Quinolones versus macrolides in the treatment of legionellosis: a systematic review and meta-analysis

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26 **Abstract**

27 Background

28 Legionellosis is a life-threatening disease. The clinical superiority of quinolones or

29 macrolides for treating patients with legionellosis has not been established.

30 Methods

31 We performed a systematic review and meta-analysis of studies reporting data for comparison

32 of quinolones versus macrolides in the treatment of proven legionellosis published from

33 01/01/1985 to 31/01/2013. We collected baseline aggregate patient characteristics. Studied

34 outcomes included mortality, clinical cure, time to apyrexia, length of hospital-stay and

35 occurrence of complication in each treatment group. Treatment effect was assessed using a

36 Mantel-Haenszel random effects model.

37 Results

38 Among 1005 abstracts reviewed, 12 studies were selected (n=879 patients). No randomized

39 controlled trial (RCT) was available. Mean age was 58.3 years, 27.7% were women and Fine

40 score was ≥4 in 35.8%. Among 253 patients with quinolone monotherapy, 10 died (4.0%).

41 Among 211 patients with macrolide monotherapy, 23 died (10.9%). The pooled odds ratio of

42 death when treated by a quinolone versus macrolide was 0.5 (95%CI=[0.2 – 1.3], n=8 studies,

43 464 patients). Length of stay was significantly lower in the quinolone monotherapy group.

44 The difference was 3.0 days (95%CI=[0.7 – 5.3], p=0.001, n=3 studies, 263 patients). Both

45 tests for heterogeneity were not significant (I^2=0% for both, p=1). Other studied outcomes

46 were not significantly different among treatment groups.

47 Conclusion

48 Few clinical data on legionellosis treatment are available. This first meta-analysis showed a

49 trend toward a lower mortality rate and a significant decrease in length of hospital-stay in

50 patients receiving quinolone. These results must be confirmed by a randomized clinical trial.

51

Introduction

Legionella pneumophila[1] is the most common intracellular bacteria responsible for severe pneumonia.[2] Its incidence was estimated to 1.2 per 100 000 inhabitants in 2010.[3] Risk factors include a male gender, a smoking habit, a history of chronic lung disease or immunosuppression, as well as travel and stay in large buildings, including hotels and hospitals.[1, 4-6] Prognosis factors include appropriateness and timing of initial antimicrobial therapy.[7, 8]

Legionellosis mostly presents as a mild-to-moderate disease. Severe systemic cases have been reported.[9-11] The overall mortality has been estimated to 12%,[12] and to 15-20% in hospitalized patients. Mortality seems higher in nosocomial cases (15-40% *versus* 10-20% in community-acquired cases).[13] As a result, when initiating an empiric antimicrobial therapy for a severe pneumonia, current guidelines recommend to perform urinary diagnostic tests and to initiate a treatment for both *Streptococcus pneumoniae*, the most frequent bacteria involved in severe pneumonia, and *Legionella spp.*[14, 15] Although erythromycin was the recommended treatment since the first reported outbreak of legionellosis, other agents have been developed. Recommended antimicrobials include quinolones and new macrolides. These recommendations are based on scarce data from *in vitro* and animal studies. Few data are available in humans and none allowed for a definitive conclusion. Consequently, the debate on which antimicrobial should be used in patients with legionellosis and/or to target *Legionella spp.* in patients with pneumonia is still ongoing.

No randomized clinical trial (RCT) has been performed for efficacy comparison. We performed a systematic review and meta-analysis to compare the clinical efficacy of a monotherapy of quinolone or macrolide in the treatment of legionellosis.

Material and methods

Data sources

77 Using Cochrane methodology,[16] we conducted a systematic search of the literature. PubMed,

78 Embase and the Cochrane Central Register of Controlled Trials databases were searched from

79 01/01/1985 to 01/31/2013.

80 Search terms included: quinolone, fluoroquinolone, ofloxacin, ciprofloxacin, pefloxacin,

81 trovafloxacin, levofloxacin, moxifloxacin, gatifloxacin, clinafloxacin, enoxacin,

82 grepafloxacin, parfloxacin, norfloxacin, cinoxacin, macrolide, azithromycin, clarithromycin,

83 erythromycin, spiramycin, roxithromycin. We also included related MeSH terms and Emtree

84 entries. Two queries were performed. The first one ('legionellosis query', Table S1 as an

85 example) aimed to identify studies providing data in legionellosis. In this query, 'legionella',

86 'legionnaire' and 'legionellosis' terms were added to those aforementioned. In the second

87 query, all RCTs performed to compare antimicrobial efficacy in community-acquired

88 pneumonia were searched ('RCTs in pneumonia query', Table S2 as an example). In this

89 second query, the term 'pneumonia' was added.

90 We searched additional references among the following scientific conferences from 2000 to

91 2012: Interscience Conference on Antimicrobial Agents and Chemotherapy, European

92 Congress of Clinical Microbiology and Infectious Diseases, Infectious Disease Society of

93 America and American Thoracic Society. Search terms included: 'legionella', 'legionnaire'

94 and 'legionellosis'.

95 *Study selection*

96 Title and abstract were independently assessed for eligibility by two authors (CB and RL).

97 Full text of eligible studies and congress abstracts were independently examined for final

98 inclusion. The opinion of a third investigator (YY) was asked in case of disagreement.

99 Original studies providing data for comparison of the efficacy of quinolones and macrolides

100 in legionellosis were included. *In vitro* and animal studies were excluded. Legionellosis

101 diagnosis had to be proven using urinary antigen, serology, sputum or tracheal aspirate

102 analyzed by culture or PCR.

103 *Data extraction*

104 Data were extracted using a standardized form: patient population, number of participating

105 centres, number of patients included, antimicrobial agents and doses used, clinical outcomes,

106 severity assessed by the Fine score and adverse effects.

107 *Outcomes*

108 Primary outcome was mortality in each treatment group. Secondary outcomes included

109 clinical cure, time to apyrexia, length of hospital stay, occurrence of complications defined by

110 studies' authors, need for mechanical ventilation and occurrence of adverse effects.

111 *Risk of bias assessment*

112 Risk of bias was assessed using the Newcastle-Ottawa scale.[17] This 8-item scale is suggested

113 by the Cochrane collaboration for risk of bias assessment of nonrandomized studies.[16]

114 However we also used this scale for included RCTs.

115 *Statistical analysis*

116 The analysis focused on patients treated by antimicrobial monotherapy. β-lactams were not

117 considered as effective anti-*Legionella* antimicrobials. We estimated pooled odds ratios and

118 their 95% confidence intervals (95%CIs) comparing between quinolones and macrolides the

119 probability of occurrence of qualitative outcomes. We estimated mean differences for time to

120 apyrexia and length of hospital stay. Estimates were determined using a Mantel-Haenszel

121 random effects model.[16] Statistical heterogeneity was assessed using the chi-square test for

122 heterogeneity and the I² statistic for measuring inconsistency. Analyses were performed using

123 Review Manager v5.2 (Cochrane Collaboration, Oxford, United Kingdom).

124 **<u>Results</u>**

125 *Identification of eligible studies*

126   Databases queries identified 1005 articles and/or congress abstracts. Most were not

127   eligible, and 96 full-text articles were retrieved and read for inclusion (Figure 1). Of those, 12

128   were finally included. All were original articles.[7, 18-28] Nine were observational cohort

129   studies,[7, 18, 20, 23-28] of which six were retrospective.[18, 20, 23, 26-28] They were performed in Spain

130   (n=4),[7, 23-25] in France (n=2),[18, 20] and Japan (n=2).[26, 27] One was international.[28] The three

131   remaining studies were RCTs conducted in patients with pneumonia.[19, 21, 22] Two of them

132   were performed in the USA,[21, 22] the third was international.[19] Five of the 12 studies were

133   conducted in a single centre.[7, 20, 23, 24, 26]

134   *Risk of bias*

135   Overall risk of bias is represented in Figure S1. Representativeness of general population was

136   satisfactory. Patients included in observational studies were all patients with a proven

137   diagnosis of legionellosis presenting in participating centres. Patients included in RCTs were

138   representative of immunocompetent patients with community-acquired pneumonia.

139   Ascertainment of therapy was performed using medical records or specific forms. All

140   outcomes were prespecified and assessed using medical records or form completion. Follow

141   up was adequate and long enough to ensure their assessment.

142   With the exception that by Dournon *et al.*,[18] no observational study controlled for

143   confounding. Dournon *et al.* matched quinolone-treated patients with erythromycin-treated

144   patient for age, duration of Legionnaires' disease, immune status and requirement of

145   mechanical ventilation. Patients treated with quinolone who received co-treatment with

146   rifampicin and/or erythromycin were excluded from their analysis. Two RCTs did not stratify

147   the randomization,[19, 21] and the other one stratified randomization on centre.[22]

148   *Patient characteristics in included studies*

149   Overall, 879 patients with legionellosis were included (10 to 292 patients per study).

150   Mean age was 58.3 years, and 27.7% of patients were women (n=223/806). All patients were

151 hospitalized at baseline, 55.1% (n=411/746) had an underlying disease, 19.8% (n=89/449)

152 had a chronic obstructive pulmonary disease, and 65.9% (n=270/410) had a smoking habit.

153 Data on immunosuppression was available in only 2 studies.[18, 27] In those, 63.6% (n=14/22)

154 and 75% (n=45/60) of patients were immunocompromised. The Fine score was $\geq$ 4 in 35.8%

155 (n=213/595).[7, 23, 26-28] Overall, 71 of the 879 patients with legionellosis enrolled in included

156 studies (8.1%) died during follow up.

157   687 patients with legionellosis were treated with a quinolone (n=377, 54.9%) or

158 macrolide (n=310, 45.1%) monotherapy (Table 1). In studies providing the information,

159 26.0% (n=47/181) of quinolone-treated patients had a Fine score $\geq$ 4, *versus* 32.7%

160 (n=36/110) of patients in the macrolide group.[23, 26-28]

161 *Outcomes*

162   Mortality was reported in 8 studies (Figure 2A).[18, 20, 23-28] Overall mortality occurred

163 in 10.9% of patients treated with a macrolide (n=23/211) *versus* 4.0% of patients treated with

164 a quinolone (n=10/253). The combined odds ratio of death when treated with quinolones

165 *versus* macrolides was 0.5 [95%CI, 0.2; 1.3].

166   Clinical cure was evaluated in 4 studies.[19, 21-23] It was defined as resolution of signs

167 and symptoms of pneumonia at the test-of-cure visit, performed depending on studies

168 between day 1 and day 21 after the end of antimicrobial therapy. One study did not provide

169 clinical cure definition.[23] Clinical cure was observed in 100% of patients in 2 studies, [19, 21]

170 which could not be used for computations. In the 2 other studies, the pooled odds ratio of

171 clinical cure for treatment with a quinolone *versus* a macrolide was 2.3 [95%CI, 0.3; 16.9]

172 (Figure 2B).[22, 23]

173   One study provided data for analysis of time to apyrexia.[23] The time to apyrexia was

174 shorter with quinolones than with macrolides, but the difference was not significant (mean

175 difference, -4.8 hours [95%CI, -22.1; 12.5], Figure 2C).

176   Three studies were available for the comparison of length of hospital-stay (Figure

177 2D).[23, 27, 28] One of them showed a significant reduction of the length of hospital-stay with

178 quinolones *versus* macrolides (-2.8, 95%CI, -5.4; -0.2).[23] We found an overall significant

179 mean reduction of 3.0 days with quinolones *versus* macrolides (95%CI, -5.3; -0.7). Test for

180 heterogeneity was not significant (I^2=0%, p=0.9).

181   Two studies were included in the analysis of complications (Figure 2E).[23, 25] These

182 studies defined complicated legionellosis either as the apparition of pleural effusion,

183 empyema, mechanical ventilation or septic shock;[25] or renal failure, pleural effusion or

184 admission to ICU.[23] The combined odds ratio of complications when treated with quinolones

185 *versus* macrolides, was 0.5 [95%CI, 0.1; 1.6]).

186 *Adverse effects*

187   In the only study providing data on adverse events,[23] the three main reported events

188 were gastrointestinal events (5 – 7%), liver abnormalities (2 – 3%) and phlebitis, which

189 occurred more frequently in patients receiving clarithromycin than in those under

190 levofloxacin therapy (p<0.01).

191 **Discussion**

192   This is the first systematic review and meta-analysis of the effectiveness of quinolones

193 *versus* macrolides in the treatment of legionellosis. We found that despite a small number of

194 studies addressing this issue in clinical settings – and a small number of patients in each study

195 – quinolones seem to have a higher effectiveness than macrolides. Quinolone therapy was

196 significantly associated with a shorter length of hospital-stay, and we observed a trend toward

197 a reduced mortality, a higher clinical cure, a lower time to apyrexia, and a lower rate of

198 complications in patients receiving a quinolone.

199   Our analysis is unique. Published reviews on this topic did not use a systematic

200 methodology for studies inclusion and results analysis.[29, 30] In the absence of RCTs, the type

201 of analysis we conducted is the most accurate way to compare quinolones and macrolides

202 effectiveness in patients with legionellosis and to improve management of this disease.

203   This question has been investigated in experimental models. In all but one of the 19

204 intracellular models reviewed by Pedro-Botet and Yu, quinolones had a higher activity on

205 *Legionella pneumophila* than macrolides.[29] Levofloxacin was the most effective quinolone

206 and azithromycin the most effective macrolide. In animal models of *Legionella pneumophila*

207 infection, treatment with quinolones resulted in an increased survival.[29] However, these

208 experimental results may not be generalisable to humans.

209   Despite a non-significant difference, results for all studied outcomes favoured

210 quinolones. The absence of significance in these comparisons may be related to a lack of

211 statistical power. However, none of the included studies attempted to control for confounding.

212 Patients treated with macrolides had higher severity of disease. This might favour quinolones.

213 Moreover, the macrolide agent used was mostly erythromycin, which is not the most effective

214 macrolide agent as observed in *in vitro* studies.[29] It was the only macrolide used in the study

215 performed by Dournon *et al,*[18] in which the number of deaths in the macrolide group

216 accounted for 40% of overall deaths observed in our review, and with a mortality rate of 50%

217 in this group.

218   This study has some other limitations. First, statistical methodology is limited by the

219 observational design of most included studies. RCTs were not designed for a proper analysis

220 in legionellosis. We used random effects modelling to limit inherent bias. Moreover, our

221 results are strengthened by the absence of heterogeneity. Second, a small number of studies

222 were included. Legionellosis is a rare disease. The systematic strategy used for inclusion

223 aimed to minimize misidentifications and to limit publication bias. However, reporting bias is

224 a recurrent problem in systematic reviews and unpublished work could not be retrieved by our

225 search strategy. Third, we were not able to perform subgroup analysis and/or to adjust on

226 disease severity or prognosis factors. Finally, we could not perform a face-to-face comparison

227 of individual quinolones and macrolides as individual data were not available.

228 In light of our results, should we prefer quinolones or macrolides when treating a

229 patient with a proven *Legionella* pneumonia? Our analysis does not provide a high level of

230 evidence for conclusion. When answering this thorny question, risks associated with the

231 administration of these antimicrobials should be considered. Quinolones are generally well-

232 tolerated drugs; serious adverse events are rare. There is a rare risk of cardiac toxicity with

233 macrolides, but azithromycin is generally considered to be free of serious adverse effects.[31-33]

234 Both quinolones and macrolides have been associated with an increased risk of developing a

235 *Clostridium difficile* infection, with a higher risk for quinolones.[34] The emergence of bacterial

236 resistance in the digestive microbiota has been documented with quinolones,[35] but such

237 consideration should not restrain their use when treating a potentially fatal infection.

238 We believe that quinolones might be preferred for proven legionellosis, especially in

239 patients with severe legionellosis. Empirical antimicrobial therapy for patients with severe

240 pneumonia might benefit of a combination of a β-lactam and a quinolone, when a *Legionella*

241 infection is suspected. However, in patients with mild pneumonia from uncertain origin, the

242 potential negative impact of quinolones on the digestive microbiota should be balanced with

243 their possible higher efficacy than macrolides.

244 This analysis should be confirmed by an international trial. With almost 5000 cases reported

245 in Europe by the European Legionnaires' Disease Surveillance Network in 2011,[36] such trial

246 would bring a definitive conclusion to the recurrent question of antimicrobial selection in

247 *Legionella* pneumonia.

248 **Funding**

250 **Meetings**

251   This work has been presented in the 53rd Interscience Conference on Antimicrobial Agents

252   and Chemotherapy, held in Denver, USA, from 10 to 13 September 2013 (Poster L-1319).

253   This work has been presented in the 15th Journées Nationales d'Infectiologie, held in

254   Bordeaux, France, from 11 to 13 June 2014 (Poster I-07).

255   **<u>Transparency declaration</u>**

256   Pr. Yazdanpanah has received travel grants, honoraria for presentation at workshops, and

257   consultancy honoraria from Bristol-Myers Squibb, Gilead, Merck, Pfizer, Roche, Tibotec, and

258   ViiV Healthcare.

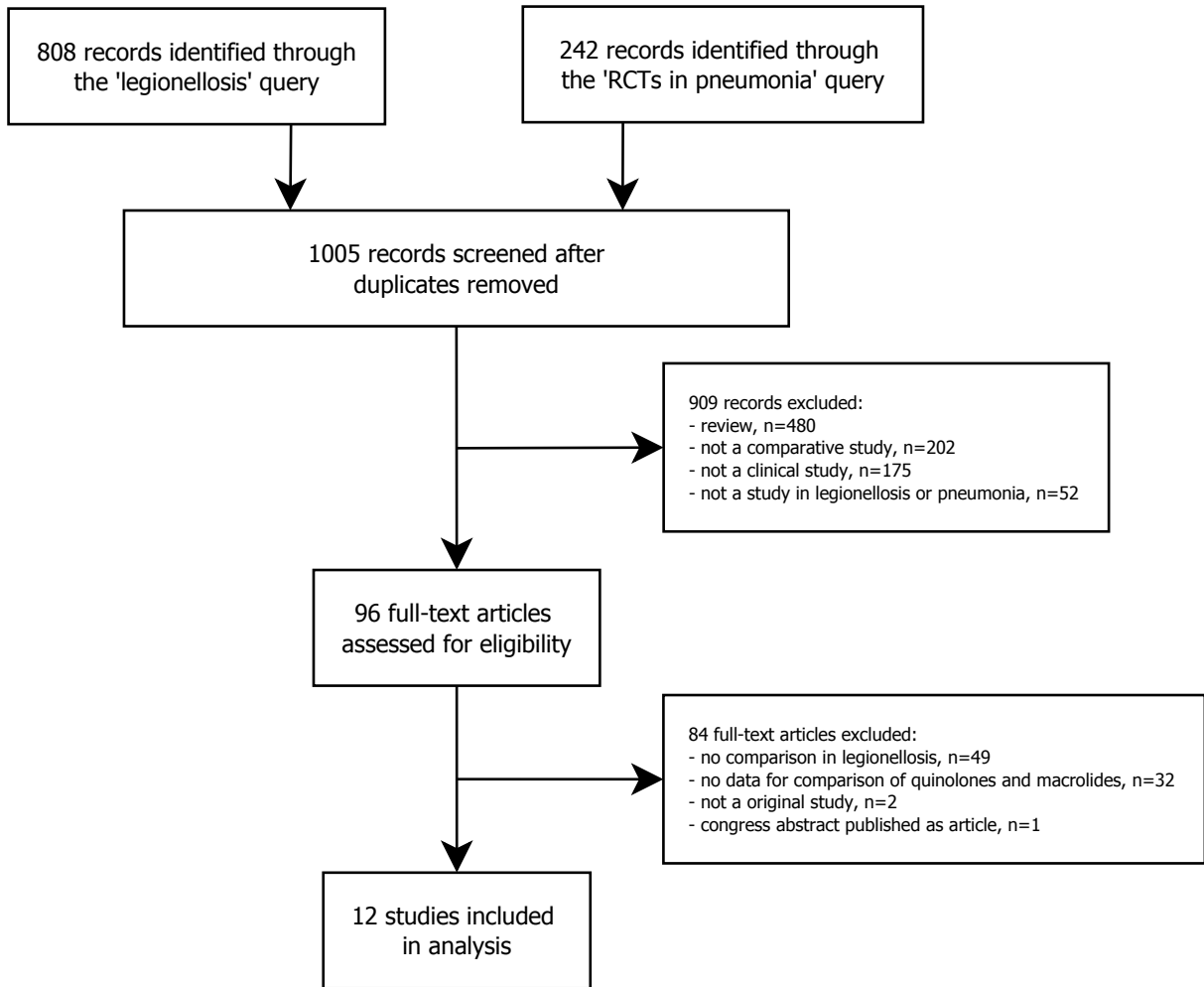259   Other authors reported no conflict of interest.

260

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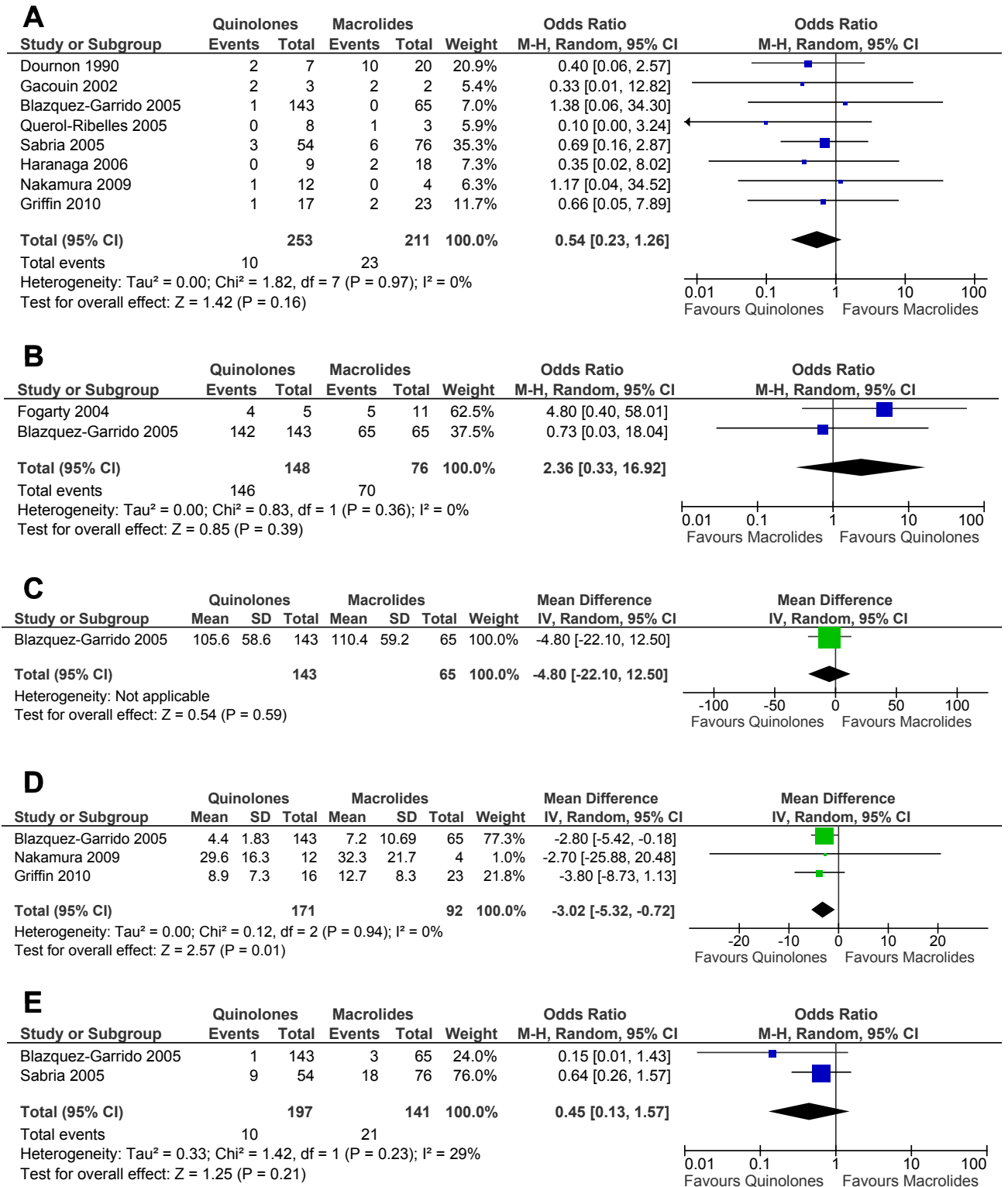353
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355 **<u>Figures</u>**

356 Figure 1. Flowchart of studies inclusion. RCTs, randomized controlled trials.

357

358

359   Figure 2. Comparison of quinolones and macrolides effectiveness in *Legionella* pneumonia.
360   A, analysis of mortality; B, analysis of clinical cure; C, analysis of the time to apyrexia
361   (hours); D, analysis of length of hospital stay (days); E, analysis of the occurrence of
362   complications.
363

A

Study or Subgroup	Quinolones Events	Total	Macrolides Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Dournon 1990	2	7	10	20	20.9%	0.40 [0.06, 2.57]
Gacouin 2002	2	3	2	2	5.4%	0.33 [0.01, 12.82]
Blazquez-Garrido 2005	1	143	0	65	7.0%	1.38 [0.06, 34.30]
Querol-Ribelles 2005	0	8	1	3	5.9%	0.10 [0.00, 3.24]
Sabria 2005	3	54	6	76	35.3%	0.69 [0.16, 2.87]
Haranaga 2006	0	9	2	18	7.3%	0.35 [0.02, 8.02]
Nakamura 2009	1	12	0	4	6.3%	1.17 [0.04, 34.52]
Griffin 2010	1	17	2	23	11.7%	0.66 [0.05, 7.89]
Total (95% CI)		253		211	100.0%	0.54 [0.23, 1.26]
Total events	10		23			

Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 7 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)

Odds Ratio M-H, Random, 95% CI — Favours Quinolones / Favours Macrolides

B

Study or Subgroup	Quinolones Events	Total	Macrolides Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Fogarty 2004	4	5	5	11	62.5%	4.80 [0.40, 58.01]
Blazquez-Garrido 2005	142	143	65	65	37.5%	0.73 [0.03, 18.04]
Total (95% CI)		148		76	100.0%	2.36 [0.33, 16.92]
Total events	146		70			

Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.39)

Odds Ratio M-H, Random, 95% CI — Favours Macrolides / Favours Quinolones

C

Study or Subgroup	Quinolones Mean	SD	Total	Macrolides Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Blazquez-Garrido 2005	105.6	58.6	143	110.4	59.2	65	100.0%	-4.80 [-22.10, 12.50]
Total (95% CI)			143			65	100.0%	-4.80 [-22.10, 12.50]

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)

Mean Difference IV, Random, 95% CI — Favours Quinolones / Favours Macrolides

D

Study or Subgroup	Quinolones Mean	SD	Total	Macrolides Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Blazquez-Garrido 2005	4.4	1.83	143	7.2	10.69	65	77.3%	-2.80 [-5.42, -0.18]
Nakamura 2009	29.6	16.3	12	32.3	21.7	4	1.0%	-2.70 [-25.88, 20.48]
Griffin 2010	8.9	7.3	16	12.7	8.3	23	21.8%	-3.80 [-8.73, 1.13]
Total (95% CI)			171			92	100.0%	-3.02 [-5.32, -0.72]

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)

Mean Difference IV, Random, 95% CI — Favours Quinolones / Favours Macrolides

E

Study or Subgroup	Quinolones Events	Total	Macrolides Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Blazquez-Garrido 2005	1	143	3	65	24.0%	0.15 [0.01, 1.43]
Sabria 2005	9	54	18	76	76.0%	0.64 [0.26, 1.57]
Total (95% CI)		197		141	100.0%	0.45 [0.13, 1.57]
Total events	10		21			

Heterogeneity: Tau² = 0.33; Chi² = 1.42, df = 1 (P = 0.23); I² = 29%
Test for overall effect: Z = 1.25 (P = 0.21)

Odds Ratio M-H, Random, 95% CI — Favours Quinolones / Favours Macrolides

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Table

Table 1. Main characteristics and outcomes of the studies included in the analysis according to monotherapy treatment group. AZM, azithromycin; CIP, ciprofloxacin; CLR, clarithromycin; ERY, erythromycin; LVX, levofloxacin; RXM, roxithromycin; M, macrolide monotherapy; OFX, ofloxacin; PEF, pefloxacin; PAZ, pazufloxacin; Q, quinolone monotherapy; SD, standard deviation; SPX, sparfloxacin; TVA, trovafloxacin. Missing data of presented variables were not available in the corresponding studies.

Study	Enrolment period	Number of patients with legionellosis		Agent(s) used (n)		Mean age (years)		Proportion of women (%)		Underlying disease, n (%)		Fine score ≥4, n (%)		Overall mortality, n (%)		Mean time to apyrexia, hours (SD)		Mean hospital stay, days (SD)		Secondary complication, n (%)		Clinical cure, n (%)	
		Q	M	Q	M	Q	M	Q	M	Q	M	Q	M	Q	M	Q	M	Q	M	Q	M	Q	M
Dournon 1990[18]	1980-1988	7	20	PEF	ERY	49.8		30						2 (28.6)	10 (50.0)								
Lode 1995[19]	1990-1992	1	7	SPX	ERY																	1 (100)	1 (100)
Gacouin 2002[20]	1990-2001	3	2											2 (66.7)	2 (100)								
Sokol 2002[21]	1998-1999	7	7	TVA	CLR																	7 (100)	7 (100)
Fogarty 2004[22]	1997-2000	5	11	LVX	ERY																	4 (80)	5 (45.5)
Blazquez-Garrido 2005[23]	2001	143	65	LVX	AZM, CLR					29 (20.3)	11 (16.9)			1 (0.7)	0 (0)	105.6 (58.6)	110.4 (59.2)	4.4 (1.8)	7.2 (10.7)	1 (0.7)	3 (4.6)	142 (99.3)	65 (100)
Querol-Ribelles 2005[24]	2000-2003	8	3	LVX	CLR									0 (0)	1 (33.3)								
Sabria 2005[25]	1995-2004	54	76	LVX (50), OFX (4)	ERY, CLR	57.4	60	33.3	18.5	37 (66.5)	59 (77.6)			3 (5.6)	6 (7.9)	48.0	77.1	7.6	9.9	9 (10.7)	18 (23.7)		
Haranaga 2006[26]	1996-2005	9	18	CIP	ERY	69.7	62.8	33	22	8 (88.9)	12 (66.7)	6 (66.7)	9 (50.0)	0 (0)	2 (11.1)	84.0	96.0	16.7	20.0				
Nakamura 2009[27]	1999-2008	12	4	CIP (10), PAZ (2)								5 (41.2)	2 (50.0)	1 (8.3)	0 (0)			29.6 (16.3)	32.3 (21.7)				
Griffin 2010[28]	2001-2008	17	23	LVX	AZM (13), CLR (10)			18.7	26.1			7 (41.2)	14 (60.9)	1 (5.9)	1 (4.3)			8.9 (7.3)	12.7 (8.3)				
Viasus 2013[7]	1995-2010	111	74	LVX	ERY, RXM, CLR, AZM													7.0	10.0				

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