

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Definition of pulmonary exacerbation and secondary end points of included studies

Author, year	Study design, phase, name	Definition of pulmonary exacerbation	Secondary endpoints
Wilson <i>et al.</i> (2013) ¹³	RCT, Phase II, n/a	Not clearly defined. (The cited reference describes four definitions. ²⁷)	Time to first exacerbation Pathogen eradication and emergence of resistance Sputum volume/color Pulmonary function Quality of life (SGRQ) AEs
De Soyza <i>et al.</i> (2018) ¹⁴ and Aksamit <i>et al.</i> (2018) ¹⁵	RCT, Phase III, RESPIRE 1 and 2	All of following three criteria 1) worsening of at least three signs or symptoms (dyspnea, wheezing, cough, 24-h sputum volume or sputum purulence) for at least 2 consecutive days 2) fever (body temperature >38.0°C) or malaise/fatigue 3) systemic antibiotic treatment	Exacerbations with a less stringent definition Pathogen eradication and emergence of resistance Pulmonary function Quality of life (SGRQ and QOL-B RSS) AEs
Serisier <i>et al.</i> (2013) ¹⁶	RCT, Phase II, ORBIT 2	Deterioration in at least four of the following criteria 1) sputum production, 2) dyspnea, 3) cough, 4) fever, 5) wheezing, 6) exercise tolerance (or fatigue/lethargy/malaise), 7) FEV1 or FVC fall of at least 10%, 8) new changes on chest radiograph, 9) changes in chest sounds	Time to first exacerbation Pulmonary function Quality of life (SGRQ) AEs
Haworth <i>et al.</i> (2019) ¹⁷	RCT, Phase III, ORBIT 3 and 4	Same as above	Total number of exacerbations, moderate or severe exacerbations <i>P aeruginosa</i> density and ciprofloxacin susceptibility Pulmonary function Quality of life (QOL-B RSS) AEs

Abbreviations: RCT, randomized controlled trial; SGRQ, St George's Respiratory Questionnaire; QOL-B RSS, Quality of Life-Bronchiectasis respiratory symptoms domain score; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; AE, adverse event

Supplementary Table 2. Definition of emergence of resistance according to each included study

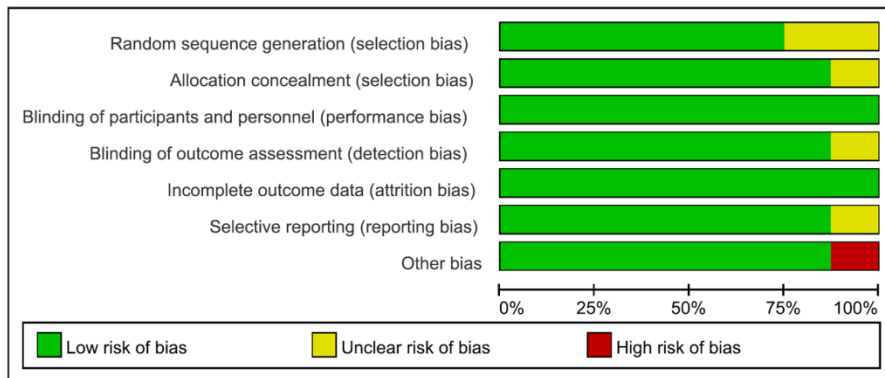
Author, year	Definition of emergence of resistance
Wilson <i>et al.</i> (2013) ¹³ , De Soyza <i>et al.</i> (2018) ¹⁴ , and Aksamit <i>et al.</i> (2018) ¹⁵	Increases in MIC to > 4 mg/L (a level defined as resistant to systemic therapy with ciprofloxacin, according to the CLSI guideline ²⁸)
Serisier <i>et al.</i> (2013) ¹⁶	Increases in MIC to \geq 2 mg/L (a level defined as intermediately susceptible to systemic therapy with ciprofloxacin, according to the CLSI guideline ²⁸)
Haworth <i>et al.</i> (2019) ¹⁷	MIC increase more than twofold

Abbreviations: MIC, minimum inhibitory concentration; CLSI, Clinical and Laboratory Standards Institute

Supplementary Table 3. Microbiologic inclusion criteria of each included study

Author, year	Microbiologic inclusion criteria
Wilson <i>et al.</i> (2013) ¹³	Isolation of a Pre-defined potential respiratory pathogen: <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , Enterobacteriaceae, <i>Stenotrophomonas maltophilia</i> , or <i>Achromobacter xylosoxidans</i> .
De Soyza <i>et al.</i> (2018) ¹⁴ and Aksamit <i>et al.</i> (2018) ¹⁵	Isolation of a pre-specified pathogen: <i>P. aeruginosa</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i> , <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>S. maltophilia</i> , or <i>Burkholderia cepacia</i> .
Serisier <i>et al.</i> (2013) ¹⁶	Isolation of a ciprofloxacin-sensitive <i>P. aeruginosa</i> strain.
Haworth <i>et al.</i> (2019) ¹⁷	Isolation of a ciprofloxacin non-resistant <i>P. aeruginosa</i> strain.

(a)



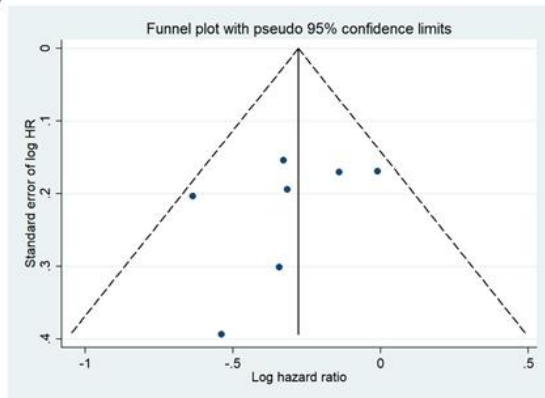
(b)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aksamit et al. (2017) ¹⁵ -14 day on/off	+	+	+	+	+	+	+
Aksamit et al. (2017) ¹⁵ -28 day on/off	+	+	+	+	+	+	+
De Soyza et al. (2017) ¹⁴ -14 day on/off	+	+	+	+	+	+	+
De Soyza et al. (2017) ¹⁴ -28 day on/off	+	+	+	+	+	+	+
Haworth et al. (2019) ¹⁷ -ORBIT 3	+	+	+	+	+	+	+
Haworth et al. (2019) ¹⁷ -ORBIT 4	+	+	+	+	+	+	+
Serisier et al. (2013) ¹⁶	?	+	+	?	+	?	-
Wilson et al. (2013) ¹³	?	?	+	+	+	+	+

Supplementary Figure 1. Risk of bias according to the Cochrane Collaboration's tool

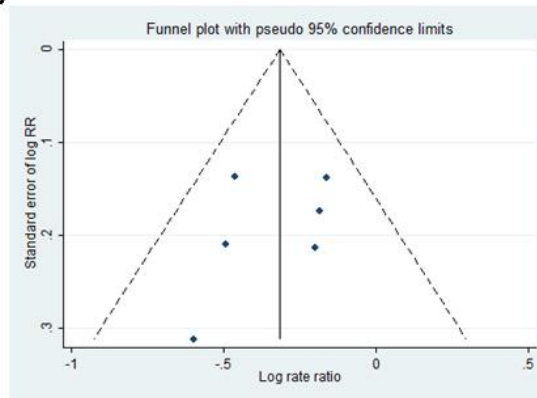
(a) Summary of overall risk of bias. (b) Risk of bias of individual studies.

(a)



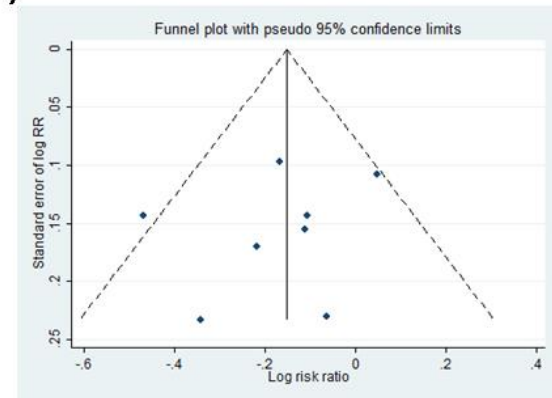
Egger test, $P = 0.362$

(b)



Egger test, $P = 0.545$

(c)

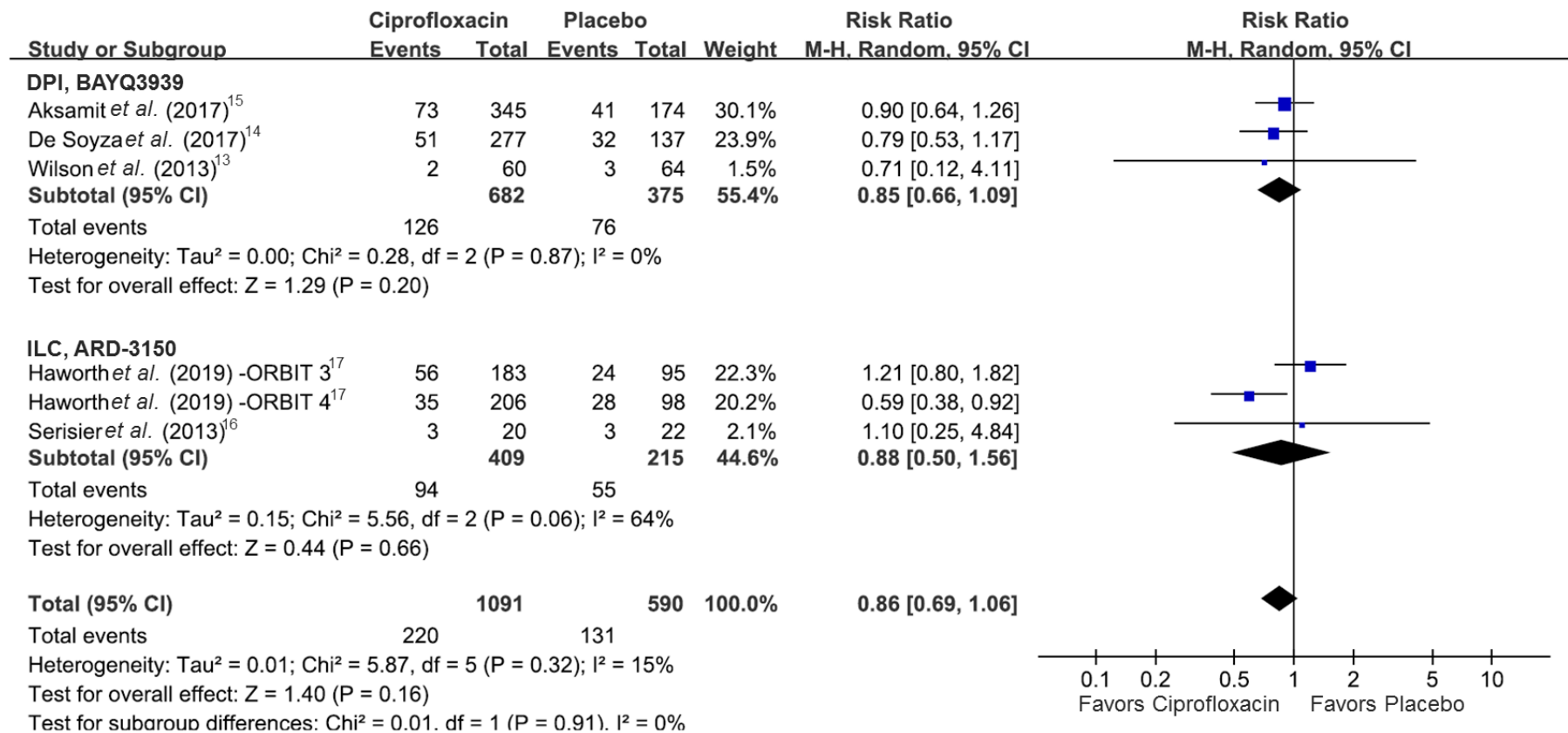


Egger test, $P = 0.464$

Supplementary Figure 2. Funnel plots for the primary outcomes and results of Egger test.

(a) Time to first exacerbation. (b) Frequency of exacerbations. (c) Exacerbation proportion

Although publication bias was suspected by the funnel plots, it was not significant by Egger's test.



Supplementary Figure 3. Forest plot presenting the RRs of serious TE-AE among bronchiectasis patients treated with inhaled ciprofloxacin versus placebo.