single surgeon. *Investig. Ophthalmol. Visual Sci.* **60** (2019).
31. Li, Z. B. *et al.* Evaluation of intracameral cefuroxime injection for endophthalmitis prophylaxis following phacoemulsification. *Int. Eye Sci.* **18**, 2282–2284 (2018).
32. Li, A., Shao, J., Gans, R., Bena, J. & Goshe, J. Postoperative endophthalmitis before and after preferred utilization of prophylactic intracameral antibiotics for phacoemulsification cataract surgeries at Cole Eye Institute. *Eye Contact Lens* **45**, 306–309 (2019).
33. Lundstrom, M., Wejde, G., Stenevi, U., Thorburn, W. & Montan, P. Endophthalmitis after cataract surgery: A nationwide prospective study evaluating incidence in relation to incision type and location. *Ophthalmology* **114**, 866–870 (2007).

34. Ma, X., Xie, L. & Huang, Y. Intraoperative cefuroxime irrigation prophylaxis for acute-onset endophthalmitis after phacoemulsification surgery. *Infect. Drug. Resist.* **13**, 1455–1463 (2020).
35. Matsuura, K., Miyoshi, T., Suto, C., Akura, J. & Inoue, Y. Efficacy and safety of prophylactic intracameral moxifloxacin injection in Japan. *J. Cataract Refract Surg.* **39**, 1702–1706 (2013).
36. Melega, M. V. *et al.* Safety and efficacy of intracameral moxifloxacin for prevention of post-cataract endophthalmitis: Randomized controlled clinical trial. *J. Cataract Refract Surg.* **45**, 343–350 (2019).
37. Moser, C. L., Lecumberri Lopez, M., Garat, M. & Martin-Baranera, M. Prophylactic intracameral cefazolin and postoperative topical moxifloxacin after cataract surgery: Endophthalmitis risk reduction and safety results in a 16-year study. *Graefes Arch. Clin. Exp. Ophthalmol.* **257**, 2185–2191 (2019).
38. Moshirfar, M. *et al.* Endophthalmitis after uncomplicated cataract surgery with the use of fourth-generation fluoroquinolones: A retrospective observational case series. *Ophthalmology* **114**, 686–691 (2007).
39. De Paiva Lucena, N., Ferreira, K. S. A., Dos Santos, B. M. A., Lynch, M. I. & Lira, R. P. C. Is Intracameral moxifloxacin a safe option for prevention of post cataract endophthalmitis?. *Invest. Ophthalmol. Vis. Sci.* **57**, 5403 (2016).
40. Porwal, A. C., Patel, A., Mathew, B. C. & Jethani, J. N. Incidence of postoperative endophthalmitis with and without use of intracameral moxifloxacin. *Indian J. Ophthalmol.* **69**, 1353–1354 (2021).
41. Råen, M., Sandvik, G. F. & Drolsum, L. Endophthalmitis following cataract surgery: The role of prophylactic postoperative chloramphenicol eye drops. *Acta Ophthalmol.* **91**, 118–122 (2013).
42. Rahman, N. & Murphy, C. C. Impact of intracameral cefuroxime on the incidence of postoperative endophthalmitis following cataract surgery in Ireland. *Ir. J. Med. Sci.* **184**, 395–398 (2015).
43. Rathi, V. M., Sharma, S., Das, T. & Khanna, R. C. Endophthalmitis Prophylaxis Study, Report 2: Intracameral antibiotic prophylaxis with or without postoperative topical antibiotic in cataract surgery. *Indian J. Ophthalmol.* **68**, 2451–2455 (2020).
44. Rodríguez-Caravaca, G., García-Sáenz, M. C., Villar-Del-Campo, M. C., Andrés-Alba, Y. & Arias-Puente, A. Incidence of endophthalmitis and impact of prophylaxis with cefuroxime on cataract surgery. *J. Cataract Refract Surg.* **39**, 1399–1403 (2013).
45. Romero-Aroca, P. *et al.* Results at seven years after the use of intracamerular cefazolin as an endophthalmitis prophylaxis in cataract surgery. *BMC Ophthalmol.* **12**, 2 (2012).
46. Rudnisky, C. J., Wan, D. & Weis, E. Antibiotic choice for the prophylaxis of post-cataract extraction endophthalmitis. *Ophthalmology* **121**, 835–841 (2014).
47. Rush, S. W., Vu, D. & Rush, R. B. The safety and efficacy of routine administration of intracameral vancomycin during cataract surgery. *J. Ophthalmol.* **2015**, 813697 (2015).
48. Sharma, S., Sahu, S. K., Dhillon, V., Das, S. & Rath, S. Reevaluating intracameral cefuroxime as a prophylaxis against endophthalmitis after cataract surgery in India. *J. Cataract Refract Surg.* **41**, 393–399 (2015).
49. Shenoy, P. *et al.* Impact of prophylactic intracameral moxifloxacin on post-cataract surgery endophthalmitis: Data from a tertiary eye care facility in rural India. *Int. Ophthalmol.* **41**, 2729–2736 (2021).
50. Shorstein, N. H., Winthrop, K. L. & Herrinton, L. J. Decreased postoperative endophthalmitis rate after institution of intracameral antibiotics in a Northern California eye department. *J. Cataract Refract Surg.* **39**, 8–14 (2013).
51. Shorstein, N. H., Liu, L., Carolan, J. A. & Herrinton, L. Endophthalmitis prophylaxis failures in patients injected with intracameral antibiotic during cataract surgery. *Am. J. Ophthalmol.* **227**, 166–172 (2021).
52. Sobaci, G. *et al.* Prophylactic usage of intracameral cefuroxime in the prevention of postoperative endophthalmitis. *Int. J. Ophthalmol.* **9**, 1439–1443 (2009).
53. Tan, C. S., Wong, H. K. & Yang, F. P. Epidemiology of postoperative endophthalmitis in an Asian population: 11-year incidence and effect of intracameral antibiotic agents. *J. Cataract Refract Surg.* **38**, 425–430 (2012).
54. Tuñí-Picado, J. *et al.* Infectious postoperative endophthalmitis after cataract surgery performed over 7 years. The role of azithromycin versus ciprofloxacin eye drops. *Rev. Esp. Quimioter.* **31**, 499–505 (2018).
55. Vieira, I. V., Boianovsky, C., Saraiva, T. J., Godoy, R. B. & Lake, J. Safety and efficacy of intracameral moxifloxacin injection for prophylaxis of endophthalmitis after phacoemulsification. *Arq. Bras. Oftalmol.* **80**, 165–167 (2017).
56. Wejde, G., Montan, P., Lundstrom, M., Stenevi, U. & Thorburn, W. Endophthalmitis following cataract surgery in Sweden: National prospective survey 1999–2001. *Acta Ophthalmol. Scand.* **83**, 7–10 (2005).
57. Yao, K. *et al.* The incidence of postoperative endophthalmitis after cataract surgery in China: A multicenter investigation of 2006–2011. *Br. J. Ophthalmol.* **97**, 1312–1317 (2013).
58. Yu-Wai-Man, P., Morgan, S. J., Hildreth, A. J., Steel, D. H. & Allen, D. Efficacy of intracameral and subconjunctival cefuroxime in preventing endophthalmitis after cataract surgery. *J. Cataract Refract Surg.* **34**, 447–451 (2008).
59. Dias, S. & Caldwell, D. M. Network meta-analysis explained. *Arch. Dis. Child Fetal Neonatal. Ed.* **104**, F8–F12 (2019).
60. Lalwani, G. A. *et al.* Acute-onset endophthalmitis after clear corneal cataract surgery (1996–2005). Clinical features, causative organisms, and visual acuity outcomes. *Ophthalmology* **115**, 473–476 (2008).
61. Fisch, A. *et al.* Epidemiology of infective endophthalmitis in France. The French Collaborative Study Group on Endophthalmitis. *Lancet* **338**, 1373–1376 (1991).
62. Bratzler, D. W. *et al.* Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg. Infect. (Larchmt).* **14**, 73–156 (2013).
63. Deramo, V. A., Lai, J. C., Fastenberg, D. M. & Udell, I. J. Acute endophthalmitis in eyes treated prophylactically with gatifloxacin and moxifloxacin. *Am. J. Ophthalmol.* **142**, 721–725 (2006).
64. Hooper, D. C. Fluoroquinolone resistance among Gram-positive cocci. *The Lancet Infect Dis.* **2**, 530–538 (2002).
65. Kato, J. M. *et al.* Surveillance of post-cataract endophthalmitis at a tertiary referral center: A 10-year critical evaluation. *Int. J. Retina Vitreous.* **7**, 14 (2021).
66. Stringham, J. D., Relhan, N., Miller, D. & Flynn, H. W. Jr. Trends in fluoroquinolone nonsusceptibility among coagulase-negative staphylococcus isolates causing endophthalmitis, 1995–2016. *JAMA Ophthalmol.* **135**, 814–815 (2017).
67. Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann. Internal Med.* **151**, 264–269, w264 (2009).
68. Agresti, A. & Coullb, B. A. Approximate is better than "Exact" for interval estimation of binomial proportions. *Am. Stat.* **52**, 8 (1998).
69. Caldwell, D. M., Ades, A. E. & Higgins, J. P. Simultaneous comparison of multiple treatments: Combining direct and indirect evidence. *BMJ* **331**, 897–900 (2005).
70. Salanti, G. & Schmid, C. H. Research Synthesis Methods special issue on network meta-analysis: Introduction from the editors. *Res. Synth. Methods.* **3**, 69–70 (2012).
71. Rücker, G. & Schwarzer, G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med. Res. Methodol.* **15**, 58 (2015).

Author contributions

A.K. and N.H. contributed equally to this paper. A.K., N.H., No. Mi. and M.T. designed the study. A.K., N.H., H.K. and M.T. contributed to the data collection. A.K., N.H. and M.T. analyzed data. A.K., N.H., E.N., Na.Ma., T.K. and M.T. wrote the manuscript. All authors reviewed the manuscript.

Competing interests

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Additional information

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Correspondence and requests for materials should be addressed to M.T.

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