**Supplementary Online Content**



This supplementary material has been provided by the authors to give readers additional information regarding their work.

**eTable 1.** Descriptive information for each included study

| Study ID | Study dates | Nation | Total (N) | Post-operative intracameral antibiotic and concentration | Post-operative topical antibiotic |
|---|---|---|---|---|---|
| **Cefuroxime** | | | | | |
| ESCRS, 2007 | 2003-2006 | 24 Nations - Multicenter | 16,211 | Cefuroxime 1 mg/0.1 mL | Levofloxacin |
| Yu-Wai-Man et al., 2008 | 2000-2006 | United Kingdom | 36,743 | Cefuroxime 1 mg/0.1 mL | None |
| Arshinoff et al., 2011 | 1993-2010 | Canada | 57,620 | Cefuroxime 1 mg/0.1 mL | None |
| Barreau et al., 2012 | 2003-2008 | France | 5,115 | Cefuroxime 1 mg/0.1 mL | Tobramycin |
| Myneni et al., 2013 | 2004-2012 | United Kingdom | 25,296 | Cefuroxime 1 mg/0.1 mL | None |
| Beselga et al., 2014 | 2005-2011 | Portugal | 15,689 | Cefuroxime 1 mg/0.1 mL | Levofloxacin |
| Rahman N et al., 2014 | 1997-2011 | Ireland | 14,043 | Cefuroxime 1 mg/0.1 mL | None |
| Rock et al., 2014 | 2002-2013 | Germany | 31,752 | Cefuroxime 1 mg/0.1 mL | Moxifloxacin |
| Sharma et al., 2015 | 2006-2012 | India | 15,122 | Cefuroxime 1 mg/0.1 mL | Ofloxacin |
| Herrinton et al., 2016 | 2007-2011 | USA | 273,490 | Cefuroxime 1 mg/0.1 mL | Gatifloxacin or surgeon preference |
| **Moxifloxacin** | | | | | |
| Arshinoff et al., 2011 | 1993-2010 | Canada | 46,941 | Moxifloxacin 100-500 mcg/0.1-0.2 mL | None |
| Matsuura et al., 2013 | 2009-2012 | Japan | 34,752 | Moxifloxacin 5-50 mcg/0.1 mL(varied dose in 19 institutions) | None |
| Galvis et al., 2014 | 2007-2012 | Colombia | 2,674 | Moxifloxacin 500 mcg/0.1 mL | Gatifloxacin or moxifloxacin |
| Rudnisky et al., 2014 | 2002-2009 | Canada | 63,477 | Moxifloxacin 100 mcg/0.1 mL | *Multiple antibiotics |
| Herrinton et al., 2016 | 2007-2011 | USA | 258,859 | Moxifloxacin 100 mcg/0.1 mL | Gatifloxacin or surgeon preference |
| Haripriya et al., 2017 | 2014-2016 | India | 194,252 | Moxifloxacin 500 mcg/0.1 mL | Ofloxacin |
| **Vancomycin** | | | | | |
| Anijeet et al., 2010 | 1998-2008 | United Kingdom | 16,606 | Vancomycin 1 mg/0.1 mL | Fusidic acid |
| Arshinoff et al., 2011 | 1993-2010 | Canada | 31,469 | Vancomycin 1 mg/0.1 mL | None |
| Rudnisky et al., 2014 | 2002-2009 | Canada | 71,557 | Vancomycin 1 mg/0.1 mL | *Multiple antibiotics |
| Rush et al., 2015 | 2010-2015 | USA | 20,719 | Vancomycin 1 mg/0.1 mL | Besifloxacin |
| Au et al., 2016 | 2000-2014 | Australia | 14,348 | Vancomycin 1 mg/0.1 mL | None |

Footnote: *Topical antibiotics include: 37.5% polymyxin B and trimethoprim, 35.1% moxifloxacin, 9.5% ofloxacin, 8.2% ciprofloxacin, 4.3% gatifloxacin, 4.0% both moxifloxacin and tobramycin, 1.0% polymyxin B, and 0.5% moxifloxacin, neomycin and polymyxin B.

**eTable 2.** Gradepro quality of evidence for intracameral antibiotic efficacy analysis.

**Intracameral antibiotics for prevention of endophthalmitis after phacoemulsification**

**Bibliography:**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects *Time frame is 1997-2017* | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Intracameral antibiotics (95% CI) |
| **Observational Studies** | 909582 (16 studies[3]) 1-90 days | ⊕⊕⊕⊖ **MODERATE**[4,5,6] due to risk of bias, large effect, plausible counfounding would change the effect | **OR 0.210** (0.153 to 0.288)[2] | **Low**[1] | |
| | | | | **2000 POE per 1000000** | **1579 fewer POE per 1,000,000** (from 1423 fewer to 1693 fewer) |
| **Randomized Controlled Trial** | 16211 (1 study) 1-90 days | ⊕⊕⊕⊕ **HIGH**[6] due to large effect | **OR 0.22** (0.08 to 0.57) | **2962 per 1000000** | **2309 fewer per 1,000,000** (from 1271 fewer to 2724 fewer) |

*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).

**CI:** Confidence interval; **OR:** Odds 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.

[1] The median assumed risk for control groups was 0.2% and the corresponding risk for intervention groups was 0.03%.

[2] P value < 0.0001

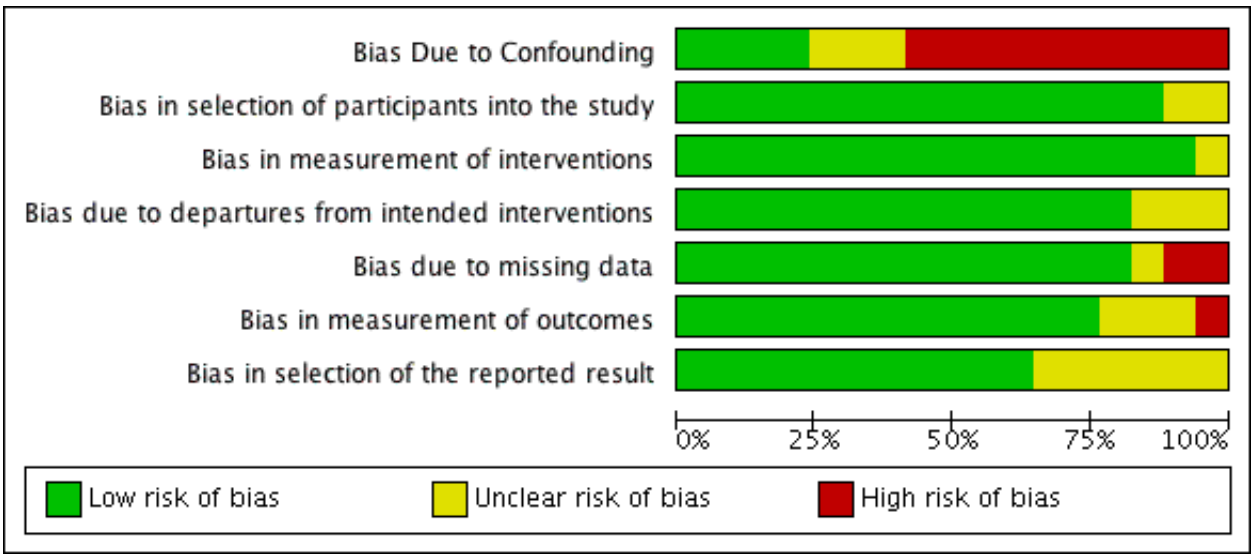
[3] The findings for non-randomized studies consists of case-control and other study designs together.

[4] Many observational studies showed no evidence of controlling for confounders.

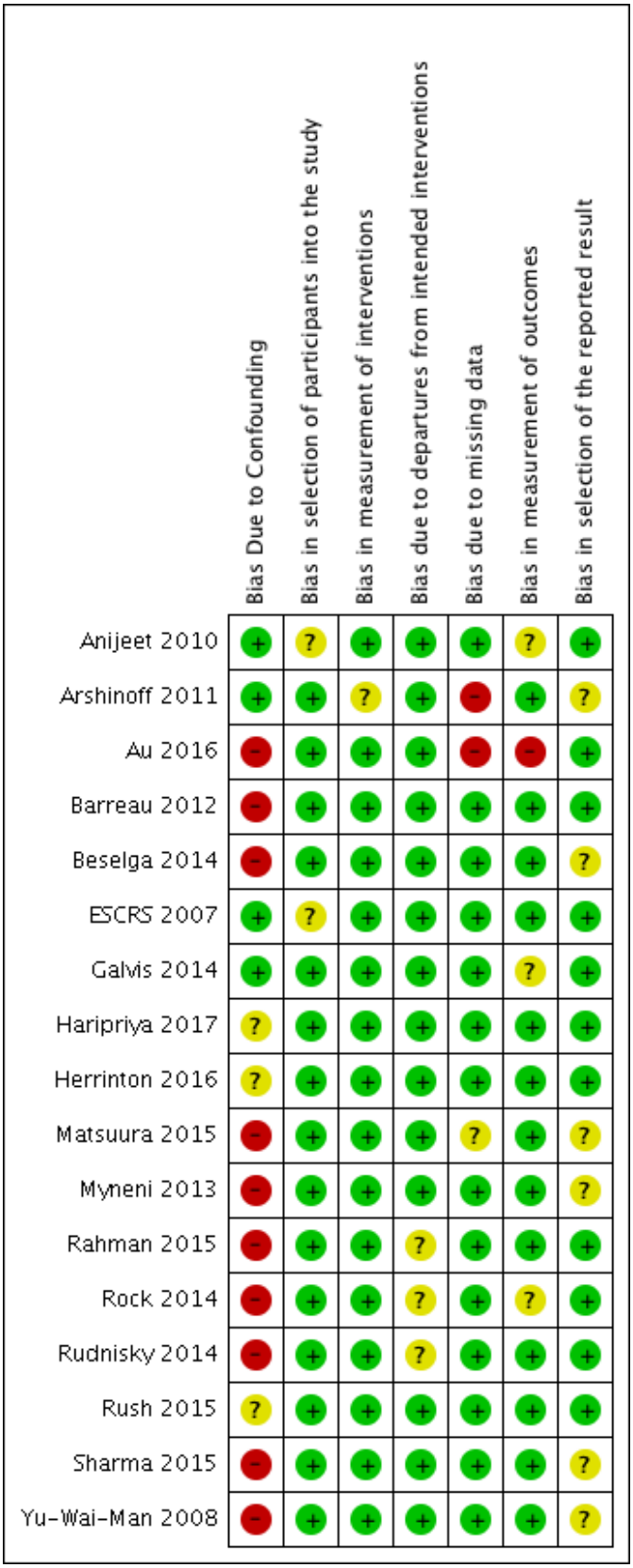
[5] Strength of this recommendation is moderate due to the existence of only one identified randomized controlled clinical trial.

[6] Our collected evidence suggests a relatively large decrease in the rates of POE when intracameral antibiotics are used.

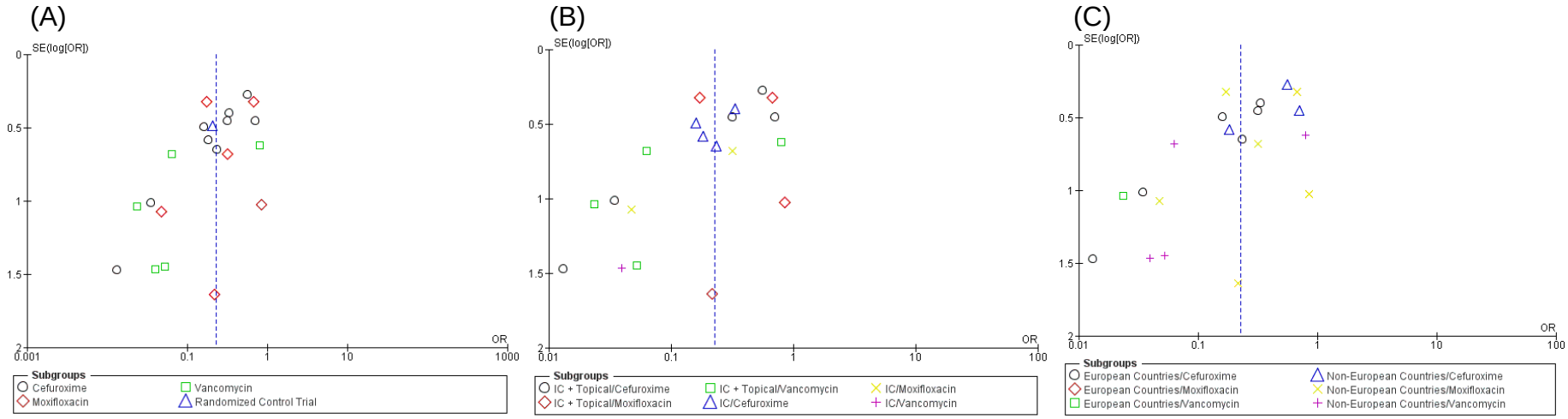
Footnote: We used the GRADEprofiler (Version 3.6.1, available at: http://tech.cochrane.org/revman/other-resources/gradepro/download) to evaluate evidence quality and strength of recommendations for each pre-specified outcome in all included studies of the meta-analysis. Regarding inconsistency among studies, only three of our studies had confidence intervals for efficacy, which crossed the midline to the range of "no effect." None of the confidence intervals for included studies showed evidence of appreciable harm due to the intervention.



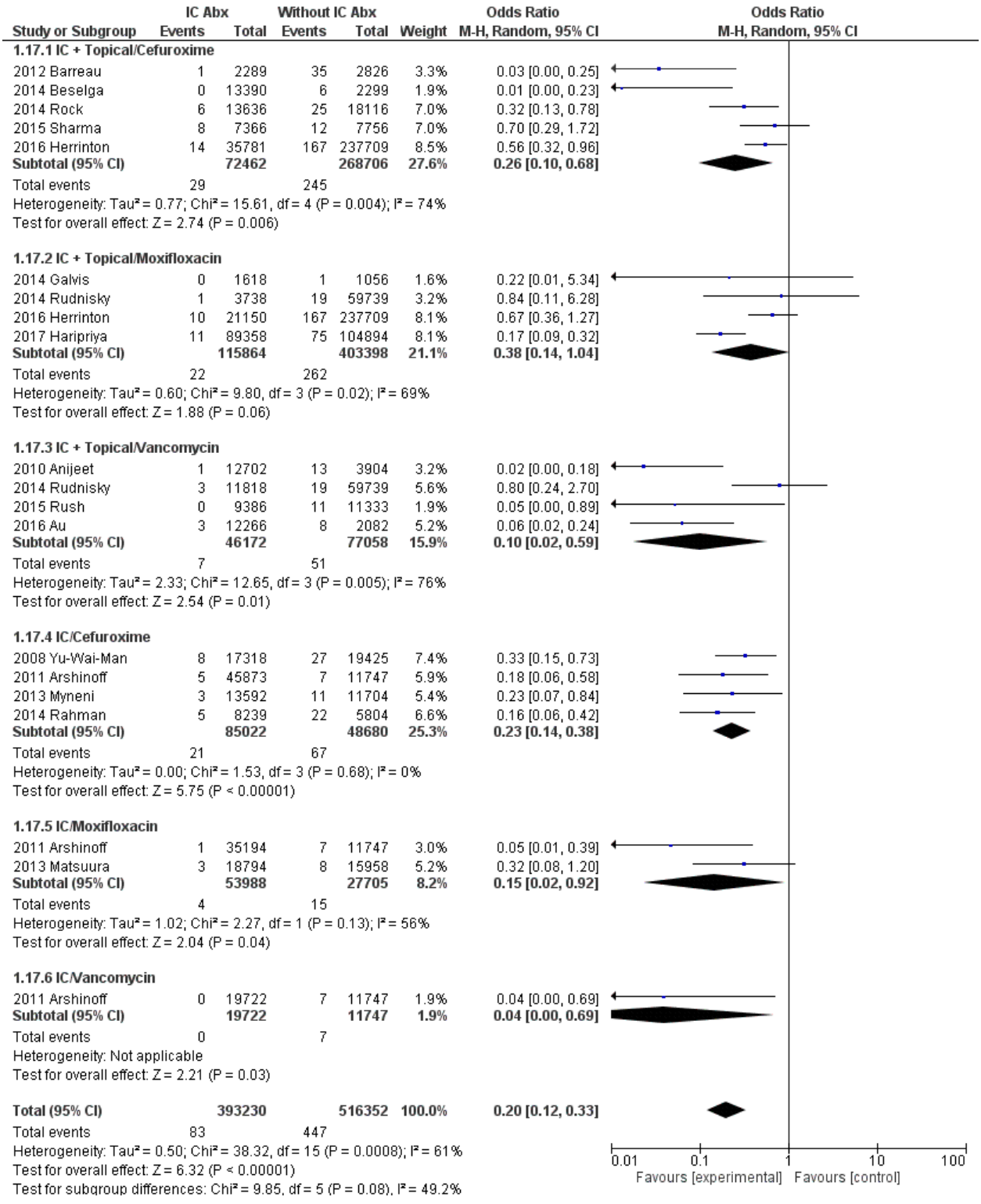

**eFigure 1.** Risk of bias summary of 17 studies included in the pooled meta-analysis.




**eFigure 2.** Risk of bias for individual studies in the pooled meta-analysis.

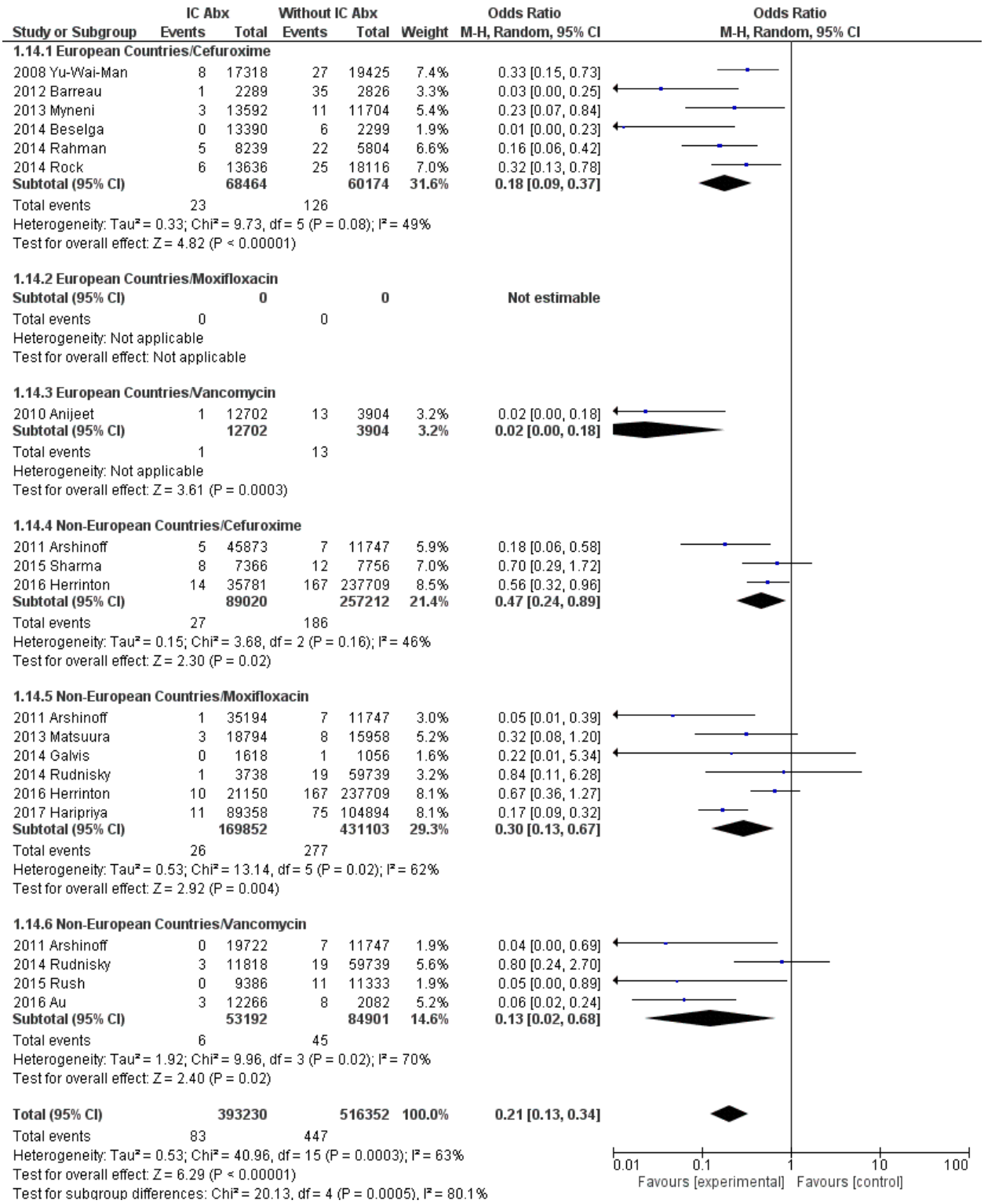



**eFigure 3.** Random effect funnel plot analysis of included studies.
(A) Minimal publication bias shown from seventeen study comparison of POE rate reduction of IC antibiotics against no IC antibiotics at the end of phacoemulsification cataract surgery. (B) Comparison of IC antibiotics with topical antibiotics compared to IC antibiotics alone. (C) Geographical comparison of POE incidence between European and non-European studies. IC = intracameral, POE = postoperative endophthalmitis.




**eFigure 4**. Random effect forest plot of postoperative endophthalmitis incidence with intracameral plus topical antibiotics versus intracameral antibiotics alone.

Figure legend: Comparison of post-phacoemulsification cataract surgery endophthalmitis in patients who received IC plus topical antibiotics versus IC antibiotics alone at the end of cataract surgery. No statistical difference was noted within cefuroxime (P = 0.85), moxifloxacin (P = 0.38), or vancomycin (P = 0.58) groups. Abx = antibiotic, IC = intracameral.




**eFigure 5.** Random effects forest plot of postoperative endophthalmitis incidence in European versus non-European studies.

Figure legend: Comparison of POE rates of European and non-European based studies that used IC antibiotics at the end of phacoemulsification cataract surgery. Average weighted POE incidence of ICC in Europe was 0.0366% compared to 0.0303% in non-European countries. The average weighted POE for Vancomycin with the one European study was 0.0079%; while the four non-European studies was 0.0113%. There were no IC moxifloxacin studies in Europe to make a comparison. Abx = antibiotic, IC = intracameral.

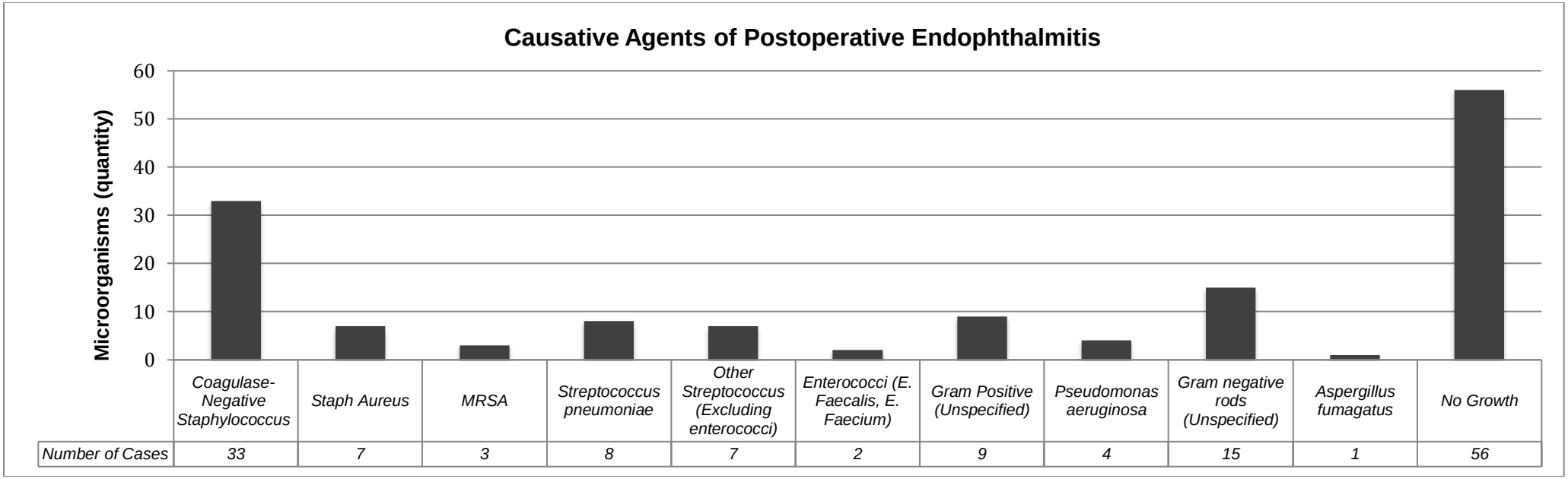

**eFigure 6.** Risk of bias summary for the safety analysis of intracameral cefuroxime.
Footnote: We used the Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool for Human and Animal Studies within the RevMan figure template. This is a graphic representation of OHAT results.


**eFigure 7.** Risk of bias summary for the safety analysis of intracameral moxifloxacin.

Footnote: We used the Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool for Human and Animal Studies within the RevMan figure template. This is a graphic representation of OHAT results.


**eFigure 8.** Risk of bias summary for the safety analysis of intracameral vancomycin.

Footnote: We used the Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool for Human and Animal Studies within the RevMan figure template. This is a graphic representation of OHAT results.




**eFigure 9.** Causative infectious agents of postoperative endophthalmitis extracted from the 17 included studies.

**eMethods.** Details of the target analysis, inclusion criteria, search strategy, risk of bias and quality of evidence.

We conducted a systematic review and meta-analysis of relevant literature using the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines[1] to determine the efficacy of intracameral (IC) cefuroxime (ICC), moxifloxacin (ICM), and vancomycin (ICV) for post-phacoemulsification cataract surgery endophthalmitis prevention. We also reviewed all articles within our literature search that reported safety or toxicity data with ICC, ICM, and ICV.

*Target Analysis (Efficacy):* A systematic review of literature for the efficacy of IC antibiotics for endophthalmitis prevention was performed. We structured our analysis based on the principles of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE).[2] The Patient, Intervention, Comparison, and Outcome (PICO) model was utilized for IC antibiotic efficacy analysis.[3]

*Eligibility criteria (Efficacy):* Inclusion criteria for the efficacy analysis of IC antibiotics for endophthalmitis prevention were: randomized controlled trials (RCTs), quasi-RCTs, cohort studies, or case-control studies; minimum sample size of n=500 eyes; phacoemulsification cataract surgery; studies reporting POE incidence with a numerator and denominator; and studies including an IC antibiotic group versus a non-IC antibiotic (topical, subconjunctival or non-specified) group. Studies were excluded if they included extracapsular cataract extraction (ECCE) surgeries in their data analysis or other non-phacoemulsification technique that could not be separated to isolate phacoemulsification only studies. Studies were excluded if they did not report original data, did not indicate POE incidence, were case reports, or were ongoing clinical trials with no published results.

*Target Analysis (Safety):* Target conditions for the analysis of IC antibiotic safety included toxicity to the cornea, anterior chamber, or retina, or a change in intraocular pressure (IOP) or visual acuity. Eligible participants consisted of animal models or post-operative human recipients of phacoemulsification cataract surgery who received ICC, ICM, or ICV.

*Eligibility criteria (Safety):* Inclusion criteria for the safety analysis of IC antibiotics for endophthalmitis prevention were: RCTs, quasi-RCTs, cohort studies, case-control studies, case series, or animal studies; minimum sample size of n=5 eyes; evaluation of ocular tissue toxicity as a result of ICC, ICM or ICV included in the outcomes; and correlation of antibiotic dose to safety or toxicity levels. We excluded *in vitro* studies and articles that did not report original data.

*Data extracted:* We extracted the following: type of study, IC antibiotic used, country of origin, incidence of POE with and without IC antibiotics, dose of antibiotic, use of topical antibiotics, location of toxicity and microorganisms isolated in POE.

*Search strategy*: Individualized search strategies by information specialist (M. M.) were utilized to optimize search criteria for each online database.

Medline / PubMed (National Library of Medicine)

Performed: 01/17/2017

(vancomycin OR vanco-mycin OR Vancomycine OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin OR Vancocine OR Vancocin HCl OR Vancomicina OR moxifloxacin OR Proflox OR moxifloxacin hydrochloride[tw] OR Octegra OR Avelox OR Avalox OR Izilox OR Actira OR BAY 12-8039 OR BAY-12-8039 OR BAY-128039 OR BAY 128039 OR cefuroxime OR Cephuroxime OR Zinacef OR Ketocef OR Glycopeptides OR Fluoroquinolones OR Cefotaxime OR Cephalosporins OR "Vancomycin"[Mesh] OR "moxifloxacin" [Supplementary Concept] OR "Cefuroxime"[Mesh] OR "Glycopeptides"[Mesh:NoExp] OR "Fluoroquinolones"[Mesh:NoExp] OR "Cefotaxime"[Mesh:NoExp] OR "Cephalosporins"[Mesh:NoExp])
AND
(Intracameral* OR Intraocular* OR Intra-Ocular* OR Periocular* OR intraorbital* OR intra-orbital* OR "Injections, Intraocular"[Mesh:NoExp OR Cataract OR Cataracts OR phacoemulsification OR anterior chamber[tw] OR "Cataract"[Mesh] OR "Cataract Extraction"[Mesh] OR "Phacoemulsification"[Mesh] OR "Anterior Chamber"[Mesh])

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Scopus (scopus.com)

Performed: 01/17/2017
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AND
TITLE-ABS-KEY ( intracameral* OR intraocular* OR intra-ocular* OR periocular* OR intraorbital* OR intra-orbital* OR cataracts OR phacoemulsification OR "anterior chamber" )
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Cochrane Library (Wiley Online Library)
Performed: 01/17/2017
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and
(intracameral* or intraocular* or intra-ocular* or periocular* or intraorbital* or intra-orbital* or Cataract or Cataracts or phacoemulsification or "anterior chamber" )
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Reviews = 2
Trials = 148
Economic Evaluations = 28

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Performed: 01/17/2017
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AND
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Performed: 01/17/2017
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AND
(Intracameral* OR Intraocular* OR Intra-Ocular* OR Periocular* OR intraorbital* OR intra-orbital*)
N = 35

ScienceDirect (Elsevier)
Performed: 01/17/2017
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AND

(intracameral* OR intraocular* OR intra-ocular* OR periocular* OR intraorbital* OR intra-orbital* OR Cataract OR Cataracts OR phacoemulsification OR "anterior chamber")

N = 1144

Dissertations & Theses (ProQuest)

Performed: 01/17/2017

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N = 481

clinicaltrials.gov

Performed: 01/17/2017

Search #1:

Search terms: (intracameral* OR intraocular* OR intra-ocular* OR periocular* OR intraorbital* OR intra-orbital* OR Cataract OR Cataracts OR phacoemulsification OR "anterior chamber")

AND

Interventions: (vancomycin OR Vancomycine OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin OR Vancocine OR Vancomicina OR moxifloxacin OR Proflox OR Octegra OR Avelox OR Avalox OR Izilox OR Actira OR cefuroxime OR Cephuroxime OR Zinacef OR Ketocef)

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Search terms: (intracameral* OR intraocular* OR intra-ocular* OR periocular* OR intraorbital* OR intra-orbital* OR Cataract OR Cataracts OR phacoemulsification OR "anterior chamber")

AND

Interventions: (Glycopeptides OR Fluoroquinolones OR Cefotaxime OR Cephalosporins)

N = 2

Embase (embase.com)

Performed: 01/17/2017

| No. | Query | Results |
|---|---|---|
| #17 | #11 OR #16 | 1,126 |
| #16 | #12 OR #13 OR #15 | 15 |
| #15 | 'cephalosporine derivative'/dd_cl,dd_io,dd_oc | 6 |
| #13 | 'quinoline derived antiinfective agent'/dd_cl,dd_io,dd_oc | 11 |
| #12 | 'polypeptide antibiotic agent'/dd_cl,dd_io,dd_oc | 0 |
| #11 | #9 OR #10 | 1,111 |
| #10 | 'vancomycin'/exp/dd_cl,dd_io,dd_oc OR 'moxifloxacin'/exp/dd_cl,dd_io,dd_oc OR 'cefuroxime'/exp/dd_cl,dd_io,dd_oc OR 'cefotaxime'/exp/dd_cl,dd_io,dd_oc | 304 |
| #9 | #3 AND #7 AND #8 | 987 |
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| #7 | #4 OR #6 | 78,966 |
| #6 | #4 OR #5 | 78,966 |
| #5 | 'anterior eye chamber'/exp | 10,169 |
| #4 | 'cataract'/exp OR 'cataract extraction'/exp OR 'phacoemulsification'/exp | 71,603 |
| #3 | #1 OR #2 | 99,999 |

| | | |
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| #1 | 'vancomycin'/exp OR 'moxifloxacin'/exp OR 'cefuroxime'/exp | 88,123 |

N = 1356

*Risk of Bias for Safety and Efficacy Analysis*

For the efficacy meta-analysis, both RCTs and observational studies were assessed using the Cochrane risk for bias tool in the Review Manager Software (Review Manager (RevMan) [Computer Program] Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, available at: http://tech.cochrane.org/revman/download [accessed July 2015]). Randomized controlled trials were evaluated utilizing the risk of bias tool in RevMan. Non-RCTs were analyzed using A Cochrane Risk of Bias Assessment Tool: For Non-Randomized Studies of Interventions (ACROBAT-NRSI) Version 1.0.0, 24 September 2014, available from http://www.riskofbias.info [accessed July 2015] and were imported into RevMan for all observational studies. The ACROBAT-NRSI tool assessed the risk of bias associated with seven criteria: confounding, selection of participants into the study, measurement of interventions, departures from intended interventions, missing data, measurement of outcomes, and selection of reported results. For the safety analysis, we used the Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool for Human and Animal Studies (January 2015 version) available from http://ntp.niehs.nih.gov/go/38673 [accessed January 2016]. The OHAT tool was selected for the safety analysis due to the integration of RCT, cohort, case-control, case series, and animal studies. The OHAT tool assessed the risk of bias associated with 6 criteria: selection, confounding, performance, attrition, detection, and reporting. For each study the risk of bias was determined independently by 2 independent reviewers. Funnel plots were evaluated for publication bias using RevMan 5.3.[4]

Results:
All post-operative topical antibiotics were given for 6 days - 1 month post operatively and included the following topical antibiotics: moxifloxacin, tobramycin, fusidic acid, levofloxacin, ofloxacin, gatifloxacin, and besifloxacin. The one exception was Beselga, et al., who gave levofloxacin immediately after surgery, without clarity if treatment was ongoing or only a one time post-operative drop. However, due to placing a topical post-op drop it was included into the topical drop category.

**References**:


1. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama.* 2000;283(15):2008-2012.
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