Cochrane Library

Cochrane Database of Systematic Reviews

Intermittent prophylactic antibiotics for bronchiectasis (Review)

Spencer S, Donovan T, Chalmers JD, Mathioudakis AG, McDonnell MJ, Tsang A, Leadbetter P

Spencer S, Donovan T, Chalmers JD, Mathioudakis AG, McDonnell MJ, Tsang A, Leadbetter P.
Intermittent prophylactic antibiotics for bronchiectasis.
Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD013254.
DOI: 10.1002/14651858.CD013254.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Intermittent prophylactic antibiotics for bronchiectasis

Sally Spencer[1], Tim Donovan[2], James D Chalmers[3], Alexander G Mathioudakis[4], Melissa J McDonnell[5], Anthony Tsang[6,7], Peter Leadbetter[8]

[1]Health Research Institute, Faculty of Health, Social Care & Medicine, Edge Hill University, Ormskirk, UK. [2]Medical Sciences, Institute of Health, University of Cumbria, Lancaster, UK. [3]University of Dundee, Ninewells Hospital and Medical School, Dundee, UK. [4]Division of Infection, Immunity and Respiratory Medicine, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. [5]Department of Respiratory Medicine, Galway University Hospital, Galway, Ireland. [6]Edge Hill University, Ormskirk, UK. [7]Department of Nursing, Faculty of Health, Social and Psychology, Manchester Metropolitan University, Manchester, UK. [8]Medical School, Faculty of Health, Social Care and Medicine, Edge Hill University, Ormskirk, UK

Contact: Sally Spencer, spencesa@edgehill.ac.uk.

Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 1, 2022.

Citation: Spencer S, Donovan T, Chalmers JD, Mathioudakis AG, McDonnell MJ, Tsang A, Leadbetter P. Intermittent prophylactic antibiotics for bronchiectasis. *Cochrane Database of Systematic Reviews* 2022, Issue 1. Art. No.: CD013254. DOI: 10.1002/14651858.CD013254.pub2.

ABSTRACT

Background

Bronchiectasis is a common but under-diagnosed chronic disorder characterised by permanent dilation of the airways arising from a cycle of recurrent infection and inflammation. Symptoms including chronic, persistent cough and productive phlegm are a significant burden for people with bronchiectasis, and the main aim of treatment is to reduce exacerbation frequency and improve quality of life. Prophylactic antibiotic therapy aims to break this infection cycle and is recommended by clinical guidelines for adults with three or more exacerbations a year, based on limited evidence. It is important to weigh the evidence for bacterial suppression against the prevention of antibiotic resistance and further evidence is required on the safety and efficacy of different regimens of intermittently administered antibiotic treatments for people with bronchiectasis.

Objectives

To evaluate the safety and efficacy of intermittent prophylactic antibiotics in the treatment of adults and children with bronchiectasis.

Search methods

We identified trials from the Cochrane Airways Trials Register, which contains studies identified through multiple electronic searches and handsearches of other sources. We also searched trial registries and reference lists of primary studies. We conducted searches on 6 September 2021, with no restriction on language of publication.

Selection criteria

We included randomised controlled trials (RCTs) of at least three months' duration comparing an intermittent regime of prophylactic antibiotics with placebo, usual care or an alternate intermittent regimen. Intermittent prophylactic administration was defined as repeated courses of antibiotics with on-treatment and off-treatment intervals of at least 14 days' duration. We included adults and children with a clinical diagnosis of bronchiectasis confirmed by high resolution computed tomography (HRCT), plain film chest radiograph, or bronchography and a documented history of recurrent chest infections. We excluded studies where participants received high dose antibiotics immediately prior to enrolment or those with a diagnosis of cystic fibrosis, allergic bronchopulmonary aspergillosis (ABPA), primary ciliary dyskinesia, hypogammaglobulinaemia, sarcoidosis, or a primary diagnosis of COPD. Our primary outcomes were exacerbation frequency and serious adverse events. We did not exclude studies on the basis of review outcomes.

Data collection and analysis

We analysed dichotomous data as odds ratios (ORs) or relative risk (RRs) and continuous data as mean differences (MDs) or standardised mean differences (SMDs). We used standard methodological procedures expected by Cochrane. We conducted GRADE assessments for the following primary outcomes: exacerbation frequency; serious adverse events and secondary outcomes: antibiotic resistance; hospital admissions; health-related quality of life.

Main results

We included eight RCTs, with interventions ranging from 16 to 48 weeks, involving 2180 adults. All evaluated one of three types of antibiotics over two to six cycles of 28 days on/off treatment: aminoglycosides, ß-lactams or fluoroquinolones. Two studies also included 12 cycles of 14 days on/off treatment with fluoroquinolones. Participants had a mean age of 63.6 years, 65% were women and approximately 85% Caucasian. Baseline FEV_1 ranged from 55.5% to 62.6% predicted. None of the studies included children. Generally, there was a low risk of bias in the included studies.

Antibiotic versus placebo: cycle of 14 days on/off. Ciprofloxacin reduced the frequency of exacerbations compared to placebo (RR 0.75, 95% CI 0.61 to 0.93; I^2 = 65%; 2 studies, 469 participants; moderate-certainty evidence), with eight people (95% CI 6 to 28) needed to treat for an additional beneficial outcome. The intervention increased the risk of antibiotic resistance more than twofold (OR 2.14, 95% CI 1.36 to 3.35; I^2 = 0%; 2 studies, 624 participants; high-certainty evidence). Serious adverse events, lung function (FEV_1), health-related quality of life, and adverse effects did not differ between groups.

Antibiotic versus placebo: cycle of 28 days on/off. Antibiotics did not reduce overall exacerbation frequency (RR 0.92, 95% CI 0.82 to 1.02; I^2 = 0%; 8 studies, 1695 participants; high-certainty evidence) but there were fewer severe exacerbations (OR 0.59, 95% CI 0.37 to 0.93; I^2 = 54%; 3 studies, 624 participants), though this should be interpreted with caution due to low event rates. The risk of antibiotic resistance was more than twofold higher based on a pooled analysis (OR 2.20, 95% CI 1.42 to 3.42; I^2 = 0%; 3 studies, 685 participants; high-certainty evidence) and consistent with unpooled data from four further studies. Serious adverse events, time to first exacerbation, duration of exacerbation, respiratory-related hospital admissions, lung function, health-related quality of life and adverse effects did not differ between study groups.

Antibiotic versus usual care. We did not find any studies that compared intermittent antibiotic regimens with usual care.

Cycle of 14 days on/off versus cycle of 28 days on/off. Exacerbation frequency did not differ between the two treatment regimens (RR 1.02, 95% CI 0.84 to 1.24; I^2 = 71%; 2 studies, 625 participants; moderate-certainty evidence) However, inconsistencies in the results from the two trials in this comparison indicate that the apparent aggregated similarities may not be reliable. There was no evidence of a difference in antibiotic resistance between groups (OR 1.00, 95% CI 0.68 to 1.48; I^2 = 60%; 2 studies, 624 participants; moderate-certainty evidence). Serious adverse events, adverse effects, lung function and health-related quality of life did not differ between the two antibiotic regimens.

Authors' conclusions

Overall, in adults who have frequent chest infections, long-term antibiotics given at 14-day on/off intervals slightly reduces the frequency of those infections and increases antibiotic resistance. Intermittent antibiotic regimens result in little to no difference in serious adverse events. The impact of intermittent antibiotic therapy on children with bronchiectasis is unknown due to an absence of evidence, and further research is needed to establish the potential risks and benefits.

PLAIN LANGUAGE SUMMARY

Long term antibiotics taken at regular intervals by people with bronchiectasis

Background

Bronchiectasis is a common condition arising from a cycle of repeated chest infections that damage the airways, leaving them susceptible to further infection. Typical symptoms include persistent cough and phlegm production. The main aim of treatment is to reduce lung infections and improve quality of life. Long term antibiotics aim to break this cycle of reinfection but this must be balanced against increased risk of developing resistance to antibiotics. Antibiotics may be taken at intervals to reduce this risk, but little is known about the length of intervals that may work best. This review will help people who develop clinical guidelines, doctors and people with bronchiectasis to decide whether to use antibiotics at regular intervals and the best interval duration.

Study characteristics

We found eight studies in September 2021 that looked at antibiotics given at intervals of 28 days on followed by 28 day off, or 14 days on then 14 days off, or a comparison between 14- and 28-day intervals, for up to 48 weeks. The studies included 2180 adults with an average age of 63.6 years. None of the studies included children.

Key results

The intervals of 14 days on/off antibiotics slightly reduced the frequency of chest infections compared to no antibiotics. We did not find these benefits with intervals of 28 days on/off antibiotics but study participants had fewer severe chest infections. Overall, antibiotic resistance was over twice as common in people receiving antibiotics, irrespective of the intervals between doses. No certain differences were found between groups for serious adverse outcomes such as deaths or hospitalisations, other aspects of lung functioning or health-related quality of life. There were enough people in the studies to assess the benefits and safety of treatment.

Quality of the evidence

In general, the included studies were of good quality. We had moderate to high confidence in the quality of the evidence for frequency of chest infections and occurrence of antibiotic resistance.

Conclusions

Overall, in adults who have frequent chest infections, long-term antibiotics given at 14-day on/off intervals slightly reduces the frequency of those infections and increases antibiotic resistance. We found little difference in the number of people who died, had to go to hospital, or had other serious problems. The benefits and safety of this type of treatment are unknown in children.

Summary of findings 1. 14 days on/off antibiotic regimen compared to 14 days on/off placebo regimen

14 days on/off antibiotic compared to 14 days on/off placebo

Patient or population: people with bronchiectasis
Setting: outpatient clinics
Intervention: 14 days on/off antibiotic regimen
Comparison: 14 days on/off placebo regimen

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without 14 days on/off antibiotic regimen	With 14 days on/off antibiotic regimen	Difference		
Exacerbation frequency assessed with: n ≥ 1 pulmonary exacerbation follow up: 48 weeks (2 RCTs; 469 participants)	RR 0.75 (0.61 to 0.93)	Study population			⊕⊕⊕⊖ MODERATE [a]	14 days on/off antibiotic regimen reduces exacerbation frequency slightly.
		51.3%	38.5% (31.3 to 47.7)	12.8% fewer (20 fewer to 3.6 fewer)		
Exacerbation frequency assessed with: rate ratio Follow-up: 48 weeks (2 RCTs; 469 participants)	In one study antibiotics reduced the frequency of exacerbations by 39% (97.5% CI 9% to 60%) over 48 weeks. There was no difference between groups in the second study.				⊕⊕⊕⊖ MODERATE [b]	14 days on/off antibiotic regimen may reduce exacerbation frequency but findings are inconclusive.
Serious adverse events assessed with: n ≥ 1 Follow-up: 48 weeks (2 RCTs; 621 participants)	OR 0.92 (0.63 to 1.33)	Study population			⊕⊕⊕⊕ HIGH	14 days on/off antibiotic regimen results in little to no difference in serious adverse events.
		23.5%	22.0% (16.2 to 29)	1.5% fewer (7.3 fewer to 5.5 more)		
Antibiotic resistance assessed with: n with elevated MICs at any point Follow-up: 48 weeks (2 RCTs; 624 participants)	OR 2.14 (1.36 to 3.35)	Study population			⊕⊕⊕⊕ HIGH	14 days on/off antibiotic regimen increases antibiotic resistance.
		10.9%	20.8% (14.3 to 29.1)	9.9% more (3.4 more to 18.2 more)		
Frequency of hospital admissions for pulmonary exacerbations - not measured	-	-	-		-	

Health-related quality of life assessed with: change in QoL-B-RS Scale from: 100 to 1; MCID: 8 Follow-up: 48 weeks (2 RCTs; 282 participants)	-	The mean change in health-related quality of life without 14 days on/off antibiotic regimen ranged from 4.45 to 10.7	-	MD 1.12 higher (3.12 lower to 5.36 higher)	⊕⊕⊕⊕ HIGH	14 days on/off antibiotic regimen results in little to no difference in health-related quality of life.
Health-related quality of life assessed with: change in SGRQ Scale from: 0 to 100; MCID: 4 Follow-up: 48 weeks (2 RCTs; 360 participants)	-	The mean change in health-related quality of life without 14 days on/off antibiotic regimen ranged from -11.5 to 2.78	-	MD 2.93 lower (7.0 lower to 1.14 higher)	⊕⊕⊕⊖ MODERATE [a]	14 days on/off antibiotic regimen results in little to no difference in health-related quality of life.

*__The risk in the intervention group__ (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; **MCID:** minimum clinically important difference; **MD:** mean difference; **MICs:** minimum inhibitory concentrations; **OR:** Odds ratio; **QOL-B-RS**: Quality of Life for Bronchiectasis respiratory symptoms; **RCTs**: randomised controlled trials; **RR:** Risk ratio; **SGRQ**: St George's Respiratory Questionnaire

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level for inconsistency due to unexplained heterogeneity between trial results.
[b]Downgraded by one level for inconsistent results.

Summary of findings 2. 28 days on/off antibiotic regimen compared to 28 days on/off placebo regimen

28 days on/off antibiotic regimen compared to 28 days on/off placebo

Patient or population: people with bronchiectasis
Setting: outpatient clinics
Intervention: 28 days on/off antibiotic regimen
Comparison: 28 days on/off placebo regimen

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	Certainty of the evidence (GRADE)	What happens

		Without 28 days on/off antibiotic regimen	With 28 days on/off antibiotic regimen	Difference		
Exacerbation frequency assessed with: n ≥ 1 pulmonary exacerbation Follow-up: range 16 to 48 weeks (8 RCTs; 1695 participants)	RR 0.92 (0.82 to 1.02)	Study population			⊕⊕⊕⊕ HIGH	28 days on/off antibiotic regimen results in little to no difference in exacerbations.
		43.2%	39.7% (35.4 to 44.1)	3.5% fewer (7.8 fewer to 0.9 more)		
Exacerbation frequency assessed with rate ratio Follow-up: range 16 to 48 weeks (8 RCTs; 1699 participants)	Two studies, with 564 participants, showed evidence of a reduction in exacerbation frequency ranging from 37% (95% CI 18% to 52%) to 45% (99% CI 70% to 102%) with ciprofloxacin over 48 weeks. Five studies, with 1105 participants, showed no evidence of difference in exacerbation frequency between antibiotics and placebo, with effects ranging from a 15% decrease to a 22% increase with the intervention.				⊕⊕⊖⊖ LOW [a,b]	28 days on/off antibiotic regimen may reduce exacerbation frequency but findings from the included studies are not in agreement.
Serious adverse events assessed with: n ≥ one Follow-up: range 16 to 48 weeks (8 RCTs; 1848 participants)	OR 1.00 (0.68 to 1.46)	Study population			⊕⊕⊖⊖ LOW [c,d]	The evidence suggests that 28 days on/off antibiotic regimen results in little to no difference in serious adverse events.
		19.6%	19.6% (14.2 to 26.3)	0.0% fewer (5.4 fewer to 6.7 more)		
Antibiotic resistance assessed with: n with elevated MICs Follow-up: range 16 to 48 weeks (3 RCTs; 685 participants)	OR 2.20 (1.42 to 3.42)	Study population			⊕⊕⊕⊕ HIGH	28 days on/off antibiotic regimen increases antibiotic resistance.
		10.5%	20.6% (14.3 to 28.7)	10.0% more (3.8 more to 18.2 more)		
Hospitalisation for pulmonary exacerbations assessed with: n ≥ 1 exacerbation Follow-up: range 16 to 48 weeks (3 RCTs; 645 participants)	OR 0.79 (0.49 to 1.29)	Study population			⊕⊕⊕⊕ HIGH	28 days on/off antibiotic regimen does not reduce hospitalisation for pulmonary exacerbations.
		14.0%	11.4% (7.4 to 17.4)	2.6% fewer (6.6 fewer to 3.4 more)		
Health-related quality of life assessed with: change in QoL-B-RS (higher = better) Scale from: 100 to 1; MCID: 8 Follow-up: range 16 to 48 weeks (7 RCTs; 1469 participants)	-	The mean change in health-related quality of life without 28 days on/off antibiotic regimen ranged from 4.0 to 8.22	-	MD 0.05 higher (1.56 lower to 1.66 higher)	⊕⊕⊕⊖ MODERATE [c]	28 days on/off antibiotic regimen probably results in little to no difference in health-related quality of life.

Health-related quality of life assessed with: change in SGRQ-S (lower = better) Scale from: 1 to 100; MCID: 4 Follow-up: range 28 days to 48 weeks (3 RCTs; 407 participants)	-	The mean change in health-related quality of life without 28 days on/off antibiotic regimen ranged from -2.91 to -6.4	-	MD 0.59 lower (4.26 lower to 3.08 higher)	⊕⊕⊖⊖ LOW [d,e]	28 days on/off antibiotic regimen may result in little to no difference in health-related quality of life.

*__The risk in the intervention group__ (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; **MCID:** minimum clinically important difference; **MD:** mean difference; **MICs**: minimum inhibitory concentrations; **OR:** Odds ratio; **QOL-B-RS**: Quality of Life for Bronchiectasis respiratory symptoms; **RCTs**: randomised controlled trials; **RR:** Risk ratio; **SGRQ**: St George's Respiratory Questionnaire

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level due to inconsistent results.
[b]Downgraded by one level for imprecision due to wide confidence intervals.
[c]Downgraded by one level to for risk of bias due to incomplete outcome data (1 study) and unclear assessment blinding and selective reporting bias (3 studies).
[d]Downgraded by one level for inconsistency due to unexplained heterogeneity between trial results.
[e]Downgraded by one level for inconsistency due to subgroup differences.

Summary of findings 3. 14 days on/off antibiotic regimen compared to 28 days on/off antibiotic regimen

14 days on/off antibiotic regimen compared to 28 days on/off antibiotic regimen

Patient or population: people with bronchiectasis
Setting: outpatient clinics
Intervention: 28 days on/off antibiotic regimen
Comparison: 14 days on/off antibiotic regimen

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		14 days on/off antibiotic regimen	28 days on/off antibiotic regimen	Difference		
Exacerbation frequency	RR 1.02 (0.84 to 1.24)	Study population			⊕⊕⊕⊖ MODERATE [a]	28 days on/off antibiotic regimen likely results in little to no

assessed with: n ≥ 1 pulmonary exacerbation Follow-up: 48 weeks (2 RCTs; 625 participants)		38.7%	39.4% (32.5 to 47.9)	0.8% more (6.2 fewer to 9.3 more)		difference in exacerbation frequency compared with 14 days on/off regimen.
Exacerbation frequency assessed with: rate ratio - not measured	-	-	-	-	-	-
Serious adverse events assessed with: n ≥ 1 Follow-up: 48 weeks (2 RCTs; 622 participants)	OR 0.83 (0.37 to 1.86)	Study population			⊕⊕⊕⊖ MODERATE [a]	28 days on/off antibiotic regimen likely results in little to no difference in serious adverse events compared with 14 days on/off regimen.
		21.9%	18.9% (9.4 to 34.3)	3.0% fewer (12.5 fewer to 12.4 more)		
Antibiotic resistance assessed with: n with elevated MICs at any point Follow-up: 48 weeks (2 RCTs; 624 participants)	OR 1.00 (0.68 to 1.48)	Study population			⊕⊕⊕⊖ MODERATE [a]	28 days on/off antibiotic regimen likely results in little to no difference in antibiotic resistance compared with 14 days on/off.
		20.8%	20.8% (15.1 to 27.9)	0.0% fewer (5.6 fewer to 7.2 more)		
Frequency of hospital admissions for pulmonary exacerbations - not measured	-	-	-	-	-	-
Health-related quality of life assessed with: change in QoL-B-RS (higher = better) Scale from: 100 to 1; MCID: 8 Follow-up: 48 weeks (2 RCTs; 384 participants)	-	The mean change in health-related quality of life with 14 days on/off antibiotic regimen ranged from 6.72 to 10.9	-	MD 0.83 higher (2.77 lower to 4.44 higher)	⊕⊕⊕⊕ HIGH	28 days on/off antibiotic regimen results in little to no difference in health-related quality of life compared with 14 days on/off.
Health-related quality of life assessed with: change in SGRQ-S (lower = better) Scale from: 1 to 100; MCID: 4 Follow-up: 48 weeks (2 RCTs; 500 participants)	-	The mean change in health-related quality of life with 14 days on/off antibiotic regimen ranged from -7.2 to -9.02	-	MD 0.34 lower (4.02 lower to 3.35 higher)	⊕⊕⊕⊕ HIGH	28 days on/off antibiotic regimen results in little to no difference in health-related quality of life compared with 14 days on/off.

*__The risk in the intervention group__ (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; **MCID:** minimum clinically important difference; **MD:** mean difference; **MICs**: minimum inhibitory concentrations; **OR:** Odds ratio; **QOL-B-RS**: Quality of Life for Bronchiectasis respiratory symptoms; **RCTs**: randomised controlled trials; **RR:** Risk ratio; **SGRQ**: St George's Respiratory Questionnaire

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for inconsistency due to unexplained heterogeneity between trial results.

BACKGROUND

Description of the condition

Bronchiectasis is a common but, until recently, under diagnosed chronic disorder characterised by permanent dilation of the large airways, bronchi and bronchioles (branches of the bronchi) (Pasteur 2010). This arises from a vicious cycle of respiratory infections that cause inflammation and damage to the bronchial walls, leading to disordered mucociliary clearance (mucus-clearing mechanism of the bronchi), that in turn renders people more susceptible to recurrent infections (Chalmers 2013; Cole 1986). Recently, the concept of a 'vicious vortex' has been introduced, which stresses the complexity of the relationships between the components of the cycle (Amati 2019). An understanding of this cycle of recurrent infection and tissue destruction is important in the management of bronchiectasis, where the central aim is to limit the progression of lung injury by arresting inflammation and bacterial colonisation (Cole 1997; Pasteur 2010). The most commonly isolated micro-organisms include non-typeable *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Moraxella catarrhalis* (Foweraker 2011). Organisms such as *P aeruginosa*, *H influenzae* and *M catarrhalis* are often resistant to antimicrobial therapy, arising from intrinsic resistance mechanisms and frequent exposure to antimicrobial agents (Menendez 2017).

Bronchiectasis presents with chronic, persistent cough, phlegm that is frequently difficult to expectorate, and recurrent respiratory infections, posing a significant health burden (Chalmers 2014). The cause of around half of presenting cases is unknown, and they are classified as idiopathic (cause is unknown), but the most common aetiology is postinfectious bronchiectasis, a diverse group that includes people with childhood respiratory infections such as pertussis, bacterial pneumonia, or tuberculosis (Pasteur 2010). Diagnosis is based on the presence of one or more abnormally dilated bronchi using high-resolution computed tomography (HRCT) (Chang 2010; Pasteur 2010). The central aims of therapeutic management are to reduce symptoms such as cough, breathlessness and expectoration, to reduce the frequency and duration of exacerbations, and to improve quality of life (Chalmers 2015; Pasteur 2010).

Recent epidemiological studies have suggested that the prevalence of bronchiectasis is increasing, particularly in women and those over 60 years old (Roberts 2010; Seitz 2010; Weycker 2005), with higher rates in low- and middle-income countries (Habesoglu 2011). In Germany, prevalence has been estimated at 67 cases per 100,000 general population (Ringshausen 2015). Recent UK figures estimate 263,000 adults living with bronchiectasis in 2013, with prevalence rates per 100,000 rising by approximately 60% over a nine-year period, from 350.5 to 566.1 in women and from 301.2 to 485.5 in men (Quint 2016). Similarly, approximately 15,000 new cases were identified in 2013, with incidence rates per 100,000 person-years rising by around 63% over the same nine-year period, from 21.2 to 35.2 in women and from 18.2 to 26.9 in men. European mortality rates, based on 2005 to 2009 data, are estimated at 0.3 per 100,000 general population in EU countries and at 0.2 per 100,000 general population in nine non-EU countries (Gibson 2013). Age-adjusted mortality in the UK is estimated to be 2.3 times higher in women and 2.1 times higher in men compared to the general population (Quint 2016).

The impact of bronchiectasis on children is significant, with worse quality of life in younger children and those with more frequent exacerbations (Kapur 2012). Global prevalence is highly variable with higher rates in some indigenous groups, such as 15 per 1000 in Australian Aboriginal and Torres Strait Islander children and 16 per 1000 among southwest Alaskan children (Chang 2002). The incidence rate in one New Zealand study was 3.7 per 100,000 per year in children under 15 years old, with an overall prevalence of 1 per 3000 children, but a much higher rate of 1 per 625 in Pacific children (Twiss 2005). These rates were almost seven times higher than those in Finland (Twiss 2005).

Higher prevalence rates may be attributable to improvements in diagnosis resulting from HRCT scans, as well as incidental diagnosis of bronchiectasis on HRCT performed for other reasons, and heightened awareness of bronchiectasis symptoms, rather than a true increase in the condition (Goeminne 2016).

Bronchiectasis is associated with high rates of exacerbations, hospital admissions, and attributable mortality, which place a considerable burden on international healthcare systems (Chalmers 2015; Redondo 2016). Approximately half of the people on the European bronchiectasis registry have at least two exacerbations per year and a third of those on the registry are hospitalised at least once a year (Polverino 2017). People with more frequent annual exacerbations and those chronically infected with *P aeruginosa* have a more rapid decline in lung function, worse health-related quality of life, and a higher risk of hospitalisation and mortality (Evans 1996; Martínez-García 2007; Polverino 2017; Wilson 1997). Other risk factors for higher hospitalisation and mortality rates include: severe exacerbations, low body mass index, chronic bacterial infection, low forced expiratory volume in one second (FEV_1) percentage of predicted, a higher proportion of affected lobes, and more breathlessness (Chalmers 2014; Rogers 2014; Seitz 2010).

The high burden of bronchiectasis is associated with substantial costs of care. The annual mean direct medical costs for an adult with bronchiectasis was estimated at EUR 4671 in a Spanish study, with higher costs associated with more severe disease (De la Rosa 2016). In a USA-based study, the additional costs of care for people with bronchiectasis compared to matched case-controls were associated with an annual increase of USD 2319 in overall costs and USD 1607 in respiratory-related costs (Joish 2013).

Bronchiectasis is the primary manifestation of genetic diseases such as cystic fibrosis, allergic bronchopulmonary aspergillosis (ABPA), primary ciliary dyskinesia (impaired movement of cilia) and hypogammaglobulinaemia (immune disorder characterised by reduced resistance to infection). Such cases are characterised by more severe clinical presentations and worse outcomes, and are beyond the scope of this systematic review. Bronchiectasis is also associated with other diseases, such as sarcoidosis or chronic obstructive pulmonary disease (COPD). People with both COPD and bronchiectasis have worse outcomes, especially those who continue to smoke, and are therefore regarded as a separate population and beyond the remit of this review (Lanza 2018Ni 2015).

Description of the intervention

Prophylactic antibiotic therapy is a cornerstone of the management of people with bronchiectasis, its goal being to suppress

bacterial infection and to break the vicious cycle of recurrent infections and exacerbations, with resultant reductions in bacterial load, inflammation, and consequent tissue destruction of the airways (Chalmers 2012). To date, randomised controlled trials (RCTs) of antibiotics in bronchiectasis have evaluated different modes (oral, intravenous (IV) and inhaled) and methods (continuous versus intermittent) of administration, using different classes of antibiotics, including but not limited to macrolides, quinolones, and polymyxins. Pooled data on the use of long-term prophylactic antibiotics administered for three or more months have demonstrated efficacy for people with frequent bronchiectasis exacerbations in decreasing the frequency and severity of exacerbations, increasing the time to first exacerbation and reducing symptom burden, offset by an increased adverse event profile and increased bacterial resistance (Hnin 2015; Polverino 2017). Continuous antibiotics are associated with more than three times the risk of bacterial resistance compared to no antibiotic prophylactic therapy (Hnin 2015).

In clinical practice, antibiotics are most frequently used in people with three or more exacerbations per year, in people with chronic *P aeruginosa* infection, and also in people with less frequent exacerbations who continue to have significant impairment of quality of life despite standard treatment (Chalmers 2015; Polverino 2017). Intermittent therapy refers to the repeated prophylactic administration of courses of antibiotics with predefined duration and intervals. Examples include antibiotics given every month or drug holidays with treatment during the winter months only, to allow for seasonal variations. As the half-life of antibiotics, such as azithromycin, is approximately one week, the off-treatment interval should last at least 14 days. Prophylactic antibiotics may be given for regimens of at least 14 days on-treatment followed by at least 14 days off treatment, for cycles lasting at least three months (Polverino 2017). In this review, we will compare the administration of intermittent long-term antibiotics using different duration periods, or compared with placebo, over three months or longer. This definition excludes short courses of antibiotics for acute exacerbations, which have been addressed in a separate review (Wurzel 2011).

How the intervention might work

Chronic airway infection is central to the pathogenesis (development) of bronchiectasis. The presence of airway bacteria results in neutrophilic (white blood cells) inflammation which promotes airway destruction and disease progression (Chalmers 2012; Chalmers 2017). It is therefore logical that suppression of bacterial load should reduce symptoms and prevent exacerbations. Antibiotic treatment has been proven to reduce bacterial load and to thereby reduce neutrophilic inflammation (Chalmers 2012). Gram-negative pathogens and *P aeruginosa,* in particular, are associated with a significant increase in the risk of death over five years compared to other pathogens, even after adjustment for confounders (Araujo 2018; Finch 2015).

As clinical outcomes are better in patients without bacterial infection, continuous long-term suppression of airway bacteria is an important aim (Polverino 2017). However, the argument against continuous exposure to antibiotics is that it leads to increased bacterial resistance and consequently treatment may lose its effectiveness (Chalmers 2015). On the contrary, intermittent administration of antibiotics might remove or limit antibiotic selection pressure and, consequently, prevent the development of resistance. There is often a fitness cost for bacteria acquiring antimicrobial resistance, which means that once the selection pressure is removed, the resistant organism is 'out-competed' by non-resistant organisms (Melnyk 2015). Indirect evidence of this concept is provided by a large retrospective analysis of mechanically-ventilated patients with hospital-acquired (nosocomial) infections (40% chronic lung disease) where an interval of at least 20 days between serial courses of antibiotics was associated with a 24% reduction in development of resistance (Hui 2013). Additionally, some antibiotic agents appear to have problems with tolerability and an increased risk of antibiotic-related adverse events, which may be minimised with intermittent therapy. Also, the treatment burden associated with nebulised therapies (inhaled as a mist), including both the time to administer the dose and to care for the machinery, are substantial; therefore, less frequent administration may improve treatment adherence and limit total costs (Chalmers 2015; McCullough 2014).

Why it is important to do this review

The 2017 ERS (European Respiratory Society) guidelines for bronchiectasis recommended the use of long-term antibiotics for people with three or more exacerbations per year following treatment of the underlying cause and regular airway clearance exercises (Polverino 2017). There are currently no clinical trials that compare the safety and efficacy of continuous administration with intermittent administration of antibiotics (Donovan 2018). The optimal delivery route (oral, inhaled, IV), dosage, and duration of intermittent antibiotics remain unclear. Given the theoretical balance between bacterial suppression and prevention of resistance, it is important to synthesise the available data on the safety and efficacy of intermittently administered antibiotic treatments in bronchiectasis to determine their impact on the prevention of exacerbations.

OBJECTIVES

To evaluate the safety and efficacy of intermittent prophylactic antibiotics in the treatment of adults and children with bronchiectasis.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to included randomised controlled trials (RCTs) and cluster-RCTs. We also planned to include cross-over studies but, to overcome potential carry-over effects from the first phase (e.g. antibiotic resistance), we only planned to use data from the first pre-cross-over phase. We included studies reported in full text, those only published as abstracts, and unpublished data.

Types of participants

We planned to include adults and children (< 18 years) with a clinical diagnosis of bronchiectasis confirmed by high resolution computed tomography (HRCT), plain film chest radiograph, or bronchography and a documented history of recurrent chest infections. We excluded studies where participants received high dose antibiotics immediately prior to enrolment or those with a diagnosis of cystic fibrosis, allergic bronchopulmonary aspergillosis (ABPA), primary ciliary dyskinesia,

hypogammaglobulinaemia, sarcoidosis, or a primary diagnosis of chronic obstructive pulmonary disease (COPD). We also excluded studies where participants received short courses of antibiotics for an acute exacerbation. We only included studies with mixed populations (different respiratory conditions) if there was a separate subgroup analysis for participants with bronchiectasis. We planned to analyse data on children and adults separately.

Types of interventions

We planned to include studies comparing the following.

- Prophylactic intermittent antibiotics versus placebo.
- Prophylactic intermittent antibiotics versus usual care. Usual care may have included bronchodilators, anti-inflammatories, mucolytics, inhaled hyperosmolar agents, or chest physiotherapy.
- Prophylactic intermittent antibiotics using regimen X versus regimen Y, e.g. 14 days of antibiotics followed by 14 days of none versus 28 days of antibiotics followed by 28 days of none.

We reported these different comparisons separately. We defined intermittent prophylactic administration as repeated courses of antibiotics with predefined on-treatment duration of at least 14 days and off-treatment intervals of at least 14 days, for a study duration of at least three months. The method of administration could have been oral or inhaled, but must have been the same for all study groups in order to isolate the effect of the antibiotic rather than the delivery device. We excluded studies that compared continuously administered prophylactic antibiotics with those administered intermittently as this has been addressed in a separate review (New Reference).

Types of outcome measures

We used exacerbation and hospitalisation rates as reported by study authors. We collected outcome data at a range of follow-up points that best reflected available evidence from included studies (e.g. end of study, end of follow-up, change from baseline).

Primary outcomes

1. Frequency of exacerbations (defined using study authors' criteria).
2. Serious adverse events defined as follows: adverse events resulting in death or life-threatening events, hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or congenital anomalies, or events considered medically important (Hansen 2015).

Secondary outcomes

1. Time to first exacerbation (defined using study authors' criteria).
2. Duration of exacerbations (defined using study authors' criteria).
3. Severity of exacerbations (defined using study authors' criteria).
4. Development of antibiotic resistance (defined using study authors' criteria).
5. Frequency of hospital admissions due to exacerbations (defined using study authors' criteria).
6. Frequency of hospital admissions (defined using study authors criteria).
7. Lung function measured as forced expiratory volume in one second (FEV_1).
8. Health-related quality of life using measures validated in a clinical setting (e.g. St George's Respiratory Questionnaire (SGRQ), Leicester Cough Questionnaire (LCQ) or Quality of Life-Bronchiectasis (QoL-B)).
9. Adverse effects and adverse reactions defined as follows. Adverse effects are unwanted outcomes of which the participant is not aware, usually detected by laboratory tests (e.g. biochemical, haematological, immunological, radiological, pathological tests) or clinical investigations (e.g. gastrointestinal endoscopy, cardiac catheterisation). Adverse reactions are unwanted outcomes that the participant experiences and are detected by their clinical manifestations (symptoms and signs) (Hansen 2015).

We did not use the above outcomes as eligibility criteria for inclusion of studies in the review. We based study selection on types of studies, participants, and interventions, to avoid excluding eligible studies with unpublished review outcomes.

Search methods for identification of studies

Electronic searches

We identified studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. At the time of the search, the Cochrane Airways Trials Register contained studies identified from the following sources:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies, all years to issue 9 of 12, 2021;
2. weekly searches of MEDLINE Ovid SP from 1946 onwards;
3. weekly searches of Embase Ovid SP from 1974 onwards;
4. monthly searches of PsycINFO Ovid SP from 1967 onwards;
5. monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) from 1937 onwards;
6. monthly searches of AMED EBSCO (Allied and Complementary Medicine) from inception;
7. handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register were identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings, are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We searched the following trials registries:

1. US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov);
2. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We searched the Cochrane Airways Trials Register and additional sources from inception to 6 September 2021, with no restriction on language of publication.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references and searched relevant manufacturers' websites for study information.

We also searched for errata or retractions from included studies published in full text on PubMed and reported the date of the search in the review.

Data collection and analysis

Selection of studies

Two review authors (TD and MMD) screened the titles and abstracts of the search results independently and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports of all potentially eligible studies and two review authors (TD and MMD) independently screened them for eligibility, recording the reasons for exclusion of ineligible studies. We resolved any disagreement through discussion or, if required, we consulted a third review author (SS). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection using a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We used a data collection form for study characteristics and outcome data, that was piloted on one study in the review. One review author (AT) extracted the following study characteristics from included studies.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

We summarised the interventions in included studies (study, adults or children, number of participants, type of antibiotic, dose, frequency, regimen, delivery mode, comparator) using a study characteristics table.

Two review authors (AT and TD) independently extracted outcome data from included studies. We noted in the Characteristics of included studies table if studies did not report outcome data in a usable way. We resolved disagreements by consensus or by involving a third review author (SS). One review author (TD) transferred data into the Review Manager file (Review Manager 2020). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (AT) spot-checked study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (SS and TD) assessed risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another author (MMD). We assessed the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We judged each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes, where necessary (e.g. for unblinded outcome assessment, risk of bias for hospital admissions may be very different than for a participant-reported health-related quality of life scale such as the SGRQ). Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the risk of bias table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol (Spencer 2019), and justified any deviations from it in the Differences between protocol and review section.

Measures of treatment effect

We analysed dichotomous data as odds ratios (OR) or risk ratios (RR) and continuous data as the mean difference (MD) or standardised mean difference (SMD). When outcomes were reported as time-to-event data (e.g. time to first exacerbation), we analysed them as hazard ratios (HR). Where we combined data from rating scales in a meta-analysis, we ensured that we entered the data with a consistent direction of effect (e.g. lower scores always indicate improvement).

We undertook meta-analyses only where meaningful; that is, if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense.

We described skewed data narratively (for example, as medians and interquartile ranges for each group).

Where a single study reported multiple trial arms, we included only the relevant arms. If it was necessary to combine two comparisons (e.g. drug A versus placebo and drug B versus placebo) in the same meta-analysis, we either combined the active arms or halved the control group to avoid double-counting.

We used adjusted data as first choice if it was available (e.g. rate ratios from Poisson regression models, mean differences from

ANOVAs, or results from cluster-RCTs adjusted for the effects of clustering), followed by change scores and endpoint scores.

We used intention-to-treat (ITT) analyses where they were reported, instead of completer or per protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we used participants, rather than events, as the unit of analysis (i.e. the number of people admitted to hospital, rather than number of admissions per person). However, if a study reported exacerbations and hospitalisations as rate ratios (number of events experienced by a participant), we analysed them on that basis.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data, where possible (e.g. when a study was identified as an abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we took this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identified substantial heterogeneity (> 50%) we reported it and explored the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

There were insufficient studies to explore possible small study and publication biases using a funnel plot. We had planned to use funnel plots if we had been able to pool 10 or more studies.

Data synthesis

We used a random-effects model, reported with 95% confidence intervals (CI), and performed a sensitivity analysis with a fixed-effect model. We synthesised and reported dichotomous and continuous data separately for each outcome, e.g. hospitalisation/no hospitalisation or duration of hospitalisation. We planned to analyse data from adults and children separately but did not find any studies that included children. For a given outcome measure, we combined effect estimates, such as differences at endpoint and change from baseline, providing that there were no reported baseline differences between groups. When outcomes were measured using different scales, e.g. health-related quality of life, we used SMD in the analyses. We used the baseline standard deviation (SD) for the SMD analyses.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses:

1. type of antibiotic (e.g. β-lactams vs fluoroquinolones);
2. study duration (≤ 6 months, < 12 months, ≥ 12 months);
3. method of administration (oral versus IV versus inhaled);
4. chronic infection with *P aeruginosa* at study enrolment versus no chronic infection.

We used the following outcomes in subgroup analyses:

1. exacerbation frequency;
2. serious adverse events.

We used the formal test for subgroup interactions in Review Manager (Review Manager 2020).

Sensitivity analysis

We planned to carry out sensitivity analyses by comparing results before and after removing studies at high risk of bias from:

1. random sequence generation;
2. allocation concealment.

We also compared the results from a fixed-effect model with results from the random-effects model.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables using the following outcomes: frequency of exacerbations, serious adverse events, development of antibiotic resistance, frequency of hospital admissions, and health-related quality of life. We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the evidence as it related to the studies that contributed data for the prespecified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We justified all decisions to downgrade the quality of studies using footnotes and we made comments to aid the reader's understanding of the review, where necessary.

RESULTS

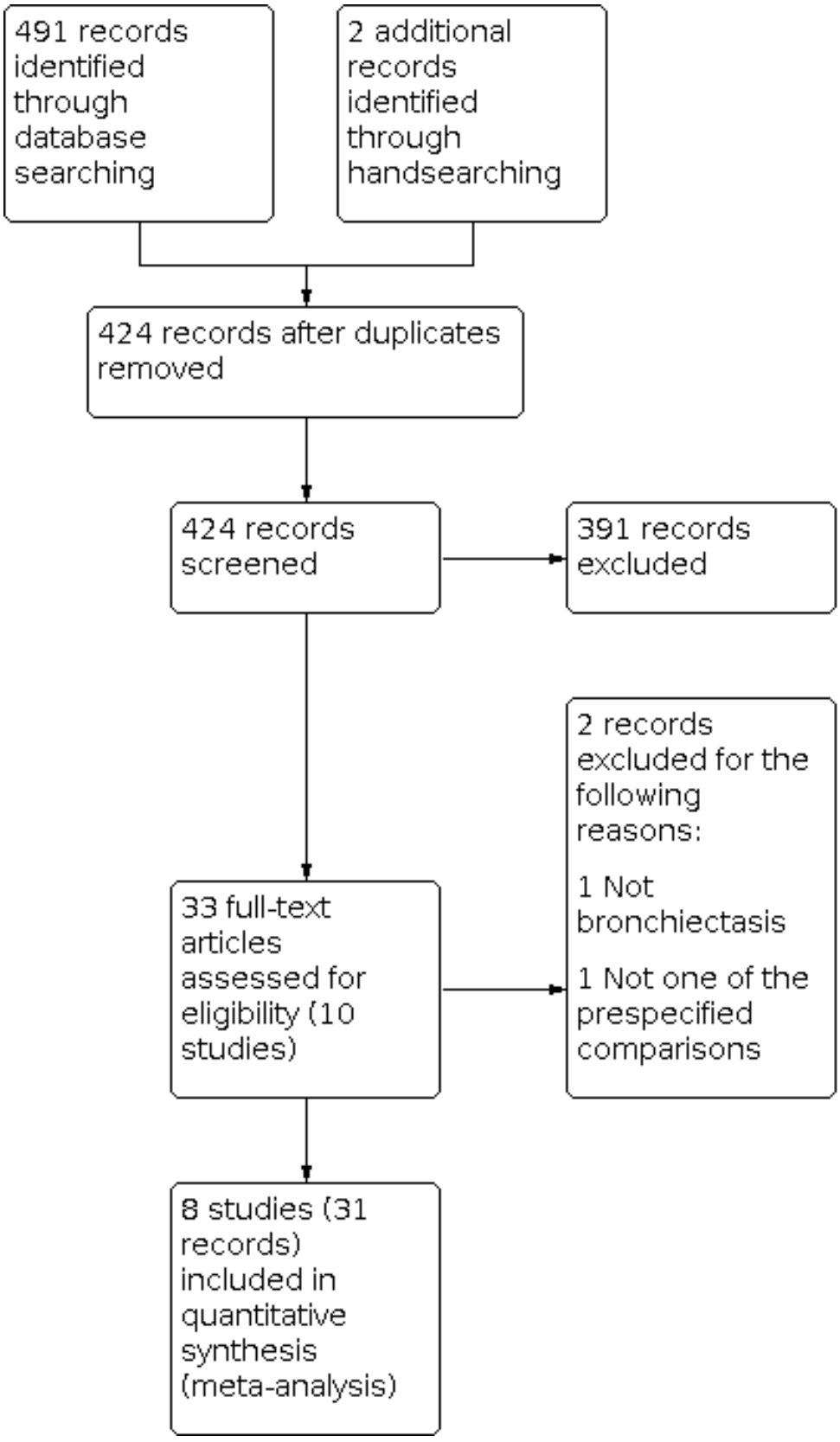
Description of studies

This review is based on a published protocol (Spencer 2019).

Results of the search

We identified 424 records after duplicates were removed following systematic searches (09 September 2021). Of these, we excluded 391 records following inspection of their titles and abstracts. We assessed 33 full-text articles for eligibility. Of these, we included eight studies, relating to 31 records, in the review (AIRBX1; AIRBX2; iBEST; ORBIT 2; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2) (see Characteristics of included studies); we formally excluded two records (documented in Excluded studies) that did not meet the review inclusion criteria (iREC; Lloberes 1990). The selection process is summarised in the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

Methods

The included studies represent four teams of investigators. AIRBX1 and AIRBX2 were identical studies conducted concurrently and results reported separately in a single main publication. iBEST was a single study with results reported in a main publication, but it is also important to note that this study was terminated early by the funder for reasons unrelated to efficacy or safety. ORBIT 2 was a precursor to the ORBIT 3 and ORBIT 4 trials and reported in a main publication. ORBIT 3 and ORBIT 4 were identical trials conducted concurrently in similar geographical areas with results reported separately and as pooled results in a single main publication. RESPIRE 1 and RESPIRE 2 were also concurrent studies, differing only in terms of analyses required by different regulatory authorities (European Medicines Agency versus US Food and Drug Administration), with main results published separately for the two trials.

All of the eight included studies were randomised, double-blind, placebo-controlled, multicentre trials (AIRBX1; AIRBX2; iBEST; ORBIT 2; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2). Six of these were phase III trials (AIRBX1; AIRBX2; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2), and two were phase II trials (iBEST; ORBIT 2). Two studies included a 4-week open-label phase at the end of the randomised treatment period that was not reported (AIRBX1; AIRBX2). Five studies were parallel group two-arm trials (AIRBX1; AIRBX2; ORBIT 2; ORBIT 3; ORBIT 4), two studies were four-arm trials (RESPIRE 1; RESPIRE 2) and one study was a nine-arm trial, though only six of those were comparisons of interest to the review (iBEST). Duration of the intervention ranged from 16 weeks (AIRBX1; AIRBX2; iBEST) to 42 weeks (ORBIT 2) and 48 weeks (ORBIT 3; ORBIT 4RESPIRE 1; RESPIRE 2). The percentage of participants who withdrew from the study after randomisation ranged from 0% in ORBIT 2 to 37% in iBEST.

One trial was conducted in Australia and New Zealand (ORBIT 2), one in Australia, Canada and the USA (AIRBX1), and one in Europe (iBEST). The remaining studies were conducted in multiple global locations ranging from 10 countries on three continents (AIRBX2) to 16 countries on six continents (ORBIT 4). All studies recruited participants through multiple sites, ranging from 11 (ORBIT 2) to 93 (ORBIT 3) centres. Of the eight studies, one did not report study start and completion dates (ORBIT 2). The oldest study concluded in 2010 (ORBIT 2), and the most recent in 2019 (iBEST).

All trials reported sample size calculations and used prespecified intention-to-treat analyses (AIRBX1; AIRBX2; iBEST; ORBIT 2; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2). Three trials used a 1:1 randomisation ratio (AIRBX1; AIRBX2; ORBIT 2), four used a 2 (intervention):1 ratio (ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2) and the remaining trial used a 1:1:1 ratio between three cohorts and a 2 (intervention):2 (intervention):1 ratio within cohorts (iBEST).

Participants

The eight studies included a total of 2180 adults with bronchiectasis confirmed by computed tomography. None of the studies included children. The number of randomised participants in each study ranged from 42 (ORBIT 2) to 521 (RESPIRE 2). However, two studies did not report population demographics for 16 participants who did not receive the study intervention after randomisation (ORBIT 3; ORBIT 4), so the following summary represents 2164 participants.

The overall mean age was 63.6 years (range of standard deviation 9.4 (ORBIT 2 to 14.0 (RESPIRE 2). 1416 participants (65%) were women, ranging from 55% (ORBIT 2) to 70% (iBEST). Ethnicity was reported by seven studies. In four of these studies an average of 85% were white/Caucasian, ranging from 77% (RESPIRE 2) to 90% (AIRBX1; AIRBX2). Two studies reported proportions of Hispanic/Latino participants: 3% (ORBIT 3) and 11% (ORBIT 4). The remaining study did not report ethnicity (ORBIT 2). Five studies reported smoking status (AIRBX1; AIRBX2; ORBIT 2; ORBIT 3; ORBIT 4). In three studies the proportion of participants with a history of smoking ranged from 2% (ORBIT 2) to 39% (AIRBX1). Approximately 1% of the population in two studies were current smokers (ORBIT 3; ORBIT 4). Three trials did not collect data on smoking status (iBEST; RESPIRE 1; RESPIRE 2).

All studies reported baseline FEV_1% predicted, with an overall mean of 59.5% predicted ranging from 55.5% (RESPIRE 2) to 62.6% (AIRBX2). Four studies reported the proportion of participants with FEV_1 < 50% predicted, and this ranged from 30% (RESPIRE 1) to 41.8% (RESPIRE 2).

Seven studies only included participants who exceeded FEV_1% predicted thresholds at screening; ≥ 20% (AIRBX1; AIRBX2), ≥ 25% (ORBIT 3; ORBIT 4) or ≥ 30% (iBEST; RESPIRE 1; RESPIRE 2). Six studies specified at least two pulmonary exacerbations in the preceding year as eligibility criteria (iBEST; ORBIT 2; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2). Six studies required positive culture of target organisms at screening (AIRBX1; AIRBX2; iBEST; ORBIT 2; RESPIRE 1; RESPIRE 2). Five studies required a previous history of infection with *P aeruginosa* at screening (AIRBX1; AIRBX2; ORBIT 2; ORBIT 3; ORBIT 4). Two studies required sputum production at least four days a week for four weeks (AIRBX1; AIRBX2).

All eight studies excluded people with tuberculosis or non-tuberculous mycobacteria infection and those requiring antibiotics within the screening period. Five studies excluded people with allergic bronchopulmonary aspergillosis (ORBIT 2; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2). Five studies excluded people with COPD (iBEST; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2). Two studies excluded people with FEV_1% predicted ≥ 90% (RESPIRE 1; RESPIRE 2).

Interventions

The eight studies evaluated three different types of prophylactic antibiotics against a matched placebo (Table 1). One trial administered 84 mg, 140 mg or 224 mg of the aminoglycoside tobramycin daily for 16 weeks (iBEST). Two trials administered 225 mg of the ß-lactam aztreonam daily for 16 weeks (AIRBX1; AIRBX2). Five trials administered the fluoroquinolone ciprofloxacin in daily doses ranging from 71 mg (RESPIRE 1; RESPIRE 2) to 210 mg (ORBIT 2), for 24 to 48 weeks. All trials used intermittent treatment regimens of 28 days on- and 28 days off treatment (AIRBX1; AIRBX2; iBEST; ORBIT 2; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2) over two (AIRBX1; AIRBX2; iBEST), three (ORBIT 2), or six (ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2) treatment cycles. In addition, two studies also included a regimen of 14 days on- and 14 days-off antibiotics for 12 treatment cycles (RESPIRE 1; RESPIRE 2). Three trials delivered the antibiotic using a breath-actuated dry-powder inhaler (iBEST; RESPIRE 1; RESPIRE 2); the remaining studies used a nebuliser (AIRBX1; AIRBX2; ORBIT 2; ORBIT 3; ORBIT 4). Two trials

excluded tizanidine as a concomitant medication (ORBIT 3; ORBIT 4).

Outcomes

No study reported all of our prespecified outcomes.

Of our planned primary outcomes, all eight studies reported serious adverse events, including deaths, and all but the ORBIT 2 study reported exacerbation frequency (the number of participants with at least one exacerbation). All studies defined exacerbations similarly, requiring deterioration in either three or four symptoms and signs (sputum, dyspnoea, cough, fever/malaise/fatigue, FEV_1); two studies also included haemoptysis as a symptom (AIRBX1; AIRBX2) and two studies included worsening chest sounds as a sign (RESPIRE 1; RESPIRE 2). In addition to signs and symptoms, five studies also included the need for additional antibiotics in the definition of an exacerbation (AIRBX1; AIRBX2; iBEST; RESPIRE 1; RESPIRE 2).

Of our planned secondary outcomes all eight studies reported time to first exacerbation and antibiotic resistance measured as proportion of participants with minimum inhibitory concentrations (MIC). All but one the iBEST study also reported lung function as measured by FEV_1 (% predicted or L). All studies reported health-related quality of life using either the Quality of Life-Bronchiectasis (QoL-B) Respiratory Symptoms score (AIRBX1; AIRBX2; iBEST; ORBIT 3; ORBIT 4), the St George's Respiratory Questionnaire (SGRQ) Symptoms score (ORBIT 2) or both (RESPIRE 1; RESPIRE 2). All included studies reported the proportion of participants with at least one adverse effect. Three studies reported exacerbation severity (ORBIT 2; ORBIT 3; ORBIT 4), three reported frequency of hospital admission for a pulmonary exacerbation (iBEST; ORBIT 3; ORBIT 4) and four reported duration of exacerbation (iBEST; ORBIT 2; ORBIT 3; ORBIT 4). No studies reported frequency of hospital admissions for any cause.

It is important to note that the two four-arm trials (RESPIRE 1; RESPIRE 2) compared some outcomes against matched placebo groups (e.g. ciprofloxacin 14 days on/off versus placebo 14 days on/off and 28 days on/off versus placebo 28 days on/off) and some against pooled placebo groups (e.g. ciprofloxacin 14 days on/off versus pooled placebo groups and 28 days on/off versus pooled placebo groups). The specific comparisons are noted in the analyses of outcomes reported below.

Studies also reported the following outcomes. Five studies reported exercise tolerance using the six-minute walk test (6MWT) (AIRBX1; AIRBX2; ORBIT 2; ORBIT 3; ORBIT 4). Four studies reported the number of antibiotics prescribed for exacerbations (AIRBX1; AIRBX2; RESPIRE 1; RESPIRE 2). Four studies reported change in *P aeruginosa* sputum density (iBEST; ORBIT 2; ORBIT 3; ORBIT 4). Two studies reported frequency of moderate/severe exacerbations (ORBIT 3; ORBIT 4). Two studies reported pathogen eradication (RESPIRE 1; RESPIRE 2).

Trial registration, conflict of interest and study funding

Seven studies were registered on a clinical trials database (clinicaltrials.gov) (AIRBX1; AIRBX2; iBEST; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2), but two studies did not report results on the database (ORBIT 3; ORBIT 4). All eight study reports included conflicts of interest statements and explicitly stated sources of study funding. Seven studies described the role of the funder in the trial (AIRBX1; AIRBX2; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2). The role of the funder was not reported in the ORBIT 2 study.

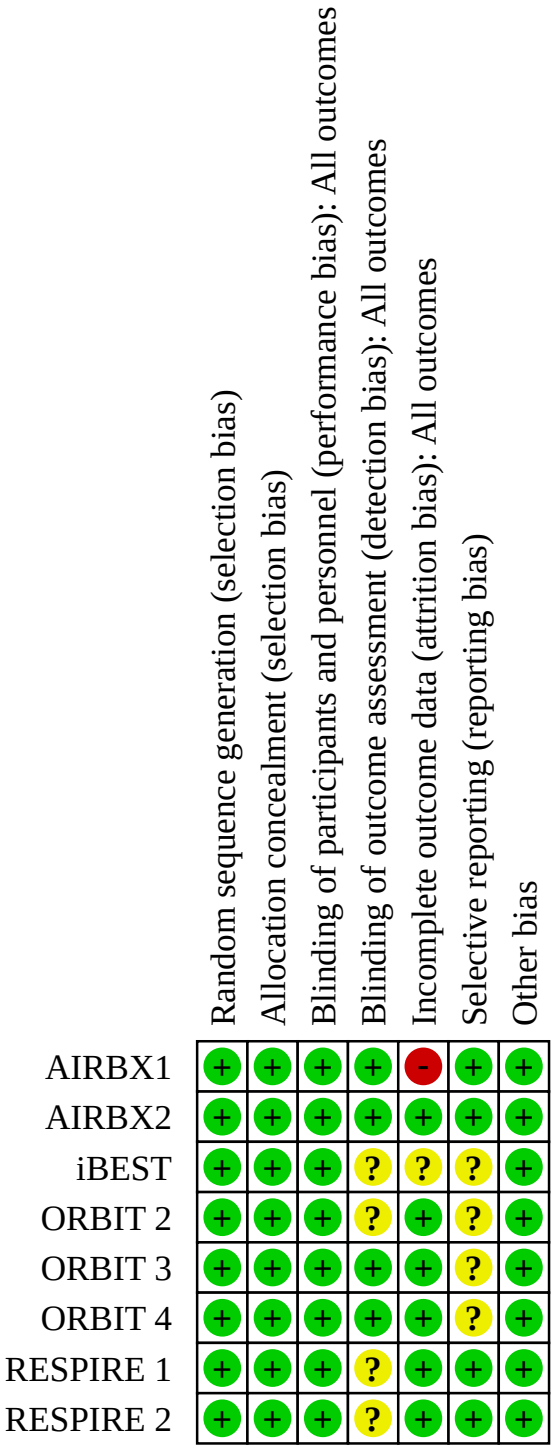
Excluded studies

We recorded reasons for exclusion of two studies in Characteristics of excluded studies. We excluded one study because participants did not meet the review definition of bronchiectasis (iREC. We excluded a second study (abstract only) because the comparisons were not one of the three predefined in the protocol (Lloberes 1990).

Risk of bias in included studies

Two review authors (SS and TD) assessed the risk of bias in each of the seven included studies using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. A summary of our judgements is in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All eight included studies reported centralised generation of the randomisation sequence and allocation of participants to treatment groups independent from the study investigators. We therefore classified the risk of selection bias as low.

Blinding

All included studies were described as double-blind, so we classified the risk of performance bias as low. Four studies reported analysis blinding so we classified these as having a low risk of detection bias (AIRBX1; AIRBX2; ORBIT 3; ORBIT 4). The four remaining studies did not explicitly report blinding of analyses, so we classified them as having an unclear risk of detection bias (iBEST; ORBIT 2; RESPIRE 1; RESPIRE 2).

Incomplete outcome data

One study analysed all randomised participants so had a low risk of attrition bias (ORBIT 2). Five studies reported withdrawals during the intervention period but this was balanced between groups, so we classified these as low risk of attrition bias (AIRBX2; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2). One study reported unbalanced withdrawals, with a higher proportion of treatment-related withdrawals in the intervention group (20%) compared to the placebo group (3%), so we classified this as a high risk of attrition bias (AIRBX1). One small study, with low event rates, was terminated early by the study funder, so we considered this to have an unclear risk of attrition bias (iBEST).

Selective reporting

Four studies had published planned outcomes either in journals or on clinical trials registries prior to the start of the study, so we classified these as having a low risk of reporting bias (AIRBX1; AIRBX2; RESPIRE 1; RESPIRE 2). One study was terminated early by the study funder and not all intended outcomes were published, we therefore classified this study as unclear risk of reporting bias (iBEST). We could not find a published study protocol or clinical trials registry entry for one study, which we classified as an unclear risk of reporting bias (ORBIT 2). Although the online publication supplement for the remaining two studies listed prespecified outcomes, we could not identify a published protocol and the clinical trials registry entry listed only two study outcomes, so we also classified these studies as having an unclear risk of reporting bias (ORBIT 3; ORBIT 4).

Other potential sources of bias

We did not identify any other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** 14 days on/off antibiotic regimen compared to 14 days on/off placebo regimen; **Summary of findings 2** 28 days on/off antibiotic regimen compared to 28 days on/off placebo regimen; **Summary of findings 3** 14 days on/off antibiotic regimen compared to 28 days on/off antibiotic regimen

Intermittent antibiotics versus placebo

14 days on followed by 14 days off

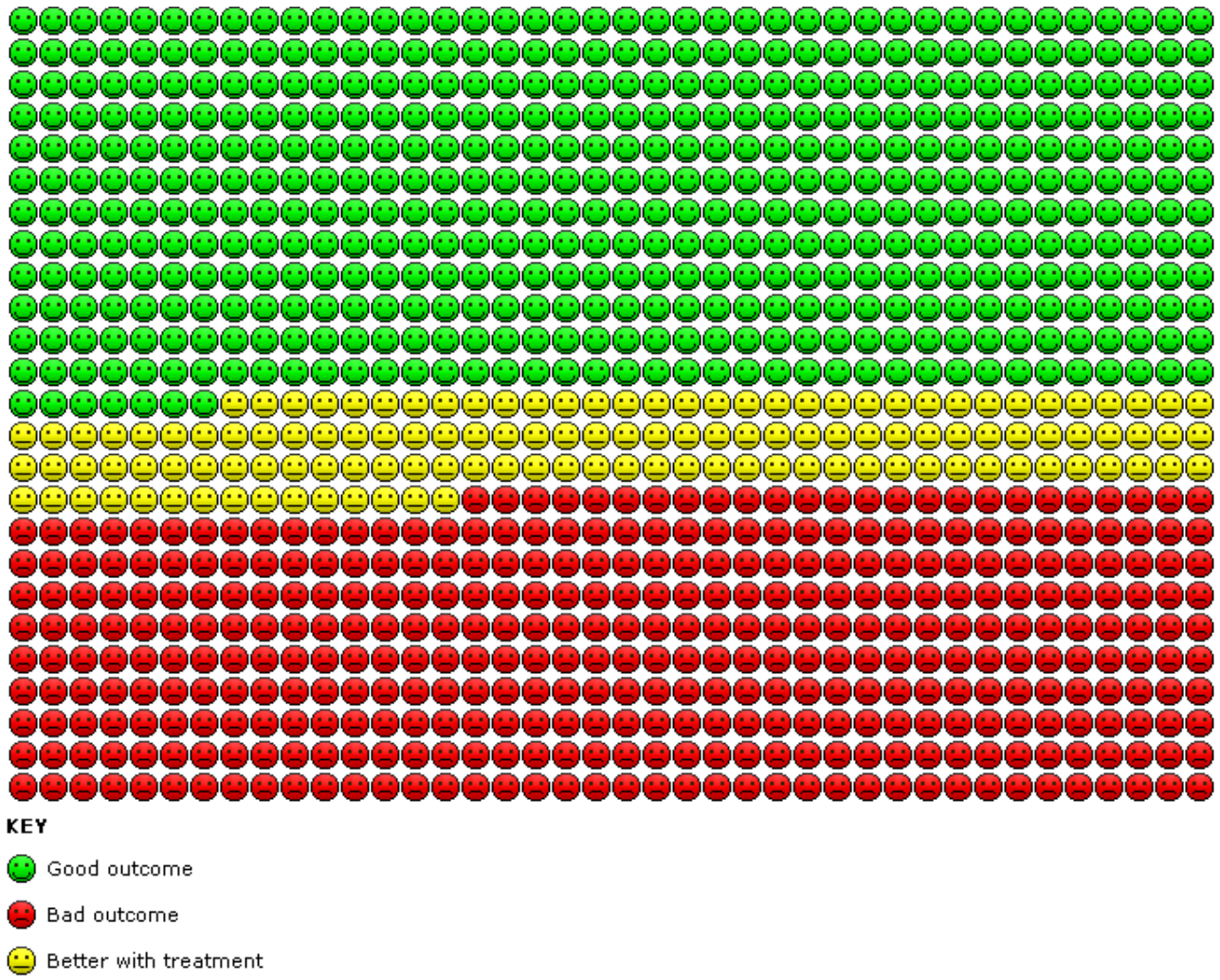
Two studies with a total of 621 adult participants compared an antibiotic regimen of 14 days on/off versus either matched or pooled placebo groups (RESPIRE 1; RESPIRE 2). We did not identify any studies that included children. This comparison is shown in Summary of findings 1.

Frequency of exacerbations

Number of participants with at least one exacerbation

We included both studies in a meta-analysis of ciprofloxacin compared to matched placebo. There was evidence that ciprofloxacin reduced the frequency of exacerbations compared to placebo (RR 0.75, 95% CI 0.61 to 0.93; I^2 = 65%; 2 studies; 469 participants; Analysis 1.1; moderate-certainty evidence). We noted the substantial heterogeneity but as there were only two studies we considered it to be relatively unimportant. The effect equates to 513 out of 1000 in the placebo group compared with 385 (95% CI 313 to 477) out of 1000 in the ciprofloxacin group with at least one exacerbation over 48 weeks, or eight people (95% CI 6 to 28) needed to treat for an additional beneficial outcome (Figure 3).

Figure 3. Cates plot: Intermittent antibiotics versus placebo: 14 days on followed by 14 days off. In the placebo group 513 people out of 1000 had at least one exacerbation over 48 weeks, compared to 385 (95% CI 313 to 477) out of 1000 for the active treatment group.



Incidence rate ratios

The studies reported incidence rate ratios (IRR) with a range of confidence intervals (CIs) due to Bonferroni and weighted Bonferroni corrections. Although we could have recalculated these for inclusion in meta-analyses with either 90%, 95% or 99% confidence intervals, this would have conflicted with the prespecified planned analyses reported by the study authors; therefore, we have included the results narratively.

Compared with matched placebo, ciprofloxacin significantly reduced the frequency of exacerbations by 39% over 48 weeks in the RESPIRE 1 study (IRR 0.61, 97.5% CI 0.40 to 0.91; P = 0.0061). In RESPIRE 2 there was no difference between the matched study arms (IRR 0.83, 95.1% CI 0.59 to 1.17; P = 0.28).

There were insufficient studies to perform planned subgroup analyses.

Serious adverse events

Both studies reported serious adverse events (SAEs) as active intervention versus pooled placebo groups. We therefore included both studies in a meta-analysis of ciprofloxacin compared to pooled placebo (RESPIRE 1; RESPIRE 2). SAEs did not differ between study groups (OR 0.92, 95% CI 0.63 to 1.33; I^2 = 44%; 2 studies, 621 participants; Analysis 1.2; high-certainty evidence).

There was one treatment-related death in the ciprofloxacin group compared with three in the pooled placebo group in RESPIRE 1, and three in the ciprofloxacin group compared with two in the pooled placebo group in RESPIRE 2.

There were insufficient studies to perform planned subgroup analyses.

Time to first exacerbation

The studies reported Bonferroni-adjusted confidence intervals for effect sizes (as above for exacerbation frequency), so we have reported these outcomes narratively.

Ciprofloxacin significantly delayed the time to first exacerbation over 48 weeks in RESPIRE 1 (HR 0.53, 97.5% CI 0.36 to 0.80; P = 0.0005), with a median time of > 336 days (97.5% CI 290 to > 336) for the ciprofloxacin arm and 186 days (97.5% CI 136 to 282) in the pooled placebo arm. In RESPIRE 2 the difference between the study arms was not statistically significant (HR 0.87, 95.1% CI 0.62 to 1.21; P = 0.39). The study did not report median days to exacerbation for each group.

Duration of exacerbations

Not an outcome in these studies.

Severity of exacerbations

Not an outcome in these studies.

Development of antibiotic resistance

The studies reported antibiotic resistance as the number of participants with an isolate with an elevated minimal inhibitory concentration (MIC) at any time between pretreatment and study endpoint at 48 weeks. We entered the two studies into a meta-analysis of ciprofloxacin compared to matched placebo. There was evidence of a higher proportion of participants with antibiotic resistance in the ciprofloxacin group compared to the placebo group (OR 2.14, 95% CI 1.36 to 3.35; I^2 = 0%; 2 studies, 624 participants; Analysis 1.3; high-certainty evidence). This equates to 109 people out of 1000 in the control group who developed antibiotic resistance over 48 weeks, compared to 208 (95% CI 143 to 291) out of 1000 in the ciprofloxacin group.

Frequency of hospital admissions

Not an outcome in these studies.

Lung function measured as FEV_1

Both studies reported mean change in FEV_1 from baseline to end of treatment, and we entered this into a meta-analysis of ciprofloxacin compared to matched placebo. There was no evidence of a difference between groups (MD -0.07 L, 95% CI -0.13 to 0.00; I^2 = 0%; 2 studies, 350 participants; Analysis 1.4).

Health-related quality of life

The two studies measured health-related quality of life as change from baseline to the 48 week study endpoint using the Quality of Life for Bronchiectasis respiratory symptoms (QOL-B-RS) scale (score of 100 = best health) and the St George's Respiratory Questionnaire symptoms (SGRQ-S) scale (score of 1 = best health). We included both studies in two meta-analyses comparing ciprofloxacin with matched placebo. There was no evidence of a difference in health-related quality of life between matched study groups: QoL-B-RS scores (MD 1.12, 95% CI -3.12 to 5.36; I^2 = 0%; 2 studies, 282 participants; Analysis 1.5; high-certainty evidence); SGRQ-S scores (MD -2.93, 95% CI -7.00 to 1.14; I^2 = 89%; 2 studies, 360 participants; Analysis 1.6; moderate-certainty evidence). The differences did not exceed the minimum clinically important threshold (QoL-B RSS ≥ 8 units; SGRQ-S ≥ -4 units).

Adverse effects

Both studies reported the number of participants with a least one treatment-related adverse effect (not including serious adverse events), and we entered the data into a meta analysis. There was evidence of more adverse effects in the ciprofloxacin group compared with pooled placebo groups (OR 1.44, 95% CI 1.04 to 2.00; I^2 = 57%; 2 studies, 621 participants; Analysis 1.7).

28 days on followed by 28 days off

All eight studies of adults with bronchiectasis compared antibiotics with placebo using a regimen of 28 days on followed by 28 days off. We did not identify any studies that included children. This comparison is shown in Summary of findings 2.

Frequency of exacerbations

Number of participants with at least one exacerbation

All eight studies reported the number of participants with one or more pulmonary exacerbations up to the study endpoint. We entered these into a meta-analysis, subgrouped by study duration and type of antibiotic. Overall, there was no evidence of a difference between antibiotic and placebo (RR 0.92, 95% CI 0.82 to 1.02; I^2 = 0%; 8 studies, 1695 participants; Analysis 2.1; high-certainty evidence), and no differences between subgroups (test for subgroup differences: Chi^2 = 3.86, df = 3, P = 0.28, I^2 = 22.2%).

We used a subgroup analysis to assess the impact of the method of administering antibiotics. Five studies used a nebuliser (AIRBX1; AIRBX2; ORBIT 2; ORBIT 3; ORBIT 4), and three studies used a dry-powder inhaler (iBEST; RESPIRE 1; RESPIRE 2). There was no evidence of a difference between groups by mode of administration (test for subgroup differences: Chi^2 = 0.96, df = 1, P = 0.33, I^2 = 0%; Analysis 2.2).

Studies did not report data subgrouped according to chronic infection with *P aeruginosa* at study enrolment, so we were unable to perform this planned analysis.

We did not perform planned sensitivity analyses as we judged all eight studies to be at low risk of bias for random sequence generation and allocation concealment.

Incidence rate ratios

The studies did not report rate ratios consistently, so we have described them narratively.

Two studies reported the relative risk of a pulmonary exacerbation with ciprofloxacin compared to placebo. In ORBIT 4 there was evidence of a 37% reduction in exacerbation with ciprofloxacin (RR 0.63, 95% CI 0.48 to 0.82; P = 0.0006; 308 participants), but in ORBIT 3 there was no evidence of a difference between groups (RR 0.85, 95% CI 0.65 to 1.12; P = 0.26; 290 participants).

Two studies reported incidence rate ratios for ciprofloxacin compared with matched placebo over 48 weeks using 97.5% CI (RESPIRE 1), and 99% CI RESPIRE 2. There was evidence of a 45 % reduction in exacerbation frequency with ciprofloxacin compared with placebo in RESPIRE 2 (IRR 0.55, 99% CI 0.30 to 1.02; P = 0.0014; 257 participants), but there was no evidence of a difference between groups in RESPIRE 1 (IRR 0.98, 97.5% CI 0.64 to 1.48; P = 0.8; 211 participants).

The iBEST study reported the rate ratio for pooled tobramycin versus pooled placebo over 16 weeks, showing no evidence of a difference between groups (RR 0.96, 95% CI 0.49 to 1.91; 63 participants).

Two studies reported the annualised risk of pulmonary exacerbation with aztreonam compared to placebo (AIRBX1; AIRBX2). There was no evidence of a difference between groups in either study (AIRBX1: RR 1.22, 95% CI 0.80 to 1.85; P = 0.35; 268 participants; AIRBX2: RR 1.05, 95% CI 0.70 to 1.56; P = 0.81; 274 participants).

ORBIT 2 did not report rate ratios for exacerbation frequency.

Serious adverse events

All eight studies reported SAEs (RESPIRE 1and RESPIRE 2 reported pooled placebo groups; iBEST reported pooled intervention and placebo groups). We entered them into a meta-analysis, subgrouped by study duration and type of antibiotic. Overall, there was no evidence of a difference between study groups (OR 1.00, 95% CI 0.68 to 1.46; I^2 = 56%; 8 studies, 1848 participants; Analysis 2.3; low-certainty evidence).

The eight studies all reported mortality. In the five ciprofloxacin trials, 11 participants in the intervention groups died compared with eight in the placebo groups. Mortality by group (intervention versus placebo) in the individual trials was as follows: RESPIRE 1 2 versus 3; RESPIRE 2 4 versus 2; ORBIT 2 no deaths; ORBIT 3 5 versus 3; ORBIT 4 1 versus 2). In the two aztreonam studies two participants in the intervention group and two in the placebo group died (intervention versus placebo: AIRBX1 2 versus 1; AIRBX2 0 versus 1). No participants in the tobramycin study died (iBEST).

We conducted a subgroup analysis to assess the impact of mode of administration on SAEs. There was no evidence of subgroup differences (test for subgroup differences: Chi^2 = 2.37, df = 1, P = 0.12, I^2 = 57.8%; Analysis 2.4).

As above, it was not possible to perform a subgroup analysis by baseline *P aeruginosa* chronic infection, or to perform sensitivity analyses.

Time to first exacerbation

The included studies did not report time to first exacerbation consistently.

Five studies reported time to first exacerbation (AIRBX1; AIRBX2; iBEST; ORBIT 3; ORBIT 4). We entered these into a meta-analysis, subgrouped by type of antibiotic. Overall, there was no evidence of a difference between study groups (HR 0.94, 95% CI 0.79 to 1.13; 5 studies, 1174 participants; Analysis 2.5).

In ORBIT 2 the median time to first pulmonary exacerbation was 134 days for ciprofloxacin and 58 days for placebo, which did not achieve statistical significance using a modified ITT population, though we note this small study was not powered to detect differences in this outcome.

As described above for the 14 days on/off outcomes in RESPIRE 1 and RESPIRE 2, confidence intervals for effect sizes were Bonferroni-adjusted, so we have reported these outcomes narratively. There was no evidence of a difference between groups in the time to first exacerbation over 48 weeks (RESPIRE 1: HR 0.73, 97.5% CI 0.50 to 1.07; P = 0.065; ciprofloxacin 336 days versus placebo 186 days; RESPIRE 2: HR 0.71, 99.9% CI 0.39 to 1.27; P = 0.051; median time to exacerbation was not estimable due to low event rates).

Duration of exacerbations

Four studies with 676 participants reported the duration of exacerbations in days (iBEST; ORBIT 2; ORBIT 3; ORBIT 4). ORBIT 2 reported median values, iBEST reported mean values, and the metric was unclear in the other two studies (ORBIT 3; ORBIT 4); we have therefore reported the results narratively. There was no evidence of a difference between groups in the average duration of exacerbations (ORBIT 2: ciprofloxacin 20.3 days versus placebo 22.3 days, P = 0.8; ORBIT 3: ciprofloxacin 39.9 days versus placebo 39.8 days, P = 0.9; ORBIT 4: ciprofloxacin 52.0 days versus placebo 57.1 days, P = 0.5; iBEST, pooled tobramycin 15.2 versus pooled placebo 14.5 days, P = 0.7).

Duration of exacerbations was not an outcome measure in the other four studies (AIRBX1; AIRBX2; RESPIRE 1; RESPIRE 2).

Severe exacerbations

The three ORBIT trials also reported the number of participants with at least one severe exacerbation during the study. We entered these into a meta-analysis, subgrouped by study duration. There was evidence of a difference between groups, with fewer severe exacerbations in the ciprofloxacin groups (OR 0.59, 95% CI 0.37 to 0.93; I^2 = 54%; 3 studies, 624 participants; Analysis 2.6). However, these results should be interpreted with caution due to low event rates in the three studies (ORBIT 2; ORBIT 3; ORBIT 4).

The other five studies did not report exacerbation data classified by severity (AIRBX1; AIRBX2; iBEST; RESPIRE 1; RESPIRE 2).

Development of antibiotic resistance

The studies did not report antibiotic resistance consistently. Three studies reported the number of participants with elevated MICs at any point during the study, and we included these in a meta-analysis (iBEST; RESPIRE 1; RESPIRE 2). Of note, RESPIRE 1 and RESPIRE 2 reported ciprofloxacin compared with pooled placebo, and iBEST reported pooled tobramycin compared with pooled placebo. There was evidence of a difference between groups, with a higher risk of developing antibiotic resistance in the intervention group (OR 2.20, 95% CI 1.42 to 3.42; I^2 = 0%; 3 studies, 685 participants; Analysis 2.7; high-certainty evidence). The effect equates to 105 out of 1000 in the placebo group compared with 205 (95% CI 143 to 286) out of 1000 in the intervention group who developed antibiotic resistance at some point during the study period, or ten people (95% CI 6 to 27) needed to treat for an additional harmful outcome.

The authors of the two ciprofloxacin studies pooled their 288 participants, and reported evidence of a higher proportion of participants in the intervention group with antibiotic resistance (≥ two-fold MIC for *P aeruginosa)* by week 48 (n/N; ciprofloxacin 62/191 (32%) versus placebo 17/97 (18%); P = 0.0078) (ORBIT 3; ORBIT 4).

Data from two aztreonam studies, with 752 participants, also reported evidence of a higher proportion of participants in the intervention group with antibiotic resistance (≥ four-fold MIC for gram-negative organisms) after 16 weeks (n/N; AIRBX1: aztreonam

14/62 (23%) versus placebo 11/76 (14%); AIRBX2: aztreonam 13/64 (20%) versus placebo 4/64 (6%)).

One ciprofloxacin study, with 42 participants, reported no evidence of a difference between groups in antibiotic resistance, based on changes in *P aeruginosa* ciprofloxacin minimal inhibitory concentrations (MIC) after 28 days (median (range): ciprofloxacin 0 (-0.5 to 31) versus placebo 0 (-0.75 to 0.5); P = 0.26) (ORBIT 2).

Frequency of hospital admissions

None of the studies reported all-cause hospital admissions; three studies reported the number of participants hospitalised for pulmonary exacerbations, and we included these in a meta-analysis (iBEST; ORBIT 3; ORBIT 4). There was no evidence of a difference between the groups ((OR 0.79, 95% CI 0.49 to 1.29; I^2 = 0%; 3 studies, 645 participants); Analysis 2.8; high-certainty evidence).

The other five studies did not report this outcome (AIRBX1; AIRBX2; ORBIT 2; RESPIRE 1; RESPIRE 2).

Lung function measured as FEV_1

Five studies reported the change in FEV_1 (L or % predicted) from baseline to endpoint (AIRBX1; AIRBX2; ORBIT 2; RESPIRE 1; RESPIRE 2). We entered these into a meta-analysis, subgrouped by study duration and type of antibiotic; of note, the RESPIRE studies compared intervention with matched placebo. There was no evidence of a difference in lung function between study groups (SMD -0.11, 95% CI -0.25 to 0.02; I^2 = 45%; 5 studies, 874 participants; Analysis 2.9).

The authors of the two ORBIT studies pooled their data (392 participants) (ORBIT 3; ORBIT 4). Mean change (SD) in FEV_1 was -0.047 L (0.19) for ciprofloxacin versus -0.064 L (0.18) for placebo. The difference was not formally tested by the study authors, but we conducted an independent t-test that showed no statistical difference between groups (MD -0.017 L, 95% CI -0.056 to 0.022; t = -0.851, df = 390; P = 0.4).

The iBEST study did not report lung function data.

Health-related quality of life

All eight studies reported health-related quality of life.

Seven studies reported the change in QoL-B-RS scores (score of 100 = best health) from baseline to study endpoint (AIRBX1; AIRBX2; iBEST; ORBIT 3; ORBIT 4; RESPIRE 1; RESPIRE 2). We combined the data in a meta-analysis, subgrouped by study duration and type of antibiotic. There was no evidence of a difference in changes in health-related quality of life between groups (MD 0.05, 95% CI -1.56 to 1.66; I^2 = 0%; 7 studies, 1469 participants; Analysis 2.10; moderate-certainty evidence). The differences did not exceed the minimum clinically important threshold (≥ 8 units). The ORBIT 2 study did not report the QoL-B as an outcome measure.

Three studies reported the change in SGRQ-S scores (score of 1 = best health) from baseline to study endpoint (ORBIT 2; RESPIRE 1; RESPIRE 2), with the two RESPIRE studies comparing intervention versus matched placebo. We entered the data into a meta-analysis subgrouped by study duration and type of antibiotic.

There was no evidence of a difference in health-related quality of life between study groups (MD -0.59, 95% CI -4.26 to 3.08; I^2 = 73%; 3 studies, 407 participants; Analysis 2.11; low-certainty evidence) and the differences did not exceed the minimum clinically important threshold (≥ -4 units) . We noted considerable heterogeneity that was not improved by fitting a random-effects model (test for subgroup differences: Chi^2 = 7.16, df = 1 (P = 0.007), I^2 = 86.0%. Sensitivity analyses showed evidence of a difference between groups in the two RESPIRE studies, with a clinically significant benefit (≥ -4 units) in health-related quality of life with ciprofloxacin (MD -5.01, 95% CI -9.90 to -0.12; I^2 = 0%; 2 studies, 370 participants; Analysis 2.11) (RESPIRE 1; RESPIRE 2).

The other five studies did not use the SGRQ (AIRBX1; AIRBX2; iBEST; ORBIT 3; ORBIT 4).

Adverse effects/reactions

All eight studies reported the number of participants with at least one treatment-related adverse event. We pooled the data in a meta-analysis, subgrouped by study duration and type of antibiotic. The two RESPIRE studies compared the intervention with pooled placebo groups, and iBEST reported pooled intervention compared with pooled placebo groups.

Overall, there was no evidence of a difference between groups (RR 1.09, 95% CI 0.91 to 1.31; I^2 = 60%; 8 studies, 1845 participants; Analysis 2.12). There was considerable heterogeneity between subgroups (test for subgroup differences: Chi^2 = 11.43, df = 3, P = 0.010, I^2 = 73.8%), but the impact of using a random-effects model was minimal (test for subgroup differences: Chi^2 = 11.94, df = 3, P = 0.008, I^2 = 74.9%).

Intermittent antibiotics versus usual care

We did not find any studies that compared intermittent regimens of antibiotics with usual care.

Intermittent antibiotics comparing regimen X with regimen Y

14 days on followed by 14 days off versus 28 days on followed by 28 days off

Two studies, with 625 adult participants, included two intervention arms of 14 days and 28 days intermittent treatment with ciprofloxacin delivered via dry-powder inhaler (RESPIRE 1; RESPIRE 2). We did not identify any studies that included children. This comparison is shown in Summary of findings 3.

Frequency of exacerbations

Number of participants with at least one exacerbation

Both studies reported the number of participants with at least one exacerbation, and we included the data in a meta-analysis. There was no evidence of a difference between the 28-day and 14-day treatment regimens (RR 1.02, 95% CI 0.84 to 1.24; I^2 = 71%; 2 studies, 625 participants; Analysis 3.1; moderate-certainty evidence).

There were insufficient studies to perform planned subgroup analyses.

We note that there are inconsistencies between the results of these head-to-head comparisons when considered alongside the individual 14-day regimen versus placebo and 28-day regimen versus placebo comparisons above, but it is not possible to draw

robust direct comparisons between one set of trials versus placebo and another set of trials versus placebo.

Incidence rate ratios

Neither of the studies reported incidence rate ratios for 28-day versus 14-day treatment regimens.

Serious adverse events

Both studies reported SAEs, and we entered their data into a meta-analysis. Overall there was no evidence of a difference between the intermittent regimens (OR 0.83, 95% CI 0.37 to 1.86; I^2 = 75%; 2 studies, 622 participants; Analysis 3.2; moderate-certainty evidence). A random-effects model did not reduce the considerable heterogeneity between studies (heterogeneity: Tau^2 = 0.25; Chi^2 = 3.97, df = 1, P = 0.05; I^2 = 75%).

There were four treatment-related deaths with the 14-day regimen and six deaths with the 28-day regimen (RESPIRE 1; RESPIRE 2).

We were unable to perform planned subgroup analyses due to an insufficient number of studies.

Time to first exacerbation

Neither of the studies reported hazard ratios for 28-day versus 14-day treatment regimens.

Duration of exacerbations

Not an outcome in these studies.

Severity of exacerbations

Not an outcome in these studies.

Development of antibiotic resistance

The studies reported antibiotic resistance as the number of participants with elevated MICs at any point during the study, and we included the data in a meta-analysis. There was no evidence of a difference between the two treatment regimens (OR 1.00, 95% CI 0.68 to 1.48; I^2 = 60%; 2 studies, 624 participants; Analysis 3.3; moderate-certainty evidence).

Frequency of hospital admissions

Not an outcome in these studies.

Lung function measured as FEV_1

Both studies reported the change in FEV_1 from baseline to the 48-week endpoint, and we pooled the data in a meta-analysis. There was no evidence of differences between the two treatment regimens (MD -0.03 L, 95% CI -0.08 to 0.01; I^2 = 43%; 2 studies, 488 participants; Analysis 3.4).

Health-related quality of life

The studies reported mean change in QOL-B-RS and SGRQ-S scores from baseline to study endpoint, which we pooled in meta-analyses. There was no difference in health-related quality of life between the 14-day and 28-day treatment regimens reported using QoL-B-RS (MD 0.83, 95% CI -2.77 to 4.44; I^2 = 0%; 2 studies, 384 participants; Analysis 3.5; high-certainty evidence) or SGRQ-S (MD 0.34, 95% CI -3.35 to 4.02; I^2 = 0%; 2 studies, 500 participants; Analysis 3.6; high-certainty evidence). The differences did not exceed the minimum clinically important threshold (QoL-B-RS ≥ 8 units; SGRQ-S ≥ -4 units).

Adverse effects/reactions

Both studies reported the number of participants with at least one treatment-related adverse effect during the 48-week study and were entered into a meta-analysis. There was no evidence of a difference between the two treatment regimens (OR 1.32, 95% CI 0.95 to 1.83; I^2 = 0%; 2 studies, 622 participants; Analysis 3.7).

DISCUSSION

Summary of main results

Eight randomised controlled trials of adults with bronchiectasis met the inclusion criteria for this systematic review. Clinical heterogeneity was observed on a range of factors, including three different types of antibiotics (aminoglycosides, ß-lactams and fluoroquinolones), with doses ranging from 71 mg to 224 mg daily, delivered via nebuliser or dry-powder inhaler for up to 48 weeks. All studies compared 28 days on/off antibiotics with matched placebo regimens and two of these studies also compared 14 days on/off antibiotics with matched placebo regimens. None of the studies compared intermittent antibiotic regimens with usual care. We did not identify any studies of intermittently administered antibiotics for children with bronchiectasis.

For our primary outcome exacerbation frequency, reported as participants with at least one exacerbation during the study, there was evidence of a slight reduction in exacerbation frequency with 14 days on/off ciprofloxacin, based on moderate-certainty evidence. There was no little to no difference in exacerbation frequency with a regimen of 28 days on/off antibiotics compared to placebo, or between 14-day and 28-day antibiotics regimens, based on moderate-certainty evidence. For our co-primary outcome serious adverse events, there was little to no difference between 14 days on/off antibiotic regimens and placebo based on high-certainty evidence, or between 28 days regimens and placebo based on low-certainty evidence, or between 14-day and 28-day regimens, based on moderate-certainty evidence. There was little to no difference in mortality rates with any antibiotic regimen.

Overall, our review provides promising but inconsistent results for our predefined primary outcomes. Antibiotics delivered at 14-day intervals slightly reduced exacerbation frequency whereas antibiotics delivered at 28-day intervals had little or no effect on exacerbation frequency, and there was little or no difference between 14-day and 28-day regimens. However, it is apparent that there are inconsistencies in the results from paired trials that used the same study designs, directly comparing 14 versus 28 day regimens, Whilst it is not possible to explain the reasons for these inconsistencies, there is a clear indication that the apparent aggregated similarities may not be reliable. Antibiotics resulted in little to no difference in adverse events with any antibiotic regimen.

For our secondary outcomes, data on time to first exacerbation with 14 days on/off ciprofloxacin was inconclusive and there was little or no difference with 28-day intermittent treatment. Analysis suggested that 28 days on/off antibiotics reduced severe exacerbations with ciprofloxacin, but there was little or no difference between groups on the duration of exacerbations with ciprofloxacin or tobramycin. Both 14-day and 28-day intermittent antibiotic therapy increased antibiotic resistance, but there was

little or no difference between 14-day and 28-day intermittent therapy. Only three studies reported data on participants admitted to hospital for at least one pulmonary exacerbation, and these showed little or no difference between groups. There was little or no difference in lung function between groups (measured using FEV_1) or health-related quality of life, for any intermittent therapy. Finally, more participants receiving 14-day intermittent therapy with ciprofloxacin had adverse effects but, for other comparison groups, there was little or no difference in the number of adverse effects between treatment and control groups.

Evidence from our predefined secondary outcomes is consistent with our primary outcome, showing that 14-day intermittent regimens slightly reduced the frequency of severe exacerbations, though intermittent therapy increased antibiotic resistance and adverse effects.

Overall completeness and applicability of evidence

We identified two studies with adult participants that investigated 14-day intermittent antibiotic therapy compared to placebo, and eight studies of 28-day intermittent antibiotic therapy compared to placebo that reported exacerbation frequency and serious adverse events. The two studies that included 28-day and 14-day antibiotic regimens also reported our two primary outcomes. Data on all-cause hospital admissions were not reported in any of the eight studies. Data on exacerbation severity and duration, and hospital admissions for pulmonary exacerbations, were not reported in the studies of 14-day intermittent therapy or 28-day versus 14-day therapy.

Our findings are based on eight studies with a total of 2164 adults. The types of antibiotics were limited, with five studies using ciprofloxacin, two using aztreonam and one using tobramycin, which may limit generalisability of the findings and, for example, the opportunity to determine the advantages of one antibiotic over another, as none of the included studies reported direct comparisons between different antibiotics. Most of the interventions lasted for at least six months, reducing the likelihood of missing small but clinically meaningful adverse reactions. Although the review provides limited evidence of benefit from intermittent antibiotics, their relative benefit compared with usual therapeutic regimens remains unknown, as we did not identify any studies that included these comparisons. All of the studies included in this review reported the risk of developing antibiotic resistance.

All included studies assessed inhaled antibiotics. We did not identify any studies evaluating oral or systemic antibiotics. Inhaled antibiotics can deliver higher concentrations of the antibiotic at the site of the infection with less systemic absorption and toxicity and, for this reason, are increasingly favoured (Geller 2009).

The populations in these studies represented the more severe end of the disease spectrum, since most of the trials only included participants with a history of at least two exacerbations during the preceding year, with a positive sputum culture at presentation, or a previous history of pseudomonas infection, and the majority of participants also had impaired spirometry (FEV_1). Participants with less severe bronchiectasis are therefore potentially underrepresented.

The impact of intermittent antibiotic therapy on children with bronchiectasis remains unknown as we did not identify any studies in children that met our study selection criteria.

Quality of the evidence

Our overall confidence in the evidence included in this review ranges from low to high for outcomes included in the GRADE assessments.

From studies comparing 14-day on/off antibiotics regimens with placebo, we are very confident in the effect estimates for serious adverse events, antibiotic resistance and health-related quality of life, measured using the QoL-B-RSS. We have moderate confidence in the effect estimates for frequency of exacerbations, measured as the number of people experiencing at least one exacerbation, and health-related quality of life, measured using the SGRQ; we downgraded the evidence due to unexplained heterogeneity. We also have moderate confidence in the estimate of exacerbation frequency, measured using rate ratios, which we downgraded due to inconsistent results.

From studies comparing 28-day on/off antibiotics regimens with placebo, we are very confident in the effect estimates for exacerbation frequency (people with at least one exacerbation), antibiotic resistance and hospitalisations for pulmonary exacerbations. We are moderately confident in the estimate of health-related quality of life (QoL-B-RSS); we downgraded the evidence due to risk of bias in the included studies. We have limited confidence in the effect estimate for frequency of exacerbations (rate ratios) due to inconsistent results and wide confidence intervals, and downgraded the evidence accordingly. We also have limited confidence in the estimate for serious adverse events; we downgraded the evidence due to risk of bias and unexplained heterogeneity. Our confidence in the effect estimate for health-related quality of life (SGRQ) was limited due to risk of bias and inconsistent results, leading to us downgrading the evidence.

Based on the two studies comparing 28-day on/off with 14-day on/off antibiotic regimens, we are very confident in the effect estimates for health-related quality of life (QoL-B-RS and SGRQ). We are moderately confident in the effect estimates for exacerbation frequency (rate ratios of people with at least one exacerbation), serious adverse events and antibiotic resistance; we downgraded the evidence due to inconsistency arising from unexplained heterogeneity.

We judged one of our eight studies to be at low risk of bias across all seven domains (AIRBX2). We considered all eight studies to be at low risk of selection, performance and other bias. The reporting of outcome assessment blinding was unclear in four studies. We considered the AIRBX1to be at high risk of attrition bias due to more treatment-related withdrawals in the intervention group. Attrition bias was unclear in another small study (iBEST). One study was at unclear risk of reporting bias due to early termination (iBEST). In three other studies, reporting bias was unclear due to lack of a prepublished trial protocol. In addition, one study was not registered on a trial registry and four studies had not reported study results on the registry. All studies performed a formal sample size calculation, though one study was terminated early before achieving the planned recruitment target (iBEST).

Potential biases in the review process

To identify potentially eligible studies, an experienced Information Specialist undertook comprehensive searches. We searched multiple resources including electronic databases, conference proceedings, reference lists of included studies and trial registries. However, we acknowledge the potential for publication bias in this review that could overestimate or underestimate effects of the intervention on outcomes. Clinical trials showing no effects or negative effects are less likely to be published, leading to bias in studies available for inclusion. However, the trials in our review also include studies reporting little positive benefit from the intervention and potential adverse effects, and we searched clinical trials registers, so are confident that our conclusions do not reflect publication bias.

Misclassification of studies during the selection process may have excluded potentially eligible studies, but we minimised this risk of bias through independent selection and verification with three review authors. We are therefore confident that our study selection processes were transparent and consistent. Similarly, it is possible that data from some full-text reports may have been entered incorrectly in analyses, but again we used three review authors to independently extract and verify the data and analyses.

As two of our comparisons included only two studies, we were unable to conduct planned subgroup or sensitivity analyses. For the third comparison we were able to explore the impact of type of antibiotic, study duration and method of administering the antibiotic. We were unable to explore the impact of baseline chronic infection with *Pseudomonas aeruginosa* on trial outcomes as this data was not reported in the included studies. We did not perform planned sensitivity analyses to determine the impact of selection bias (random sequence generation and allocation concealment) on the effects of interventions as we judged all of the included studies to be at low risk of this type of bias.

Agreements and disagreements with other studies or reviews

The potential benefits of prophylactic antibiotics for people with bronchiectasis include a 50% reduction in the odds of an exacerbation or hospitalisation (Hnin 2015). A review of continuous versus intermittent antibiotics for severe acute infections reported no differences in benefits or harms between regimens (Shiu 2013), but there was insufficient evidence to assess the impact of these different regimens in people with bronchiectasis (Donovan 2018). However, a retrospective analysis of hospitalised patients with nosocomial infections found that lower resistance rates were associated with longer antibiotic-free intervals (20 days +) between courses of antibiotics (Hui 2013), which suggested that potential benefits from intermittent antibiotic regimens in people with bronchiectasis may vary according to interval duration. Our review showed no differences in serious adverse events or antibiotic resistance between 14- and 28-day regimens, which does not support the findings from the nosocomial study.

AUTHORS' CONCLUSIONS

Implications for practice

Prophylactic long-term administration of antibiotics is recommended for adults with bronchiectasis who have three or more exacerbations per year (Polverino 2017). In clinical practice these antibiotics are most often administered to people with chronic *Pseudomonas aeruginosa* infection (Chalmers 2015). Intermittent antibiotic regimens are often used to limit antimicrobial resistance, side effects and improve treatment adherence, but this practice has been based on limited evidence. Our findings suggest that intermittent prophylactic antibiotics administered at 14-day on/off intervals slightly reduces the frequency of exacerbations, but there was little or no difference between comparisons of 14-day versus 28-day on/off antibiotics regimens. When compared to placebo, 14-day on/off regimens resulted in a greater reduction (25%) in the number of participants experiencing at least one exacerbation (RR 0.75, 95% CI 0.61 to 0.93) based on moderate-certainty evidence, compared to the reduction (8%) with the 28-day on/off regimen (RR 0.92, 95% CI 0.82 to 1.02) based on high-certainty evidence. Therefore, based on currently available evidence, 14-day on/off regimens are favoured.

Intermittent antibiotic regimens probably result in little to no difference in serious adverse events compared to placebo, but our confidence in this evidence ranges from low with 28-day regimens to high with 14-day regimens. However, they are associated with an increase in antimicrobial resistance compared to placebo (90% increase with 14-day and 95% with 28-day regimens), based on high-certainty evidence. While direct comparisons between continuous and intermittent regimens are still lacking (New Reference), the risk of antimicrobial resistance does not appear to differ between intermittent and continuous regimens, as summarised in the recent European Respiratory Society Bronchiectasis guidelines (Polverino 2017).

Overall, administration of 14-day on/off regimens of prophylactic antibiotics for adults experiencing frequent exacerbations slightly reduces exacerbation frequency and increases antimicrobial resistance.

The impact of intermittent antibiotic therapy on children with bronchiectasis is unknown due to an absence of evidence.

Implications for research

All of the studies included in this review were high quality and provided robust evidence of the benefits and harms of different intermittent regimens. However, none of the studies reported data on all-cause hospital admissions. The severity and duration of exacerbations and hospital admissions for pulmonary exacerbations were not reported in the studies of 14-day intermittent therapy or 28-day versus 14-day therapy. The impact on these outcomes therefore remains unclear, and merits further research. We did not include cost-benefit or participant preference as outcomes in this review, but these could also be considered in further research. The key area of uncertainty concerns the potential benefits and harms of different intermittent regimens for children with bronchiectasis, where we did not identify any studies, and these issues certainly require clarification in high quality clinical trials.

ACKNOWLEDGEMENTS

The Background and Methods sections of this review were based on a standard template used by Cochrane Airways. We would like to thank the Cochrane Airways Group for its support.

We and the Cochrane Airways Editorial Team are grateful to Philip Ind (UK) and Pieter C Goeminne (Belgium) for their peer review of this Cochrane Review.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Airways Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health and Social Care.

REFERENCES

References to studies included in this review

AIRBX1 *{published data only}*

* Barker AF, O'Donnell AE, Flume P, Thompson PJ, Ruzi JD, de Gracia J, et al. Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): Two randomised double-blind, placebo-controlled phase 3 trials. *Lancet Respiratory Medicine* 2014;**2**:738-49. [DOI: 10.1016/S2213-2600(14)70165-1]

Crichton M, Lonergan M, Barker A, Sibila O, Goeminne P, Shoemark A, et al. Inhaled antibiotics improve symptoms of cough and sputum in patients with bronchiectasis: a post-hoc analysis of the AIR-BX studies. *European Respiratory Journal* 2020;**56**(Suppl 64):2365. [DOI: 10.1183/13993003.congress-2020.2365]

Crichton ML, Lonergan M, Barker AF, Sibila O, Goeminne P, Shoemark A, et al. Inhaled aztreonam improves symptoms of cough and sputum production in patients with bronchiectasis: a post hoc analysis of the AIR-BX studies. *European Respiratory Journal* 2020;**56**(1):2000608. [DOI: 10.1183/13993003.00608-2020]

NCT01313624. Safety and effectiveness of AZLI (an inhaled antibiotic) in adults with non-cystic fibrosis bronchiectasis (AIR-BX1) [A phase 3, double-blind, multicenter, randomized, placebo-controlled trial evaluating repeated courses of aztreonam for inhalation solution in subjects with non-CF bronchiectasis and gram-negative endobronchial infection]. clinicaltrials.gov/ct2/show/NCT01313624 (first received 14 March 2011).

Vidal OS, Laserna E, Shoemark A, Keir HR, Finch S, Rodrigo-Troyano A, et al. Airway bacterial load and response to inhaled aztreonam in bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2019;**199**:A5714. [DOI: 10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A5714]

AIRBX2 *{published data only}*

* Barker AF, O'Donnell AE, Flume P, Thompson PJ, Ruzi JD, de Gracia J, et al. Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. *Lancet Respiratory Medicine* 2014;**2**:738-49. [DOI: 10.1016/S2213-2600(14)70165-1]

NCT01314716. Safety and Effectiveness of AZLI (an Inhaled Antibiotic) in Adults With Non-Cystic Fibrosis Bronchiectasis (AIR-BX2) [A phase 3, double-Blind, multicenter, randomized, placebo-controlled trial evaluating repeated courses of aztreonam for inhalation solution/aztreonam 75 mg powder and solvent for nebuliser solution in subjects with non-CF bronchiectasis and gram-negative endobronchial infection (AIR-BX2)]. clinicaltrials.gov/ct2/show/NCT01314716 (first received 14 March 2011).

iBEST *{published data only}*

Loebinger M, Polverino E, Blasi F, Elborn JS, Chalmers JD, Tiddens HAWM, et al. Efficacy and safety of different doses of tobramycin inhalation powder in patients with bronchiectasis and pulmonary pseudomonas aeruginosa infection: results from the ibest-1 study. *American Journal of Respiratory and Critical Care Medicine* 2020;**201**:A6201. [DOI: https://doi.org/10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A6201]

Loebinger M, Polverino E, Blasi F, Elborn S, Chalmers J, Tiddens H, et al. Efficacy of inhaled dry powder tobramycin (TOBI Podhaler) in P. aeruginosa infected patients with bronchiectasis - iBEST study. *European Respiratory Journal* Sep 2020;**56**(Suppl 64):4105. [DOI: 10.1183/13993003.congress-2020.4105]

Loebinger MR, Polverino E, Blasi F, Elborn SJ, Chalmers JD, Tiddens HAWM, et al. A randomised placebo-controlled dose finding study of tobramycin inhalation powder (TIP) in patients with bronchiectasis (BE) and pulmonary P. aeruginosa Pa) infection (iBEST-1). *European Respiratory Journal* 2018;**52**(suppl 62):PA2669. [DOI: 10.1183/13993003.congress-2018.PA2669]

Loebinger MR, Polverino E, Blasi F, Elborn SJ, Chalmers JD, Tiddens HAWM, et al. Efficacy and safety of tobramycin inhalation powder in bronchiectasis patients with P. aeruginosa infection: Design of a dose-finding study (iBEST-1). Pulmonary Pharmacology and Therapeutics 2019;**58**:101834. [DOI: 10.1016/j.pupt.2019.101834]

* Loebinger MR, Polverino E, Chalmers JD, Tiddens HAWM, Goossens H, Tunney M, et al. Efficacy and safety of TOBI Podhaler® in pseudomonas aeruginosa-infected bronchiectasis patients: iBEST study. *European Respiratory Journal* 2021;**57**:2001451. [DOI: https://doi.org/10.1183/13993003.01451-2020]

NCT02712983. Dose-finding study to assess the efficacy, safety and tolerability of tobramycin inhalation powder in patients with non-cystic fibrosis bronchiectasis and pulmonary p. aeruginosa infection (iBEST-1) [A randomized, blinded, parallel group, multi-center dose-finding study, to assess the efficacy, safety and tolerability of different doses of tobramycin inhalation powder in patients with non-cystic fibrosis bronchiectasis and pulmonary p. aeruginosa infection]. clinicaltrials.gov/ct2/show/NCT02712983 (first received 18 March 2016).

ORBIT 2 *{published data only}*

Cipolla DC, Gonda I, Serisier D, Bruinenberg P. Dual release ciprofloxacin for inhalation (DRCFI) improves time to first exacerbation in bronchiectasis. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 2011;**24**(3):A27. [CN-00792702]

Serisier D, Kolbe J, Greville H, Gonda I, Bruinenberg P. Inhaled liposomal ciprofloxacin significantly reduces sputum Pseudomonas aeruginosa density and increases time to first exacerbation in a 168 day placebo controlled study in non-cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2011;**183**:A4866.

* Serisier DJ, Bilton D, De Soyza A, Thompson PJ, Kolbe J, Greville HW, et al. Inhaled, dual release liposomal ciprofloxacin in non-cystic fibrosis bronchiectasis (ORBIT-2): A randomised,

double-blind, placebo-controlled trial. *Thorax* 2013;**68**(9):812-7. [DOI: 10.1136/thoraxjnl-2013-203207]

Serisier DJ, Thompson PJ, Greville H, Kolbe J, Bruinenberg PR. Dual release ciprofloxacin for inhalation (DRCFI) reduces sputum p *seudomonas aeruginosa* (PA) density and delays time to infective pulmonary exacerbation in non-cystic fibrosis (CF) bronchiectasis (BE). *European Respiratory Journal* 2011;**38**(8):1928. [CN-01163771]

ORBIT 3 *{published data only}*

Chalmers JD, Cipolla D, Thompson B, Davis AM, O'Donnell A, Tino G, et al. Changes in respiratory symptoms during 48 weeks treatment with ARD-3150 (inhaled liposomal ciprofloxacin) in bronchiectasis: results from the ORBIT-3 and -4 studies. *European Respiratory Journal* 2020;**56**(4):2000110. [DOI: 10.1183/13993003.00110-2020]

Chalmers JD, Davis AM, Tino G, Gonda I, Froehlich J. Inhaled ciprofloxacin (ARD-3150) in patients with non-cystic fibrosis bronchiectasis and frequent pulmonary exacerbations: a pooled analysis from ORBIT-3 and ORBIT-4. *American Journal of Respiratory and Critical Care Medicine* 2020;**201**:A5713. [DOI: 10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A5713]

Froehlich J, Dahms J, Cipolla D, Gonda I. Reduction in frequency of pulmonary exacerbations (PE) with inhaled ARD-3150 in non-cystic fibrosis bronchiectasis (NCFB) patients is independent of pseudomonas aeruginosa (PA) susceptibility at baseline. *European Respiratory Journal* 2017;**50**:OA466. [DOI: 10.1183/1393003.congress-2017.OA466]

* Haworth CS, Bilton D, Chalmers JD, Davis AM, Froehlich J, Gonda I, et al. Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with pseudomonas aeruginosa (ORBIT-3 and ORBIT-4): Two phase 3, randomised controlled trials. *Lancet Respiratory Medicine* 2019;**7**(3):213-26. [DOI: 10.1016/S2213-2600(18)30427-2]

O'Donnell A, Bilton D, Serisier D, Wanner A, Froehlich J, Bruinenberg P, et al. A phase 3 study design of Pulmaquin in non-cystic fibrosis bronchiectasis (NCFBE) patients chronically colonized with pseudomonas aeruginosa (PA). *Pneumologie* 2016;**70**:A11. [DOI: 10.1055/s-0036-1592235]

O'Donnell A, Froehlich J, Thompson B, Dahms J, Cipolla D, Davis A, et al. Robustness of assessment of pulmonary endpoints in phase 3 trials with ARD-3150 in non-cystic fibrosis bronchiectasis (NCFB) patients with chronic Pseudomonas aeruginosa (PA) infections. *European Respiratory Journal* 2018;**52**:PA2682. [DOI: 10.1183/13993003.congress-2018.PA2682]

O'Donnell A, Gonda I, Cipolla D, Froehlich J, Davis A, Haworth C. Open-label extension (OLE) of ORBIT-3 and ORBIT-4 trials of ARD-3150 in non-cystic fibrosis bronchiectasis (NCFB). *European Respiratory Journal* 2018;**52**:PA357. [DOI: 10.1183/13993003.congress-2018.PA357]

O'Donnell AE, Bilton D, Serisier D, Wanner A, Froehlich J, Bruinenberg P, et al. ORBIT-3 and ORBIT-4: Design of a phase 3 program to investigate safety and efficacy of pulmaquin® in non-cystic fibrosis bronchiectasis (NCFBE) patients chronically colonized with pseudomonas aeruginosa (PA). *American Journal of Respiratory and Critical Care Medicine* 2016;**193**:A1775.

Phase 3 study with ciprofloxacin dispersion for inhalation in non-CF bronchiectasis (ORBIT-3) [A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Pulmaquin® in the management of chronic lung infections with pseudomonas aeruginosa in subjects with non-cystic fibrosis bronchiectasis, including 28 day open-label extension and pharmacokinetic substudy (ORBIT-3)]. clinicaltrials.gov/ct2/show/NCT01515007 (first received 23 January 2012).

VanDevanter DR, Gonda I, Dahms J, Cipolla D, Davis AM, Chalmers JD, et al. Microbiological changes observed over 48 weeks of treatment with inhaled liposomal ciprofloxacin in individuals with non-cystic fibrosis bronchiectasis and chronic Pseudomonas aeruginosa lung infection. *Clinical Microbiology and Infection* 2019;**25**(12):1532-8. [DOI: 10.1016/j.cmi.2019.04.017]

ORBIT 4 *{published data only}*

Froehlich J, Dahms J, Cipolla D, Gonda I. Reduction in frequency of pulmonary exacerbations (PE) with inhaled ARD-3150 in non-cystic fibrosis bronchiectasis (NCFB) patients is independent of pseudomonas aeruginosa (PA) susceptibility at baseline. *European Respiratory Journal* 2017;**50**:OA466. [DOI: 10.1183/1393003.congress-2017.OA466]

* Haworth CS, Bilton D, Chalmers JD, Davis AM, Froehlich J, Gonda I, et al. Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with pseudomonas aeruginosa (ORBIT-3 and ORBIT-4): Two phase 3, randomised controlled trials. *Lancet Respiratory Medicine* 2019;**7**(3):213-26.

NCT02104245. Phase 3 study with ciprofloxacin dispersion for inhalation in non-CF bronchiectasis (ORBIT-4) [A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Pulmaquin® in the management of chronic lung infections with pseudomonas aeruginosa in patients with non-cystic fibrosis bronchiectasis, including 28 day open-label extension]. clinicaltrials.gov/ct2/show/NCT02104245 (first received 4 April 2014).

O'Donnell A, Bilton D, Serisier D, Wanner A, Froehlich J, Bruinenberg P, et al. A phase 3 study design of Pulmaquin in non-cystic fibrosis bronchiectasis (NCFBE) patients chronically colonized with pseudomonas aeruginosa (PA). *Pneumologie* 2016;**70**:A11. [DOI: 10.1055/s-0036-1592235]

O'Donnell A, Froehlich J, Thompson B, Dahms J, Cipolla D, Davis A, et al. Robustness of assessment of pulmonary endpoints in phase 3 trials with ARD-3150 in non-cystic fibrosis bronchiectasis (NCFB) patients with chronic Pseudomonas aeruginosa (PA) infections. *European Respiratory Journal* 2018;**52**:PA2682. [DOI: 10.1183/13993003.congress-2018.PA2682]

O'Donnell A, Gonda I, Cipolla D, Froehlich J, Davis A, Haworth C. Open-label extension (OLE) of ORBIT-3 and

ORBIT-4 trials of ARD-3150 in non-cystic fibrosis bronchiectasis (NCFB). *European Respiratory Journal* 2018;**52**:PA357. [DOI: 10.1183/13993003.congress-2018.PA357]

O'Donnell AE, Bilton D, Serisier D, Wanner A, Froehlich J, Bruinenberg P, et al. ORBIT-3 and ORBIT-4: design of a phase 3 program to investigate safety and efficacy of Pulmaquin® in non-cystic fibrosis bronchiectasis (NCFBE) patients chronically colonized with pseudomonas aeruginosa (PA). *American Journal of Respiratory and Critical Care Medicine* 2016;**193**:A1775.

VanDevanter DR, Gonda I, Dahms J, Cipolla D, Davis AM, Chalmers JD, et al. Microbiological changes observed over 48 weeks of treatment with inhaled liposomal ciprofloxacin in individuals with non-cystic fibrosis bronchiectasis and chronic Pseudomonas aeruginosa lung infection. *Clinical Microbiology and Infection* 2019;**25**(12):1532-8. [DOI: 10.1016/j.cmi.2019.04.017]

RESPIRE 1 *{published data only}*

Akasamit T, Bandel TJ, Criollo M, De Soyza A, Elborn JS, Operschall E, et al. The RESPIRE trials: Two phase III, randomized, multicentre, placebo-controlled trials of ciprofloxacin dry powder for inhalation (Ciprofloxacin DPI) in non-cystic fibrosis bronchiectasis. *Contemporary Clinical Trials* 2017;**58**:78-85. [DOI: 10.1016/j.cct.2017.05.007]

* De Soyza A, Aksamit T, Bandel T, Criollo M, Elborn JS, Operschall E, et al. RESPIRE 1: A phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *European Respiratory Journal* 2018;**51**(1):1702052. [DOI: 10.1183/13993003.02052-201]

De Soyza A, Aksamit T, Bandel TJ, Criollo M, Elborn JS, Krahn U, et al. RESPIRE 1: Ciprofloxacin DPI 32.5mg b.d. administered 14 day on/off or 28 day on/off vs placebo for 48 weeks in subjects with non-cystic fibrosis bronchiectasis (NCFB). *European Respiratory Journal* 2016;**48**:OA272. [DOI: 10.1183/13993003.congress-2016.OA272]

De Soyza A, Aksamit T, Bandel TJ, Criollo M, Elborn JS, Operschall E, et al. Baseline therapies for bronchiectasis (non-CF etiology) vary by country-data from the RESPIRE 1 trial of ciprofloxacin dry powder for inhalation (DPI). *Pneumologie* 2016;**70**:A14. [DOI: 10.1055/s-0036-1592238]

De Soyza A, Aksamit T, Operschall E, Bandel TJ, Krahn U, Criollo M, et al. Baseline demographic profile of subjects of the phase 3 RESPIRE 1 trial of ciprofloxacin dry powder for inhalation (DPI) in non-cystic fibrosis bronchiectasis (NCFB). *European Respiratory Journal* 2015;**46**:PA2617. [DOI: 10.1183/13993003.congress-2015.PA2617]

NCT01764841. Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis (Non-CF BE) (RESPIRE 1). clinicaltrials.gov/ct2/show/results/NCT01764841 (first received 10 January 2013).

Quittner A, De Soyza A, Aksamit T, Bandel TJ, Criollo M, Elborn JS, et al. Effects of ciprofloxacin dry powder for inhalation (ciprofloxacin DPI) on health-related quality of life in patients with non-cystic fibrosis bronchiectasis (NCFB): Results from the phase 3 respire 1 study. *American Journal of Respiratory and Critical Care Medicine* 2017;**195**:A7303.

RESPIRE 2 *{published data only}*

Akasamit T, Bandel TJ, Criollo M, De Soyza A, Elborn JS, Operschall E, et al. The RESPIRE trials: Two phase III, randomized, multicentre, placebo-controlled trials of ciprofloxacin dry powder for inhalation (Ciprofloxacin DPI) in non-cystic fibrosis bronchiectasis. *Contemporary Clinical Trials* 2017;**58**:78-85. [DOI: 10.1016/j.cct.2017.05.007]

Aksamit T, Bandel TJ, Criollo M, Elborn JS, Lau M, Operschall E, et al. RESPIRE 2: Ciprofloxacin DPI 32.5 Mg B.i.d. administered 14 days on/off Or 28 days on/off vs. placebo for 48 weeks in patients with non-cystic fibrosis bronchiectasis (NCFB). *American Journal of Respiratory and Critical Care Medicine* 2017;**195**:A7642.

* Aksamit T, De Soyza A, Bandel TJ, Criollo M, Elborn JS, Operschall E, et al. RESPIRE 2: A phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *European Respiratory Journal* 2018;**51**(1):1702053. [DOI: 10.1183/13993003.02053-2017]

Aksamit T, De Soyza A, Operschall E, Bandel TJ, Krahn U, Montegriffo E, et al. Baseline demographic profile of subjects of the phase 3 RESPIRE 2 trial of ciprofloxacin dry powder for inhalation (DPI) in non-cystic fibrosis bronchiectasis (NCFB). *ATS Journals* 2016;**193**:A1768.

NCT02106832. Ciprofloxacin dry powder for inhalation (DPI) in non-cystic fibrosis bronchiectasis (Non-CF BE) (RESPIRE 2) [Randomized, double-blind, placebo-controlled, multicenter study comparing ciprofloxacin DPI 32.5 mg BID (twice a day) intermittently administered for 28 days on / 28 days off or 14 days on / 14 days off versus placebo to evaluate the time to first pulmonary exacerbation and frequency of exacerbations in subjects with non-cystic fibrosis bronchiectasis]. clinicaltrials.gov/ct2/show/NCT02106832 (first received 8 April 2014).

References to studies excluded from this review

iREC *{published data only}*

jRCTs031190008. Intermittent versus daily therapy for nodular bronchiectatic Mycobacterium avium complex lung disease (iREC). rctportal.niph.go.jp/en/detail?trial_id=jRCTs031190008 (first received 15 April 2019).

Nakagawa T, Hashimoto H, Yagi M, Kogure Y, Sekimizu M, Saito AM, et al. Multicentre, open label, randomised controlled trial comparing intermittent versus daily treatment for non-cavitary nodular/bronchiectatic Mycobacterium avium complex lung disease with rifampicin, ethambutol and clarithromycin (iREC): study protocol. *BMJ Open Respiratory Research* 2019;**6**(1):e000434. [DOI: 10.1136/bmjresp-2019-000434]

Lloberes 1990 *{published data only}*

Lloberes P, Barber E, Montserrat JM, Picado C. Intermittent antibiotic treatment in patients with stable bronchiectasis: A comparative study between amoxycillin and cefonicid.

European Respiratory Journal 1990;**3**(Suppl 10):88S. [CN-00383510]

Additional references

Amati 2019

Amati F, Simonetta E, Gramegna A, Tarsia P, Contarini M, Blasi F, et al. The biology of pulmonary exacerbations in bronchiectasis. *European Respiratory Review* 2019;**28**(154):e190055. [DOI: 10.1183/16000617.0055-2019]

Araujo 2018

Araújo D, Shteinberg M, Aliberti S, Goeminne PC, Hill AT, Fardon TC, et al. The independent contribution of *Pseudomonas aeruginosa* infection to long-term clinical outcomes in bronchiectasis. *European Respiratory Journal* 2018;**51**(2):e1701953. [DOI: 10.1183/13993003.01953-2017]

Chalmers 2012

Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2012;**186**(7):657-65. [PMID: 22744718]

Chalmers 2013

Chalmers JD, Hill AT. Mechanisms of immune dysfunction and bacterial persistence in non-cystic fibrosis bronchiectasis. *Molecular Immunology* 2013;**55**(1):27-34. [PMID: 23088941]

Chalmers 2014

Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index. An international derivation and validation study. *American Journal of Respiratory and Critical Care Medicine* 2014;**189**(5):576-85. [PMID: 24328736]

Chalmers 2015

Chalmers JD, Aliberti S, Blasi F. Management of bronchiectasis in adults. *European Respiratory Journal* 2015;**45**(5):1446-62. [PMID: 25792635]

Chalmers 2017

Chalmers JD, Moffitt KL, Suarez-Cuartin G, Sibila O, Finch S, Furrie E, et al. Neutrophil elastase activity is associated with exacerbations and lung function decline in bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2017;**195**(10):1384-93. [DOI: 10.1164/rccm.201605-1027OC]

Chang 2002

Chang AB, Grimwood K, Mulholland EK, Torzillo PJ. Bronchiectasis in indigenous children in remote Australian communities. *Medical Journal of Australia* 2002;**177**(4):200-4. [PMID: 12175325]

Chang 2010

Chang AB, Bell SC, Byrnes CA, Grimwood K, Holmes PW, King PT, et al. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand. *Medical Journal of Australia* 2010;**193**(6):356-65. [PMID: 20854242]

Cole 1986

Cole PJ. Inflammation: a two-edged sword - the model of bronchiectasis. *European Journal of Respiratory Diseases* 1986;**147 Suppl**:6-15. [PMID: 3533593]

Cole 1997

Cole P. The damaging role of bacteria in chronic lung infection. *Journal of Antimicrobial Chemotherapy* 1997;**40**(Suppl A):5-10. [PMID: 9484867]

De la Rosa 2016

De la Rosa D, Martínez-García MA, Olveira C, Girón R, Máiz L, Prados C. Annual direct medical costs of bronchiectasis treatment: impact of severity, exacerbations, chronic bronchial colonization and chronic obstructive pulmonary disease coexistence. *Chronic Respiratory Disease* 2016;**13**(4):361-71. [PMID: 27072020]

Donovan 2018

Donovan T, Felix LM, Chalmers JD, Milan SJ, Mathioudakis AG, Spencer S. Continuous versus intermittent antibiotics for bronchiectasis. *Cochrane Database of Systematic Reviews* 2018, Issue 6. Art. No: CD012733. [DOI: 10.1002/14651858.CD012733.pub2]

Evans 1996

Evans SA, Turner SM, Bosch BJ, Hardy CC, Woodhead MA. Lung function in bronchiectasis: the influence of Pseudomonas aeruginosa. *European Respiratory Journal* 1996;**9**(8):1601-4. [PMID: 8866579]

Finch 2015

Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A comprehensive analysis of the impact of Pseudomonas aeruginosa colonization on prognosis in adult bronchiectasis. *Annals of the American Thoracic Society* 2015;**12**(11):1602-11. [PMID: 26356317]

Foweraker 2011

Foweraker J, Wat D. Microbiology of non-CF bronchiectasis. In: Floto RA, Haworth CS, editors(s). Bronchiectasis. European Respiratory Society Monographs. Vol. **52**. European Respiratory Society, 2011:68-96.

Geller 2009

Geller DE. Aerosol antibiotics in cystic fibrosis. *Respiratory Care* 2009;**54**(5):658-70. [DOI: 10.4187/aarc0537]

Gibson 2013

Gibson GJ, Loddenkemper R, Sibille Y, Lundbäck B, editor(s). European Lung White Book: Respiratory Health and Disease in Europe. Sheffield, UK: European Respiratory Society, 2013.

Goeminne 2016

Goeminne PC, De Soyza A. Bronchiectasis: how to be an orphan with many parents? *European Respiratory Journal* 2016;**47**(1):10-3. [PMID: 26721955]

GRADEpro GDT [Computer program]

Grade Working Group, McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed prior to 31

July 2021. Hamilton (ON): Grade Working Group, McMaster University (developed by Evidence Prime), 2015. Available at gradepro.org.

Habesoglu 2011

Habesoglu MA, Ugurlu AO, Eyuboglu FO. Clinical, radiologic, and functional evaluation of 304 patients with bronchiectasis. *Annals of Thoracic Medicine* 2011;**6**(3):131-6. [PMID: 21760844]

Hansen 2015

Hansen MP, Thorning S, Aronson JK, Beller EM, Glasziou PP, Hoffmann TC, et al. Adverse events in patients taking macrolide antibiotics versus placebo for any indication. *Cochrane Database of Systematic Reviews* 2015, Issue 8. Art. No: CD011825. [DOI: 10.1002/14651858.CD011825]

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hnin 2015

Hnin K, Nguyen C, Carson KV, Evans DJ, Greenstone M, Smith BJ. Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults. *Cochrane Database of Systematic Reviews* 2015, Issue 8. Art. No: CD001392. [DOI: 10.1002/14651858.CD001392.pub3]

Hui 2013

Hui C, Lin MC, Jao MS, Liu TC, Wu RG. Previous antibiotic exposure and evolution of antibiotic resistance in mechanically ventilated patients with nosocomial infections. *Journal of Critical Care* 2013;**28**(5):728-34. [DOI: 10.1016/j.jcrc.2013.04.008]

Joish 2013

Joish VN, Spilsbury-Cantalupo M, Operschall E, Luong B, Boklage S. Economic burden of non-cystic fibrosis bronchiectasis in the first year after diagnosis from a US health plan perspective. *Applied Health Economics and Health Policy* 2013;**11**(3):299-304. [PMID: 23580074]

Kapur 2012

Kapur N, Masters IB, Newcombe P, Chang AB. The burden of disease in pediatric non-cystic fibrosis bronchiectasis. *Chest* 2012;**141**(4):1018-24. [PMID: 21885727]

Lanza 2018

Lanza FC, Castro RA, De Camargo AA, Zanatta DJ, Rached S, Athanazio R, et al. COPD Assessment Test (CAT) is a valid and simple tool to measure the impact of bronchiectasis on affected patients. *COPD* 2018;**15**(5):512-9. [DOI: 10.1080/15412555.2018.1540034]

Martínez-García 2007

Martínez-García MA, Soler-Cataluña JJ, Perpiñá-Tordera M, Román-Sánchez P, Soriano J. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. *Chest* 2007;**132**(5):1565-72. [PMID: 17998359]

McCullough 2014

McCullough AR, Tunney MM, Quittner AL, Elborn JS, Bradley JM, Hughes CM. Treatment adherence and health outcomes in patients with bronchiectasis. *BMC Pulmonary Medicine* 2014;**14**:107. [PMID: 24980161]

Melnyk 2015

Melnyk AH, Wong A, Kassen R. The fitness costs of antibiotic resistance mutations. *Evolutionary Applications* 2015;**8**(3):273–83.

Menendez 2017

Menéndez R, Méndez R, Polverino E, Rosales-Mayor E, Amara-Elori I, Reyes S, et al. Risk factors for multidrug-resistant pathogens in bronchiectasis exacerbations. *BMC Infectious Diseases* 2017;**17**(1):e659. [DOI: 10.1186/s12879-017-2754-5]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Medicine* 2009;**6**(7):e1000097. [DOI: 10.1371/journal.pmed.1000097]

Ni 2015

Ni Y, Shi G, Yu Y, Hao J, Chen T, Song H. Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis. *International Journal of Chronic Obstructive Pulmonary Disease* 2015;**10**:1465-75.

Pasteur 2010

Pasteur MC, Bilton D, Hill AT, British Thoracic Society Bronchiectasis (non-CF) Guideline Group. British Thoracic Society guidelines for non-CF bronchiectasis. *Thorax* 2010;**65**(Suppl 1):i1–58.

Polverino 2017

Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *European Respiratory Journal* 2017;**50**(3):pii: 1700629. [DOI: 10.1183/13993003.00629-2017]

Quint 2016

Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *European Respiratory Journal* 2016;**47**(1):186-93. [PMID: 26541539]

Redondo 2016

Redondo M, Keyt H, Dhar R, Chalmers JD. Global impact of bronchiectasis and cystic fibrosis. *Breathe* 2016;**12**(3):222-35.

Review Manager 2020 [Computer program]

Nordic Cochrane Centre, the Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.4. Copenhagen: Nordic Cochrane Centre, the Cochrane Collaboration, 2020.

Ringshausen 2015

Ringshausen FC, De Roux A, Diel R, Hohmann D, Welte T, Rademacher J. Bronchiectasis in Germany: a population-based estimation of disease prevalence. *European Respiratory Journal* 2015;**46**(6):1805-7. [PMID: 26293498]

Roberts 2010

Roberts HJ, Hubbard R. Trends in bronchiectasis mortality in England and Wales. *Respiratory Medicine* 2010;**104**:981-5.

Rogers 2014

Rogers GB, Zain NM, Bruce KD, Burr LD, Chen AC, Rivett DW, et al. A novel microbiota stratification system predicts future exacerbations in bronchiectasis. *Annals of the American Thoracic Society* 2014;**11**(4):496-503. [PMID: 24592925]

Seitz 2010

Seitz AE, Olivier KN, Steiner CA, Montes de Oca R, Holland SM, Prevots DR. Trends and burden of bronchiectasis-associated hospitalizations in the United States, 1993-2006. *Chest* 2010;**138**(4):944-9. [PMID: 20435655]

Shiu 2013

Shiu JR, Wang E, Tejani AM, Wasdell M. Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections. *Cochrane Database of Systematic Reviews* 2013, Issue 3. Art. No: CD008481. [DOI: 10.1002/14651858.CD008481.pub2]

Twiss 2005

Twiss J, Metcalfe R, Edwards E, Byrnes C. New Zealand national incidence of bronchiectasis "too high" for a developed country. *Archives of Disease in Childhood* 2005;**90**(7):737-40. [PMID: 15871981]

Weycker 2005

Weycker D, Edelsberg J, Oster G, Tino G. Prevalence and economic burden of bronchiectasis. *Clinical Pulmonary Medicine* 2005;**12**(4):205-9.

Wilson 1997

Wilson CB, Jones PW, O'Leary CJ, Hansell DM, Cole PJ, Wilson R. Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. *European Respiratory Journal* 1997;**10**(8):1754-60. [PMID: 9272915]

Wurzel 2011

Wurzel D, Marchant JM, Yerkovich ST, Upham JW, Masters IB, Chang AB. Short courses of antibiotics for children and adults with bronchiectasis. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No: CD008695. [DOI: 10.1002/14651858.CD008695.pub2]

References to other published versions of this review

Spencer 2019

Spencer S, Donovan T, Chalmers JD, Mathioudakis AG, McDonnell MJ, Tsang A, Pilkington G. Intermittent prophylactic antibiotics for bronchiectasis. *Cochrane Database of Systematic Reviews* 2019, Issue 1. Art. No: CD013254. [DOI: 10.1002/14651858.CD013254]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

AIRBX1

Study characteristics	
Methods	**Study design:** double-blind, multicentre, randomised, placebo-controlled trial **Total study duration:** 16 weeks **Number of study centres and locations:** 57; Australia, Canada and USA. **Screening period:** 2 weeks **Study setting:** ambulatory clinics **Date of study:** April 2011 to June 2013
Participants	266 adults randomised. **Inclusion criteria:** people aged ≥ 18 years with bronchiectasis confirmed by CT chest scan, history of positive sputum or bronchoscopic culture for target gram-negative organism or treatment of exacerbation (in the previous 5 years) with antibiotics with gram-negative coverage, positive sputum culture for target gram-negative bacteria (at screening), chronic sputum production (≥ 4 days/week in the previous 4 weeks), FEV_1 of 20% predicted or higher after bronchodilator (at screening), recent chest X-ray at screening or between screening and baseline without substantial acute findings (e.g. no new infiltrate).

AIRBX1 *(Continued)*

	Exclusion criteria: recent (in the 2 weeks before screening) hospital admission; previous hospital admission for embolisation for treatment of haemoptysis; antibiotic use for respiratory symptoms (apart from chronic stable macrolide treatment) or haemoptysis of more than 30 mL (from 2 weeks before screening until baseline); serious adverse event (from screening to baseline); changes in other treatments (bronchodilator, corticosteroid, macrolide or bronchial hygiene; 4 weeks before screening to study completion); change in systemic corticosteroid treatment (4 weeks before screening through to baseline; after baseline, ≤ 14-day courses allowed for worsening respiratory signs or symptoms); current treatment for non-tuberculous mycobacteria infection; active *Mycobacterium tuberculosis* infection (previous year); previous AZLI treatment; history of cystic fibrosis; pregnancy, lactation or no acceptable birth control **Diagnostic criteria:** CT chest scan **Mean age:** intervention 64.2 (SD 12.9; range 23 to 83); control 64.9 (12.1; range 20 to 88) **Gender:** intervention 84 women (63%); control 97 women (73%) **Ethnicity:** 240 (90%) white; 9 African-American; 8 Asian; 1 American Indian; 7 other; 1 not stated **History of smoking:** intervention 63 (47%); control 40 (30%). **Baseline lung function:** mean FEV_1 % predicted: intervention 60.4 (SD 22.6); 64.5 (SD 18.7). Proportion < 50% predicted: intervention 39%; control 25% **Baseline medication:** Use of non-antibiotic inhaled medications, LAMA 27%, LABA/ICS 38%, LAMA/LABA/ICS 22%
Interventions	**Intervention:** two consecutive cycles of 28 days 75 mg AZLI three times a day, followed by 4 weeks off treatment **Comparison:** two consecutive cycles of 28 days matched placebo three times a day, followed by 4 weeks off treatment **Concomitant medications:** All participants received a β-2 agonist bronchodilator prior to the intervention. **Excluded medications:** none
Outcomes	**Primary outcomes (prespecified):** change from baseline to day 28 in QoL-B-RSS. **Secondary outcomes (prespecified):** frequency (rate per participant/year) of protocol defined exacerbation (acute worsening of respiratory disease requiring a non-study antibiotic meeting and at least 3 major criteria (increased sputum volume and discolouration, dyspnoea and cough) or 2 major and at least 2 minor criteria (fever > 38° C, increased malaise or fatigue, FEV_1 L or FVC decreased > 10% from baseline, new or increased haemoptysis); time to the first protocol-defined exacerbation up to day 112; number of participants with protocol defined exacerbation; change in QoL-B-RSS from baseline to day 84; EQ-5D change from baseline to end of treatment; FEV_1 L percentage change from baseline to end of treatment; changes in MIC of aztreonam; change from baseline in 6MWT; number of participants with non-study antibiotic prescribed for protocol-defined exacerbation; percentage and number of days of antibiotic use for protocol-defined exacerbation. **Adverse events:** Number of participants with any AE (baseline to 30 days after last study drug), number of participants with any serious adverse event and deaths. **Withdrawals:** intervention: 38; control: 10 **Study time points:** baseline, 4, 12, 16 and 20 weeks **Adherence to treatment:** intervention 89.8% (SD 16.6); 93.5% (SD 10.4)
Notes	This is one of two trials completed by the AIRBX team of investigators **Funding:** Gilead Sciences

AIRBX1 *(Continued)*

Role of the funding source: involved in study design, collection, analysis and interpretation of data, and in writing of the report. LS, JZ, LH, SAL, SL, MTM, DG and TGOR (Gliead employees) had access to the raw data.

Notable conflicts of interest of trial authors:

AFB, AEOD, ALQ, PF, JdG had grants or funding from Gilead, during the conduct of the study. ALQ, PF and ADS had grants from Gilead, outside the submitted work. LS, JZ, LH, SAL, SL, MTM, DG and TGOR are employees of and own stock in Gilead Sciences. ABM was a previous employee of Gilead Sciences. ALQ has a patent copyright to QOL-B Version 3.1 issued.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done without stratification and the code was generated by a Gilead designee. Randomisation was done at baseline with an interactive voice and web response system."
Allocation concealment (selection bias)	Low risk	"Randomisation was done without stratification and the code was generated by a Gilead designee. Randomisation was done at baseline with an interactive voice and web response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treatment assignments were masked to patients, site personnel, study vendors, and the sponsor...AZLI and placebo appeared identical"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Treatment assignments were masked to patients, site personnel, study vendors, and the sponsor, apart from designated personnel reviewing randomisation and drug allocation; such personnel were independent of the data analyses."
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomisation ratio 1:1 "Discontinuations for safety or tolerability were higher in the AZLI group (27 [20%] participants) than in the placebo group (four [3%) participants)."
Selective reporting (reporting bias)	Low risk	No published protocol but results consistent with planned outcomes on trials registry (clinical trials.gov)
Other bias	Low risk	None identified

AIRBX2

Study characteristics

Methods

Study design: double-blind, multicentre, randomised, placebo-controlled trial

Total study duration: 16 weeks

Number of study centres and locations: 90; Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, UK and USA

Screening period: 2 weeks

Study setting: ambulatory clinics

AIRBX2 *(Continued)*

	Date of study: April 2011 to July 2013
Participants	274 adults randomised **Inclusion criteria:** people aged ≥18 years with bronchiectasis confirmed by CT chest scan, history of positive sputum or bronchoscopic culture for target gram-negative organism or treatment of exacerbation (in the previous 5 years) with antibiotics with gram-negative coverage, positive sputum culture for target gram-negative bacteria (at screening), chronic sputum production (≥ 4 days/week in the previous 4 weeks), FEV_1 of 20% predicted or higher after bronchodilator (at screening), recent chest X-ray at screening or between screening and baseline without substantial acute findings (e.g. no new infiltrate). **Exclusion criteria:** recent (in the 2 weeks before screening) hospital admission; previous hospital admission for embolisation for treatment of haemoptysis; antibiotic use for respiratory symptoms (apart from chronic stable macrolide treatment) or haemoptysis of more than 30 mL (from 2 weeks before screening until baseline); serious adverse event (from screening to baseline); changes in other treatments (bronchodilator, corticosteroid, macrolide or bronchial hygiene; 4 weeks before screening to study completion); change in systemic corticosteroid treatment (4 weeks before screening through to baseline; after baseline, ≤ 14-day courses allowed for worsening respiratory signs or symptoms); current treatment for non-tuberculous mycobacteria infection; active *Mycobacterium tuberculosis* infection (previous year); previous AZLI treatment; history of cystic fibrosis; pregnancy, lactation or no acceptable birth control **Diagnostic criteria:** CT chest scan **Mean age:** intervention 63.3 (SD 14.2; range 22 to 85); control 62.7 (SD 13.3; range 18 to 87) **Gender:** intervention 89 women (65%); control 101 women (73%) **Ethnicity:** 247 white (90%); 2 African-American; 1 Asian; 6 American Indian; 3 other; 15 not stated **History of smoking:** intervention 44 (32%); control 57 (41%) **Baseline lung function:** mean FEV_1 % predicted: intervention 63.8 (SD 19.5); 63.4 (SD 21.6). Proportion < 50% predicted: intervention 27%; control 30% **Baseline medication:** Use of non-antibiotic inhaled medications, LAMA 32%, LABA/ICS 36%, LAMA/LABA/ICS 23%
Interventions	**Intervention:** two consecutive cycles of: 28 days 75 mg AZLI three times a day, followed by 4 weeks off treatment **Comparison:** two consecutive cycles of 28 days matched placebo three times a day, followed by 4 weeks off treatment **Concomitant medications:** all participants received a β-2 agonist bronchodilator prior to the intervention. **Excluded medications:** none
Outcomes	**Primary outcomes (prespecified):** change from baseline to day 28 in QoL-B-RSS **Secondary outcomes (prespecified):** frequency (rate per participant/year) of protocol defined exacerbation (acute worsening of respiratory disease requiring a non-study antibiotic meeting and at least 3 major criteria (increased sputum volume and discolouration, dyspnoea and cough) or 2 major and at least 2 minor criteria (fever > 38° C, increased malaise or fatigue, FEV_1 L or FVC decreased > 10% from baseline, new or increased haemoptysis); time to the first protocol-defined exacerbation up to day 112; number of participants with protocol defined exacerbation; change in QoL-B-RSS from baseline to day 84; EQ-5D change from baseline to end of treatment; FEV_1 L percentage change from baseline to end of treatment; changes in MIC of aztreonam; change from baseline 6 MWT; number of participants with non-study antibiotic prescribed for protocol-defined exacerbation; percentage and number of days of antibiotic use for protocol-defined exacerbation.

AIRBX2 *(Continued)*

Adverse events: Number of participants with any AE (baseline to 30 days after last study drug) and number of participants with any serious adverse event.

Withdrawals: intervention group: 16; control group: 14

Study time points: baseline, 4, 12, 16 and 20 weeks

Adherence to treatment: intervention 94.4% (SD 10.1); 90.7% (SD 17.6)

Notes

This is one of two trials completed by the AIR-BX team of investigators

Funding: Gilead Sciences

Role of the funding source: involved in study design, collection, analysis and interpretation of data, and in writing of the report. LS, JZ, LH, SAL, SL, MTM, DG and TGOR (Gliead employees) had access to the raw data.

Notable conflicts of interest of trial authors:

AFB, AEOD, ALQ, PF, JdG had grants or funding from Gilead Sciences, during the conduct of the study. ALQ, PF and ADS had grants from Gilead, outside the submitted work. LS, JZ, LH, SAL, SL, MTM, DG and TGOR are employees of and own stock in Gilead Sciences. ABM was a previous employee of Gilead Sciences. ALQ has a patent copyright to QOL-B Version 3.1 issued.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done without stratification and the code was generated by a Gilead designee. Randomisation was done at baseline with an interactive voice and web response system."
Allocation concealment (selection bias)	Low risk	"Randomisation was done without stratification and the code was generated by a Gilead designee. Randomisation was done at baseline with an interactive voice and web response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treatment assignments were masked to patients, site personnel, study vendors, and the sponsor...AZLI and placebo appeared identical"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Treatment assignments were masked to patients, site personnel, study vendors, and the sponsor, apart from designated personnel reviewing randomisation and drug allocation; such personnel were independent of the data analyses."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomisation ratio 1:1 "Discontinuations for safety or tolerability were higher in the AZLI group (ten [7%] participants) than in the placebo group (five [4%] participants)." Withdrawal was less than 10% in each group and the small difference (5 participants) was considered unlikely to bias study outcomes.
Selective reporting (reporting bias)	Low risk	No published protocol but results consistent with planned outcomes on trials registry (clinical trials.gov)
Other bias	Low risk	None identified

iBEST

Study characteristics	
Methods	**Study design:** randomised, double-blind, parallel-group, multicentre study **Total study duration:** 168 days **Number of study centres and locations:** 34 centres across 6 countries; Belguim, France, Germany, Italy, Spain, UK **'Run in' period:** 28 days **Study setting:** not reported **Date of study:** February 2017 to March 2019
Participants	**Inclusion criteria:** aged ≥ 18 years; bronchiectasis; FEV_1 ≥ 30% predicted; history of ≥ 2 exacerbations treated with oral antibiotics or ≥ 1 exacerbation requiring parenteral antibiotics in the past 12 months; ≥ 1 positive sputum or throat culture at screening **Exclusion criteria:** cystic fibrosis; active or actively treated non-tuberculous mycobacterial infection or tuberculosis; primary diagnosis of bronchial asthma or COPD; regularly inhaled anti-pseudomonal antibiotics; any significant medical condition that is either recently diagnosed or was not stable during the last 3 months other than pulmonary exacerbations; clinically significant hearing loss, chronic tinnitus or history of hearing loss **Diagnostic criteria:** chest CT **Mean age:** Cohort A intervention 57.5 (SD 11.8; range 40 to 80), control 61.3 (SD 7.5; range 52 to 71); Cohort B intervention 62.4 (SD 16.7; range 19 to 82), control 69.1 (SD 13.2; range 40 to 77); Cohort C intervention 60.8 (SD 13.0; range 35 to 75), control 71.3 (SD 10.4; range 49 to 81) **Gender:** Cohort A intervention (intermittent) 10 women (77%), control 3 women (43%); Cohort B intervention 7 women (50%), control 6 women (86%); Cohort C intervention 8 women (53%), control 4 women (57%) **Ethnicity:** 96 Caucasian (90%); 11 other **History of smoking:** not reported **Baseline lung function:** mean FEV_1 % predicted. Cohort A intervention (intermittent) 64.0 (SD 16.5), control 64.3 (SD 25.5); Cohort B intervention 58.7 (SD 22.4), control 54.7 (SD 16.6); Cohort C intervention 53.9 (SD 17.4), control 59.5 (SD 11.4) **Baseline medication:** not reported
Interventions	107 randomised (63 from comparisons of interest: intermittent tobramycin and placebo arms). The study was terminated early before achieving the target of 180 participants **Intervention and comparisons:** capsules containing 28mg TIP delivered by breath-actuated T-326 inhaler delivered in the following doses and regimens for 16 weeks (112 days): Cohort A (three capsules once daily. A total of 84 mg tobramycin daily) • three capsules of TIP once daily continuously for 112 days, or • three capsules of TIP or placebo once daily for two treatment cycles of 28 days on TIP and 28 days on placebo, or • three capsules of matched placebo Cohort B (five capsules once daily. A total of 140 mg tobramycin daily) • five capsules of TIP once daily continuously for 112 days, or

iBEST *(Continued)*

	• five capsules once daily of TIP or placebo for two treatment cycles of 28 days on TIP and 28 days on placebo, or • five capsules of matched placebo Cohort C (four capsules twice daily Total of 224 mg tobramycin daily) • four capsules of TIP twice daily in the morning and evening continuously for 112 days, or • four capsules of TIP or placebo b.i.d for two treatment cycles of 28 days on TIP and 28 days on placebo, or • four capsules of matched placebo **Concomitant medications:** macrolides, inhaled corticosteroids, and bronchodilators (including both short- and long-acting bronchodilators) **Excluded medications:** not reported
Outcomes	**Primary outcomes (prespecified):** change in sputum *P aeruginosa* density from baseline to day 29 **Secondary outcomes (prespecified):** frequency, rate, severity and time to first pulmonary exacerbation; use of anti-pseudomonal antibiotics; serum and sputum tobramycin concentrations; changes in spirometry; number and duration of hospitalisations; QoL-B-RSS; safety **Adverse events:** Number of participants with any adverse event **Withdrawals:** all (comparisons of interest): Cohort A intervention 7 (1), control 1; Cohort B intervention 12 (4), control 0; Cohort C intervention 18 (9), control 2. **Study time points:** day 1, day 8, day 29 then monthly to end of treatment at day 113. Two visits during 56-day follow-up period at day 141 and day 169 **Adherence to treatment:** not reported
Notes	This study was terminated early by the funder and study authors state this was unrelated to efficacy or safety results. The original sample size estimate required 180 participants. Phase II trial **Funding source:** Novartis Pharmaceuticals. **Role of the funding source:** The protocol was designed by Novartis in collaboration with the authors. Novartis was responsible for data collection, analysis, interpretation and writing of the articles. **Notable conflicts of interest of trial authors:** EP, FB, MT, CSH, HAVMT and SJE received fees and/or grants from Novartis. GA and WZ are employees of Novartis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomised via interactive response technology to one of nine treatment arms"
Allocation concealment (selection bias)	Low risk	Concealed allocation sequence from those assigning participants.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blinding is implemented within each cohort"

iBEST *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	180 participants required (assuming a discontinuation rate of 20%). However, recruitment was closed for administrative reasons (acquisition of the product by another company) when only 107 participants recruited (reduced sample power is 81%). 14/42 withdrew in the intermittent antibiotics group and 3/21 in the placebo group.
Selective reporting (reporting bias)	Unclear risk	Although the smaller sample (due to early termination) and lack of power did not change the study protocol it did mean that some planned analyses were not reported.
Other bias	Low risk	None identified

ORBIT 2

Study characteristics	
Methods	**Study design:** double-blind, multicentre, randomised, placebo-controlled trial **Total study duration:** 24 weeks **Number of study centres and locations:** 11; Australia and New Zealand **Screening period:** 14 days **Study setting:** not reported **Recruitment period:** November 2009 to September 2010
Participants	42 adults randomised. **Inclusion criteria:** clinically stable adults (18 to 80 years) with bronchiectasis confirmed by CT scan; documented *Paeruginosa* airway infection within 6 months of screening; ≥ 2 pulmonary exacerbations requiring antibiotic therapy within last 12 months; clinically stable able to perform 6 MWT with oxygen; negative pregnancy test and use of contraception where relevant. At least one ciprofloxacin-sensitive *P aeruginosa* strain cultured from sputum during screening to be eligible for randomisation. **Exclusion criteria:** cystic fibrosis; pulmonary exacerbation requiring treatment during screening, allergic bronchopulmonary aspergillosis; pulmonary non-tuberculous mycobacterial infection; anti-pseudomonal antibiotic within 28 days prior to baseline **Mean age:** intervention, 70 (SD 5.6); control 59.5 (SD 13.2) **Gender:** intervention 10 (50%) women; control 13 (59.1%) **Ethnicity:** not reported **Diagnostic criteria:** CT chest scan **Baseline lung function:** mean FEV_1 % predicted: intervention 60.7 (SD 24.1); 53.1 (SD 22.7) **Smoking history:** intervention 1/20; control 0/22 **Baseline medications**: oral macrolides 21%, inhaled corticosteroids 24%, ICS/LABA inhalers 48%, inhaled LABA 9.5%, inhaled SABA 55%, inhaled long-acting anticholinergic 29%, inhaled short-acting anticholinergic 12%, inhaled mannitol 1 person.

ORBIT 2 *(Continued)*

Interventions	**Intervention:** up to 3 consecutive cycles of: 28 days DRCFI comprising 150 mg in 3 mL solution of liposomal ciprofloxacin for inhalation and 60 mg in 3 mL solution of free ciprofloxacin once a day, followed by 28 days off treatment. **Comparison:** up to 3 consecutive cycles of: matched placebo for inhalation comprising control liposomes (15 mg in 3 mL) and normal saline (0.9%, 3 mL) once a day, followed by 28 days off treatment. Note:Trial medication was discontinued once participants reached pulmonary exacerbation endpoint. **Concomitant medications:** none **Excluded medications:** Tizanidine. Changes to or new prescription of azithromycin, hypertonic saline, mucolytics, bronchodilator medications or oral corticosteroids within 28 days of baseline
Outcomes	**Primary outcomes:** mean change in sputum *P aeruginosa* bacterial density (as $\log_{10}$ CFU/g) from baseline to end of first treatment cycle (day 28) **Secondary outcomes:** time to first protocol-defined pulmonary exacerbation (deterioration in four of the following: sputum, dyspnoea, cough, fever, wheezing, exercise tolerance (or fatigue/lethargy/malaise), ≥ 10% FEV_1 or FVC, chest radiograph, chest sounds on auscultation); number of people with pulmonary exacerbations by day 168; severity of pulmonary exacerbations (mild/moderate/severe) to day 28; time to resolve pulmonary exacerbations between baseline and day 28; change in FEV_1 from baseline to day 28, change in SGRQ from baseline to day 28, changes in ciprofloxacin MIC for *P aeruginosa* in sputum; change in 6 MWT from baseline to day 28. **Adverse events:** Serious, respiratory-related adverse events leading to withdrawal, non-respiratory adverse events and deaths. **Withdrawals:** discontinued trial medication before primary endpoint at 28 days: intervention 2; control 3 (1 protocol violation). 39 participants (except protocol violation) completed all planned assessments. **Time points:** baseline, 14 and 28 days then every 28 days to end of 3rd cycle at 168 days
Notes	This phase II trial is one of three trials completed by the ORBIT team of investigators **Funding:** Aradigm Corporation, Hayward, USA **Role of the funding source:** not reported **Notable conflicts of interest of trial authors:** The funder reimbursed organisations of DJS, PJT, JK and HG for all study related procedures. DB received fees for serving on the medical advisory board of Aradigm Corporation. PB was an employee of Aradigm when the study was designed, conducted and analysed. IG and DC are employees of Aradigm and shareholders in the company.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Central randomisation was used in this study to protect the planned balanced 1:1 active to placebo ratio."
Allocation concealment (selection bias)	Low risk	"No study centre personnel involved in the day-to-day clinical conduct of the study had access to the [randomisation] code"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"This study was performed in a double-blind manner. The study drugs were supplied in identical 5-mL vials. The CFI formulation was similar in appearance to the CLI formulation lid concentration, and the FCI formulation was similar in appearance to the normal saline."

ORBIT 2 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific statement about analysis blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All 42 randomised subjects were included in the mITT analysis"
Selective reporting (reporting bias)	Unclear risk	No published protocol and trial not on a clinical trials registry.
Other bias	Low risk	None identified

ORBIT 3

Study characteristics	
Methods	**Study design:** double-blind, multicentre, randomised, placebo-controlled trial **Total study duration:** 48 weeks **Number of study centres and locations:** 93; Australia, Canada, Germany, Hungary, Ireland, Israel, Italy, Latvia, Poland, Romania, South Africa, South Korea, Spain, Taiwan, UK and USA. **Screening period:** not reported **Study setting:** hospitals, private practices and clinical research units **Date of study:** April 2014 to October 2016
Participants	290 adults randomised **Inclusion criteria:** ≥ 18 years of age; non-CF bronchiectasis confirmed by chest CT; at least two pulmonary exacerbations treated with courses of antibiotics in past 12 months; FEV_1 ≥ 25% of predicted at screening; lab-confirmed history of chronic *P aeruginosa* lung infection; positive culture for *P aeruginosa* with at least one isolate non-resistant to ciprofloxacin at screening **Exclusion criteria:** pulmonary exacerbation requiring antibiotics within 28 days of study treatment; COPD related to smoking history of greater than 10 pack years; active allergic bronchopulmonary aspergillosis, tuberculosis, or non-tuberculous mycobacterial infection requiring treatment; anti-pseudomonal antibiotics (stable macrolides use was permitted if treatment was not initiated within the previous 2 months) **Diagnostic criteria:** chest CT scan **Mean age:** intervention 64.3 (SD 13.6); control 66.7 (SD 10.7) **Gender:** intervention 127 (69%) women; control 67 (71%) **Ethnicity:** Hispanic/Latino 3% **Baseline lung function:** FEV_1 % predicted intervention 57.3 (21.9); control 57.4 (20.2) **Current smokers:** intervention 3; control 1 **Baseline medications:** not reported Note: population characteristics only reported for participants who received at least one dose of study medication.

ORBIT 3 *(Continued)*

Interventions	**Intervention:** six consecutive treatment cycles of: 3 mL liposome encapsulated ciprofloxacin 135 mg and 3 ml free ciprofloxacin 54 mL by nebulizer once daily for 28 days, followed by 28 days off treatment. **Comparison:** six consecutive treatment cycles of: 6 mL placebo (3 mL dilute empty liposomes with 3 mL of saline) by nebuliser once daily for 28 days, followed by 28 days off treatment **Concomitant medications permitted:** fluoroquinolones, macrolides, penicillins, combinations (including beta-lactamase), cephalosporin (third generation), penicillins with extended spectrum, tetracyclines, combinations of sulphonamides and trimethoprim, including derivatives, aminoglycosides, carbapenems, glucocorticoids (includes all routes of administration), corticosteroids (includes all routes of administration), anticholinergics, selective beta-2-adrenoreceptor agonists, adrenergics in combination with other corticosteroids, adrenergics in combination with anticholinergics **Excluded medications:** tizanidine
Outcomes	**Primary outcomes (prespecified):** time to first pulmonary exacerbation (deterioration in four of the following: sputum, dyspnoea, cough, fever, wheezing, exercise tolerance (or fatigue/lethargy/malaise), ≥ 10% FEV_1 or FVC, chest radiograph, chest sounds on auscultation) from date of randomisation to week 48. **Secondary outcomes (prespecified):** frequency of pulmonary exacerbations to week 48; frequency of severe pulmonary exacerbations (treatment with intravenous antibiotics or hospitalisation) to week 48; frequency of moderate (treatment with oral or inhaled antibiotics or an increase in macrolide dose) and severe pulmonary exacerbations to week 48; number of pulmonary exacerbations per participant to week 48; number of severe and moderate/severe pulmonary exacerbations per participant to week 48; change from baseline to week 48 in QoL-B-RSS; change in *P aeruginosa* sputum density from baseline to the start of each on/off treatment period; FEV_1 and FVC L and % predicted to week 48; antibiotic resistance (ciprofloxacin inhibitory concentration > 4 µg/mL for *P aeruginosa*); change in lung function (FVC, FEV_1, DLCO) from baseline to week 48; hospitalisation for pulmonary exacerbation to week 48; change from baseline 6 MWT; number of pulmonary exacerbations requiring intravenous antibiotics; number of participants with antibiotics to resolve a pulmonary exacerbation **Adverse events:** number of participants with any adverse event, any serious adverse event and deaths. **Withdrawals:** intervention 52 (41 withdrawn, 11 discontinuation); control 24 (18 withdrawn, 6 discontinuation) **Time points:** day 1, 7, 14, 28 and then approximately every 28 days to end of study.
Notes	This phase III trial is one of three trials completed by the ORBIT team of investigators **Funding:** Aradigm Corporation **Role of the funding source:** study design, data collection, data interpretation and writing of the report. **Notable conflicts of interest of trial authors:** JF and IG were employed by funder during conduct of the study. AEO'D reported grants from funder during the conduct of the study. CSH, JDC and AW reported personal fees from funders during conduct of the study. BT reported consultancy with funder.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"After a subject met all entry criteria, sites accessed SynteractHCR's interactive web randomisation system (IWRS), which assigned a randomisation number to the subject."
Allocation concealment (selection bias)	Low risk	"Treatment assignment was accomplished by a computer generated random sequence implemented through the IWRS. The study coordinator accessed the IWRS during visits when study drug was dispensed (i.e., at Visits 1, 4, 6, 8, 10,

ORBIT 3 *(Continued)*

		12, and 14) to register the visit and obtain the study drug kit assignment for the subject."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"This study was performed in a double-blind manner. Neither the investigator nor the subject knew the subject's treatment assignment. The study drug was supplied in 5-mL vials colour coded with red and blue vial caps to ascertain that each dose was a mixture of the liposomal and non-liposomal components."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Aradigm staff and designees involved in clinical management, data management, and statistical evaluation remained blinded until a database lock memo was issued and identification of the analysis populations was agreed upon and documented."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomisation ratio 2:1 Intervention 41 withdrew/193 randomised (21%): Placebo 18 withdrew/97 randomised (19%)
Selective reporting (reporting bias)	Unclear risk	Outcomes stated as prespecified in the online supplement but we could not find a published protocol and the trials registry (clinicaltrials.gov) record does not list all outcomes described as prespecified in the published supplement
Other bias	Low risk	None identified

ORBIT 4

Study characteristics	
Methods	**Study design:** double-blind, multicentre, randomised, placebo-controlled trial **Total study duration:** 48 weeks **Number of study centres and locations:** 88, Australia, Canada, France, Georgia, Hungary, Israel, Italy, New Zealand, Peru, Poland, Romania, Serbia, South Korea, Spain, UK and USA **Screening period:** not reported **Study setting:** hospitals, private practices and clinical research units **Date of study:** April 2014 to October 2016
Participants	308 adults randomised **Inclusion criteria:** ≥ 18 years of age; non-CF bronchiectasis confirmed by chest CT; at least two pulmonary exacerbations treated with courses of antibiotics in past 12 months; FEV_1 ≥ 25% of predicted at screening; lab-confirmed history of chronic *P aeruginosa* lung infection; positive culture for *P aeruginosa* with at least one isolate non-resistant to ciprofloxacin at screening **Exclusion criteria:** pulmonary exacerbation requiring antibiotics within 28 days of study treatment; COPD related to smoking history of greater than 10 pack years; active allergic bronchopulmonary aspergillosis, tuberculosis, or non-tuberculous mycobacterial infection requiring treatment; anti-pseudomonal antibiotics (stable macrolides use was permitted if treatment was not initiated within the previous 2 months) **Diagnostic criteria:** chest CT scan **Mean age:** intervention 63.3 (SD 13.5); control 64.2 (SD 12.6)

ORBIT 4 *(Continued)*

	Gender: intervention 134 (65%) women; control 63 (64%) **Ethnicity:** Hispanic/Latino 34 (11%) **Baseline lung function:** FEV_1% predicted intervention 62.6 (22.2); control 59.8 (20.8) **Current smokers:** intervention 2; control 0 **Baseline medications:** not reported Note: population characteristics only reported for participants who received at least one dose of study medication.
Interventions	**Intervention:** six consecutive treatment cycles of: 3 mL liposome encapsulated ciprofloxacin 135 mg and 3 mL free ciprofloxacin 54 ml by nebulizer once daily for 28 days, followed by 28 days off treatment. **Comparison:** six consecutive treatment cycles of: 6 mL placebo (3 mL dilute empty liposomes with 3 mL of saline) by nebuliser once daily for 28 days, followed by 28 days off treatment. **Concomitant medications permitted:** fluoroquinolones, macrolides, penicillins, combinations (including beta-lactamase), cephalosporin (third generation), penicillins with extended spectrum, tetracyclines, combinations of sulphonamides and trimethoprim, including derivatives, aminoglycosides, carbapenems, glucocorticoids (includes all routes of administration), corticosteroids (includes all routes of administration), anticholinergics, selective beta-2-adrenoreceptor agonists, adrenergics in combination with other corticosteroids, adrenergics in combination with anticholinergics **Excluded medications:** tizanidine
Outcomes	**Primary outcomes (prespecified):** time to first pulmonary exacerbation (deterioration in four of the following: sputum, dyspnoea, cough, fever, wheezing, exercise tolerance (or fatigue/lethargy/malaise), ≥ 10% FEV_1 or FVC, chest radiograph, chest sounds on auscultation) from date of randomisation to week 48. **Secondary outcomes (prespecified):** frequency of pulmonary exacerbations to week 48; frequency of severe pulmonary exacerbations (treatment with intravenous antibiotics or hospitalisation) to week 48; frequency of moderate (treatment with oral or inhaled antibiotics or an increase in macrolide dose) and severe pulmonary exacerbations to week 48; number of pulmonary exacerbations per participant to week 48; number of severe and moderate/severe pulmonary exacerbations per participant to week 48; change from baseline to week 48 in QoL-B-RSS; change in *P aeruginosa* sputum density from baseline to the start of each on/off treatment period; FEV_1 and FVC L and % predicted to week 48; antibiotic resistance (ciprofloxacin inhibitory concentration > 4 µg/mL for *P aeruginosa*); change in lung function (FVC, FEV_1, DLCO) from baseline to week 48; hospitalisation for pulmonary exacerbation to week 48; change from baseline 6 MWT; number of pulmonary exacerbations requiring IV antibiotics; number of participants with antibiotics to resolve a pulmonary exacerbation **Adverse events:** number of participants with any adverse event, any serious adverse event and deaths. **Withdrawals:** intervention 37 (28 withdrawn, 9 discontinuation); control 21 (17 withdrawn, 4 discontinuation) **Time points:** Day 1, 7, 14, 28 and then approximately every 28 days to end of study.
Notes	This phase III trial is one of three trials completed by the ORBIT team of investigators **Funding:** Aradigm Corporation **Role of the funding source:** study design, data collection, data interpretation and writing of the report. **Notable conflicts of interest of trial authors:** JF and IG were employed by funder during conduct of the study. AEO'D reported grants from funder during the conduct of the study. CSH, JDC and AW reported personal fees from funders during conduct of the study. BT reported consultancy with funder.

ORBIT 4 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"After a subject met all entry criteria, sites accessed SynteractHCR's interactive web randomisation system (IWRS), which assigned a randomisation number to the subject."
Allocation concealment (selection bias)	Low risk	"Treatment assignment was accomplished by a computer generated random sequence implemented through the IWRS. The study coordinator accessed the IWRS during visits when study drug was dispensed (i.e., at Visits 1, 4, 6, 8, 10, 12, and 14) to register the visit and obtain the study drug kit assignment for the subject."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"This study was performed in a double-blind manner. Neither the investigator nor the subject knew the subject's treatment assignment. The study drug was supplied in 5-mL vials colour coded with red and blue vial caps to ascertain that each dose was a mixture of the liposomal and non-liposomal components."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Aradigm staff and designees involved in clinical management, data management, and statistical evaluation remained blinded until a database lock memo was issued and identification of the analysis populations was agreed upon and documented."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomisation ratio 2:1 Intervention 28 withdrew/207 randomised (14%): Placebo 17 withdrew/101 randomised (17%)
Selective reporting (reporting bias)	Unclear risk	Outcomes stated as prespecified in the online supplement but we could not find a published protocol and the trials registry (clinicaltrials.gov) record does not list all outcomes described as prespecified in the published supplement
Other bias	Low risk	None identified

RESPIRE 1

Study characteristics

Methods	**Study design:** double-blind, multicentre, randomised, placebo-controlled trial (4 arms) **Total study duration:** 48 weeks **Number of study centres and locations:** 124 centres in 14 countries: Argentina, Australia, Denmark, France, Germany, Israel, Italy, Japan, Latvia, New Zealand, Slovakia, Spain, UK, USA **Screening period:** 4 weeks **Study setting:** outpatient clinics **Date of study:** May 2013 to March 2016
Participants	416 adults randomised **Inclusion criteria:** primary diagnosis of non-cystic fibrosis bronchiectasis (idiopathic or postinfectious aetiology as determined by the investigator) confirmed by CT scan with stable disease (no exacerbation in last 30 days); ≥ 2 exacerbations in previous 12 months; positive culture at screening for one of

RESPIRE 1 *(Continued)*

	the following *P aeruginosa, H. influenzae, Moraxella catarrhalis, S aureus, Streptococcus pneumoniae, Stenotrophomonas maltophilia or Burkholderia cepaci;* sputum production on most days; people with stable chronic macrolide treatment (at least 6 months prior to screening), bronchodilators, anticholinergics, inhaled corticosteroids or mucolytics (for at least 4 weeks prior to screening) **Exclusion criteria:** post-bronchodilator FEV_1 < 30% or ≥ 90% predicted; systemic or inhaled antibiotic treatments within 4 weeks of study drug administration; active allergic bronchopulmonary aspergillosis, active or actively treated nontuberculous mycobacterial lung infection or tuberculosis; primary diagnosis of COPD; chronic asthma; allergy to fluoroquinolones or quinolones **Mean age:** 14 days on/off arm, intervention 65.2 (SD 13.5); control 65.5 (12.9). 28 days on/off arm, Intervention 64.2 (SD 12.1); control 64.0 (SD 13.5) **Gender:** 14 days on/off arm, intervention 88 (64.2%) women; control 44 (64.7%) women. 28 days on/off arm, intervention 101 (71.6%) women; control 52 (74.3%) women **Ethnicity:** White 363 (87%), Black 4, Asian 34, American Indian 1, Native Hawaiian 8, not reported 6 **Diagnostic criteria:** CT chest scan **Baseline lung function:** FEV_1 % predicted, 14 days on/off arm, intervention 59.42 (SD 16.7); control 57.37 (SD 15.5): 28 days on/off arm, intervention 59.48 (SD 15.1); control 61.7 ± (SD 16.7). Proportion < 50% predicted: 14 days on/off arm, intervention 29.9%; control 32.4%: 28 days on/off arm, intervention 31.2%; control 25.7% **Smoking history:** not reported **Baseline medications:** mucolytics 18%, bronchodilators 61%, ICS 37%, low dose systemic corticosteroids 3%, long term oral macrolides 16%, theophylline 2%, other respiratory 1%.
Interventions	**Intervention:** 12 consecutive treatment cycles of 35.5 mg of ciprofloxacin by dry powder inhaler twice daily for 14 days, followed by 14 days off treatment **or** six consecutive treatment cycles of 35.5 mg of ciprofloxacin by dry powder inhaler twice daily for 28 days, followed by 28 days off treatment **Comparison:** twelve consecutive treatment cycles of placebo by dry powder inhaler twice daily for 14 days, followed by 14 days off treatment **or** six consecutive treatment cycles of placebo by dry powder inhaler twice daily for 28 days, followed by 28 days off treatment **Concomitant medications:** > 80% of participants received at least one concomitant respiratory medication including: mucolytics, bronchodilators (long acting β-agonist bronchodilators, short acting β-agonist bronchodilators, long-acting anticholinergic bronchodilators and short-acting anticholinergic bronchodilators), inhaled corticosteroids, low-dose systemic corticosteroids, long-term oral macrolides and theophylline. **Excluded medications:** none stated
Outcomes	**Primary outcomes (prespecified):** 1) time to first protocol-defined exacerbation (worsening of at least 3 of the following; dyspnoea, wheeze, cough, sputum volume, sputum purulence, and fever or malaise/fatigue and requiring systemic antibiotics) within 48 weeks after start of treatment. 2) frequency of protocol-defined exacerbations during the 48 week study period. **Secondary outcomes (prespecified):** frequency of exacerbations (systemic antibiotic use and worsening of at least one sign/symptom) over 48 weeks; pathogen eradication at end of last treatment cycle; occurrence of new pathogens, not present at baseline, by 48 weeks; Quality of life measured by SGRQ Symptoms and QoL-B-RSS at end of treatment; improvement in FEV_1 from baseline to end of treatment; antibiotic resistance (MIC against ciprofloxacin) **Adverse events:** treatment-emergent adverse events, treatment-emergent serious adverse events and deaths. **Withdrawals:** 82 did not complete the study: 14-day intervention 26; 14-day placebo 19; 28-day intervention 23; 28-day placebo 14

RESPIRE 1 *(Continued)*

	Time points: baseline, end of on-treatment cycle 6 (14 day regimen) and cycle 3 (28 day regimen), QoL-B-RSS collected nine (28 day regimen) or ten (14 day regimen) times, 48 weeks (end of treatment), 8 weeks after last dose for both the 14 days on/off and 28 days on/off regimen (end of study)
Notes	This trial was one of two studies completed by the RESPIRE team of investigators **Funding:** Bayer HealthCare AG **Role of the funding source:** involved in the design of the study and the decision to publish **Notable conflicts of interest of trial authors:** MC, TJB, EO and KR were employed by the funder at the time of the study. ADS, EP, JSE, KW and RW received fees from the funder. Payments received by ADS sent to Queens University Belfast. TA reported all remuneration for participation in clinical trials sponsored by the funder was sent to Mayo Foundation for Medical Research and Education.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization and medication kit numbers are generated by Bayer's Randomization Management."
Allocation concealment (selection bias)	Low risk	″Drug dispensation is managed by an interactive voice response system and interactive web response system run by an external vendor."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study is blinded for treatment assignment"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific statement about analysis blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomisation ratio 2:1 28 days regimen: intervention 23 withdrew/141 randomised (16%): placebo 14 withdrew/70 randomised (20%) 14 days regimen: intervention 26 withdrew/137 randomised (19%): placebo 19 withdrew/68 randomised (28%)
Selective reporting (reporting bias)	Low risk	Prepublished study protocol
Other bias	Low risk	None identified.

RESPIRE 2

Study characteristics

Methods	**Study design:** double-blind, multicentre, randomised, placebo-controlled trial (4 arms) **Total study duration:** 48 weeks **Number of study centres and locations:** 160 centres across 24 countries; Argentina, Australia, Austria, Brazil, Bulgaria, China, Czech Republic, Germany, Hong Kong, Latvia, Lithuania, Netherlands, Philip-

RESPIRE 2 *(Continued)*

	pines, Poland, Portugal, Romania, Russia, Serbia, South Africa, South Korea, Taiwan, Thailand, Turkey, USA **Screening period:** 4 weeks **Study setting:** outpatient clinics **Date of study:** April 2014 to October 2016
Participants	521 adults randomised. **Inclusion criteria:** primary diagnosis of non-cystic fibrosis bronchiectasis (idiopathic or postinfectious aetiology as determined by the investigator) confirmed by CT scan with stable disease (no exacerbation in last 30 days); ≥ 2 exacerbations in previous 12 months; positive culture at screening for one of the following *P aeruginosa, H influenzae, Moraxella catarrhalis, S aureus, Streptococcus pneumoniae, Stenotrophomonas maltophilia or Burkholderia cepaci;* sputum production on most days; people with stable chronic macrolide treatment (at least 6 months prior to screening), bronchodilators, anticholinergics, inhaled corticosteroids or mucolytics (for at least 4 weeks prior to screening) **Exclusion criteria:** post-bronchodilator FEV_1 < 30% or ≥ 90% predicted; systemic or inhaled antibiotic treatments within 4 weeks of study drug administration; active allergic bronchopulmonary aspergillosis, active or actively treated nontuberculous mycobacterial lung infection or tuberculosis; primary diagnosis of COPD; chronic asthma; allergy to fluoroquinolones or quinolones **Mean age:** 14 days on/off arm, intervention 60.4 (SD 13.7); control 60.4 (15.0). 28 days on/off arm, intervention 59.3 (SD 14.2); control 60.6 (SD 13.7) **Gender:** 14 days on/off arm, intervention 96 (54.5%) women; control 62 (70.5%) women. 28 days on/off arm, intervention 92 (53.8%) women; control 52 (60.5%) women **Ethnicity:** White 403 (77%); Black/African 5; Asian 111; multiple 2 **Diagnostic criteria:** CT chest scan **Baseline lung function:** FEV_1% predicted, 14 days on/off arm, intervention 54.3 (SD 17.3); control 55.8 (SD 18.6): 28 days on/off arm, intervention 56.4 (SD 18.8); control 56.2 ± (SD 18.2). Proportion < 50% predicted: 14 days on/off arm, intervention 44.3%; control 44.3%: 28 days on/off arm, intervention 38.0%; control 41.9% **Smoking history:** not reported **Baseline medications:** mucolytics 25%, bronchodilators 45%, ICS 35%, low dose systemic corticosteroids 1%, long term oral macrolides 8%, theophylline 8%, other respiratory 0.7%.
Interventions	**Intervention:** 12 consecutive treatment cycles of 35.5 mg of ciprofloxacin by dry powder inhaler twice daily for 14 days, followed by 14 days off treatment **or** six consecutive treatment cycles of 35.5 mg of ciprofloxacin by dry powder inhaler twice daily for 28 days, followed by 28 days off treatment **Comparison:** twelve consecutive treatment cycles of placebo by dry powder inhaler twice daily for 14 days, followed by 14 days off treatment **or** six consecutive treatment cycles of placebo by dry powder inhaler twice daily for 28 days, followed by 28 days off treatment **Concomitant medications:** > 80% of participants received at least one concomitant respiratory medication including: mucolytics, bronchodilators (long acting β-agonist bronchodilators, short acting β-agonist bronchodilators, long-acting anticholinergic bronchodilators and short-acting anticholinergic bronchodilators), inhaled corticosteroids, low-dose systemic corticosteroids, long-term oral macrolides and theophylline. **Excluded medications:** none stated
Outcomes	**Primary outcomes (prespecified):** 1) time to first protocol-defined exacerbation (worsening of at least 3 of the following; dyspnoea, wheeze, cough, sputum volume, sputum purulence, and fever or malaise/

RESPIRE 2 *(Continued)*

	fatigue and requiring systemic antibiotics) within 48 weeks after start of treatment. 2) frequency of protocol-defined exacerbations during the 48 week study period. **Secondary outcomes (prespecified):** frequency of exacerbations (systemic antibiotic use and worsening of at least one sign/symptom) over 48 weeks; pathogen eradication at end of last treatment cycle; occurrence of new pathogens, not present at baseline, by 48 weeks; Quality of life measured by SGRQ Symptoms and QoL-B-RSS at end of treatment; improvement in FEV_1 from baseline to end of treatment; antibiotic resistance (MIC against ciprofloxacin). **Adverse events:** Treatment-emergent adverse events, treatment-emergent serious adverse events and deaths. **Withdrawals:** 79 did not complete the study: 14 day intervention 25; 14 day placebo 15; 28 day intervention 23; 28 day placebo 16; **Time points:** baseline, end of on-treatment cycle 6 (14 day regimen) and cycle 3 (28 day regimen), QoL-B-RSS collected 9 (28 day regimen) or 10 (14 day regimen) times, 48 weeks (end of treatment), 8 weeks after last dose for both the 14 days on/off and 28 days on/off regimen (end of study)
Notes	This trial was one of two studies completed by the RESPIRE team of investigators. **Funding:** Bayer HealthCare AG **Role of the funding source:** involved in the design of the study and the decision to publish **Notable conflicts of interest of trial authors:** MC, TJB, EO and KR were employed by the funder at the time of the study. ADS, EP, JSE, KW and RW received fees from the funder. Payments received by ADS sent to Queens University Belfast. TA reported all remuneration for participation in clinical trials sponsored by the funder was sent to Mayo Foundation for Medical Research and Education.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization and medication kit numbers are generated by Bayer's Randomization Management."
Allocation concealment (selection bias)	Low risk	"Drug dispensation is managed by an interactive voice response system and interactive web response system run by an external vendor."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study is blinded for treatment assignment"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific statement about analysis blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomisation ratio 2:1 28 days regimen: Intervention: 23 withdrew/171 randomised (13%): placebo: 16 withdrew/86 randomised (19%) 14 days regimen: Intervention: 25 withdrew/176 randomised (14%): placebo: 15 withdrew/88 randomised (17%)

RESPIRE 2 *(Continued)*

Selective reporting (reporting bias)	Low risk	Prepublished study protocol
Other bias	Low risk	None identified.

Abbreviations
6 MWT: 6-minute walk test
AZLI: Aztreonam for inhalation solution
CFU/g colony forming units per gram of sputum
COPD: chronic obstructive pulmonary disease
CT: computerised tomography
DLCO: diffusing capacity for carbon monoxide
DRCFI: dual release ciprofloxacin for inhalation
EQ-5D: Euroqol-5D
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
ICS: inhaled corticosteroid
LABA: long-acting beta-agonist
LAMA: long-acting muscarinic antagonist
MIC: minimum inhibitory concentrations
mITT: modified intention-to-treat
non-CF: non-cystic fibrosis
SABA: short-acting beta-agonist
SD: standard deviation
SGRQ: St George's Respiratory Questionnaire
TIP: tobramycin inhalation powder
QoL-B-RSS: Quality of Life-Bronchiectasis Respiratory Symptoms Score

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
iREC	Not bronchiectasis as defined by the review. All participants had nodular/bronchiectatic mycobacterium avium complex lung disease.
Lloberes 1990	The study compared intermittent treatment regimens between two different antibiotics, which was not one of our predefined comparisons.

DATA AND ANALYSES

Comparison 1. 14 days on/off vs placebo

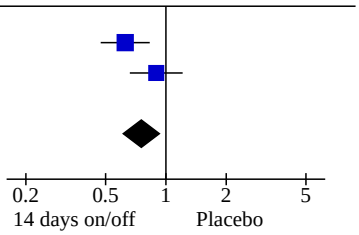
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Frequency of exacerbations: n ≥ 1	2	469	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.61, 0.93]
1.2 Serious adverse events: n ≥ 1	2	621	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.63, 1.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Development of antibiotic resistance: n with elevated MICs at any point	2	624	Odds Ratio (M-H, Fixed, 95% CI)	2.14 [1.36, 3.35]
1.4 Lung function: mean change in FEV_1 L	2	350	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.13, 0.00]
1.5 Health-related quality of life: mean change in QoL-B Respiratory Symptoms	2	282	Mean Difference (IV, Fixed, 95% CI)	1.12 [-3.12, 5.36]
1.6 Health-related quality of life: mean change in SGRQ Symptoms	2	360	Mean Difference (IV, Fixed, 95% CI)	-2.93 [-7.00, 1.14]
1.7 Adverse effects/reactions: n ≥ 1	2	621	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [1.04, 2.00]

Analysis 1.1. Comparison 1: 14 days on/off vs placebo, Outcome 1: Frequency of exacerbations: n ≥ 1

Study or Subgroup	14 days on/off Events	14 days on/off Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESPIRE 1	53	137	42	68	52.6%	0.63 [0.47 , 0.83]
RESPIRE 2	68	176	38	88	47.4%	0.89 [0.66 , 1.21]
Total (95% CI)		**313**		**156**	**100.0%**	**0.75 [0.61 , 0.93]**
Total events:	121		80			

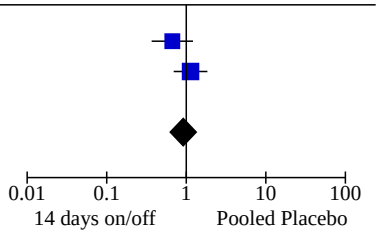
Heterogeneity: $Chi^2 = 2.88$, df = 1 (P = 0.09); $I^2 = 65\%$
Test for overall effect: Z = 2.68 (P = 0.007)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: 14 days on/off vs placebo, Outcome 2: Serious adverse events: n ≥ 1

Study or Subgroup	14 days on/off Events	14 days on/off Total	Pooled placebo Events	Pooled placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
RESPIRE 1	23	136	32	137	46.6%	0.67 [0.37 , 1.21]
RESPIRE 2	45	174	41	174	53.4%	1.13 [0.69 , 1.84]
Total (95% CI)		**310**		**311**	**100.0%**	**0.92 [0.63 , 1.33]**
Total events:	68		73			

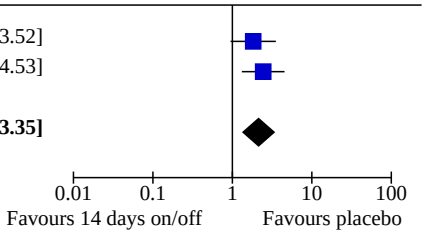
Heterogeneity: $Chi^2 = 1.79$, df = 1 (P = 0.18); $I^2 = 44\%$
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: 14 days on/off vs placebo, Outcome 3: Development of antibiotic resistance: n with elevated MICs at any point

Study or Subgroup	14 days on/off Events	14 days on/off Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
RESPIRE 1	28	137	17	138	49.9%	1.83 [0.95 , 3.52]
RESPIRE 2	37	176	17	173	50.1%	2.44 [1.32 , 4.53]
Total (95% CI)		**313**		**311**	**100.0%**	**2.14 [1.36 , 3.35]**
Total events:	65		34			

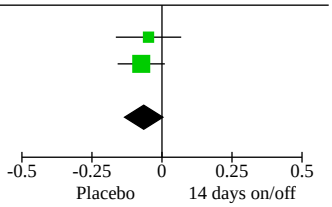
Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 3.31 (P = 0.0009)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: 14 days on/off vs placebo, Outcome 4: Lung function: mean change in FEV_1 L

Study or Subgroup	14 days on/off Mean	14 days on/off SD	14 days on/off Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
RESPIRE 1	-0.026	0.226	98	0.022	0.352	41	34.3%	-0.05 [-0.16 , 0.07]
RESPIRE 2	-0.037	0.287	140	0.037	0.299	71	65.7%	-0.07 [-0.16 , 0.01]
Total (95% CI)			**238**			**112**	**100.0%**	**-0.07 [-0.13 , 0.00]**

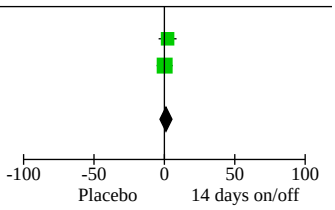
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.87 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: 14 days on/off vs placebo, Outcome 5: Health-related quality of life: mean change in QoL-B Respiratory Symptoms

Study or Subgroup	14 days on/off Mean	14 days on/off SD	14 days on/off Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
RESPIRE 1	6.72	17.9	95	4.45	17.78	44	44.4%	2.27 [-4.10 , 8.64]
RESPIRE 2	10.9	18.07	94	10.7	15.58	49	55.6%	0.20 [-5.49 , 5.89]
Total (95% CI)			**189**			**93**	**100.0%**	**1.12 [-3.12 , 5.36]**

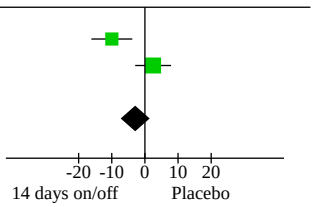
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.61)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: 14 days on/off vs placebo, Outcome 6: Health-related quality of life: mean change in SGRQ Symptoms

Study or Subgroup	14 days on/off Mean	14 days on/off SD	14 days on/off Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
RESPIRE 1	-7.2	20.41	101	2.78	16.16	45	43.4%	-9.98 [-16.16 , -3.80]
RESPIRE 2	-9.02	20.1	142	-11.5	18.54	72	56.6%	2.48 [-2.93 , 7.89]
Total (95% CI)			**243**			**117**	**100.0%**	**-2.93 [-7.00 , 1.14]**

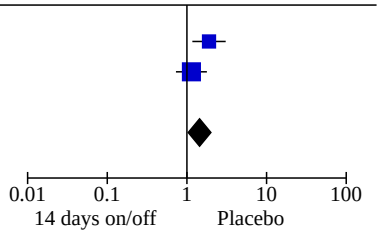
Heterogeneity: Chi² = 8.85, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: 14 days on/off vs placebo, Outcome 7: Adverse effects/reactions: n ≥ 1

Study or Subgroup	14 days on/off Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
RESPIRE 1	83	136	62	137	40.1%	1.89 [1.17 , 3.07]
RESPIRE 2	60	174	55	174	59.9%	1.14 [0.73 , 1.78]
Total (95% CI)		**310**		**311**	**100.0%**	**1.44 [1.04 , 2.00]**
Total events:	143		117			

Heterogeneity: Chi² = 2.30, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable



Comparison 2. 28 days on/off vs placebo

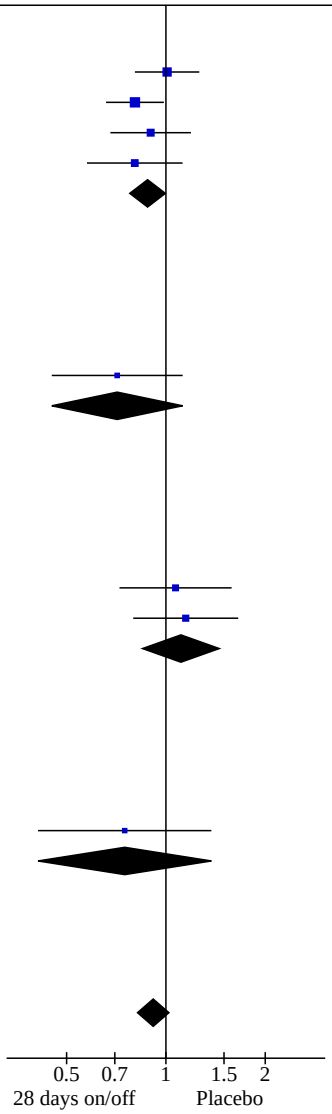
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Frequency of exacerbations: n ≥ 1	8	1695	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.02]
2.1.1 Ciprofloxacin over 48 weeks	4	1050	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.78, 1.00]
2.1.2 Ciprofloxacin over 42 weeks	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.45, 1.12]
2.1.3 Aztreonam over 16 weeks	2	540	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.85, 1.45]
2.1.4 Tobramycin over 16 weeks (pooled data)	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.41, 1.37]
2.2 Frequency of exacerbations: n ≥ 1; by mode of administration	8	1695	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.02]
2.2.1 Dry powder inhaler	3	531	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.69, 1.03]
2.2.2 Nebuliser	5	1164	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.83, 1.08]
2.3 Serious adverse events: n ≥ 1	8	1848	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.68, 1.46]
2.3.1 Ciprofloxacin over 48 weeks	4	1205	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.52, 1.13]
2.3.2 Ciprofloxacin over 42 weeks	1	42	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.20, 6.30]
2.3.3 Aztreonam over 16 weeks	2	538	Odds Ratio (M-H, Random, 95% CI)	1.68 [0.82, 3.45]
2.3.4 Tobramycin over 16 weeks (pooled data)	1	63	Odds Ratio (M-H, Random, 95% CI)	1.64 [0.39, 6.82]
2.4 Serious adverse events: n ≥ 1; by mode of administration	8	1848	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4.1 Nebuliser	5	1162	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.82, 1.50]
2.4.2 Dry powder inhaler	3	686	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.52, 1.10]
2.5 Time to 1st exacerbation	5	1174	Hazard Ratio (IV, Fixed, 95% CI)	0.94 [0.79, 1.13]
2.5.1 Ciprofloxacin over 48 weeks	2	598	Hazard Ratio (IV, Fixed, 95% CI)	0.83 [0.67, 1.04]
2.5.2 Aztreonam over 16 weeks	2	540	Hazard Ratio (IV, Fixed, 95% CI)	1.24 [0.91, 1.71]
2.5.3 Tobramycin for 16 weeks (pooled data)	1	36	Hazard Ratio (IV, Fixed, 95% CI)	0.76 [0.34, 1.71]
2.6 Severe exacerbations: n ≥ 1	3	624	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.37, 0.93]
2.6.1 Ciprofloxacin over 42 weeks	1	42	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.14, 8.72]
2.6.2 Ciprofloxacin over 48 weeks	2	582	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.36, 0.91]
2.7 Development of antibiotic resistance: n with elevated MICs at any point	3	685	Odds Ratio (M-H, Fixed, 95% CI)	2.20 [1.42, 3.42]
2.7.1 Ciprofloxacin for 48 weeks	2	622	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [1.37, 3.37]
2.7.2 Tobramycin for 16 weeks (pooled data)	1	63	Odds Ratio (M-H, Fixed, 95% CI)	3.33 [0.37, 29.68]
2.8 Frequency of hospital admissions for pulmonary exacerbation: n ≥ 1	3	645	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.49, 1.29]
2.8.1 Ciprofloxacin for 48 weeks	2	582	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.44, 1.23]
2.8.2 Tobramycin for 16 weeks (pooled data)	1	63	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [0.29, 8.62]
2.9 Lung function: mean change in FEV_1	5	874	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.25, 0.02]
2.9.1 Ciprofloxacin over 28 days	1	39	Std. Mean Difference (IV, Fixed, 95% CI)	-0.44 [-1.08, 0.19]
2.9.2 Ciprofloxacin over 48 weeks	2	357	Std. Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.16, 0.29]
2.9.3 Aztreonam over 16 weeks	2	478	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.38, -0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.10 Health-related quality of life: mean change in QoL-B Respiratory Symptoms	7	1469	Mean Difference (IV, Fixed, 95% CI)	0.05 [-1.56, 1.66]
2.10.1 Tobramycin for 16 weeks (pooled data)	1	63	Mean Difference (IV, Fixed, 95% CI)	-5.40 [-13.74, 2.94]
2.10.2 Ciprofloxacin over 48 weeks	4	866	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-2.18, 1.81]
2.10.3 Aztreonam over 16 weeks	2	540	Mean Difference (IV, Fixed, 95% CI)	1.19 [-1.69, 4.07]
2.11 Health-related quality of life: mean change in SGRQ Symptoms	3	407	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-4.26, 3.08]
2.11.1 Ciprofloxacin over 28 days	1	37	Mean Difference (IV, Fixed, 95% CI)	5.10 [-0.46, 10.66]
2.11.2 Ciprofloxacin over 48 weeks	2	370	Mean Difference (IV, Fixed, 95% CI)	-5.01 [-9.90, -0.12]
2.12 Adverse effects/reactions: n ≥ 1	8	1845	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.91, 1.31]
2.12.1 Ciprofloxacin over 28 days	1	39	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.29, 1.11]
2.12.2 Ciprofloxacin over 48 weeks	4	1205	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.85, 1.26]
2.12.3 Aztreonam over 16 weeks	2	538	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.19, 2.04]
2.12.4 Tobramycin for 16 weeks (pooled data)	1	63	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.81, 1.24]

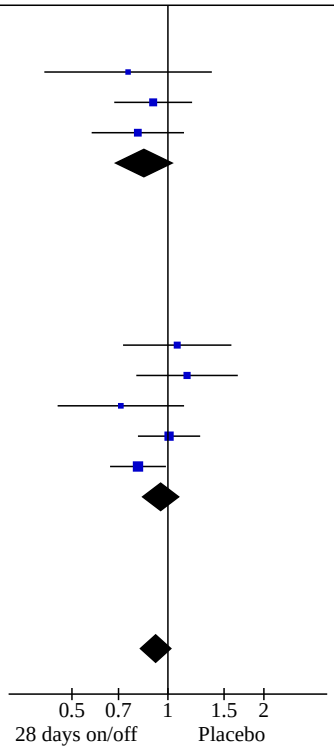
Analysis 2.1. Comparison 2: 28 days on/off vs placebo, Outcome 1: Frequency of exacerbations: n ≥ 1

Study or Subgroup	28 days on/off Events	28 days on/off Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Ciprofloxacin over 48 weeks						
ORBIT 3	101	183	52	95	19.5%	1.01 [0.81 , 1.26]
ORBIT 4	105	206	62	98	23.9%	0.81 [0.66 , 0.99]
RESPIRE 1	67	141	37	70	14.1%	0.90 [0.68 , 1.19]
RESPIRE 2	56	171	35	86	13.3%	0.80 [0.58 , 1.12]
Subtotal (95% CI)		**701**		**349**	**70.8%**	**0.88 [0.78 , 1.00]**
Total events:	329		186			
Heterogeneity: Chi² = 2.44, df = 3 (P = 0.49); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
2.1.2 Ciprofloxacin over 42 weeks						
ORBIT 2	11	20	17	22	4.6%	0.71 [0.45 , 1.12]
Subtotal (95% CI)		**20**		**22**	**4.6%**	**0.71 [0.45 , 1.12]**
Total events:	11		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.14)						
2.1.3 Aztreonam over 16 weeks						
AIRBX1	38	134	35	132	10.0%	1.07 [0.72 , 1.58]
AIRBX2	43	136	38	138	10.7%	1.15 [0.80 , 1.66]
Subtotal (95% CI)		**270**		**270**	**20.8%**	**1.11 [0.85 , 1.45]**
Total events:	81		73			
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
2.1.4 Tobramycin over 16 weeks (pooled data)						
iBEST	15	42	10	21	3.8%	0.75 [0.41 , 1.37]
Subtotal (95% CI)		**42**		**21**	**3.8%**	**0.75 [0.41 , 1.37]**
Total events:	15		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
Total (95% CI)		**1033**		**662**	**100.0%**	**0.92 [0.82 , 1.02]**
Total events:	436		286			
Heterogeneity: Chi² = 6.49, df = 7 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.59 (P = 0.11)						
Test for subgroup differences: Chi² = 3.86, df = 3 (P = 0.28), I² = 22.2%						



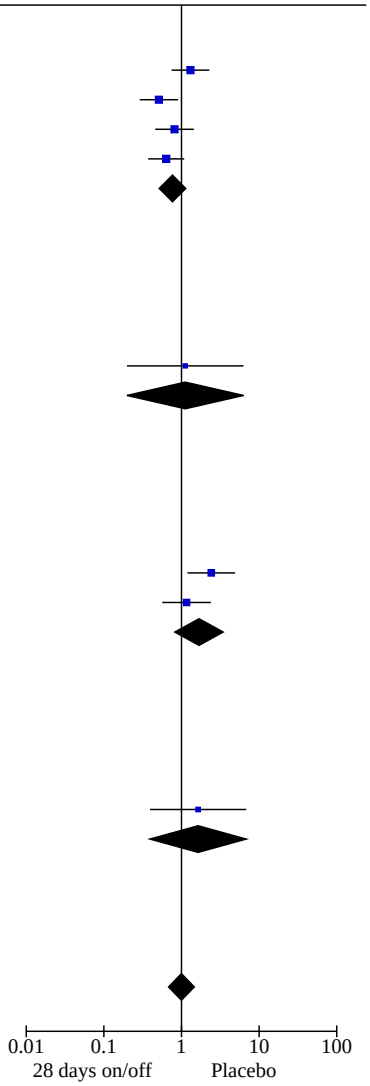
Analysis 2.2. Comparison 2: 28 days on/off vs placebo, Outcome 2: Frequency of exacerbations: n ≥ 1; by mode of administration

Study or Subgroup	28 days on/off Events	28 days on/off Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Dry powder inhaler						
iBEST	15	42	10	21	3.8%	0.75 [0.41 , 1.37]
RESPIRE 1	67	141	37	70	14.1%	0.90 [0.68 , 1.19]
RESPIRE 2	56	171	35	86	13.3%	0.80 [0.58 , 1.12]
Subtotal (95% CI)		**354**		**177**	**31.2%**	**0.84 [0.69 , 1.03]**
Total events:	138		82			
Heterogeneity: Chi² = 0.42, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.67 (P = 0.09)						
2.2.2 Nebuliser						
AIRBX1	38	134	35	132	10.0%	1.07 [0.72 , 1.58]
AIRBX2	43	136	38	138	10.7%	1.15 [0.80 , 1.66]
ORBIT 2	11	20	17	22	4.6%	0.71 [0.45 , 1.12]
ORBIT 3	101	183	52	95	19.5%	1.01 [0.81 , 1.26]
ORBIT 4	105	206	62	98	23.9%	0.81 [0.66 , 0.99]
Subtotal (95% CI)		**679**		**485**	**68.8%**	**0.95 [0.83 , 1.08]**
Total events:	298		204			
Heterogeneity: Chi² = 5.73, df = 4 (P = 0.22); I² = 30%						
Test for overall effect: Z = 0.80 (P = 0.43)						
Total (95% CI)		**1033**		**662**	**100.0%**	**0.92 [0.82 , 1.02]**
Total events:	436		286			
Heterogeneity: Chi² = 6.49, df = 7 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.59 (P = 0.11)						
Test for subgroup differences: Chi² = 0.96, df = 1 (P = 0.33), I² = 0%						



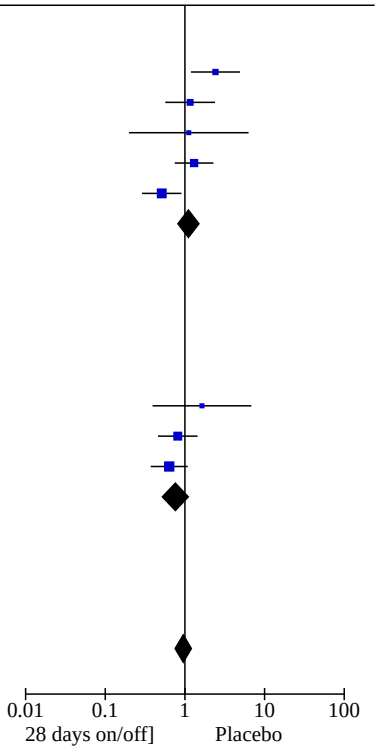
Analysis 2.3. Comparison 2: 28 days on/off vs placebo, Outcome 3: Serious adverse events: n ≥ 1

Study or Subgroup	28 days on/off Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2.3.1 Ciprofloxacin over 48 weeks						
ORBIT 3	56	183	24	95	16.0%	1.30 [0.75 , 2.28]
ORBIT 4	35	206	28	98	15.8%	0.51 [0.29 , 0.90]
RESPIRE 1	28	141	32	137	15.8%	0.81 [0.46 , 1.44]
RESPIRE 2	28	171	41	174	16.5%	0.64 [0.37 , 1.08]
Subtotal (95% CI)		**701**		**504**	**64.1%**	**0.77 [0.52 , 1.13]**
Total events:	147		125			
Heterogeneity: Tau² = 0.08; Chi² = 5.92, df = 3 (P = 0.12); I² = 49%						
Test for overall effect: Z = 1.33 (P = 0.18)						
2.3.2 Ciprofloxacin over 42 weeks						
ORBIT 2	3	20	3	22	4.1%	1.12 [0.20 , 6.30]
Subtotal (95% CI)		**20**		**22**	**4.1%**	**1.12 [0.20 , 6.30]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
2.3.3 Aztreonam over 16 weeks						
AIRBX1	28	134	13	132	13.3%	2.42 [1.19 , 4.91]
AIRBX2	18	135	16	137	13.1%	1.16 [0.57 , 2.39]
Subtotal (95% CI)		**269**		**269**	**26.3%**	**1.68 [0.82 , 3.45]**
Total events:	46		29			
Heterogeneity: Tau² = 0.14; Chi² = 2.02, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 1.42 (P = 0.16)						
2.3.4 Tobramycin over 16 weeks (pooled data)						
iBEST	9	42	3	21	5.5%	1.64 [0.39 , 6.82]
Subtotal (95% CI)		**42**		**21**	**5.5%**	**1.64 [0.39 , 6.82]**
Total events:	9		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**1032**		**816**	**100.0%**	**1.00 [0.68 , 1.46]**
Total events:	205		160			
Heterogeneity: Tau² = 0.16; Chi² = 15.82, df = 7 (P = 0.03); I² = 56%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Test for subgroup differences: Chi² = 4.19, df = 3 (P = 0.24), I² = 28.4%						



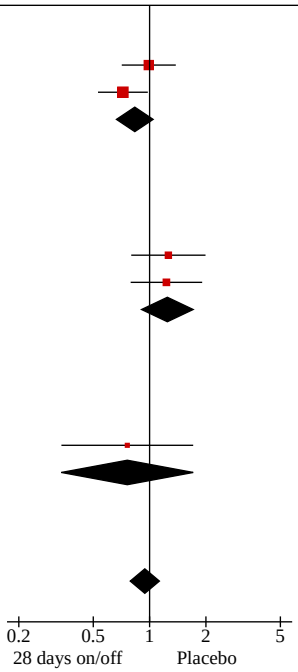
Analysis 2.4. Comparison 2: 28 days on/off vs placebo, Outcome 4: Serious adverse events: n ≥ 1; by mode of administration

Study or Subgroup	28 days on/off Events	28 days on/off Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.4.1 Nebuliser						
AIRBX1	28	134	13	132	7.2%	2.42 [1.19 , 4.91]
AIRBX2	18	135	16	137	9.6%	1.16 [0.57 , 2.39]
ORBIT 2	3	20	3	22	1.7%	1.12 [0.20 , 6.30]
ORBIT 3	56	183	24	95	15.3%	1.30 [0.75 , 2.28]
ORBIT 4	35	206	28	98	22.0%	0.51 [0.29 , 0.90]
Subtotal (95% CI)		**678**		**484**	**55.9%**	**1.11 [0.82 , 1.50]**
Total events:	140		84			
Heterogeneity: Chi² = 12.08, df = 4 (P = 0.02); I² = 67%						
Test for overall effect: Z = 0.65 (P = 0.51)						
2.4.2 Dry powder inhaler						
iBEST	9	42	3	21	2.2%	1.64 [0.39 , 6.82]
RESPIRE 1	28	141	32	137	18.2%	0.81 [0.46 , 1.44]
RESPIRE 2	28	171	41	174	23.7%	0.64 [0.37 , 1.08]
Subtotal (95% CI)		**354**		**332**	**44.1%**	**0.76 [0.52 , 1.10]**
Total events:	65		76			
Heterogeneity: Chi² = 1.59, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 1.45 (P = 0.15)						
Total (95% CI)		**1032**		**816**	**100.0%**	**0.95 [0.75 , 1.20]**
Total events:	205		160			
Heterogeneity: Chi² = 15.82, df = 7 (P = 0.03); I² = 56%						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Chi² = 2.37, df = 1 (P = 0.12), I² = 57.8%						



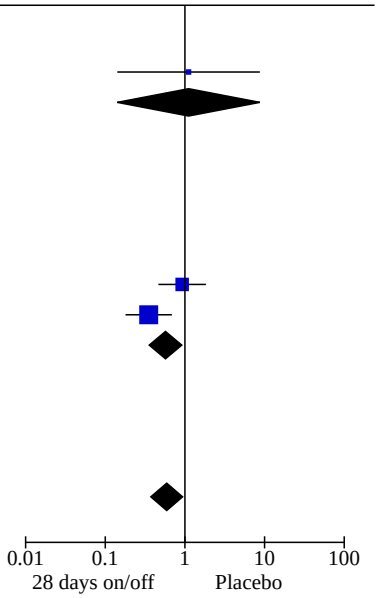
Analysis 2.5. Comparison 2: 28 days on/off vs placebo, Outcome 5: Time to 1st exacerbation

Study or Subgroup	log[Hazard Ratio]	SE	28 days on/off Total	Placebo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
2.5.1 Ciprofloxacin over 48 weeks						
ORBIT 3	-0.0101	0.1696	193	97	29.0%	0.99 [0.71 , 1.38]
ORBIT 4	-0.3285	0.1563	207	101	34.2%	0.72 [0.53 , 0.98]
Subtotal (95% CI)			**400**	**198**	**63.2%**	**0.83 [0.67 , 1.04]**
Heterogeneity: Chi² = 1.91, df = 1 (P = 0.17); I² = 48%						
Test for overall effect: Z = 1.59 (P = 0.11)						
2.5.2 Aztreonam over 16 weeks						
AIRBX1	0.2311	0.2332	134	132	15.4%	1.26 [0.80 , 1.99]
AIRBX2	0.207	0.2245	136	138	16.6%	1.23 [0.79 , 1.91]
Subtotal (95% CI)			**270**	**270**	**31.9%**	**1.24 [0.91 , 1.71]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.35 (P = 0.18)						
2.5.3 Tobramycin for 16 weeks (pooled data)						
iBEST	-0.2744	0.4137	23	13	4.9%	0.76 [0.34 , 1.71]
Subtotal (95% CI)			**23**	**13**	**4.9%**	**0.76 [0.34 , 1.71]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Total (95% CI)			**693**	**481**	**100.0%**	**0.94 [0.79 , 1.13]**
Heterogeneity: Chi² = 6.28, df = 4 (P = 0.18); I² = 36%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Chi² = 4.37, df = 2 (P = 0.11), I² = 54.2%						



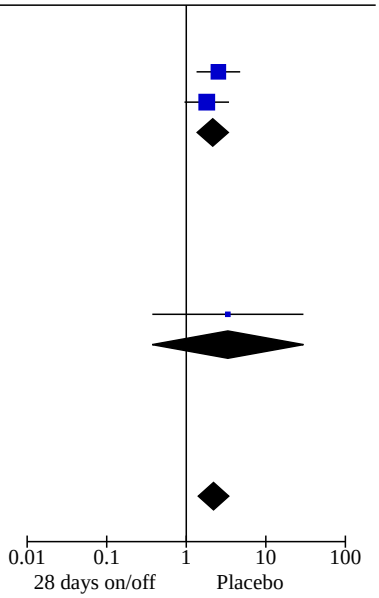
Analysis 2.6. Comparison 2: 28 days on/off vs placebo, Outcome 6: Severe exacerbations: n ≥ 1

Study or Subgroup	28 days on/off Events	28 days on/off Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.6.1 Ciprofloxacin over 42 weeks						
ORBIT 2	2	20	2	22	3.8%	1.11 [0.14 , 8.72]
Subtotal (95% CI)		**20**		**22**	**3.8%**	**1.11 [0.14 , 8.72]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
2.6.2 Ciprofloxacin over 48 weeks						
ORBIT 3	27	183	15	95	36.9%	0.92 [0.46 , 1.83]
ORBIT 4	19	206	22	98	59.3%	0.35 [0.18 , 0.69]
Subtotal (95% CI)		**389**		**193**	**96.2%**	**0.57 [0.36 , 0.91]**
Total events:	46		37			
Heterogeneity: Chi² = 3.91, df = 1 (P = 0.05); I² = 74%						
Test for overall effect: Z = 2.34 (P = 0.02)						
Total (95% CI)		**409**		**215**	**100.0%**	**0.59 [0.37 , 0.93]**
Total events:	48		39			
Heterogeneity: Chi² = 4.31, df = 2 (P = 0.12); I² = 54%						
Test for overall effect: Z = 2.25 (P = 0.02)						
Test for subgroup differences: Chi² = 0.38, df = 1 (P = 0.54), I² = 0%						



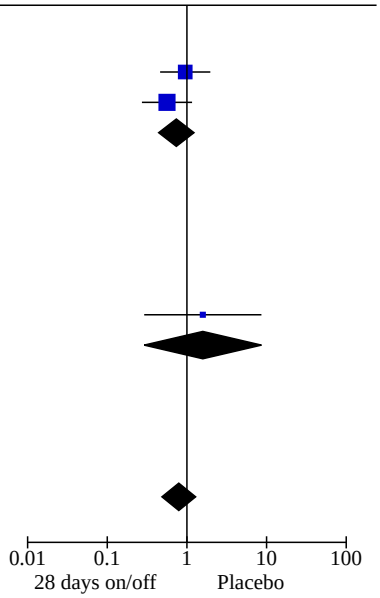
Analysis 2.7. Comparison 2: 28 days on/off vs placebo, Outcome 7: Development of antibiotic resistance: n with elevated MICs at any point

Study or Subgroup	28 days on/off Events	28 days on/off Total	Pooled placebo Events	Pooled placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.7.1 Ciprofloxacin for 48 weeks						
RESPIRE 1	37	141	17	138	45.4%	2.53 [1.35 , 4.76]
RESPIRE 2	28	170	17	173	50.5%	1.81 [0.95 , 3.45]
Subtotal (95% CI)		**311**		**311**	**95.9%**	**2.15 [1.37 , 3.37]**
Total events:	65		34			
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 3.34 (P = 0.0008)						
2.7.2 Tobramycin for 16 weeks (pooled data)						
iBEST	6	42	1	21	4.1%	3.33 [0.37 , 29.68]
Subtotal (95% CI)		**42**		**21**	**4.1%**	**3.33 [0.37 , 29.68]**
Total events:	6		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
Total (95% CI)		**353**		**332**	**100.0%**	**2.20 [1.42 , 3.42]**
Total events:	71		35			
Heterogeneity: Chi² = 0.68, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 3.51 (P = 0.0004)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%						



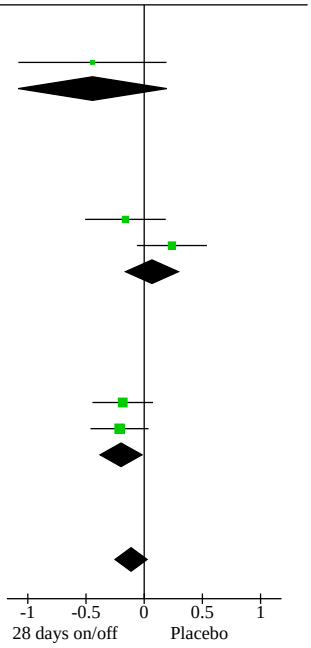
Analysis 2.8. Comparison 2: 28 days on/off vs placebo, Outcome 8: Frequency of hospital admissions for pulmonary exacerbation: n ≥ 1

Study or Subgroup	28 days on/off Events	28 days on/off Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.8.1 Ciprofloxacin for 48 weeks						
ORBIT 3	24	183	13	95	41.8%	0.95 [0.46 , 1.97]
ORBIT 4	19	206	15	98	51.8%	0.56 [0.27 , 1.16]
Subtotal (95% CI)		**389**		**193**	**93.6%**	**0.74 [0.44 , 1.23]**
Total events:	43		28			
Heterogeneity: Chi² = 1.01, df = 1 (P = 0.31); I² = 1%						
Test for overall effect: Z = 1.18 (P = 0.24)						
2.8.2 Tobramycin for 16 weeks (pooled data)						
iBEST	6	42	2	21	6.4%	1.58 [0.29 , 8.62]
Subtotal (95% CI)		**42**		**21**	**6.4%**	**1.58 [0.29 , 8.62]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.59)						
Total (95% CI)		**431**		**214**	**100.0%**	**0.79 [0.49 , 1.29]**
Total events:	49		30			
Heterogeneity: Chi² = 1.75, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Test for subgroup differences: Chi² = 0.72, df = 1 (P = 0.40), I² = 0%						



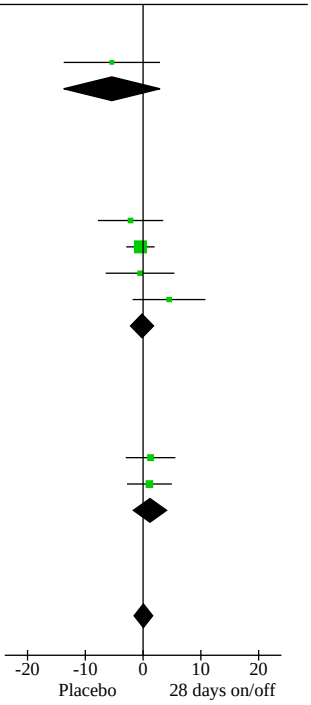
Analysis 2.9. Comparison 2: 28 days on/off vs placebo, Outcome 9: Lung function: mean change in FEV $_1$

Study or Subgroup	28 days on/off Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
2.9.1 Ciprofloxacin over 28 days								
ORBIT 2	-0.05	0.12	19	0	0.1	20	4.7%	-0.44 [-1.08 , 0.19]
Subtotal (95% CI)			**19**			**20**	**4.7%**	**-0.44 [-1.08 , 0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.37 (P = 0.17)								
2.9.2 Ciprofloxacin over 48 weeks								
RESPIRE 1	-0.012	0.149	112	0.024	0.344	45	15.8%	-0.16 [-0.51 , 0.19]
RESPIRE 2	0.038	0.336	138	-0.038	0.272	62	21.0%	0.24 [-0.06 , 0.54]
Subtotal (95% CI)			**250**			**107**	**36.8%**	**0.07 [-0.16 , 0.29]**
Heterogeneity: Chi² = 2.91, df = 1 (P = 0.09); I² = 66%								
Test for overall effect: Z = 0.58 (P = 0.56)								
2.9.3 Aztreonam over 16 weeks								
AIRBX1	-2.51	10.551	107	-0.54	10.714	122	28.0%	-0.18 [-0.44 , 0.08]
AIRBX2	-1.69	12.1996	123	0.91	12.2352	126	30.5%	-0.21 [-0.46 , 0.04]
Subtotal (95% CI)			**230**			**248**	**58.5%**	**-0.20 [-0.38 , -0.02]**
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%								
Test for overall effect: Z = 2.17 (P = 0.03)								
Total (95% CI)			**499**			**375**	**100.0%**	**-0.11 [-0.25 , 0.02]**
Heterogeneity: Chi² = 7.26, df = 4 (P = 0.12); I² = 45%								
Test for overall effect: Z = 1.60 (P = 0.11)								
Test for subgroup differences: Chi² = 4.33, df = 2 (P = 0.11), I² = 53.8%								



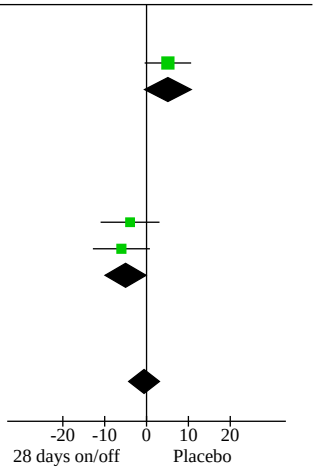
Analysis 2.10. Comparison 2: 28 days on/off vs placebo, Outcome 10: Health-related quality of life: mean change in QoL-B Respiratory Symptoms

Study or Subgroup	28 days on/off Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.10.1 Tobramycin for 16 weeks (pooled data)								
iBEST	-1.4	21.59	42	4	12.12	21	3.7%	-5.40 [-13.74 , 2.94]
Subtotal (95% CI)			**42**			**21**	**3.7%**	**-5.40 [-13.74 , 2.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.27 (P = 0.20)								
2.10.2 Ciprofloxacin over 48 weeks								
ORBIT 3	4.25	22.8	183	6.42	22.8	95	8.1%	-2.17 [-7.82 , 3.48]
ORBIT 4	7.74	10.2	206	8.2	10.2	98	43.1%	-0.46 [-2.91 , 1.99]
RESPIRE 1	7.7	18.5	110	8.22	16.74	46	7.3%	-0.52 [-6.47 , 5.43]
RESPIRE 2	11.57	17.49	85	7.08	17	43	6.5%	4.49 [-1.81 , 10.79]
Subtotal (95% CI)			**584**			**282**	**65.0%**	**-0.18 [-2.18 , 1.81]**
Heterogeneity: Chi² = 2.65, df = 3 (P = 0.45); I² = 0%								
Test for overall effect: Z = 0.18 (P = 0.86)								
2.10.3 Aztreonam over 16 weeks								
AIRBX1	5.7	18.5213	134	4.4	17.2337	132	14.0%	1.30 [-3.00 , 5.60]
AIRBX2	5.2	16.3267	136	4.1	16.4463	138	17.2%	1.10 [-2.78 , 4.98]
Subtotal (95% CI)			**270**			**270**	**31.2%**	**1.19 [-1.69 , 4.07]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%								
Test for overall effect: Z = 0.81 (P = 0.42)								
Total (95% CI)			**896**			**573**	**100.0%**	**0.05 [-1.56 , 1.66]**
Heterogeneity: Chi² = 4.95, df = 6 (P = 0.55); I² = 0%								
Test for overall effect: Z = 0.06 (P = 0.95)								
Test for subgroup differences: Chi² = 2.30, df = 2 (P = 0.32), I² = 12.9%								

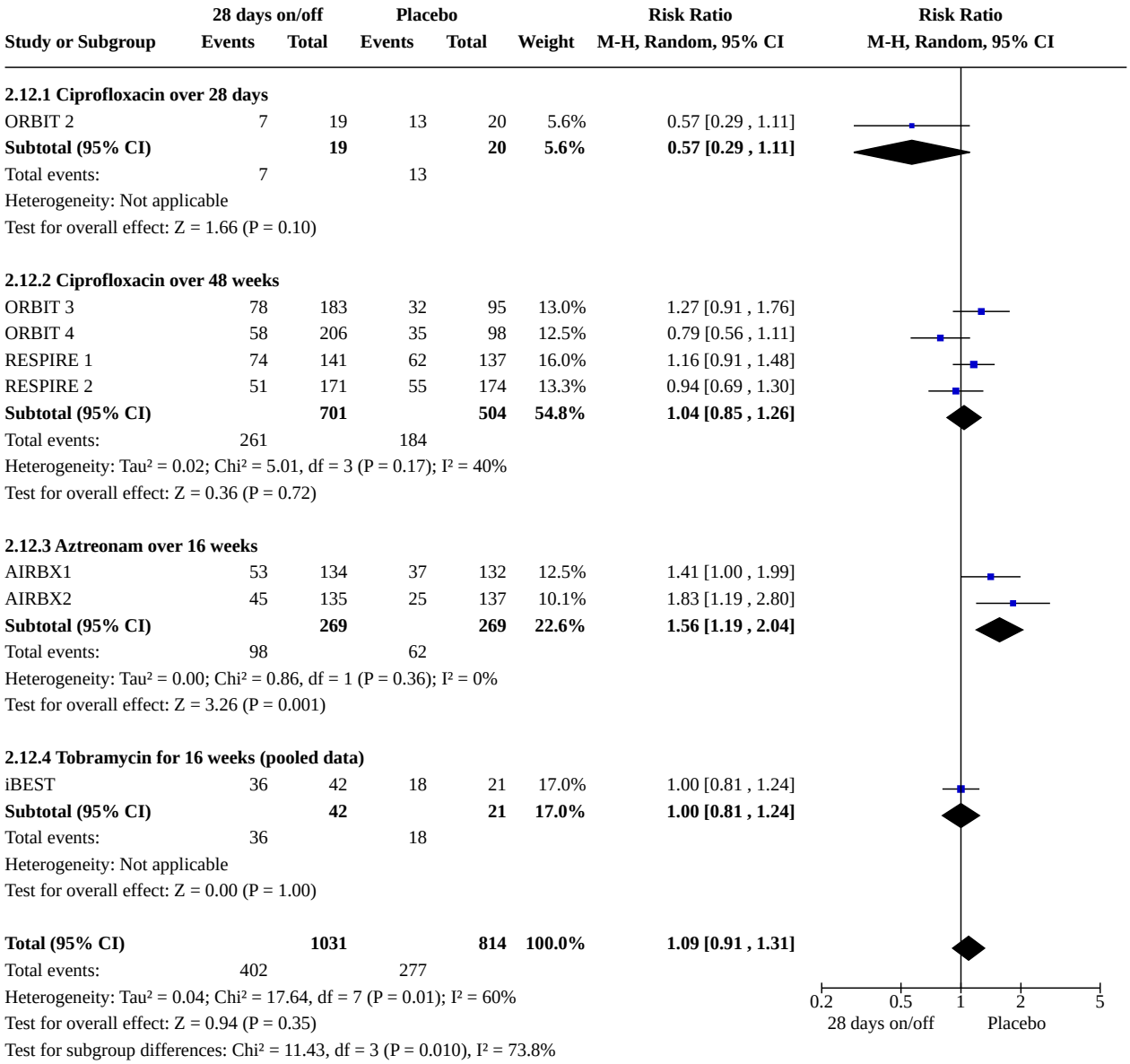


Analysis 2.11. Comparison 2: 28 days on/off vs placebo, Outcome 11: Health-related quality of life: mean change in SGRQ Symptoms

Study or Subgroup	28 days on/off Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.11.1 Ciprofloxacin over 28 days								
ORBIT 2	-1.3	7.16	19	-6.4	9.8	18	43.7%	5.10 [-0.46 , 10.66]
Subtotal (95% CI)			**19**			**18**	**43.7%**	**5.10 [-0.46 , 10.66]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.80 (P = 0.07)								
2.11.2 Ciprofloxacin over 48 weeks								
RESPIRE 1	-8.17	22.92	115	-4.23	19.55	46	27.2%	-3.94 [-10.97 , 3.09]
RESPIRE 2	-8.92	21.06	142	-2.91	24.48	67	29.1%	-6.01 [-12.82 , 0.80]
Subtotal (95% CI)			**257**			**113**	**56.3%**	**-5.01 [-9.90 , -0.12]**
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%								
Test for overall effect: Z = 2.01 (P = 0.04)								
Total (95% CI)			**276**			**131**	**100.0%**	**-0.59 [-4.26 , 3.08]**
Heterogeneity: Chi² = 7.34, df = 2 (P = 0.03); I² = 73%								
Test for overall effect: Z = 0.32 (P = 0.75)								
Test for subgroup differences: Chi² = 7.16, df = 1 (P = 0.007), I² = 86.0%								



Analysis 2.12. Comparison 2: 28 days on/off vs placebo, Outcome 12: Adverse effects/reactions: n ≥ 1



Comparison 3. 14 days on/off vs 28 days on/off

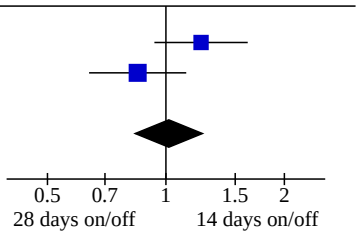
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Frequency of exacerbations: n ≥ 1	2	625	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.84, 1.24]
3.2 Serious adverse events: n ≥ 1	2	622	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.37, 1.86]
3.3 Development of antibiotic resistance: n with elevated MICs at any point	2	624	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 Lung function: mean change in FEV$_1$L	2	488	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.08, 0.01]
3.5 Health-related quality of life: mean change in QoL-B Respiratory Symptoms	2	384	Mean Difference (IV, Fixed, 95% CI)	0.83 [-2.77, 4.44]
3.6 Health-related quality of life: mean change in SGRQ Symptoms	2	500	Mean Difference (IV, Fixed, 95% CI)	-0.34 [-4.02, 3.35]
3.7 Adverse effects/reactions: n ≥ 1	2	622	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.95, 1.83]

Analysis 3.1. Comparison 3: 14 days on/off vs 28 days on/off, Outcome 1: Frequency of exacerbations: n ≥ 1

Study or Subgroup	28 days on/off Events	28 days on/off Total	14 days on/off Events	14 days on/off Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESPIRE 1	67	141	53	137	44.5%	1.23 [0.93 , 1.61]
RESPIRE 2	56	171	68	176	55.5%	0.85 [0.64 , 1.13]
Total (95% CI)		**312**		**313**	**100.0%**	**1.02 [0.84 , 1.24]**
Total events:	123		121			

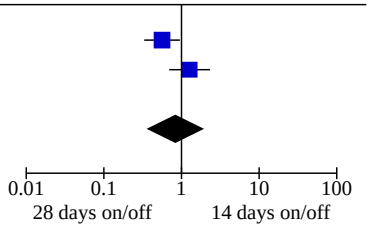
Heterogeneity: Chi² = 3.41, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: 14 days on/off vs 28 days on/off, Outcome 2: Serious adverse events: n ≥ 1

Study or Subgroup	28 days on/off Events	28 days on/off Total	14 days on/off Events	14 days on/off Total	Weight	Odds Ratio M-H, Random, 95% CI
RESPIRE 1	28	171	45	174	51.7%	0.56 [0.33 , 0.95]
RESPIRE 2	29	141	23	136	48.3%	1.27 [0.69 , 2.33]
Total (95% CI)		**312**		**310**	**100.0%**	**0.83 [0.37 , 1.86]**
Total events:	57		68			

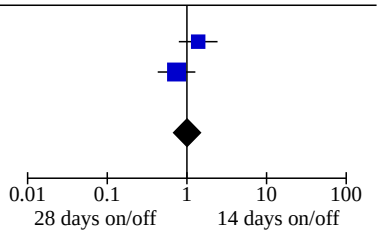
Heterogeneity: Tau² = 0.25; Chi² = 3.97, df = 1 (P = 0.05); I² = 75%
Test for overall effect: Z = 0.45 (P = 0.66)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: 14 days on/off vs 28 days on/off, Outcome 3: Development of antibiotic resistance: n with elevated MICs at any point

Study or Subgroup	28 days on/off Events	28 days on/off Total	14 days on/off Events	14 days on/off Total	Weight	Odds Ratio M-H, Fixed, 95% CI
RESPIRE 1	37	141	28	137	40.8%	1.38 [0.79 , 2.42]
RESPIRE 2	28	170	37	176	59.2%	0.74 [0.43 , 1.28]
Total (95% CI)		**311**		**313**	**100.0%**	**1.00 [0.68 , 1.48]**
Total events:	65		65			

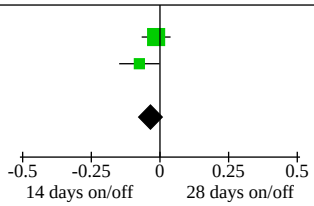
Heterogeneity: Chi² = 2.47, df = 1 (P = 0.12); I² = 60%
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: 14 days on/off vs 28 days on/off, Outcome 4: Lung function: mean change in FEV$_1$L

Study or Subgroup	14 days on/off Mean	14 days on/off SD	14 days on/off Total	28 days on/off Mean	28 days on/off SD	28 days on/off Total	Weight	Mean Difference IV, Fixed, 95% CI
RESPIRE 1	-0.026	0.226	98	-0.012	0.149	112	66.2%	-0.01 [-0.07 , 0.04]
RESPIRE 2	-0.037	0.287	140	0.038	0.336	138	33.8%	-0.07 [-0.15 , -0.00]
Total (95% CI)			**238**			**250**	**100.0%**	**-0.03 [-0.08 , 0.01]**

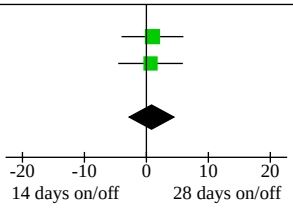
Heterogeneity: Chi² = 1.75, df = 1 (P = 0.19); I² = 43%
Test for overall effect: Z = 1.59 (P = 0.11)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: 14 days on/off vs 28 days on/off, Outcome 5: Health-related quality of life: mean change in QoL-B Respiratory Symptoms

Study or Subgroup	28 days on/off Mean	28 days on/off SD	28 days on/off Total	14 days on/off Mean	14 days on/off SD	14 days on/off Total	Weight	Mean Difference IV, Fixed, 95% CI
RESPIRE 1	7.7	18.5	110	6.72	17.9	95	52.2%	0.98 [-4.01 , 5.97]
RESPIRE 2	11.57	17.49	85	10.9	18.07	94	47.8%	0.67 [-4.54 , 5.88]
Total (95% CI)			**195**			**189**	**100.0%**	**0.83 [-2.77 , 4.44]**

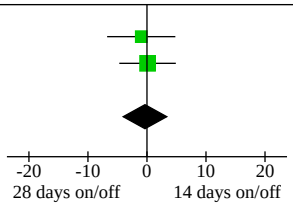
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: 14 days on/off vs 28 days on/off, Outcome 6: Health-related quality of life: mean change in SGRQ Symptoms

Study or Subgroup	28 days on/off Mean	28 days on/off SD	28 days on/off Total	14 days on/off Mean	14 days on/off SD	14 days on/off Total	Weight	Mean Difference IV, Fixed, 95% CI
RESPIRE 1	-8.17	22.92	115	-7.2	20.41	101	40.7%	-0.97 [-6.75 , 4.81]
RESPIRE 2	-8.92	21.06	142	-9.02	20.1	142	59.3%	0.10 [-4.69 , 4.89]
Total (95% CI)			**257**			**243**	**100.0%**	**-0.34 [-4.02 , 3.35]**

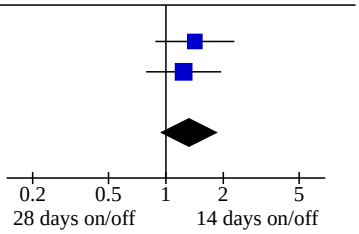
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: 14 days on/off vs 28 days on/off, Outcome 7: Adverse effects/reactions: n ≥ 1

Study or Subgroup	28 days on/off Events	Total	14 days on/off Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
RESPIRE 1	83	136	74	141	45.7%	1.42 [0.88 , 2.29]
RESPIRE 2	60	174	51	171	54.3%	1.24 [0.79 , 1.95]
Total (95% CI)		**310**		**312**	**100.0%**	**1.32 [0.95 , 1.83]**
Total events:	143		125			

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Study intervention characteristics

Study	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6
Aminoglycosides						
iBEST	84 mg daily tobramycin via DPI 4 cycles of 28 days on intervention/28 days on placebo for 16 weeks	84 mg daily matched placebo via DPI continuously for 16 weeks	140 mg daily tobramycin via DPI 4 cycles of 28 days on intervention/28 days on placebo for 16 weeks	140 mg daily matched placebo via DPI continuously for 16 weeks)	112 mg twice daily tobramycin via DPI 4 cycles of 28 days on intervention/28 days on placebo for 16 weeks	112 mg twice daily matched placebo via DPI continuously for 16 weeks
β-lactams						
AIRBX1; AIRBX2	75 mg 3 times daily aztreonam inhalation solution via Altera nebulizer 2 cycles of 28 days on/28 days off for 16 weeks)	3 times daily matched placebo inhalation solution via Altera nebulizer 2 cycles of 28 days on/28 days off for 16 weeks	–	–	–	–
Fluoroquinolones						
ORBIT 2	150 mg liposomal ciprofloxacin in 3 mL plus 60 mg free ciprofloxacin in 3 mL once daily via PARI LC Sprint nebulizer Up to 3 cycles of 28 days on/28 days off for 24 weeks	15 mg liposomes in 3 mL plus 0.9% saline in 3 mL once daily via PARI LC Sprint nebulizer Up to 3 cycles of 28 days on/28 days off for 24 weeks	–	–	–	–

Table 1. Study intervention characteristics *(Continued)*

ORBIT 3; ORBIT 4	135 mg liposomal ciprofloxacin in 3 mL plus 54 mg free ciprofloxacin in 3 mL once daily via PARI LC Sprint nebulizer 6 cycles of 28 days on/28 days off for 48 weeks	3 mL dilute empty liposomes plus 3 mL saline once daily via PARI LC Sprint nebulizer 6 cycles of 28 days on/28 days off for 48 weeks	–	–	–	–
RESPIRE 1; RESPIRE 2	35.5 mg ciprofloxacin twice daily via DPI 6 cycles of 28 days on/28 days off for 48 weeks	35.5 mg placebo twice daily via DPI 6 cycles of 28 days on/28 days off for 48 weeks	35.5 mg ciprofloxacin twice daily via DPI 12 cycles of 14 days on/14 days off for 24 weeks	35.5 mg placebo twice daily via DPI 12 cycles of 14 days on/14 days off for 24 weeks	–	–

DPI: breath actuated dry powder inhaler

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Trials Register

Electronic searches: core databases

Database	Dates searched	Frequency of search
Cochrane Central Register of Controlled Trials (CENTRAL; via the Cochrane Register of Studies (CRS))	From inception	Monthly
MEDLINE (Ovid) ALL	1946 onwards	Weekly
Embase (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (Cumulative Index to Nursing and Allied Health Literature; EBSCO)	1937 onwards	Monthly
AMED (Allied and Complementary Medicine; EBSCO)	From inception	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards

(Continued)

Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

Bronchiectasis search

1. exp Bronchiectasis/
2. bronchiect$.mp.
3. bronchoect$.mp.
4. kartagener$.mp.
5. (ciliary adj3 dyskinesia).mp.
6. (bronchial$ adj3 dilat$).mp.
7. or/1-6

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to identify relevant studies from the Cochrane Airways Trials Register

Search line	Search terms	Comments

(Continued)

#1	BRONCH:MISC1	MISC1 denotes the field in the record where the record has been coded for condition, in this case, bronchiectasis
#2	MeSH DESCRIPTOR Bronchiectasis Explode All	Index term for bronchiectasis, exploded to retrieve all narrower terms
#3	bronchiect*	
#4	#1 or #2 or #3	Search line combines all population terms
#5	MeSH DESCRIPTOR Anti-Bacterial Agents Explode 1	Index term for antibiotics, exploded to retrieve all narrower terms
#6	antibiotic* or anti-biotic*	
#7	anti-bacteri* or antibacteri*	
#8	*cillin	
#9	*mycin OR *micin	
#10	*oxacin	
#11	*tetracycline	
#12	macrolide*	
#13	quinolone*	
#14	trimethoprim	
#15	ceph*	
#16	sulpha*	
#17	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	Search line combines all intervention terms
#18	#4 and #17	Search line brings together population and intervention terms

Appendix 3. Search strategies for trial registries

ClinicalTrials.gov

Study type: interventional
Condition: bronchiectasis
Intervention: antibiotic* OR antibacterial OR *cillin OR *mycin OR *micin OR macrolide OR quinolone OR trimethoprim OR ceph* OR sulpha*

WHO Trials Portal

Condition: bronchiectasis
Intervention: antibiotic* OR antibacterial OR *cillin OR *mycin OR *micin OR macrolide OR quinolone OR trimethoprim OR ceph* OR sulpha*

HISTORY

Protocol first published: Issue 1, 2019

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the Background section. TD, AT and SS contributed to the Methods section.

AT searched trial registries, TD and MMD screened the search results, AT and PL extracted data, TD and SS completed risk of bias assessments, SS and TD did the data analysis, and all review authors contributed to writing the report.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor) edited the review; advised on methodology; approved the review prior to publication.

Katy Pike (Contact Editor): edited the review; advised on methodology, interpretation and content.

Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on interpretation and content; edited the review.

Emma Jackson (Assistant Managing Editor): conducted peer review; edited the references and other sections of the protocol and the review.

Elizabeth Stovold (Information Specialist): designed the search strategy; ran the searches; edited the search methods section.

DECLARATIONS OF INTEREST

S Spencer was the lead investigator on a study to develop a series of reviews on bronchiectasis, funded by Edge Hill University. She is an editor for the Cochrane Airways Group and the Cochrane Dementia and Cognitive Improvement Group.

JD Chalmers is a member of the EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration) group that sets research priorities in bronchiectasis. He also receives grant support from Pfizer, AstraZeneca, and GlaxoSmithKline. In addition, he is part of an innovative medicines initiative consortium that includes Novartis and Basilea Pharmaceutica. He has participated in advisory boards for Bayer HealthCare, Chiesi, and Raptor Pharmaceuticals. He has received speaker fees from Napp, AstraZeneca, BI, and Pfizer. None of these conflicts of interest are related to the work of this review and are unrelated to the topic of the review.

T Donovan: none known

P Leadbetter: none known

AG Mathioudakis: none known

MJ McDonnell: none known

A Tsang: none known

SOURCES OF SUPPORT

Internal sources

- Sally Spencer and Anthony Tsang, UK

  Employees of Edge Hill University
- Alexander G Mathioudakis, UK

  AGM was supported by the National Institute for Health Research Manchester Biomedical Research Centre (NIHR Manchester BRC).

External sources

- All authors, UK

  The authors declare that no such funding was received for this systematic review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We noted clinical heterogeneity between included studies according to type of antibiotic and duration of the trials, so we included these as two additional subgroup analyses. We specified that time-to-event data were analysed as hazard ratios.