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[Intervention Review]

Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

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ABSTRACT

Background

Respiratory tract infection with *Pseudomonas aeruginosa* occurs in most people with cystic fibrosis. Once chronic infection is established, *Pseudomonas aeruginosa* is virtually impossible to eradicate and is associated with increased mortality and morbidity. Early infection may be easier to eradicate.

This is an update of a Cochrane review first published in 2003, and previously updated in 2006, 2009 and 2014.

Objectives

To determine whether antibiotic treatment of early *Pseudomonas aeruginosa* infection in children and adults with cystic fibrosis eradicates the organism, delays the onset of chronic infection, and results in clinical improvement. To evaluate whether there is evidence that a particular antibiotic strategy is superior to or more cost-effective than other strategies and to compare the adverse effects of different antibiotic strategies (including respiratory infection with other micro-organisms).

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

Most recent search: 10 October 2016.

Selection criteria

We included randomised controlled trials of people with cystic fibrosis, in whom *Pseudomonas aeruginosa* had recently been isolated from respiratory secretions. We compared combinations of inhaled, oral or intravenous antibiotics with placebo, usual treatment or other combinations of inhaled, oral or intravenous antibiotics. We excluded non-randomised trials, cross-over trials, and those utilising historical controls.

Data collection and analysis

Both authors independently selected trials, assessed risk of bias and extracted data.

Main results

The search identified 60 trials; seven trials (744 participants) with a duration between 28 days and 27 months were eligible for inclusion. Three of the trials are over 10 years old and their results may be less applicable today given the changes in standard treatment. Some of the trials had low numbers of participants and most had relatively short follow-up periods; however, there was generally a low risk of bias from missing data. In most trials it was difficult to blind participants and clinicians to treatment given the interventions and comparators used. Two trials were supported by the manufacturers of the antibiotic used.

Evidence from two trials (38 participants) at the two-month time-point showed treatment of early *Pseudomonas aeruginosa* infection with inhaled tobramycin results in microbiological eradication of the organism from respiratory secretions more often than placebo, odds ratio 0.15 (95% confidence interval (CI) 0.03 to 0.65) and data from one of these trials, with longer follow up, suggested that this effect may persist for up to 12 months.

One randomised controlled trial (26 participants) compared oral ciprofloxacin and nebulised colistin versus usual treatment. Results after two years suggested treatment of early infection results in microbiological eradication of *Pseudomonas aeruginosa* more often than no anti-pseudomonal treatment, odds ratio 0.12 (95% CI 0.02 to 0.79).

One trial comparing 28 days to 56 days treatment with nebulised tobramycin solution for inhalation in 88 participants showed that both treatments were effective and well-tolerated, with no notable additional improvement with longer over shorter duration of therapy. However, this trial was not powered to detect non-inferiority or equivalence .

A trial of oral ciprofloxacin with inhaled colistin versus nebulised tobramycin solution for inhalation alone (223 participants) failed to show a difference between the two strategies, although it was underpowered to show this. A further trial of inhaled colistin with oral ciprofloxacin versus nebulised tobramycin solution for inhalation with oral ciprofloxacin also showed no superiority of the former, with increased isolation of *Stenotrophomonas maltophilia* in both groups.

A recent, large trial in 306 children aged between one and 12 years compared cycled nebulised tobramycin solution for inhalation to culture-based therapy and also ciprofloxacin to placebo. The primary analysis showed no difference in time to pulmonary exacerbation or proportion of *Pseudomonas aeruginosa* positive cultures. An analysis performed in this review (not adjusted for age) showed fewer participants in the cycled therapy group with one or more isolates of *Pseudomonas aeruginosa,* odds ratio 0.51 (95% CI 0.31 to 0.28).

Using GRADE, the quality of evidence for outcomes was downgraded to moderate to very low. Downgrading decisions for *Pseudomonas aeruginosa* eradication and lung function were based on applicability (participants mostly children) and limitations in study design, with imprecision an additional limitation for lung function, growth parameters and adverse effects.

Authors' conclusions

We found that nebulised antibiotics, alone or in combination with oral antibiotics, were better than no treatment for early infection with *Pseudomonas aeruginosa*. Eradication may be sustained for up to two years. There is insufficient evidence to determine whether antibiotic strategies for the eradication of early *Pseudomonas aeruginosa* decrease mortality or morbidity, improve quality of life, or are associated with adverse effects compared to placebo or standard treatment. Four trials comparing two active treatments have failed to show differences in rates of eradication of *Pseudomonas aeruginosa.* There have been no published randomised controlled trials that investigate the efficacy of intravenous antibiotics to eradicate *Pseudomonas aeruginosa* in cystic fibrosis. Overall, there is still insufficient evidence from this review to state which antibiotic strategy should be used for the eradication of early *Pseudomonas aeruginosa* infection in cystic fibrosis.

PLAIN LANGUAGE SUMMARY

Different ways of giving antibiotics to eradicate *Pseudomonas aeruginosa* infection in people with cystic fibrosis

Review question

What is the best way of using antibiotics to eliminate lung infections caused by a germ called *Pseudomonas aeruginosa* in people with cystic fibrosis?

Background

Cystic fibrosis is an inherited condition where the airways often become blocked with mucus. It is associated with chest infections, which can lead to progressive breathing failure and death. A germ called *Pseudomonas aeruginosa* is often the cause of infection and is difficult to treat successfully, once infection has become established.

We wanted to compare different combinations of inhaled, oral and intravenous (IV) antibiotics for eliminating *Pseudomonas aeruginosa* in people with cystic fibrosis to see if any single treatment works best and is more cost-effective.

Search date

The evidence is current to 10 October 2016.

Study characteristics

We included seven trials with 744 people with cystic fibrosis of both sexes, any age and both mild and more severe lung disease. The trials lasted from 28 days to 27 months. We could not combine many results as trials used different treatments. Two trials compared tobramycin to placebo (a dummy treatment). Three trials combined oral ciprofloxacin and inhaled colistin in the experimental group but used different comparators - one compared the antibiotic combination to no treatment, one to inhaled tobramycin and the third to oral ciprofloxacin with inhaled tobramycin. Another trial considered inhaled tobramycin and compared 28 days of treatment to 56 days. The final trial compared regular cycles of inhaled tobramycin (plus oral ciprofloxacin or placebo) to only treating with inhaled tobramycin (plus oral ciprofloxacin or placebo) based on the results of cultures grown in the laboratory.

Key results

Two small trials (38 people) treating early infection showed that after two months inhaled antibiotics were better than no treatment and eliminated *Pseudomonas aeruginosa* in most people. One of these trials reported for longer and suggested that this effect may last for up to 12 months. Another small trial (26 people) which lasted two years showed that treating early infection with a combination of inhaled and oral antibiotics was better than no treatment for eliminating *Pseudomonas aeruginosa*. A trial comparing 28 days of nebulised tobramycin solution for inhalation (88 people) to 56 days showed both were equally tolerated and successful at eliminating *Pseudomonas aeruginosa*. Four direct comparisons of oral or inhaled antibiotics (or combinations of both), including one with 223 people, did not find a difference between different antibiotic combinations. A recent trial in 306 children (aged up to 12 years) compared a regular cycle of inhaled tobramycin (with either oral ciprofloxacin or placebo) to treatment only when it was shown that a child was infected with *Pseudomonas aeruginosa* and showed that when children were given a regular cycle of inhaled tobramycin (with either oral ciprofloxacin or placebo) fewer of them grew *Pseudomonas aeruginosa* from their sputum. The trial report made an adjustment for age and did not show any difference in the number of times *Pseudomonas aeruginosa* was grown from samples between the groups, nor was there any difference in the length of time until the children had their next chest infection.

Quality of the evidence

Some trials were conducted up to 20 years ago and the results may not be applicable today. Some trials were small. All the trials had quite a short follow-up period, so we could not show whether treatment made people with cystic fibrosis feel better or live longer. Given the treatments compared in most of the trials, it would have been easy for people to guess which treatment they were receiving, which might have influenced some of the results. Two trials were supported by the pharmaceutical industry. Further research is still needed to see whether eliminating the bacteria completely improves the well-being and quality of life in people with cystic fibrosis and to establish which antibiotic combination provides the best way of eliminating *Pseudomonas aeruginosa*.

Overall the quality of evidence was moderate to very low, meaning that further research is likely to change the estimate of the size of the treatment effect. Future, larger trials (with greater power) may show one treatment is more effective in eradicating *Pseudomonas aeruginosa* than another.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Inhaled tobramycin compared with placebo

Inhaled tobramycin compared with placebo for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis

Patient or population: adults and children with cystic fibrosis and a positive microbiological isolate of *Pseudomonas aeruginosa* from a respiratory tract specimen

Settings: outpatients

Intervention: inhaled tobramycin

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Inhaled tobramycin				
Eradication of *P aeruginosa* from the respiratory tract: Proportion with positive respiratory culture for *P aeruginosa* **Follow-up:** 2 months (further results reported up to 2 years)	682 per 1000	102 per 1000 (20 to 443 per 1000)	**OR** 0.15 (95% CI 0.03 to 0.65)	38 (2 RCTs)	⊕⊖⊖⊖ **very low[1,2,3]**	The two studies gave very different doses of inhaled tobramycin (80 mg or 300 mg 2x daily). Results across different time points and sensitivity analyses to account for missing data in one trial were variable, showing no consistently significant advantage to inhaled tobramycin over placebo.
FEV_1 **Follow-up:** up to 2 years	There were no changes in spirometric pulmonary function during or after the treatment period.		NR	up to 22[4] (1 RCT)	⊕⊖⊖⊖ **very low[1,3,5]**	No numerical data were reported.
FVC **Follow-up:** up to 2 years	There were no changes in spirometric pulmonary function during or after the treatment period.		NR	up to 22[4] (1 RCT)	⊕⊖⊖⊖ **very low[1,3,5]**	No numerical data were reported.
Growth and nutritional status: change in weight (kg) from baseline **Follow-up:** up to 2 months	The mean change in weight from baseline was 0.3 kg in the placebo group.	The mean change in weight from baseline was 0.1 kg higher (0.38 kg lower to 0.58 kg higher)	NA	21 (1 RCT)	⊕⊕⊖⊖ **low[1,3]**	There was also no difference in the mean change in weight from baseline between groups at 1 month MD 0.20 kg (95% CI -0.28 to 0.68).

		in the inhaled tobramycin group.				
Frequency of infective pulmonary exacerbations: number of exacerbations per patient year **Follow-up:** NA	Outcome not reported.		NA	NA	NA	
Isolation of other micro-organisms from the respiratory tract: number of positive cultures per patient year **Follow-up:** up to 2 months	There were no changes in the prevalence of other micro-organisms, including multi-resistant organisms, cultured from respiratory secretions.		NR	21 (1 RCT)	⊕⊖⊖⊖ **very low[1,3,5]**	No numerical data were reported.
Adverse effects to antibiotics: cough **Follow-up:** up to 2 months	923 per 1000	535 per 1000 (28 to 1000 per 1000)	**OR** 0.58 (95% CI 0.03 to 10.86)	21 (1 RCT)	⊕⊖⊖⊖ **very low[1,3,6]**	No other specific adverse events were reported. The other included study in this comparison stated that there was no evidence of a difference in serum creatinine levels or auditory threshold between the groups.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEV_1:** forced expiratory volume in one second; **FVC**: forced vital capacity;**MD**: mean difference; **NA**: not applicable; **NR**: not reported **OR**: odds ratio; ***P aeruginosa****: Pseudomonas aeruginosa*; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Downgraded once due to risk of bias; methodological information was limited and unclear in the included studies and there were concerns regarding incomplete outcome data, selective reporting and other biases due to the early termination of one study.
2. Downgraded once due to imprecision: wide confidence intervals around the pooled effect and variable results shown at different time points.
3. Downgraded once due to applicability: the included studies recruited only children; results are not applicable to adults.
4. In the included trial, 22 participants were randomised but it is not clear if all participants contributed to this outcome.
5. Downgraded once due to imprecision: no numerical results available.
6. Downgraded once due to imprecision: very wide confidence intervals around the effect size.

Summary of findings 2. Oral ciprofloxacin and inhaled colistin compared with no treatment

Oral ciprofloxacin and inhaled colistin compared with no treatment for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis

Patient or population: adults and children with cystic fibrosis and a positive microbiological isolate of *P. aeruginosa* from a respiratory tract specimen

Settings: outpatients

Intervention: oral ciprofloxacin and inhaled colistin

Comparison: no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Oral ciprofloxacin and inhaled colistin				
Eradication of *P aeruginosa* from the respiratory tract **Follow-up:** NA	Outcome not reported		NA	NA	NA	
FEV_1 **Follow-up:** NA	Outcome not reported		NA	NA	NA	
FVC **Follow-up:** NA	Outcome not reported		NA	NA	NA	
Growth and nutritional status **Follow-up:** NA	Outcome not reported		NA	NA	NA	
Frequency of infective pulmonary exacerbations: number of exacerbations per patient year **Follow-up:** NA	Outcome not reported		NA	NA	NA	
Isolation of other micro-organisms from the respiratory tract: number of positive cultures per patient year **Follow-up:** NA	Outcome not reported		NA	NA	NA	

Adverse effects to antibiotics **Follow-up:** 27 months	No adverse effects were reported in either group	NR	26 (1 RCT)	⊕⊖⊖⊖ **very low**[1,2,3]	No numerical data were reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
FEV_1: forced expiratory volume in one second; **FVC**: forced vital capacity; **NA**: not applicable; **NR**: not reported; ***P aeruginosa***: *Pseudomonas aeruginosa*; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Downgraded once due to risk of bias; methodological information was limited and unclear in the included study and there was a high risk of bias due to lack of blinding.
2. Downgraded once due to applicability: the included study recruited only children; results are not applicable to adults.
3. Downgraded once due to imprecision: no numerical results available.

Summary of findings 3. Oral ciprofloxacin and inhaled colistin compared to inhaled tobramycin

Oral ciprofloxacin and inhaled colistin compared to inhaled tobramycin for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis

Patient or population: adults and children with cystic fibrosis and a positive microbiological isolate of *P aeruginosa* from a respiratory tract specimen

Settings: outpatients

Intervention: oral ciprofloxacin and inhaled colistin

Comparison: inhaled tobramycin

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Inhaled tobramycin	**Oral ciprofloxacin and inhaled colistin**				
Eradication of *P aeruginosa* from the respiratory tract: Proportion with positive respiratory culture for *P aeruginosa*	458 per 1000	348 per 1000 (110 to 1000 per 1000)	**OR** 0.76 (95% CI 0.24 to 2.42)	up to 58[1] (1 RCT)	⊕⊖⊖⊖ **very low**[2,3,4]	There was also no significant difference between treatment groups within the first 6 months, OR 0.43 (95% CI 0.15 to 1.23).

Follow-up: up to 24 months						
FEV_1: change from baseline (% predicted) **Follow-up**: up to 24 months	Median change from baseline in FEV_1 (% predicted) for all the participants was -1%.		NR	up to 58[1] (1 RCT)	⊕⊖⊖⊖ **very low**[2,3,5]	Changes in FEV_1 are not reported separately for each treatment arm.
FVC **Follow-up**: NA	Outcome not reported.		NA	NA	NA	
Growth and nutritional status: BMI and weight z score **Follow-up**: up to 24 months	Both BMI z score and weight z score were reported not to have changed significantly for trial participants as a whole.		NR	up to 58[1] (1 RCT)	⊕⊖⊖⊖ **very low**[2,3,5]	Numerical data were not reported for comparative results across the treatment groups.
Frequency of infective pulmonary exacerbations: number of exacerbations per patient year **Follow-up**: up to 24 months	During the first six months of follow up, there was no difference between the two treatment arms in number of oral antibiotic treatment days.		NR	up to 58[1] (1 RCT)	⊕⊖⊖⊖ **very low**[2,3,5]	These oral antibiotics were given for symptoms and not because of failed eradication. No numerical data were reported
Isolation of other micro-organisms from the respiratory tract: number of positive cultures per patient year **Follow-up**: NA	Outcome not reported.		NA	NA	NA	
Adverse effects to antibiotics: severe cough **Follow-up**: up to 24 months	34 per 1000	11 per 1000 (0 to 280 per 1000)	**OR** 0.32 (95% CI 0.01 to 8.24)	up to 58[1] (1 RCT)	⊕⊖⊖⊖ **very low**[2,3,4]	No other specific adverse events were reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CI:** confidence interval; **FEV_1:** forced expiratory volume in one second; **FVC**: forced vital capacity; **NA**: not applicable; **NR**: not reported **OR**: odds ratio; ***P aeruginosa****: Pseudomonas aeruginosa*; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. In the included trial, 58 participants were randomised but not all participants contributed to all outcomes (unclear how many participants contributed to some outcomes).
2. Downgraded once due to risk of bias; methodological information was limited and unclear in the included study and there were concerns of bias due to selective reporting of results.
3. Downgraded once due to applicability: the included studies recruited only children; results are not applicable to adults.
4. Downgraded once due to imprecision: very wide confidence intervals around the effect size.
5. Downgraded once due to imprecision: no numerical comparative results available.

Summary of findings 4. Inhaled tobramycin (28 days) compared with inhaled tobramycin (56 days)

Inhaled tobramycin (28 days) compared with inhaled tobramycin (56 days) for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis

Patient or population: adults and children with cystic fibrosis and a positive microbiological isolate of *P aeruginosa* from a respiratory tract specimen

Settings: outpatients

Intervention: inhaled tobramycin (28 days)

Comparison: inhaled tobramycin (56 days)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Inhaled tobramycin (56 days)	Inhaled tobramycin (28 days)				
Eradication of *P aeruginosa* from the respiratory tract: time to next isolation of *P aeruginosa* from BAL, sputum or oropharyngeal cultures **Follow-up:** 27 months	By 26.12 months, 50% of people in the 56 day group can expect to have experienced a recurrence of *P aeruginosa.*	By 25.18 months, 50% of people in the 28 day group can expect to have experienced a recurrence of *P aeruginosa.*	**HR** 0.81 (95% CI 0.37 to 1.76)	65[1] (1 RCT)	⊕⊕⊖⊖ **low**[2,3]	
FEV_1: % predicted **Follow-up:** 27 months	There were no major short- or long-term changes in spirometric parameters were observed during the study period.		NR	up to 88[1] (1 RCT)	⊕⊖⊖⊖ **very low**[2,3,4]	Changes in lung function were not reported separately for each treatment arm.
FVC: % predicted **Follow-up:** 27 months	There were no major short- or long-term changes in spirometric parameters were observed during the study period.		NR	up to 88[1] (1 RCT)	⊕⊖⊖⊖ **very low**[2,3,4]	Changes in lung function were not reported separately for each treatment arm.

Growth and nutritional status: weight, height and BMI **Follow-up:** 27 months	No significant differences in weight, height or body mass index were reported.		NR	up to 88[1] (1 RCT)	⊕⊖⊖⊖ **very low**[2,3,4]	Numerical data were not reported or comparative results across the treatment groups.
Frequency of infective pulmonary exacerbations: number of exacerbations per patient year **Follow-up:** 27 months	47 per 1000	9 per 1000 (0 to 188 per 1000)	**OR** 0.19 (95% CI 0.01 to 4.00)	77[1] (1 RCT)	⊕⊖⊖⊖ **very low**[2,3,5]	
Isolation of other micro-organisms from the respiratory tract: number of positive cultures per patient year **Follow-up:** 27 months	There were no consistent trends reported in the isolation of non-*P aeruginosa* organisms (one isolate only of *Stenotrophomonas maltophilia* which was seen in the 28-day arm).		NR	up to 88[1] (1 RCT)	⊕⊖⊖⊖ **very low**[2,3,4]	Numerical data were not reported or comparative results across the treatment groups.
Adverse effects to antibiotics **Follow-up:** up to 27 months	There were no significant differences between treatment groups in terms of any reported adverse events at any time point.		NA	up to 77[1] (1 RCT)	⊕⊖⊖⊖ **very low**[2,3,6]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BAL: bronchial lavage **CI:** confidence interval; **FEV_1:** forced expiratory volume in one second; **FVC**: forced vital capacity; **HR**: hazard ratio; **NA**: not applicable; **NR**: not reported **OR**: odds ratio; ***P aeruginosa***: *Pseudomonas aeruginosa*; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. In the included trial, 88 participants were randomised but not all participants contributed to all outcomes (unclear how many participants contributed to some outcomes).
2. Downgraded once due to risk of bias; methodological information was limited and unclear in the included study and there were concerns of bias due to selective reporting of results and lack of blinding.
3. Downgraded once due to applicability: the included studies recruited only children; results are not applicable to adults.
4. Downgraded once due to imprecision: no numerical comparative results available.
5. Downgraded once due to imprecision: very wide confidence intervals around the effect size
6. Downgraded once due to imprecision: some wide confidence intervals around effects sizes (small event rates) and a lot of adverse events analysed increasing the statistical chance of a spurious finding.

Summary of findings 5. Inhaled colistin plus oral ciprofloxacin compared to inhaled tobramycin plus oral ciprofloxacin

Inhaled colistin plus oral ciprofloxacin compared to inhaled tobramycin plus oral ciprofloxacin for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis

Patient or population: adults and children with cystic fibrosis and a positive microbiological isolate of *P aeruginosa* from a respiratory tract specimen

Settings: outpatients

Intervention: inhaled colistin plus oral ciprofloxacin

Comparison: inhaled tobramycin plus oral ciprofloxacin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Inhaled tobramycin plus oral ciprofloxacin	Inhaled colistin plus oral ciprofloxacin				
Eradication of *P aeruginosa* from the respiratory tract: proportion with positive respiratory culture for *P aeruginosa* **Follow-up:** median 16 months	315 per 1000	403 per 1000 (227 to 721 per 1000)	**OR** 1.28 (95% CI 0.72 to 2.29)	up to 223[1] (1 RCT)	⊕⊕⊖⊖ **low[2,3]**	There was also no significant difference between treatment groups within the first 6 months, OR 1.11 (95% CI 0.64 to 1.92).
FEV_1: relative change in % predicted FEV_1 from baseline **Follow-up:** mean 54 days	The mean relative change in % predicted FEV_1 from baseline was 4.55% in the inhaled tobramycin plus oral ciprofloxacin group.	The mean relative change in % predicted FEV_1 from baseline was 2.4% lower (5.89% lower to 1.09% higher) in the inhaled colistin plus oral ciprofloxacin group.	NA	128[1] (1 RCT)	⊕⊕⊖⊖ **low[2,4]**	
FVC **Follow-up:** NA	Outcome not reported.		NA	NA	NA	
Growth and nutritional status **Follow-up:** NA	Outcome not reported.		NA	NA	NA	

Frequency of infective pulmonary exacerbations: number of exacerbations per patient year **Follow-up:** NA	Outcome not reported.		NA	NA	NA	
Isolation of other micro-organisms from the respiratory tract: number of positive cultures per patient year **Follow-up:** median 16 months	There were no differences during follow up between the two groups for isolation of: *Stenotrophomonas maltophilia, Achromobacter xylosoxidans* or *Aspergillus* species.		NA	205[1] (1 RCT)	⊕⊕⊕⊖ **moderate[2]**	
Adverse effects to antibiotics: leading to trial discontinuation **Follow-up:** median 16 months	21 out of 118 (18%) participants discontinued the trial early due to adverse events in the inhaled tobramycin plus oral ciprofloxacin group.	17 out of 105 (16%) participants discontinued the trial early due to adverse events in the inhaled colistin plus oral ciprofloxacin group.	NA	223 (1 RCT)	⊕⊕⊕⊖ **moderate[2]**	Reasons for discontinuations included vomiting, photosensitivity, wheeze and pulmonary exacerbation.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **FEV_1:** forced expiratory volume in one second; **FVC**: forced vital capacity; **NA**: not applicable; **NR**: not reported **OR**: odds ratio; ***P aeruginosa***: *Pseudomonas aeruginosa*; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. In the included trial, 223 participants were randomised but not all participants contributed to all outcomes (unclear how many participants contributed to some outcomes, spirometry not performed in very young children).
2. Downgraded once due to risk of bias; methodological information was limited and unclear in the included study and there were potential concerns of bias due to selective reporting of results and lack of blinding.
3. Downgraded once due to imprecision: wide confidence intervals around the effect size.
4. Downgraded once due to applicability: a large proportion of the randomised participants (95 out of 223, 42%) did not contribute to this outcome.

Summary of findings 6. Cycled inhaled tobramycin compared to culture-based inhaled tobramycin

Cycled inhaled tobramycin compared to culture-based inhaled tobramycin for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis
Patient or population: adults and children with cystic fibrosis and a positive microbiological isolate of *P aeruginosa* from a respiratory tract specimen

Settings: outpatients

Intervention: cycled inhaled tobramycin

Comparison: culture-based inhaled tobramycin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Culture-based inhaled tobramycin	Cycled inhaled tobramycin				
Eradication of *P aeruginosa* from the respiratory tract: proportion of participants with one or more isolates of *P aeruginosa* from the respiratory tract **Follow-up:** 18 months	467 per 1000	228 per 1000 (145 to 383 per 1000)	**OR** 0.51 (95% CI 0.31 to 0.82)	298[1] (1 RCT)	⊕⊕⊕⊖ **moderate[2]**	The original trial report published age group–adjusted ORs which are slightly different to the results of this review.
FEV_1: mean 70-week % change in FEV_1 (% predicted) **Follow-up:** 70 weeks	The mean 70-week % change in FEV_1 (% predicted) was -1.61% in the culture-based inhaled tobramycin group.	The mean 70-week % change in FEV_1 (% predicted) was 2.38% higher (2% lower to 6.76% higher) in the cycle-based inhaled tobramycin group.	NA	143[1] (1 RCT)	⊕⊕⊖⊖ **low[2,3]**	
FVC **Follow-up:** NA	Outcome not reported.		NA	NA	NA	
Growth and nutritional status: mean 70-week change from baseline in weight (kg) and height (cm) **Follow-up:** 70 weeks	There were no significant differences between treatment groups in mean 70-week change from baseline in weight (kg) or height (cm).		NA	304[1] (1 RCT)	⊕⊕⊕⊖ **moderate[2]**	
Frequency of infective pulmonary exacerbations: proportion of participants with one or more pulmonary exacerbations (any severity) **Follow-up:** 18 months	533 per 1000	400 per 1000 (256 to 624 per 1000)	**OR** 0.75 (95% 0.48 to 1.17)	304[1] (1 RCT)	⊕⊕⊕⊖ **moderate[2]**	There was also no significant difference between groups in terms of proportion of participants with one

						or more severe pulmonary exacerbation or in terms of time to pulmonary exacerbation (severe or any severity).
Isolation of other micro-organisms from the respiratory tract: proportion of participants with new isolates of *Stenotrophomonas maltophilia* **Follow-up:** 18 months	184 per 1000	217 per 1000 (118 to 390 per 1000)	**OR** 1.18 (95% CI 0.65 to 2.12)	279[1] (1 RCT)	⊕⊕⊕⊖ **moderate[2]**	
Adverse effects to antibiotics: proportion of participants with one or more serious adverse events **Follow-up:** 18 months	289 per 1000	246 per 1000 (147 to 405 per 1000)	**OR** 0.85 (95% 0.51 to 1.40)	304[1] (1 RCT)	⊕⊕⊕⊖ **moderate[2]**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEV_1:** forced expiratory volume in one second; **FVC**: forced vital capacity; **NA**: not applicable; **NR**: not reported **OR**: odds ratio; ***P aeruginosa***: *Pseudomonas aeruginosa*; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. In the included trial, 306 participants were randomised, 304 received treatment but not all participants contributed to all outcomes (unclear how many participants contributed to some outcomes, spirometry not performed in very young children (less than 4 years of age)).
2. Downgraded once due to applicability: the included studies recruited only children; results are not applicable to adults. Also the included trial required patients to have been free of *P aeruginosa* for at least two years so results may not be applicable to a wider population.
3. Downgraded once due to applicability: a large proportion of the randomised and treated participants (161 out of 304, 53%) did not contribute to this outcome.

Summary of findings 7. Ciprofloxacin compared to placebo added to cycled and culture-based inhaled tobramycin therapy

Ciprofloxacin compared to placebo added to cycled and culture-based inhaled tobramycin therapy for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis

Patient or population: adults and children with cystic fibrosis and a positive microbiological isolate of *P aeruginosa* from a respiratory tract specimen

Settings: outpatients

Intervention: ciprofloxacin added to cycled and culture-based inhaled tobramycin therapy

Comparison: placebo added to cycled and culture-based inhaled tobramycin therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo added to cycled and culture-based inhaled tobramycin therapy	Ciprofloxacin added to cycled and culture-based inhaled tobramycin therapy				
Eradication of *P aeruginosa* from the respiratory tract: proportion of participants with one or more isolates of *P aeruginosa* from the respiratory tract **Follow-up:** 18 months	362 per 1000	322 per 1000 (199 to 521 per 1000)	**OR** 0.89 (95% CI 0.55 to 1.44)	298[1] (1 study)	⊕⊕⊕⊖ **moderate[2]**	The original trial report published age group–adjusted ORs which are slightly different to the results of this review.
FEV_1: mean 70-week % change in FEV_1 (% predicted) **Follow-up:** 70 weeks	The mean 70-week % change in FEV_1 (% predicted) was -1.85% in the placebo added to cycled and culture-based inhaled tobramycin therapy group.	The mean 70-week % change in FEV_1 (% predicted) was 3.02% higher (1.33% lower to 7.37% higher) in the ciprofloxacin added to cycled and culture-based inhaled tobramycin therapy group.	NA	143[1] (1 RCT)	⊕⊕⊖⊖ **low[2,3]**	
FVC **Follow-up:** NA	Outcome not reported.		NA	NA	NA	
Growth and nutritional status: mean 70-week change from baseline in weight (kg) and height (cm) **Follow-up:** 70 weeks	There were no significant differences between treatment groups in mean 70-week change from baseline in weight (kg) or height (cm).		NA	304[1] (1 RCT)	⊕⊕⊕⊖ **moderate[2]**	
Frequency of infective pulmonary exacerbations: proportion of participants	447 per 1000	666 per 1000	**OR** 1.49 (95% CI 0.95 to 2.33)	304[1] (1 RCT)	⊕⊕⊕⊖ **moderate[2]**	There was also no significant dif-

with one or more pulmonary exacerbations (any severity) **Follow-up:** 18 months		(425 to 1000)				ference between groups in terms of proportion of participants with one or more severe pulmonary exacerbation or in terms of time to pulmonary exacerbation (severe or any severity).
Isolation of other micro-organisms from the respiratory tract: proportion of participants with new isolates of *Stenotrophomonas maltophilia* **Follow-up:** 18 months	183 per 1000	220 per 1000 (121 to 395 per 1000)	**OR** 1.20 (95% CI 0.66 to 2.16)	279[1] (1 RCT)	⊕⊕⊕⊖ **moderate**[2]	
Adverse effects to antibiotics: proportion of participants with one or more serious adverse event **Follow-up:** 18 months	230 per 1000	354 per 1000 (214 to 591 per 1000)	**OR** 1.54 (95% CI 0.93 to 2.57)	304[1] (1 RCT)	⊕⊕⊕⊖ **moderate**[2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEV_1:** forced expiratory volume in one second; **FVC**: forced vital capacity; **NA**: not applicable; **NR**: not reported **OR**: odds ratio; ***P aeruginosa***: *Pseudomonas aeruginosa*; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. In the included trial, 306 participants were randomised, 304 received treatment but not all participants contributed to all outcomes (unclear how many participants contributed to some outcomes, spirometry not performed in very young children (less than 4 years of age)).
2. Downgraded once due to applicability: the included studies recruited only children; results are not applicable to adults. Also the included trial required patients to have been free of *P. aeruginosa* for at least two years so results may not be applicable to a wider population.
3. Downgraded once due to applicability: a large proportion of the randomised and treated participants (161 out of 304, 53%) did not contribute to this outcome.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common life-limiting, autosomal recessively inherited disease in white populations. Although this is a multisystem disease, the primary cause of death in CF is respiratory failure resulting from chronic pulmonary infection (FitzSimmons 1993). The most frequent cause of chronic pulmonary infection beyond infancy in people with CF is *Pseudomonas aeruginosa* (*P aeruginosa*) and, once established, appears to be permanent in the majority of cases (Fitzsimmons 1996). A number of definitions have been used for chronic *P aeruginosa* infection in CF.

1. The presence of *P. aeruginosa* in monthly specimens for six successive months or the development of precipitating antibodies to *P. aeruginosa* or both (Valerius 1991).
2. The culture of *P aeruginosa* from the sputum or respiratory secretions, on two or more occasions extending over six months or a shorter period if accompanied by a sustained rise of anti-pseudomonal antibodies (UK CF Trust 2004).
3. The isolation of *P aeruginosa* in more than 50% of months over a 12-month period (Lee 2003) - the second and subsequent positive specimens in the same month do not count. Conversely, eradication is defined as all monthly specimens negative for *P aeruginosa* over 12 months.
4. Three or more isolates of *P aeruginosa* in a 12-month period (UK CF Registry 2012).

We have used the first definition in this systematic review.

The age-specific prevalence of *P aeruginosa* in pre-school children is under 5%, rising to 30% at aged 16 years (UK CF Registry 2015). Some authors have suggested that the use of prophylactic anti-staphylococcal antibiotic therapy in early childhood may predispose to chronic *P aeruginosa* infection (Ratjen 2001b; Stutman 2002). However, this effect was not seen in a systematic review of prophylactic antibiotic use, including over 400 participants (Smyth 2017).

In children who are too young to expectorate, cough swabs or oropharyngeal swabs are the only respiratory specimens which can be easily obtained. These do not reliably predict the presence of *P aeruginosa* in the lower respiratory tract (Armstrong 1996; Rosenfeld 1999), whereas flexible fibreoptic bronchoscopy with bronchoalveolar lavage (BAL) may detect positive *P aeruginosa* in children with negative cough swabs or oropharyngeal swabs (Douglas 2009; Hilliard 2007). Sputum cultures have been shown to accurately reflect lower respiratory tract organisms in expectorating children and adults (Iacocca 1963; Thomassen 1984). Over half of people with CF have chronic infection with *P aeruginosa* by their mid-twenties (UK CF Registry 2015), although prior to chronic infection *P aeruginosa* is often isolated intermittently from respiratory tract specimens. This may represent transient colonies of *P aeruginosa* within the lower respiratory tract or alternatively it may reflect the difficulties in accurately detecting *P aeruginosa* in the lungs of young people with CF (Burns 2001). The quantity and type of *P aeruginosa* present in the lower respiratory tract changes as infection becomes established. It is known that *P aeruginosa* has two major phenotypes - mucoid and non-mucoid. Following first isolation there is a progressive increase in the density of *P aeruginosa* colonies in the lower respiratory tract (Rosenfeld 2001). Initial isolates often show a non-mucoid phenotype; however, as infection progresses a mucoid phenotype may prevail and will be more difficult to eradicate. Douglas has reported a relatively high prevalence (18.2%) of mucoid *P aeruginosa* at first isolation in newborn screened infants, speculating that the notion of transformation from non-mucoid to mucoid phenotype under environmental pressure may be inaccurate in young children (Douglas 2009). It has been reported that *P aeruginosa* provokes an inflammatory response of the lower respiratory tract (Muhlebach 1999) and there is a marked step up in this inflammatory response as the number of *P aeruginosa* colonies increases (Armstrong 1996).

The presence of *P aeruginosa* in respiratory secretions is a major predictor of mortality in children with CF (Emerson 2002). Individuals with CF infected with *P aeruginosa* also suffer greater morbidity with a more rapid deterioration in lung function (Emerson 2002; Pamukcu 1995) and a more rapid decline in chest radiograph score (Kosorok 2001), poor growth, reduced quality of life, increased hospitalisation and increased need for antibiotic treatment (Ballman 1998; Nixon 2001; Winnie 1991). Some studies suggest there is a temporal relationship between the onset of chronic infection and increased morbidity (Abman 1991; Hudson 1993; Kosorok 2001; Parad 1999), whilst others do not support these findings (Kerem 1990; Rosenfeld 2001). On balance, there seems to be good evidence from well-designed non-experimental studies that clinical state deteriorates after first isolation of *P aeruginosa*.

Description of the intervention

Several strategies exist to treat early infection with *P aeruginosa* and include the use of the inhaled antibiotics such as colistin and tobramycin (Littlewood 1985; Ratjen 2001a), oral quinolones such as ciprofloxacin (Taccetti 2005) and intravenous (IV) antibiotics usually consisting of combination of an aminoglycoside with a beta-lactam (Döring 2000; Douglas 2009).

How the intervention might work

As well as antibiotic treatment of *P aeruginosa* given at the time of first isolation, other strategies have the potential to prevent or delay infection of the respiratory tract. These include avoidance of contact with people who carry *P aeruginosa* (UK CF Trust 2004) and the development of vaccines against *P. aeruginosa* (Johansen 2015). Uncontrolled series have indicated that a variety of anti-pseudomonal antibiotics either singly (Littlewood 1985; Ratjen 2001a) or in combination (Vazquez 1993) at first isolation may delay the onset of chronic infection. A trial using historical controls suggested that oral ciprofloxacin and nebulised colistin are effective in delaying or preventing chronic infection (Frederiksen 1997). An uncontrolled pilot study of IV therapy suggested that IV treatment alone was less effective in delaying the onset of chronic infection (Steinkamp 1989). There is also evidence supporting eradication therapy from long-term observational studies of chronic infection with *P aeruginosa* in CF clinics such as the study reported by Lee (Lee 2004).

Why it is important to do this review

There are differences in the approach to detection and management of first isolation of *P aeruginosa*. Some CF centres advocate frequent microbiological surveillance with attempts to eradicate *P aeruginosa* when it first appears in the lung (Döring

2000), whereas others treat only when clinical or radiological signs of pulmonary infection are present (Ramsey 1996). There is evidence that, when *P aeruginosa* is cleared from respiratory secretions it is not simply suppressed because, when infection recurs, this is with a genetically distinct organism in most cases (Munck 2001). Evidence that eradication strategies result in increased survival or improved quality of life for people with CF are from observational studies alone. There are multiple different eradication regimens that have been described using different anti-pseudomonal antibiotics in different combinations of IV, oral or nebulised (or both) and with varying doses and duration of therapy (Lee 2009). Given the expense of chronic anti-pseudomonal suppressive therapy, there is a clear rationale for early eradication from a cost-effectiveness perspective and this is supported by observational data (Taccetti 2005); however, there has not been any formal evaluation of cost effectiveness to date.

This is an update of a Cochrane review first published in 2003, and previously updated in 2006, 2009 and 2014 (Wood 2003; Wood 2006; Langton-Hewer 2009; Langton-Hewer 2014).

OBJECTIVES

To determine whether antibiotic treatment of early *P aeruginosa* infection in children and adults with CF alters clinical and microbiological outcome when compared to usual treatment.

To test the hypotheses that antibiotics against *P aeruginosa*, given at the time of first isolation, reduce CF-related mortality; improve quality of life; improve pulmonary function; nutritional status; and reduce the need for subsequent hospitalisation and consumption of antibiotics.

To investigate whether these antibiotics prevent or delay the onset of chronic infection of the respiratory tract with *P aeruginosa*; increase the incidence of isolates of other micro-organisms from the respiratory tract; and are associated with adverse effects which are either important to the individual with CF or have long-term sequelae.

To investigate whether there is evidence of superior *P aeruginosa* eradication efficacy or improved cost-effectiveness between different antibiotic strategies.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Children and adults with CF, diagnosed clinically and by sweat or genetic testing (or both) with a first ever positive microbiological isolate of *P aeruginosa* from a respiratory tract specimen. Trials will also be included where the participants have been proven to be free of *P aeruginosa* for at least six months before a new isolation and should not be currently receiving *Pseudomonas*-suppressing treatment such as daily inhaled antibiotic therapy. Participants should be enrolled into a trial within six months (post hoc change - previously not more than two months) from isolation of *P aeruginosa.* In a further post hoc change, we have also altered our eligibility criteria to allow trials where all participants receive some eradication therapy before randomisation (*see* Differences between protocol and review). People with CF of all ages and disease severity will be included.

Types of interventions

Combinations of inhaled, oral or IV antibiotics with the aim of eradicating first pulmonary isolates of *P aeruginosa* compared with placebo or usual treatment (or both) or other combinations of inhaled, oral or IV antibiotics.

Types of outcome measures

Primary outcomes

1. Eradication of *P aeruginosa* from the respiratory tract as defined by
   a. clearance of *P aeruginosa* from bronchoalveolar lavage (BAL), sputum or oropharyngeal cultures at 1, 2, 3, 6, 12 and 24 months after commencement of therapy
   b. time to next isolation of *P aeruginosa* from BAL, sputum or oropharyngeal cultures

Secondary outcomes

1. Mortality
2. Quality of life assessment
3. Spirometric lung function (e.g. forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)) expressed as % predicted values for age, sex and height
4. Growth and nutritional status as measured by weight, height (children), body mass index (BMI) or z score
5. Frequency of respiratory exacerbations as defined by:
   a. frequency of infective pulmonary exacerbations expressed as the number of exacerbations per patient year
   b. time to next course of IV antibiotics from commencement of therapy
   c. days in hospital expressed as days in hospital per patient year
   d. days of antibiotic usage expressed as days of antibiotic usage per patient year
6. Isolation of other micro-organisms from the respiratory tract expressed as the number of positive cultures per patient year (where available, the microbiology detection method will be described in view of the differences in sensitivity and specificity of oropharyngeal, sputum and BAL samples for bacteriology, mycology and non-tuberculous mycobacteria)
7. Adverse effects to antibiotics, e.g. renal or auditory impairment and hypersensitivity reactions

Additional outcomes which have arisen during the review

1. Time to chronic infection (as defined above in Description of the condition)
2. Clinical and radiological scores
3. Cost effectiveness (trials looking at cost effectiveness will be compared, where possible)

Search methods for identification of studies

Relevant trials were identified from the Group's Cystic Fibrosis Trials Register using the terms: antibiotics AND (pseudomonas aeruginosa OR mixed infections) AND (eradication OR unknown).

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the*Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major CF conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the Trials Register, please see the relevant sections of the Group's website.

Date of the most recent search of the Group's trials register: 10 October 2016.

We have also searched the relevant clinical trials databases clinicaltrials.gov/, WHO ICTRP and ISRCTN. We used the search terms "cystic fibrosis" AND "Pseudomonas aeruginosa" AND "eradication".

Date of last search: 19 April 2017.

Data collection and analysis

Selection of studies

For the original review, two authors (DW, AS) independently selected the trials to be included in the review. From Issue 3, 2009 of *The Cochrane Library* two authors (SLH, AS) selected the trials to be included in the review. Where there was disagreement on the suitability of a trial for inclusion in the review, or on its risk of bias, the authors reached a consensus by discussion.

Data extraction and management

Each author independently extracted data using standard data acquisition forms. Where there was disagreement on the suitability of a trial for inclusion in the review, or on its risk of bias, the authors reached a consensus by discussion.

We planned to group outcome data into those measured at one, three, six, 12 months and annually thereafter. In addition, we previously stated that if outcome data were recorded at other time periods as well, that we would also consider examining these data. Some trials reported data at two months for some outcomes and we have included these data within the review. In the Taccetti trial, cumulative data were reported at six months and final follow-up data at a median of 16 months (range 12 to 28 months); we have included both time points in our analysis (Taccetti 2012). In the Treggiari trial, cumulative data for pulmonary exacerbations and isolates of *P aeruginosa* are presented for the 70-week follow-up period and these have been reported and analysed in this review (Treggiari 2011).

Assessment of risk of bias in included studies

For earlier versions of this review, in order to assess the risk of bias, each author independently assessed the methodological quality of each trial, based on the method described by Schulz (Schulz 1995). From the 2011 update, each author independently assessed the risk of bias using the tool recommended by Cochrane (Higgins 2011). The risk of bias was judged to be high, unclear or low for the domains of:

- sequence generation;
- allocation concealment;
- blinding (risk of bias increased as the level of blinding decreased);
- incomplete outcome data (the risk of bias increased if any withdrawals were not adequately described and reasons for withdrawals given, or if the withdrawals were not equal across groups);
- selective outcome reporting (bias increased if stated outcome measures were only partially reported or not reported at all);
- other potential sources of bias.

Where there was disagreement on the quality and risk of bias of a trial, the authors reached a consensus by discussion.

Measures of treatment effect

For binary outcome measures (eradication of *P aeruginosa*, mortality, isolation of micro-organisms and adverse effects), in order to allow an intention-to-treat analysis, the authors sought data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up. We calculated a pooled estimate of the treatment effect for each outcome across trials - the odds ratio (OR) or the ratio of the odds of an outcome among treatment allocated participants to the corresponding odds among controls with 95% confidence intervals (CIs). We presented binary data on clearance of *P aeruginosa* from BAL, sputum or oropharyngeal cultures and occurrence of chronic infection with *P aeruginosa* at multiple time points. We calculated the OR at each time point separately, thus ignoring the correlation between time points.

For continuous outcomes (quality of life, lung function, weight, height, BMI, number of respiratory exacerbations, days in hospital, days of antibiotic use, clinical and radiological scores), in order to allow an intention-to-treat analysis, we sought outcome data by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up. We recorded either mean change from baseline for each group or mean post-treatment or intervention values and standard deviation (SD). We calculated a pooled estimate of treatment effect by calculating the mean difference (MD) with 95% CIs.

In this version of the review, we entered time-to-event data into the meta-analysis using the log hazard ratio. This was possible for the outcome 'time to pulmonary exacerbation' (severe or any), in the comparison of cycled versus culture-based therapy (Analysis 6.5; Analysis 6.7) and ciprofloxacin versus placebo (Analysis 7.5; Analysis 7.7). We used the generic inverse variance (GIV) to analyse the data for time to next isolation of *P aeruginosa* from the Ratjen trial (Ratjen 2010). For future updates of this review, for time-to-event data, such as time to next *P aeruginosa* infection or time to chronic infection, we will attempt to obtain individual patient data (IPD). We will use these IPD to provide estimates of the log hazard ratio and its standard error and plan to combine time-to-event data from trials in a meta-analysis.

The authors have reported longitudinal data as individual time points. We realise that this method ignores any correlation between the participants; however, we have been unable to analyse these data using more appropriate methods as we do not have the

correlation co-efficient for these data. If in the future, we are able to obtain the correlation co-efficient, we will analyse these data more appropriately.

If trials include a health economic component, we will conduct a full or partial economic evaluation of interventions to eradicate *P aeruginosa,* depending on the available data.

Unit of analysis issues

Cross-over trials are not eligible for inclusion within this review.

The natural history of infection with *P aeruginosa* in CF comprises an initial infection with the organism usually in planktonic form, followed by chronic infection (in which the *P aeruginosa* frequently exists in the mucoid state). In the planktonic form, antibiotics can eradicate the organism; however, persistent infection is associated with biofilm growth and adaptive evolution mediated by genetic variation. The development of mucoidy, hypermutability and the acquisition of mutational antibiotic resistance are important factors associated with persistent infection and are associated with increased difficulty in eradication (Ciofu 2012).

In a cross-over trial comparing active treatment with placebo, given the progression of infections due to of *P aeruginosa,* the group receiving the active treatment after placebo will be at a disadvantage compared with those receiving active treatment first. The*P aeruginosa* may form a biofilm during placebo treatment and so it would not be able to be eradicated during the active treatment phase. Hence, a cross-over trial is an inappropriate design and we have not included cross-over trials in this review.

Dealing with missing data

In trials where outcome data were unavailable for randomised participants, we performed an available-case analysis. This available-case analysis included data on only those participants whose results are known, using as a denominator the total number of people who completed the trial for the particular outcome in question.

When data were incomplete, we imputed the missing data to provide best-case and worst-case scenarios, in order to show the range of possible results for the combined analysis (*see* Analysis 1.4; Analysis 1.5). The best-case scenario analysis is based on the assumption that all the missing data points represented beneficial clinical outcomes, whereas the worst-case analysis assumes that all missing data points had a negative clinical outcome.

Assessment of heterogeneity

For future updates of this review, if we are able to combine data from different trials we will test for heterogeneity using the I^2 statistic (Higgins 2003). We will consider values of I^2 up to 30% to indicate little or no heterogeneity, values between 30% and 60% to represent moderate heterogeneity, values from 60% to 90% to represent substantial heterogeneity and values over 90% to represent considerable heterogeneity. We accept that the importance of the observed value of I^2 depends firstly on the magnitude and direction of effects and secondly on strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for I^2). In a future version of this review (with more trials included in the meta-analysis of individual treatment comparisons), if we find evidence of at least substantial clinical heterogeneity (as defined above) in the included trials, we will perform a random-effects analysis.

Assessment of reporting biases

We sought evidence of reporting bias by comparison of the reported outcomes with those listed in the trial's methodological description. Where important outcomes have not been identified, we have requested the original trial protocol from the authors.

Data synthesis

We have analysed the data using a fixed-effect model. If, in future updates of this review, we find evidence of at least substantial clinical heterogeneity (as defined above) in the included trials, we plan to perform a random-effects analysis.

Subgroup analysis and investigation of heterogeneity

If we identify a moderate degree of heterogeneity or higher (Higgins 2003) and are able to combine a sufficient number of trials (at least 10), then we will investigate this with subgroup analyses. We plan to categorise participants if possible as *P aeruginosa*-free and *P aeruginosa*-naive according to the definition by Lee (Lee 2003). These subgroups will be analysed separately.

Sensitivity analysis

We also plan to test the robustness of our results with the following sensitivity analyses:

- trials where participants receive treatment within three months of isolation of *P aeruginosa* versus those where the interval is between three and 12 months;
- trials with high risk of bias versus low risk of bias for generation of allocation sequence;
- trials with a high risk of bias versus a low risk of bias for concealment of allocation;
- multi-centre versus single centre trials.

Summary of Findings and Quality of the Evidence (GRADE)

In a post hoc change in line with current Cochrane guidance, at the 2017 update, we added a summary of findings table for each comparison presented in the review. We selected the following seven outcomes to report (chosen based on relevance to clinicians and consumers):

- eradication of *P aeruginosa* from the respiratory tract;
- FEV_1;
- FVC;
- growth and nutritional status;
- frequency of infective pulmonary exacerbations;
- isolation of other micro-organisms from the respiratory tract; and
- adverse effects to antibiotics, e.g. renal or auditory impairment and hypersensitivity reactions.

We determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by

one level if they considered the limitation to be serious and by two levels if very serious.

RESULTS

Description of studies

Results of the search

Our search identified a total of 60 trials, none of these were cross-over trials. Of these 60 trials, seven met our inclusion criteria (Gibson 2003; Proesmans 2013; Ratjen 2010; Taccetti 2012; Treggiari 2011; Valerius 1991; Wiesemann 1998); we identified two trials which are still ongoing and will include data from these trials in a future update of this review once they have been published (TORPEDO Trial; Ratjen 2016); 50 trials were excluded (see below) and one trial is listed as 'Awaiting classification' (Noah 2010). We have contacted the investigators of this trial for further information to allow us to include or exclude it at a future update.

Included studies

The seven included trials enrolled a total of 744 participants (Gibson 2003; Proesmans 2013; Ratjen 2010; Taccetti 2012; Treggiari 2011; Valerius 1991; Wiesemann 1998).

Trial characteristics

All seven included trials were randomised controlled trials of parallel design. One trial reported stratification for age and participating centre (Gibson 2003), another trial reported stratification by age and FEV_1 values as an expression of illness severity (Taccetti 2012); the remaining five trials did not use stratification (Proesmans 2013; Ratjen 2010; Treggiari 2011; Valerius 1991; Wiesemann 1998). Two trials stated that they were double-blind (Gibson 2003; Wiesemann 1998); the Treggiari trial used placebo to blind for ciprofloxacin but not for TSI (Treggiari 2011); the other trials could not be blinded due to differing treatment regimens.

Five trials were multicentre (Gibson 2003; Ratjen 2010; Taccetti 2012; Treggiari 2011; Wiesemann 1998) and the other two were single-centre trials (Proesmans 2013; Valerius 1991). Five trials were based in Europe (Proesmans 2013; Ratjen 2010; Taccetti 2012; Valerius 1991; Wiesemann 1998) and two in North America (Gibson 2003; Treggiari 2011).

The duration of the trials varied and ranged from 28 days (Gibson 2003) to 27 months (Valerius 1991). The duration of the intervention has varied greatly, from three weeks (Valerius 1991) to one year (Wiesemann 1998).

Participant characteristics

The number of participants in each trial ranged from 21 to 306 and were as follows: 306 in the Treggiari trial (Treggiari 2011); 223 in the Taccetti trial (Taccetti 2012); 88 in the Ratjen trial (Ratjen 2010); 26 in the Proesmans trial (Proesmans 2013); 26 in the Valerius trial (Valerius 1991); 22 in the Wiesemann trial (Wiesemann 1998); and 21 in the Gibson trial (Gibson 2003). The Gibson trial reported that the planned sample size was 98 participants, but randomisation was stopped after an early interim analysis by the Data Monitoring Committee was undertaken due to poor accrual. This analysis showed a statistically significant treatment effect and so the trial was stopped (Gibson 2003).

Only two trials recruited adult participants; Taccetti recruited participants aged from 1 to 35 years (Taccetti 2012) and in the Ratjen trial any patient over six months of age was eligible for inclusion (Ratjen 2010). Two trials were restricted to younger children: six months to six years (Gibson 2003) and 1 to 12 years (Treggiari 2011).

All seven trials had approximately equal numbers of males and females.

All seven trials specified that participants had to have microbiological evidence of recent onset of airway infection with *P aeruginosa.* However, the interval allowed between isolation of *P aeruginosa* and randomisation to study treatment varied greatly, from four weeks (Proesmans 2013; Wiesemann 1998) to as long as six months (Treggiari 2011). Two trials additionally specified that individuals with raised titres to anti-pseudomonal antibodies were excluded from the trial (Ratjen 2010; Wiesemann 1998). Other data from the EPIC trial (Treggiari 2011) have shown that raised antibodies to *P aeruginosa* (anti-alkaline protease and anti-exotoxin A) are associated with an increased risk of recurrence in the 60 weeks following eradication treatment (Anstead 2013). Trials excluding participants with raised antibodies might therefore be expected to achieve higher eradication rates.

Intervention

Trials have used various combinations of inhaled tobramycin, inhaled colistin, oral ciprofloxacin, placebo and no treatment. Two trials were placebo-controlled (Gibson 2003; Wiesemann 1998); one trial compared active treatment to no treatment (Valerius 1991); and three open-label trials compared different active treatments (Proesmans 2013; Ratjen 2010; Taccetti 2012). The design of the Treggiari trial was complex, with randomisation to cycled treatment with tobramycin solution for inhalation (TSI) or culture-based treatment and further randomisation to additional oral ciprofloxacin or placebo (Treggiari 2011).

Two trials compared tobramycin to placebo (Gibson 2003; Wiesemann 1998). One trial used tobramycin solution for inhalation (TSI) TOBI® (now marketed by Novartis) at a dose of 300 mg twice-daily for 28 days (Gibson 2003); the second trial used aerosolised tobramycin parenteral preparation (Eli Lilly, Bad Homburg, Germany) at a dose of 80 mg twice-daily for 12 months (Wiesemann 1998).

Ratjen also used TSI and evaluated a short (28 days) versus a longer (56 days) course of treatment (Ratjen 2010).

Participants in the Treggiari trial were randomised to one of four arms; they received either cycles of four weeks of treatment with nebulised TSI (with or without ciprofloxacin) in every 12-week period or TSI (with or without ciprofloxacin) only when respiratory culture was positive for *P aeruginosa* (Treggiari 2011). All trial participants had an initial 28-day course of TSI, with an additional 28 days given if the patient remained positive after initial treatment. Ciprofloxacin or placebo was not given with second course of TSI and follow up was for 18 months from randomisation and first treatment with TSI (Treggiari 2011).

Three trials evaluated inhaled colistin in combination with oral ciprofloxacin (Proesmans 2013; Taccetti 2012; Valerius 1991). Proesmans compared colistin 2 million units (MU) twice daily for three months (in combination with oral ciprofloxacin 30 mg/kg/day) to TSI 300 mg twice daily for 28 days (Proesmans 2013). The

Taccetti trial compared 28 days of inhaled colistin with 28 days TSI; both arms also had oral ciprofloxacin 30 mg/kg/day for 28 days (Taccetti 2012). Valerius compared colistin 1 MU (plus ciprofloxacin 250 mg to 750 mg), both given twice daily for three weeks, for initial and any subsequent isolate of *P aeruginosa* to no treatment (Valerius 1991).

Outcome measures

The most widely used primary outcome measure was eradication of *P aeruginosa* from respiratory secretions, though definitions of eradication differ considerably between trials. In the Gibson trial, the primary outcome was the change in *P aeruginosa* density in BAL from baseline to 28 days (Gibson 2003). However, the trial also looked at eradication at 28 days, and defined eradication as a density of *P aruginosa* in BAL of less than 20 colony forming units (CFU). Proesmans defined eradication as a negative culture result for *P aeruginosa* (from sputum, cough swab or BAL) at 28 days or three months (depending on which intervention the participant received) (Proesmans 2013). Both trials based successful eradication on a single specimen (Gibson 2003; Proesmans 2013). In contrast, Taccetti used a more stringent definition of eradication as per guidance published by the UK CF Trust of three negative cultures in a six-month period (Taccetti 2012; UK CF Trust 2004). Ratjen used the median time to recurrence of any strain of *P aeruginosa* during a 27-month follow-up period (Ratjen 2010). In the oldest trial, the primary outcome measure was time to chronic infection with *P aeruginosa,* defined as the presence of *P aeruginosa* in monthly sputum samples for six consecutive months or the development of precipitating serum antibodies against *P aeruginosa* or both (*see* Description of the condition for other definitions of chronic infection) (Valerius 1991). There were two primary outcomes in the Treggiari trial, time to pulmonary exacerbation requiring IV antibiotics and proportion of *P aeruginosa* positive cultures over the 18-month trial period (Treggiari 2011).

Other measured outcomes included less severe pulmonary exacerbations, *Pseudomonas* antibody levels, lung function, nutritional status, modified Shwachman score and monitoring for adverse clinical and microbiological effects.

Excluded studies

We excluded 50 trials from our analysis for a number of reasons. Three trials were excluded because therapy was not randomised (Gibson 2007; Postnikov 2000; Schelstraete 2010) and one trial was excluded because it was an observational study (Ballman 1998). Four trials were excluded as they did not have a control group (Heinzl 2002; Littlewood 1985; Ratjen 2001a; Steinkamp 1989) and a further five because they used a historical control group (Frederiksen 1997; Griese 2002; Kenny 2009; Taccetti 2005; Vazquez 1993). A total of 23 trials were excluded as they involved participants with chronic *P aeruginosa* infection (Clancy 2013; Coates 2011; Elborn 2015; Flume 2015a; Flume 2015b; Flume 2016; Geller 2011; Goss 2009; Konstan 2010; Konstan 2011; Konstan 2015; Latzin 2008; Lenoir 2007; Mazurek 2012; Oermann 2009; Postnikov 2007; Prayle 2013; Ramsey 1999; Retsch-Bogart 2008; Retsch-Bogart 2009; Steinkamp 2007; Stockmann 2015; Trapnell 2012; Wainwright 2011b). Two trials were excluded as they were designed to evaluate a diagnostic technique for *P aeruginosa* (Brett 1992; Wainwright 2011a). A further two trials were excluded as they evaluated symptomatic rather than eradication treatment (Church 1997; Schaad 1997) and one was of a prophylactic antibiotic regimen to prevent infection with *P aeruginosa* (Tramper-Stranders 2009). Seven trials looked at pharmacokinetics and drug tolerability (Alothman 2002; Alothman 2005; Geller 2007; Rietschel 2009; Ruddy 2013; Stass 2013; Schuster 2013) and the final trial was excluded as it looked at antibiotic sinonasal nebulisation aiming to eradicate from the sinuses only (Mainz 2014).

Studies awaiting assessment

One single-centre, randomised, prospective trial is currently awaiting assessment (Noah 2010). The trial enrolled children with CF (stable disease) and positive surveillance cultures for *P aeruginosa*. Investigators compared twice-daily nebulised tobramycin (300 mg) for four weeks or intravenous ceftazidime with tobramycin for two weeks at standard weight-adjusted doses.The primary efficacy endpoint was change in BAL fluid percentage neutrophils from the most affected lobe at bronchoscopy. Secondary outcomes included change in BAL fluid differential cell counts, cytokines and bacterial quantity.

Eight out of 15 participants had a first ever isolate of *P aeruginosa* and their data are eligible to be included in this review; however these outcome data are not published separately and we have contacted the lead author for them.

Ongoing studies

Two trials are listed as ongoing (Ratjen 2016; TORPEDO Trial).

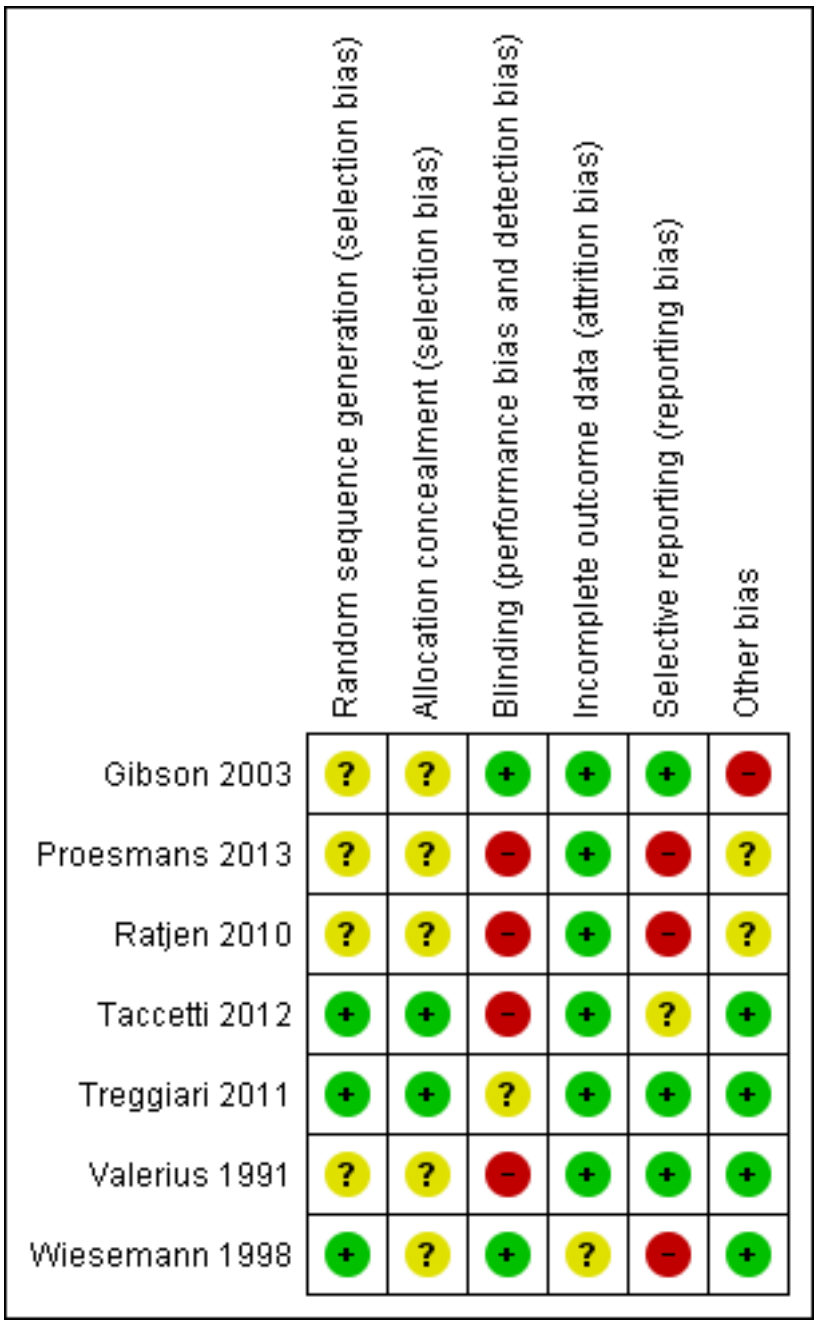
Ratjen is conducting a randomised, double-Blind, placebo-controlled trial in several centres in Europe and Canada (Ratjen 2016). The aim is to enrol 50 participants with CF (males and females) aged three months to six years who have an early lower respiratory tract infection with *P aeruginosa.* The trial will compare twice-daily TOBI to twice-daily placebo (0.9 % saline) for 28 days. The primary outcome is the proportion of participants who are *P aeruginosa*-free at Day 29. Secondary outcome measures include remaining *P aeruginosa*-free at three months. The trial is being sponsored by Novartis Pharmaceuticals.

The TORPEDO Trial (Trial of Optimal Therapy for Pseudomonas Eradication in Cystic Fibrosis) is a multicentre randomised trial of parallel design (TORPEDO Trial). Participants with CF older than 28 days are eligible for enrolment and should have isolated *P aeruginosa* either for the first time or after having been *P aeruginosa*-free (i.e. a minimum of four consecutive cough or sputum samples should be *P aeruginosa*-free within a 12-month period. Treatment will commence no later than 21 days from the date of a positive microbiology report for *P aeruginosa* and will compare 10 days IV ceftazidime together with IV tobramycin to three months of oral ciprofloxacin. Both treatment regimens will be in conjunction with three months nebulised colistin. The primary outcome is the successful eradication of *P aeruginosa* infection three months after treatment has started, remaining infection-free through to 15 months after the start of treatment. Secondary outcomes include the time to reoccurrence of the original *P aeruginosa* infection or re-infection with a different genotype of *P aeruginosa*, lung function, oxygen saturation, growth and nutritional status, number of pulmonary exacerbations, hospitalisation (frequency and duration), QoL, adverse events, other sputum or cough microbiology, costs, burden of treatment (carers and participants).

Risk of bias in included studies

Please see further information in the risk of bias sections of the tables (Characteristics of included studies) and the graphical risk of bias summary (Figure 1).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All seven trials were described as randomised controlled trials; in four, the method of generation of allocation sequence was not stated; hence the trials are judged to have an unclear risk of bias (Gibson 2003; Proesmans 2013; Ratjen 2010; Valerius 1991). The remaining three trials are judged to have a low risk of bias (Taccetti 2012; Treggiari 2011; Wiesemann 1998). In the first of these, Taccetti describes a balanced randomisation sequence that was created using statistical software using permuted blocks of size 10 (Taccetti 2012). Treggiari employed a computer random number generator to assign treatments within permuted blocks of 12 (Treggiari 2011). In the Wiesemann trial, the allocation sequence was generated using a coin flip (Wiesemann 1998). There is no information as to who was responsible for the coin flip or what controls were in place

to ensure validity of the result of the coin flip; however we have still judged this to have a low risk of bias.

In five trials it was not reported how allocation was concealed and we judged these to have an unclear risk of bias (Gibson 2003; Proesmans 2013; Ratjen 2010; Valerius 1991; Wiesemann 1998). In the Taccetti trial, the staff involved in randomisation and in treatment assignments were "kept separate" and we judged this trial to have a low risk of selection bias (Taccetti 2012). In the Treggiari trial, randomisation was remote and so allocation was concealed (Treggiari 2011).

Blinding

Two trials were reported as double-blind trials (Gibson 2003; Wiesemann 1998). Gibson did not provide any details in the published paper regarding who was blinded or the method of blinding (Gibson 2003). However, in response to a request for further information, Dr Gibson confirmed that drugs and placebo were sufficiently masked that neither participants or clinicians were able to differentiate between them. Wiesemann reported that participants were blinded by providing a placebo inhalation with a similar taste to the treatment inhalation, but it is not clear whether the clinicians administering the treatment were blinded to treatment allocation; however, we still judged this to have a low risk of bias (Wiesemann 1998).

In the Treggiari trial, the oral ciprofloxacin treatment was blinded but the TSI was open label and so we judged this to have an unclear risk of bias (Treggiari 2011).

The remaining four trials did not utilise blinding and were judged to have a high risk of bias (Proesmans 2013; Ratjen 2010; Taccetti 2012; Valerius 1991). The Proesmans trial compared an inhaled intervention to a combination of inhaled and oral treatment, so blinding of participants and clinicians was not possible; there is no information available as to whether the outcome assessors were blinded (Proesmans 2013). The Ratjen trial was open label comparing 28 or 56 days of nebulised therapy and made no attempt at blinding (Ratjen 2010). The Taccetti trial was also open label comparing 28 days of inhaled colistin with 28 days of TSI, both groups also receiving 28 days of oral ciprofloxacin (Taccetti 2012). Valerius compared a combination of inhaled and oral treatment to no treatment, so again blinding of participants and clinicians was not possible and no information is available with regards to the outcome assessors (Valerius 1991).

Incomplete outcome data

Six trials were judged to have a low risk of bias (Gibson 2003; Proesmans 2013; Ratjen 2010; Taccetti 2012; Treggiari 2011; Valerius 1991). Four trials were analysed on an intention-to-treat basis; all four reported data on all participants who were randomised (Gibson 2003; Proesmans 2013; Taccetti 2012; Valerius 1991). In the Ratjen trial, 65 of the 88 randomised participants were included in the primary outcome (time to recurrence of *P. aeruginosa*). A total of 52 participants were prematurely withdrawn from the trial, but these were approximately evenly distributed across the two treatment groups and reasons were given for each withdrawal; we therefore judge there to be a low risk of bias (Ratjen 2010). In the Treggiari trial only two of 306 randomised participants were excluded from the analysis (because they did not receive treatment) (Treggiari 2011).

One trial had an unclear risk of bias (Wiesemann 1998). Five participants withdrew from this trial after randomisation and only baseline data at entry to the trial were presented for these participants; to date we have been unable to obtain further outcome data. The trial was therefore analysed on an available-case basis and we judged it to have an unclear risk of bias (Wiesemann 1998).

Selective reporting

It is current practice for newer trials to publish a protocol, but we have not been able to locate a published protocol for the Taccetti trial and have therefore judged this trial to have an unclear risk of bias (Taccetti 2012).

We judged three trials to have a high risk of bias (Proesmans 2013; Ratjen 2010; Wiesemann 1998). Although a protocol for the Proesmans trial was available online and we were able to confirm from the full paper that all outcomes from the protocol were measured, the paper did not provide actual data for BMI z score, weight z score or frequency of exacerbations and simply reported that none of these changed significantly for trial participants (Proesmans 2013). Ratjen reported that there were no major short-term (at three months) or long-term (at 27 months) changes in spirometry, but did not record the figures for either of the two groups. In addition, only summary statements and no numerical data were provided for weight, height or BMI (Ratjen 2010). Wiesemann reported no change in spirometric pulmonary function during or after the treatment period, but again no data were given (Wiesemann 1998).

We judged three trials to have a low risk of bias from selective reporting (Gibson 2003; Treggiari 2011; Valerius 1991). The trial protocol for the EPIC trial was published as a separate paper; primary and secondary outcome measures were clearly described in the protocol and data on all of these outcomes were presented in either the main paper, related papers or in the online supplement (Treggiari 2011). We have compared the 'Methods' sections of the reports from the remaining trials with the 'Results' sections of the same and have not found any evidence of selective reporting (Gibson 2003; Valerius 1991).

Other potential sources of bias

We judged one trial to have a high risk due to other potential sources of bias (Gibson 2003). The Gibson trial planned to recruit to a sample size of 98 participants, but was stopped early by the Data Monitoring Committee after interim analysis of the first 21 participants showed a statistically significant microbiological effect in favour of the tobramycin-treated group (Gibson 2003). This trial was supported in part by Chiron, the manufacturer of the inhaled tobramycin (Gibson 2003).

We judged the Ratjen trial to have an unclear risk due to other potential sources of bias (Ratjen 2010). This trial recruited fewer participants than planned, the total number of planned randomised participants was 100, but 35 from the recruited cohort of 123 were not randomised: 31 because of high *P aeruginosa* antibody levels (which led the investigators to believe that they were chronically infected with *P aeruginosa*); one for an adverse event; one where consent was withdrawn; one for a protocol deviation; and one 'other' (unspecified) reason (Ratjen 2010). Therefore the trial investigators actually randomised 88 participants and the primary outcome was evaluable in 65 of

these (Ratjen 2010). The trial results cannot be generalised to a population where anti-*Pseudomonas* antibodies are not measured. Furthermore, like the earlier Gibson trial, this trial was initially supported by Chiron and later Novartis Pharma, the manufacturer of TSI (Ratjen 2010).

The Proesmans study was judged to have an unclear risk of bias in view of the different time-points at which the primary outcome was measured - at 28 days in the inhaled tobramycin group and three months in the colistin with ciprofloxacin group (Proesmans 2013).

In four trials no other potential source of bias was identified and these were judged to have a low risk of bias (Taccetti 2012; Treggiari 2011; Valerius 1991; Wiesemann 1998).

Effects of interventions

See: **Summary of findings for the main comparison** Inhaled tobramycin compared with placebo; **Summary of findings 2** Oral ciprofloxacin and inhaled colistin compared with no treatment; **Summary of findings 3** Oral ciprofloxacin and inhaled colistin compared to inhaled tobramycin; **Summary of findings 4** Inhaled tobramycin (28 days) compared with inhaled tobramycin (56 days); **Summary of findings 5** Inhaled colistin plus oral ciprofloxacin compared to inhaled tobramycin plus oral ciprofloxacin; **Summary of findings 6** Cycled inhaled tobramycin compared to culture-based inhaled tobramycin; **Summary of findings 7** Ciprofloxacin compared to placebo added to cycled and culture-based inhaled tobramycin therapy

Inhaled tobramycin versus placebo

This comparison included two trials with 43 participants (Gibson 2003; Wiesemann 1998).

Primary outcome

1. Eradication of *P aeruginosa* from the respiratory tract

a. Clearance of P aeruginosa from BAL, sputum or oropharyngeal cultures

The intervention (inhaled tobramycin) was given in a very different dose in the Wiesemann trial (80 mg twice daily) compared to the Gibson trial (300 mg twice daily) (Gibson 2003; Wiesemann 1998). In the Gibson trial, significantly fewer children who received TSI had a positive BAL at one month, OR 0.01 (95% CI 0.00 to 0.30), but not at two months (Analysis 1.1). Results were not available for all the participants in the Wiesemann trial, thereby precluding an intention-to-treat analysis (Wiesemann 1998). Wiesemann was able to demonstrate a statistically significant reduction in the odds of a positive culture from the respiratory tract specimen at 2 months, OR 0.10 (95% CI 0.01 to 0.90); six months, OR 0.06 (95% CI 0.00 to 0.92); and 12 months of treatment, OR 0.02 (95% CI 0.00 to 0.67) but not at one or three months (Analysis 1.2). An available-case analysis of the data presented in the Wiesemann trial showed that, when combined with the data from the Gibson trial, there was a statistically significant reduction in the odds of a positive culture in the treatment group compared to the placebo group both at one month, OR 0.06 (95% CI 0.01 to 0.33); and two months, OR 0.15 (95% CI 0.03 to 0.65) (Analysis 1.3).

A sensitivity analysis following imputation of the missing data to provide best-case and worst case-scenarios for the combined analysis showed a range of possible results. The best-case scenario showed a reduction in the odds of a positive culture of *P aeruginosa* in the treatment group at both one month, OR 0.06 (95% CI 0.01 to 0.30); and two months, OR 0.14 (95% CI 0.03 to 0.60) (Analysis 1.4). Furthermore, these imputed data also showed a significant difference in favour of tobramycin at six months, OR 0.04 (95% CI 0.00 to 0.48) and 12 months, OR 0.01 (95% CI 0.00 to 0.26), but not at three months (Analysis 1.4). In the worst-case scenario the odds of a positive culture was reduced at one month, OR 0.08 (95% CI 0.02 to 0.38) and two months, OR 0.18 (95% CI 0.04 to 0.73), but was not statistically significant for Wiesemann alone at three, six or 12 months (Analysis 1.5).

b. Time to next isolation of P. aeruginosa from BAL, sputum or oropharyngeal cultures

Neither trial assessed or reported on this outcome.

Secondary Outcomes

1. Mortality

Mortality was not included as an outcome in either trial, but there were no reported deaths during any of the trial periods (Gibson 2003; Wiesemann 1998).

2. Quality of life

Neither trial assessed or reported on this outcome.

3. Spirometric lung function

Wiesemann reported no change in spirometric pulmonary function during or after the treatment period, but no data were given (Wiesemann 1998). Gibson did not assess or report on spirometric lung function; most of the participants in this trial were too young to perform spirometry reliably (Gibson 2003).

4. Growth and nutritional status

Only the trial by Gibson presented data on weight (kg) (Gibson 2003). There was no significant difference found between the two groups in the change in weight from baseline (trial entry) and subsequent weights measured at one month and two months (Analysis 1.6).

5. Frequency of respiratory exacerbations

Neither trial assessed or reported on this outcome.

6. Isolation of other micro-organisms

Gibson reported no changes in the prevalence of other micro-organisms, including multi-resistant organisms, cultured from respiratory secretions (Gibson 2003). Wiesemann did not collect data on this outcome (Wiesemann 1998).

7. Adverse effects of antibiotics

Gibson reported cough in association with inhalation in seven out of eight participants in the treatment group and in 12 out of 13 in the placebo group, but this result was not statistically significant (Analysis 1.7) . There was no evidence of a difference in serum creatinine levels or auditory threshold between the groups, however the numbers of participants was small (Gibson 2003). Wiesemann reported one withdrawal from the placebo group because of cough, however the authors did not report on the presence or absence of cough in other participants (Wiesemann 1998).

Additional outcomes which have arisen during the review

1. Time to chronic infection

Neither trial assessed or reported on this outcome.

2. Clinical and radiological scores

Only the Gibson trial reported modified Shwachmann scores, which were recorded at one month and two months from enrolment and were expressed as both mean scores with SDs and mean change from baseline with SDs (Gibson 2003). There were no significant differences between the two groups in changes in either mean scores or modified Schwachman scores from baseline at either one month or two months (Analysis 1.8).

3. Cost

Neither trial reported a health economic analysis.

Oral ciprofloxacin and inhaled colistin versus no treatment

This intervention included only one trial with 26 participants (Valerius 1991).

Primary outcome

1. Eradication of P aeruginosa from the respiratory tract

a. Clearance of P aeruginosa from BAL, sputum or oropharyngeal cultures

The included trial did not report on this outcome.

b. Time to next isolation of P aeruginosa from BAL, sputum or oropharyngeal cultures

The included trial did not report on this outcome.

Secondary Outcomes

1. Mortality

The included trial did not report on this outcome.

2. Quality of life

The included trial did not report on this outcome.

3. Spirometric lung function

The included trial did not report on this outcome.

4. Growth and nutritional status

The included trial did not report on this outcome.

5. Frequency of respiratory exacerbations

The included trial did not report on this outcome.

6. Isolation of other micro-organisms

The included trial did not report on this outcome.

7. Adverse effects of antibiotics

Valerius did not describe cough specifically, but reported that there were no adverse effects in either group (Valerius 1991).

Additional outcomes which have arisen during the review

1. Time to chronic infection

We defined this as the presence of *P aeruginosa* in each monthly sputum sample for six consecutive months or the presence of precipitating antibodies to *P aeruginosa* or both. From the data provided for the Valerius trial, it was possible to calculate the proportion of participants in each group who were defined as chronically infected with *P aeruginosa* from respiratory secretions at 3, 6, 12 and 24 month time points (Valerius 1991). The odds of being chronically infected with *P aeruginosa* were reduced in the treatment group compared to the placebo group after 24 months, OR 0.12 (95% CI 0.02 to 0.79) (Analysis 2.1). No significant difference was detected between the two groups at the other time points. No other trials in the review used this outcome measure to express their findings.

2. Clinical and radiological scores

The included trial did not report on this outcome.

3. Cost

The Valerius trial did not include a health economic analysis.

Oral ciprofloxacin and inhaled colistin versus inhaled tobramycin

This intervention comparing oral ciprofloxacin and inhaled colistin (three months) with inhaled tobramycin (28 days) included only one trial including 58 participants (29 in each treatment group) (Proesmans 2013).

Primary outcome

1. Eradication of P aeruginosa from the respiratory tract

a. Clearance of P aeruginosa from BAL, sputum or oropharyngeal cultures

At some point in the six months following treatment, *P aeruginosa* was isolated in 10 out of 29 participants enrolled to the inhaled colistin with oral ciprofloxacin arm compared to 16 out of 29 in the TSI arm. The difference between groups was not statistically significant (Analysis 3.1).

b. Time to next isolation of P aeruginosa from BAL, sputum or oropharyngeal cultures

The included trial did not report on this outcome.

Secondary Outcomes

1. Mortality

There were no deaths in either arm (Proesmans 2013).

2. Quality of life

The included trial did not report on this outcome.

3. Spirometric lung function

The median change from baseline in FEV_1 (% predicted) for all the participants was -1%. The changes are not reported separately for each treatment arm (Proesmans 2013).

4. Growth and nutritional status

Both BMI z score and weight z score were reported not to have changed significantly for trial participants as a whole, but numerical data are not reported (Proesmans 2013).

5. Frequency of respiratory exacerbations

The authors report that, during the first six months of follow up, there was no difference between the two treatment arms in number of oral antibiotic treatment days. These oral antibiotics were given for symptoms and not because of failed eradication. However, numerical data are not reported (Proesmans 2013).

6. Isolation of other micro-organisms

The included trial did not report on this outcome.

7. Adverse effects of antibiotics

One participant is reported to have developed a severe cough with TSI, but this result was not statistically significant (Analysis 3.2). No other adverse effects are reported.

Additional outcomes which have arisen during the review

1. Time to chronic infection

The included trial did not report on this outcome.

2. Clinical and radiological scores

The included trial did not report on this outcome.

3. Cost

The included trial did not include a health economic analysis.

Inhaled tobramycin (28 days) versus inhaled tobramycin (56 days)

This intervention comparing 28 days TSI with 56 days TSI included one trial of 123 participants, of whom 88 were randomised (Ratjen 2010).

Primary outcome

1. Eradication of P aeruginosa from the respiratory tract

a. Clearance of P aeruginosa from BAL, sputum or oropharyngeal cultures

This outcome was not evaluated; data are presented in the paper at one month when participants were all given the initial 28 days of TSI before randomisation and were excluded if they had raised anti *P aeruginosa* antibody levels (Ratjen 2010).

b. Time to next isolation of P aeruginosa from BAL, sputum or oropharyngeal cultures

The median time to recurrence was 26.12 months in the 28-day treatment group and 25.82 months in the 56-day treatment group. Differences between groups were not significant (Analysis 4.1).

Secondary Outcomes

1. Mortality

There were no deaths reported (Ratjen 2010).

2. Quality of life

The included trial did not report on this outcome.

3. Spirometric lung function

The paper presented data in a table for the median change from baseline to three months and to 27 months for FEV_1 % predicted, FVC % predicted and FEF_{25-75} % predicted; however, reported data were combined for both the 28-day and the 56-day treatment groups. The paper states that there were "no major short- or long-term changes in spirometric parameters observed during the study period" (Ratjen 2010).

4. Growth and nutritional status

No significant differences in weight, height or BMI were reported. Only a summary statement was presented, indicating that the no significant difference was found in weight, height or BMI and no data were provided (Ratjen 2010).

5. Frequency of respiratory exacerbations

Two participants allocated to the 56-day treatment group were hospitalised on one occasion, each for a pulmonary exacerbation. One of these isolated *P aeruginosa* and was treated with IV ceftazidime and tobramycin. When entered into the analysis this gave a non-significant result (Analysis 4.2).

6. Isolation of other micro-organisms

There were no consistent trends reported in the isolation of non-*P aeruginosa* organisms (one isolate only of *Stenotrophomonas maltophilia* (*S maltophilia*) which was seen in the 28-day arm).

7. Adverse effects of antibiotics

Adverse events up to three months that were considered possibly or probably related to treatment were reported by 14 participants in each treatment group, with the majority being related to dysphonia in both treatment groups (11% and 14%, respectively) and cough in the 28-day group (9%). There were no significant differences between treatment groups for any of the reported adverse events at any time-point; however we note that given the number of different events measured and the increased probability of type I statistical error and spurious group differences, numerical results of these two analyses must be carefully interpreted (Analysis 4.3; Analysis 4.4).

Additional outcomes which have arisen during the review

1. Time to chronic infection

The included trial did not report on this outcome.

2. Clinical and radiological scores

The included trial did not report on this outcome.

3. Cost

The included trial did not have a health economic analysis.

Inhaled colistin plus oral ciprofloxacin versus inhaled tobramycin plus oral ciprofloxacin

This comparison of inhaled colistin plus oral ciprofloxacin with inhaled tobramycin plus oral ciprofloxacin included one trial with 223 participants (Taccetti 2012).

Primary outcome

1. Eradication of P aeruginosa from the respiratory tract

a. Clearance of P aeruginosa from BAL, sputum or oropharyngeal cultures

In the inhaled colistin plus oral ciprofloxacin group, *P aeruginosa* was isolated within the first six months from 39 out of 105 participants (37.1%) and in the the inhaled tobramycin plus oral ciprofloxacin group from 41 out of 118 participants (34.7%) (Taccetti 2012). When data were analysed, the rate of isolation of *P aeruginosa* between the two arms was not significantly different (Analysis 5.1). At a median follow-up period of 16 months, *P aeruginosa* had been isolated from 36 out of 97 participants in the colistin with ciprofloxacin arm for whom data were available and from 24 out of 108 participants in the tobramycin with ciprofloxacin arm; the two arms were not significantly different. The trial authors report that subgroup analyses by gender, age (one to five years; five to 12 years and over 12 years), lung function (FEV_1 less than or greater than 70%) and participants with first ever isolation of *P aeruginosa* failed to show any significant differences between groups (Taccetti 2012).

b. Time to next isolation of P aeruginosa from BAL, sputum or oropharyngeal cultures

The trial did not report on this outcome.

Secondary Outcomes

1. Mortality

No deaths were reported (Taccetti 2012).

2. Quality of life

The trial did not report on this outcome.

3. Spirometric lung function

Following treatment, after a mean (SD) time of observation of 54 (39) days, the mean (SD) relative change in FEV_1 % predicted from baseline was 2.15 (8.50)% in the inhaled colistin plus oral ciprofloxacin group compared to 4.55 (11.54)% in the the inhaled tobramycin plus oral ciprofloxacin group (not statistically significant) (Analysis 5.2).

4. Growth and nutritional status

The trial did not report these outcomes.

5. Frequency of respiratory exacerbations

The trial did not report this outcome.

6. Isolation of other micro-organisms

There was an observation that *S maltophilia* was isolated more frequently in the follow-up period than before eradication treatment. There were no differences during follow up between the two groups for isolation of: *S maltophilia, Achromobacter xylosoxidans* or *Aspergillus* species (Analysis 5.3).

7. Adverse effects to antibiotics

There were a total of 38 out of 223 randomised participants (17%) who discontinued treatment early; of these 17 were from the inhaled colistin plus oral ciprofloxacin group and 21 from the inhaled tobramycin plus oral ciprofloxacin group (Analysis 5.4). There were a number of reasons for these discontinuations including vomiting, photosensitivity, wheeze and pulmonary exacerbation.

Additional outcomes which have arisen during the review

1. Time to chronic infection

The trial did not report on this outcome.

2. Clinical and radiological scores

The trial did not report on this outcome.

3. Cost

A health economic analysis was not undertaken in the included trial.

Cycled inhaled tobramycin versus culture-based inhaled tobramycin

This comparison of cycled inhaled tobramycin (with oral ciprofloxacin or placebo) with culture-based inhaled tobramycin (with oral ciprofloxacin or placebo) included one trial, with 306 participants randomised and data analysed on 304 participants who received treatment (Treggiari 2011).

Primary outcome

1. Eradication of *P aeruginosa* from the respiratory tract

a. Clearance of P aeruginosa from BAL, sputum or oropharyngeal cultures

Treggiari reported 43 out of 148 children on cycled therapy had one or more isolates of *P aeruginosa* compared to 67 out of 150 children on culture-based therapy giving a statistically significant effect in favour of cycled therapy, OR 0.51 (95% CI 0.31 to 0.82) (Analysis 6.1). The main trial publication reports an age-adjusted OR, using generalised estimating equations, with robust variance, specifying a logit link and assuming an independence working correlation (Treggiari 2011). This may explain the difference between the trial publication and the findings of this review.

b. Time to next isolation of P aeruginosa from BAL, sputum or oropharyngeal cultures

This was not reported in the included trial.

Secondary Outcomes

1. Mortality

No deaths were reported in either arm (Treggiari 2011).

2. Quality of life

This outcome was not reported in the included trial.

3. Spirometric lung function

The included trial reports the mean 70-week change in FEV_1 % predicted, but the mean difference between the two arms was not significant (Analysis 6.2).

4. Growth and nutritional status

The Treggiari trial reports the mean 70-week change from baseline in weight (kg) for each treatment arm, but the MD between arms was not significant (Analysis 6.3). The trial also reports data for the

change from baseline in height (cm) for each arm at the same time point; again the MD between arms was not significant (Analysis 6.4).

5. Frequency of respiratory exacerbations

A primary outcome in the Treggiari trial was the time to a severe pulmonary exacerbation (i.e. an exacerbation requiring IV antibiotics or hospitalisation or both) (Treggiari 2011). The analysis shows no significant difference in time to a severe exacerbation (Analysis 6.5).

Data on the frequency of severe exacerbations, during the 70-week follow-up period, are also presented in the paper. From our analysis, the data indicate no significant difference between groups (Analysis 6.6).

Treggiari also reported a secondary outcome of time to pulmonary exacerbation of any severity (including any exacerbation treated with IV, inhaled or oral antibiotics or requiring hospitalisation). The results of our analysis are slightly different to those reported in the paper, but still show no statistically significant difference in time to any exacerbation (Analysis 6.7).

Finally, the number of exacerbations of any severity was also reported. In our analysis, the OR was not significantly different between cycled and culture-based therapy (Analysis 6.8).

6. Isolation of other micro-organisms

The Treggiari trial reported the number of participants in each arm with one or more isolates of the emerging pathogen *S maltophilia* (Treggiari 2011). There was no significant difference between cycled and culture-based therapy (Analysis 6.9).

7. Adverse effects to antibiotics

With regards to the incidence of serious adverse effects, Treggiari did not report any significant difference between treatment arms, although adverse events attributable to antibiotic therapy were not recorded separately from adverse events which were unlikely to be related to the study intervention (Treggiari 2011). Our results were also not statistically significant (Analysis 6.10).

Additional outcomes which have arisen during the review

1. Time to chronic infection

This was not reported in the one included trial.

2. Clinical and radiological scores

These outcomes were not reported in the one included trial.

3. Cost

A health economic analysis was not undertaken in the one included trial.

Ciprofloxacin *versus* placebo added to cycled and culture-based inhaled tobramycin therapy

As discussed under Description of studies, the Treggari trial randomised participants to cycled versus culture-based inhaled tobramycin therapy and then to oral ciprofloxacin versus placebo for two weeks with each 28-day course of TSI (Treggiari 2011). This section presents the comparison of outcomes in the ciprofloxacin and placebo arms.

Primary outcome

1. Eradication of *P aeruginosa* from the respiratory tract

a. Clearance of P aeruginosa from BAL, sputum or oropharyngeal cultures

Treggiari reported that 49 out of 146 children on oral ciprofloxacin had one or more isolates of *P aeruginosa* compared to 55 out of 150 children on placebo (Treggiari 2011). The data for this outcome show a non-statistically significant effect (Analysis 7.1). Age group–adjusted ORs are reported in the trial paper; in our analysis, we did not adjust for age.

b. Time to next isolation of P aeruginosa from BAL, sputum or oropharyngeal cultures

This was not reported in the included trial.

Secondary Outcomes

1. Mortality

No deaths were reported in either arm (Treggiari 2011).

2. Quality of life

This outcome was not reported in the included trial.

3. Spirometric lung function

The included trial reports the mean 70-week change in FEV_1 % predicted, but the MD between the two arms was not significant (Analysis 7.2).

4. Growth and nutritional status

The Treggiari trial reports the mean 70-week change from baseline in weight (kg) for each treatment arm; the MD between arms was not significant (Analysis 7.3). The trial also reports data for the change from baseline in height (cm) for each arm; again the MD between arms was not significant (Analysis 7.4).

5. Frequency of respiratory exacerbations

A primary outcome in the Treggiari trial was the time to a severe pulmonary exacerbation (i.e. an exacerbation requiring IV antibiotics or hospitalisation, or both) (Treggiari 2011). Again, for the ciprofloxacin versus placebo comparison, there was no significant difference in time to a severe exacerbation (Analysis 7.5).

Data on the frequency of severe exacerbations, during the 70-week follow-up period, are also presented in the paper. From our analysis, the OR is not significantly different between groups (Analysis 7.6).

We analysed the outcome 'time to pulmonary exacerbation (any severity)', including any exacerbation treated with IV, inhaled or oral antibiotics or requiring hospitalisation (Analysis 7.7). There was no difference between ciprofloxacin and placebo in time to exacerbation (any severity).

Finally, the number of exacerbations of any severity was not significantly different between ciprofloxacin and placebo (Analysis 7.8).

6. Isolation of other micro-organisms

In the Treggiari trial, there was no significant difference between ciprofloxacin and placebo in the number of isolates of *S maltophilia* (Analysis 7.9).

7. Adverse effects to antibiotics

Treggiari did not report any significant difference between treatment arms in the incidence of adverse events, although adverse events attributable to antibiotic therapy were not recorded separately from adverse events which were unlikely to be related to the trial intervention (Treggiari 2011). Our analysis showed no difference between arms in the number of participants with one or more serious adverse events (Analysis 7.10).

Additional outcomes which have arisen during the review

1. Time to chronic infection

This was not reported in the one included trial.

2. Clinical and radiological scores

These outcomes were not reported in the one included trial.

3. Cost

A health economic analysis was not undertaken in the one included trial.

DISCUSSION

Summary of main results

Our review includes seven trials (with data from 744 participants) of antibiotic strategies for the eradication of *Pseudomonas aeruginosa* (*P aeruginosa*) infection in cystic fibrosis (CF), conducted over a period of over 20 years. Each trial used a different intervention and only two trials could be combined in a meta-analysis of the same treatment comparison. An early interim analysis was performed due to slow accrual in one trial (Gibson 2003).

Cumulative data from 43 participants in two of the seven included trials indicate that *P aeruginosa* was more frequently eradicated from the respiratory secretions in the participants receiving antibiotics than from those receiving placebo (Gibson 2003; Wiesemann 1998). This reduction in the number of isolates of *P aeruginosa* was noted at both one month and two months after the start of treatment. A further trial suggests that the onset of chronic infection with *P aeruginosa* is delayed in those individuals who have received antibiotic therapy compared to those receiving no therapy (Valerius 1991). There was evidence from the trials by Valerius and Wiesemann that this effect may persist for up to 24 months (Valerius 1991; Wiesemann 1998). We found no difference in adverse events. In two trials, an increased incidence of the emerging pathogen *S maltophilia* was reported following treatment, but no difference was found between eradication regimens in either of these trials (Taccetti 2012; Treggiari 2011) .

The trial by Proesmans, which randomised 58 participants, was associated with a low rate of short-term eradication of *P aeruginosa* from both groups of children treated with nebulised high-dose tobramycin and a combination of oral ciprofloxacin with inhaled colistin (Proesmans 2013). The numbers of participants in each group were too low to allow comparisons of superiority between the two eradication regimens to be made. A further possible cause of the low eradication rate in this trial may be that participants were recruited if they had been free of *P aeruginosa* for at least six months (with negative microbiology samples for at least six months), which is shorter than the 12-month *P aeruginosa*-free interval used by the Leeds definition of '*Pseudomonas*-free' (Lee 2003).

The Ratjen trial (n = 88) ran from November 2003 until January 2008 and has reported both 28-day and 56-day treatment with inhaled tobramycin to be effective and safe; with no additional advantage to 56 days of therapy over 28 days (Ratjen 2010). The authors of this trial concluded that head-to-head comparisons will clarify whether adding either oral ciprofloxacin or IV antibiotic therapy can further increase treatment success in people with CF with early *P aeruginosa* infection.

The Taccetti trial randomised 223 participants and failed to demonstrate superiority of inhaled tobramycin with oral ciprofloxacin over inhaled colistin with oral ciprofloxacin, both treatments given over 28 days (Taccetti 2012). As in the Ratjen trial, the included participants had been free of *P aeruginosa* for at least six months, again at variance with the Leeds definition of *Pseudomonas*-free (Lee 2003).

The Treggiari trial was the largest trial of *P aeruginosa* eradication in CF reported so far randomising 306 children (aged 1 to 12 years) and reporting data on 304 children (Treggiari 2011). The trial used a complex, four-arm design, comparing cycled with culture-based treatment with TSI and also additional oral ciprofloxacin versus placebo. The trial was adequately powered for its two primary outcome measures (time to severe pulmonary exacerbation and proportion of *P. aeruginosa* positive cultures) and found no difference between arms for either outcome. In contrast, our analysis (which was not corrected for age) did find a significant difference in the proportion of *P aeruginosa* positive cultures in favour of cycled therapy. There was no difference between ciprofloxacin and placebo for this outcome.

No deaths were reported in any of the trials.

Overall completeness and applicability of evidence

The aim of antibiotic therapy for early *P aeruginosa* infection in CF should be both eradication of the micro-organism and improvement in (or slowing in the rate of decline of) clinical parameters, whilst minimising adverse effects and the isolation of new micro-organisms. If *P aeruginosa* is successfully eradicated, but there is no measurable clinical benefit, it is likely that current measures of clinical status are not sufficiently sensitive or that the duration of follow up is too short to show a difference.

There are differences in the type and dose of drug administered to the treatment groups in the two trials where nebulised tobramycin was compared to placebo. In the Wiesemann trial, tobramycin injectable solution was administered by nebuliser, at a low dose (80 mg twice daily) for a long duration (12 months) (Wiesemann 1998); whereas Gibson used TSI TOBI® (now marketed by Novartis) at a high dose (300 mg twice daily) for a short duration (28 days) (Gibson 2003). This is a potential source of heterogeneity between the trials. It is of interest that significant heterogeneity was detected between the trials at the one-month time point but this was not detected at the two-month time point.

The Proesmans and Taccetti trials included participants who were *Pseudomonas*-naive and those that had not isolated *P aeruginosa* for at least six months (Proesmans 2013; Taccetti 2012), which is at variance with the 12-month definition proposed by Lee to define a person as '*Pseudomonas*-free' (Lee 2003). It was not possible for the authors of this review to extract IPD for those participants who fit this longer definition of *Pseudomonas*-free. The Treggiari trial required participants to have been free of *P aeruginosa* for at least two years (Treggiari 2011).

Eradication of isolates of *P aeruginosa* is easiest in people with CF with recent onset of *P aeruginosa* infection of the respiratory tract, in particular in those who have non-mucoid isolates of *P aeruginosa* as they seem particularly susceptible to antibiotic therapy. Two trials included in this review have recruited adults suggesting that early *P aeruginosa* infection can be eradicated from adults as well as from children and therefore adults should be included in future studies.

Finally, it should be noted that some of the trials were conducted between 10 and 20 years ago and the results may be less applicable to people with CF today.

Quality of the evidence

The quality of the trials was variable with important deficiencies identified in some. For example, in four out of the seven included trials we judged there to be a high risk from a lack of blinding of participants and clinicians; in two of these trials the different interventions used in the treatment and control groups precluded blinding (Proesmans 2013; Valerius 1991) and two trials were open label and no attempt was made at blinding. We also judged there to be a high risk of bias due to selective reporting in three of the trials, which only reported summary statements with no actual data for a number of outcomes (Proesmans 2013; Ratjen 2010; Wiesemann 1998).

While we generally judged there to be a low risk of bias due to incomplete outcome data, there was incomplete follow up of a number of participants in one of the older and smaller trials (Wiesemann 1998). The absence of these data has complicated the combined analysis of the two trials that compare inhaled tobramycin with placebo (Gibson 2003; Wiesemann 1998); one trial was analysed on an intention-to-treat basis (Gibson 2003) and another on an available-case basis (Wiesemann 1998). A sensitivity analysis based on best- and worst-case scenarios demonstrated similar results to the available-case analysis. The available-case analysis revealed a reduction in the odds of a positive culture for *P aeruginosa* in the group treated with tobramycin inhalation when compared to the odds in the placebo group at both one and two months from the start of treatment (Wiesemann 1998).

The Gibson trial was stopped early because of evidence of significant treatment effect (Gibson 2003). It has been suggested that the results of randomised controlled trials stopped early for benefit should be interpreted with caution particularly when the number of events is small (Montori 2005).

In the Ratjen trial, the authors wished to enrol 120 participants in order to randomise 100 participants. They succeeded in recruiting 123 individuals of whom 88 were randomised and 65 could be included in the analysis of the primary outcome (time to recurrence of *P aeruginosa*). This trial is potentially subject to bias because of the exclusion of non-randomised individuals, including 31 people in whom there were elevated antibody titres to *P aeruginosa* (Ratjen 2010).

The relationship between the presence of *P aeruginosa* in secretions from the upper respiratory tract and the isolation of *P aeruginosa* from the lower respiratory tract is inconsistent. Reporting of the presence of organisms in respiratory secretions is difficult to standardise, dependent on the sampling methods used and on the number of samples taken. The trials included in this review used a heterogeneous mix of methods to sample respiratory secretions from both the lower and upper respiratory tracts. No two trials used the same methods and more than one method was used in two trials. There was no subgroup analysis based on sampling method in any of the trials, probably owing to relatively small numbers of participants in individual trials. Wiesemann used a combination of oropharyngeal swabs and sputum samples, whereas Gibson used oropharyngeal swabs and BAL fluid (Gibson 2003; Wiesemann 1998). Proesmans used sputum, throat swab and BAL (Proesmans 2013). The Taccetti study did not describe the technique used for culture collection (Taccetti 2012). The Treggiari trial enrolled younger children and used oropharyngeal swabs or sputum samples (Treggiari 2011). Armstrong has shown that the results of oropharyngeal specimens are poorly predictive of the presence of organisms in the lower respiratory tract (Armstrong 1996). Valerius relied on sputum samples which can be of poor quality in younger children (Valerius 1991).

The quality of evidence ranged from moderate to very low, based on GRADE criteria (see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7).

Potential biases in the review process

The original review stated that trials would be included only where eradication begins within two months of isolation of *P aeruginosa*. In a post hoc change, this has now been altered to include those where eradication has been initiated up to six months since isolation. Whilst prompt treatment of new *P aeruginosa* infection is recommended (Smyth 2014), there is no robust evidence for a specific time limit for initiation of treatment.

The review now also includes patients from two distinct groups, those that are *Pseudomonas*-naive and those that are *Pseudomonas*-free.

Agreements and disagreements with other studies or reviews

We are not aware of any other studies or reviews which recommend specific eradication treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Significantly more children with cystic fibrosis (CF) show clearance of *Pseudomonas aeruginosa* (*P aeruginosa*) from their respiratory secretions up to three months after commencing antibiotic therapy aimed at eradication of the organism from their respiratory tract when compared to placebo. This effect may last for several months. This review has not established any improvement in

clinical outcome measures following treatment. The small numbers of participants in some trials and the short duration of follow up mean that this review may have insufficient statistical power to detect changes in these clinical outcomes. However, there are many observational studies which have shown a decline in clinical status once chronic *P aeruginosa* infection occurs and so clinical benefit from eradication is likely. There was no significant difference in the rate of common adverse effects detected. An increased incidence of the emerging pathogen *Stenotrophomonas maltophilia* (*S maltophilia*) was seen after eradication treatment in two trials, but there was no statistically significant difference between regimens (Taccetti 2012; Treggiari 2011).

We found that nebulised antibiotics (or a combination of nebulised and oral antibiotics) were better than no treatment in treating early infection with *P aeruginosa*, which was eliminated in the majority of individuals. Eradication may be sustained in the short term. We were unable to determine whether there is an associated clinical benefit to people with CF, though data from observational studies suggest that benefit is likely. Overall, there is insufficient evidence from this review to state which antibiotic strategy should be used for the eradication of early *P aeruginosa* infection in CF.

Implications for research

Whilst there is evidence that eradication treatment is more effective than placebo or no treatment, there is no evidence to help the clinician choose which regimen to use. There remains an urgent need for well-designed and well-executed trials, comparing eradication regimens. Where possible these should evaluate whether eradication results in appreciable clinical benefit to people with CF, without causing them harm. Trials should also explore the influence of prior infection with *P aeruginosa* ('*Pseudomonas*-free' compared to '*Pseudomonas*-naive') and whether there is an advantage in early institution of therapy (within weeks rather than within months). This might be accomplished, using a stratified trial design. Consideration should be given to appropriate outcome measures, particularly spirometric lung function, nutritional status, socio-economic outcomes (including quality of life) and duration of follow up. Long-term follow-up trials with careful clinical and bacteriological surveillance are required. These trials will be challenging to design and deliver. Randomisation should include two active treatments that are both believed to be effective and safe and would still need to recruit a sufficient number of participants to show differences in efficacy with adequate power. Adults as well as children should be included in such trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Gibson 2003

Methods	Double-blind RCT. Placebo-controlled. Parallel design. Duration: 28 days. Multicentre based in USA.
Participants	21 participants with a recent positive oropharyngeal culture and isolation of *P aeruginosa* from BAL at study entry. Age: 6 months - 6 years. Gender: 11 males, 10 females.
Interventions	Treatment: Tobramycin solution for inhalation (300 mg 2x daily for 28 days). Control: placebo inhalations.

Gibson 2003 *(Continued)*

Outcomes	Eradication of *P aeruginosa*, nutritional status, modified Shwachman score, adverse effects.
Notes	Oropharyngeal cultures performed at entry and on days 14, 28, 42 and 56 of the study. BAL from the same lobar segment on entry and day 28. Enrolement was discontinued due to an interim analysis, precipitated by poor accrual of participants, which showed a statistically significant microbiological effect of treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as a randomised controlled trial stratified by study centre and age (≦ 36 months; > 36 months), but the method of generation of allocation sequence was not stated.
Allocation concealment (selection bias)	Unclear risk	Did not report how allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Reported as double blind, but paper did not provide any details regarding who was blinded or the method of blinding. We received the following helpful response from trial authors, regarding placebo: Active: Preservative free tobramycin sulfate, 60 mg/mL in 5 mL excipient (1/4 normal saline, pH 6.0) in low density polyethylene plastic ampoules inside a foil pouch (PathoGenesis Corporation). Placebo: 5 mL of vehicle with 1.25 mg of quinine sulfate added as a flavouring agent, packaged identically. PathoGenesis Corporation were responsible for the manufacture of the tobramycin and placebo for inhalation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed on an intention-to-treat basis. Reported data on all participants who were randomised. There were no dropouts reported.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting found.
Other bias	High risk	Study was stopped early by the Data Monitoring Committee after recruitment of 21 from an anticipated 98 participants because of statistically significant treatment effect in favour of the tobramycin group. Study received sponsorship support from Chiron, manufacturer of tobramycin for inhalation as used in the study.

Proesmans 2013

Methods	RCT. Parallel design. Duration: 3 months. Single centre based in Europe.
Participants	58 children with CF, all with new isolation of *P aeruginosa* (sputum or cough swabs).

Proesmans 2013 *(Continued)*

	Age: median age 9 years, interquartile range (4.7 - 13.1 years). Gender: 31 male, 27 female. Lung function: median FEV_1 at inclusion 98% predicted.
Interventions	Treatment (n = 29): Inhaled TSI (300 mg 2x daily for 28 days). Control (n = 29): 3 months combination therapy with inhaled colistin (2 MU 2x daily) + oral ciprofloxacin (10 mg/kg 3x daily).
Outcomes	**Primary outcomes** Eradication of *P aeruginosa* at the end of treatment. **Secondary outcomes** Time to *P aeruginosa* relapse; antibodies (Ab); IgG; FEV_1; BMI; and *P aeruginosa* status at 2-year follow up.
Notes	Participants were then switched to the other arm or treated with IV antibiotics if clinically indicated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised in blocks of 10. No description given of method of randomisation, nor of any stratification.
Allocation concealment (selection bias)	Unclear risk	Did not report how allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding not possible for participants and clinicians as treatments compared were inhaled versus inhaled and oral. No details regarding whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis on all 58 randomised participants.
Selective reporting (reporting bias)	High risk	Protocol published on ClinicalTrials.gov (identifier: NCT01400750). All pre-specified outcomes reported. BMI z score, weight z score and frequency of exacerbations were reported not to have changed significantly for trial participants, but numerical data are not reported.
Other bias	Unclear risk	Primary outcome was assessed at end of treatment which was different for the 2 treatment groups 28 days for TSI participants versus 3 months for colistin/ciprofloxacin participants.

Ratjen 2010

Methods	RCT. Parallel design. Duration: 27 months. Multicentre (21 centres) based in Europe (Germany, France, Spain, Austria, UK, Netherlands).

Ratjen 2010 *(Continued)*

Participants	123 participants with CF free of *P aeruginosa* (88 randomised - 31 participants not randomised because of high *P aeruginosa* antibody titres and 4 for other reasons). Age (mean (SD)): 28-day TIS 8.7 (7.2) years, 56-day TIS 8.7 (10.5) years. Gender: 28-day TIS 26 (58%) males, 19 (42%) females; 56-day TIS 22 (51%) males, 21 (49%) females. Lung function (mean (SD) FEV_1 % predicted): 28-day TIS 80.2 (18.9), 56-day TIS 87.0 (19.2).
Interventions	Group 1 (n = 45): 28 days of tobramycin solution for inhalation (TSI) (300 mg 2x daily), then stopped treatment. Group 2 (n = 43): 28 days of tobramycin solution for inhalation (TSI) (300 mg 2x daily), then randomised to a further 28 days (56 days in total).
Outcomes	**Primary outcome** Median time to recurrence of any strain of *P aeruginosa.* **Secondary outcomes** Proportion of patients free of *P aeruginosa* 1 month after the end of treatment Number and length of hospital admissions for respiratory indications Occurrence of other pathogens Changes in FEV_1, FVC & FEF_{25-75} Weight, height and BMI.
Notes	Also known as ELITE trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no description of randomisation techniques given.
Allocation concealment (selection bias)	Unclear risk	Did not report how allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study, no attempt at blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	65 participants from 88 randomised achieved primary outcome. A total of 52 participants prematurely withdrawn from trial. 27 participants withdrew from the 28-day treatment group with the following reasons: loss to follow up (n = 1); protocol deviation (n = 4); recurrence/non-eradication (n = 21); other (n = 1). 25 participants withdrew from the 56-day treatment group for the following reasons: withdrawn consent (n = 1); loss to follow up (n = 2); protocol deviation (n = 2); recurrence/no eradication (n = 19); abnormal audiology test (n = 1).
Selective reporting (reporting bias)	High risk	Study reports there were no major short- or long-term (3 and 27 months) changes in spirometry, but does not record the figures for either of the 2 groups. Also, only summary statements and no numerical data are provided for weight, height or BMI.

Ratjen 2010 *(Continued)*

Other bias	Unclear risk	Recruited fewer participants than planned; actually randomised 88 participants (primary outcome evaluable in 65) - planned randomisation of 100 participants. Did not randomise 35 participants from the recruited cohort of 123 participants: 31 because of high *P aeruginosa* antibody levels, one for an adverse event, one where consent was withdrawn, one for a protocol deviation and one 'other' (unspecified) reason. Participants with raised antibody levels were not included because the investigators believed that they were chronically infected with *P aeruginosa* based on their antibody results. This trial was initially supported by Chiron and later Novartis Pharma, the manufacturer of TSI.

Taccetti 2012

Methods	RCT. Parallel design. Duration: 28 days. Multicentre (13 centres) in Italy.
Participants	223 participants with first ever or new *P aeruginosa* infection. New infection defined as *P aeruginosa* isolation following bacterial clearance documented by 3 negative cultures within the previous 6 months. Age: over 1 year. Gender: 116 male, 107 female.
Interventions	Group A (n = 105; 52 male and 53 female): 28 days 2x daily inhalation of 2 MU colistin with 2x daily doses of ciprofloxacin 15 mg/kg/dose. Group B (n = 118; 64 male and 54 female): 28 days therapy with TSI (300 mg 2x daily) with 2x daily doses of ciprofloxacin 15 mg/kg/dose.
Outcomes	**Primary outcome** *P aeruginosa* eradication defined as 3 negative cultures over 6 months. **Secondary outcomes** Lung function (FEV_1). Period of time free of *P aeruginosa.* Isolation of other pathogens including gram-negative and aspergillus.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence generated by statistical software within permuted blocks of size 10, stratified according to age and FEV_1.
Allocation concealment (selection bias)	Low risk	Separation of individuals responsible for randomisation and treatment assignment.

Taccetti 2012 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Open-label trial so no blinding of participants nor researchers.
Incomplete outcome data (attrition bias) All outcomes	Low risk	38 of 223 randomised participants (17%) dropped out of the trial. The biggest reason for dropping out was lack of compliance with follow up protocol (11 from Group A and 13 from Group B) and identification of a pulmonary exacerbation during early eradication therapy (4 from Group A and 5 from Group B). Analysis was by intention-to-treat.
Selective reporting (reporting bias)	Unclear risk	We have been unable to locate a published protocol for this trial. The details published on the EudraCT database (number 2008-006502-42) describe objectives but not outcomes. In the main paper, the methods section does not describe all the trial objectives. Only eradication, time free of *P aeruginosa* and spirometry are described in the methods section. These outcomes plus the additional outcomes of isolation of other organisms and adverse events are described in the results.
Other bias	Low risk	No evidence of other bias identified.

Treggiari 2011

Methods	RCT. Multi-centre (57 centres) in the USA. Trial duration for each participant is 18 months. Parallel design. Inhaled tobramycin was provided in an open-label fashion, while oral ciprofloxacin was provided in a double-blinded fashion.
Participants	306 participants with CF, previously free of *P aeruginosa* or had not had positive isolates for 2 years or more. Age: 1 year or older and 12 years and younger. Gender: 150 male, 154 female.
Interventions	All participants received eradication therapy with inhaled tobramycin (Novartis Pharmaceutical Corp) for 28 days with or without ciprofloxacin (Bayer Healthcare AG). The main randomised intervention of nebulised tobramycin, with or without oral ciprofloxacin, commenced after this initial 28 days of treatment: Group A: cycled therapy; Group B: culture-based therapy. Furthermore, the time from isolation of *P. aeruginosa* to commencing trial therapy was up to 6 months and in this interval, some participants received antimicrobial therapy.
Outcomes	**Primary outcomes** Time to first exacerbation requiring IV therapy. Proportion of positive cultures in each group. **Secondary outcomes** *Clinical* Time to pulmonary exacerbation not requiring IV antibiotic usage or hospitalization.

Treggiari 2011 *(Continued)*

	Frequency of pulmonary exacerbations, hospitalizations, and use of concomitant oral, inhaled, and IV antibiotics. Anthropometric measures (linear growth, weight gain). Pulmonary function tests including FVC, $FEF_{25\%-75\%}$, and FEV_1 (participants 4 years of age and older, able to reproducibly perform spirometry). Total hospitalization days. *Microbiological* Changes in antibiotic susceptibility patterns (minimal inhibitory concentrations of 12 antibiotics). Colony morphology. Presence of mucoid isolates from baseline to the end of the trial. Emergence of intrinsically aminoglycoside and ciprofloxacin-resistant non-pseudomonal organisms (e.g. *B cepacia*, *A xylosoxidans* and *S maltophilia*). Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was carried out by permuted blocks, and performed using a computer-generated sequence.
Allocation concealment (selection bias)	Low risk	Randomization assignment was available at the sites via an interactive voice response system with e-mail confirmation of the treatment assignment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Inhaled tobramycin was provided in an open-label fashion, while oral ciprofloxacin was provided in a double-blinded fashion. All trial personnel and participants were blinded to oral therapy assignment but not to cycled or culture-based treatment allocation. The core trial investigators were blinded to all treatment allocation for the entire study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 of 306 randomised participants excluded from the analysis (because they did not receive study treatment).
Selective reporting (reporting bias)	Low risk	Data on all primary and secondary outcomes reported.
Other bias	Low risk	No imbalance in baseline characteristics. Central trial team (not local investigators) blinded.

Valerius 1991

Methods	RCT. Parallel design. Duration: 27 months.

Valerius 1991 *(Continued)*

	Single-centre trial based in Europe.
Participants	26 participants with a recent positive culture who have never received anti-pseudomonal therapy. Age: 2 - 9 years. Gender: 13 males, 13 females.
Interventions	Treatment: oral ciprofloxacin (250 - 750 mg) 2x daily and inhaled colistin (1 MU) for 3 weeks at entry and each time *P aeruginosa* isolated. Control: no anti-pseudomonas chemotherapy.
Outcomes	Time to chronic colonisation with *P aeruginosa* (defined as the presence of *P aeruginosa* in monthly routine sputum specimens for 6 consecutive months and/or the development of precipitating serum antibodies against *P aeruginosa*).
Notes	Monthly sputum samples.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as a RCT without stratification, but the method of generation of allocation sequence was not stated.
Allocation concealment (selection bias)	Unclear risk	Did not report how allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	High risk	Did not use blinding, interventions different.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed on an intention-to-treat basis. Reported data on all participants who were randomised. There were no dropouts reported.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting found.
Other bias	Low risk	No evidence of other bias identified.

Wiesemann 1998

Methods	RCT. Double-blind, placebo-controlled trial. Parallel design. Duration: 2 years. Multicentre trial based in Europe.
Participants	22 children with *P aeruginosa*-negative throat swabs or sputum cultures for > 1 year and negative serum antibody titers were eligible. Age: 4 - 18 years.

Wiesemann 1998 *(Continued)*

	Gender: 9 males, 13 females.
Interventions	Treatment: nebulised tobramycin 80 mg inhaled 2x daily. Control: inhaled placebo.
Outcomes	Time to clearance of *P aeruginosa* from the airway.
Notes	Monthly sputum or oropharyngeal swabs during trial period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation sequence was generated using a coin flip for pairs of participants. There is no information as to who was responsible for the coin flip or what controls were in place to ensure validity of the result of the coin flip.
Allocation concealment (selection bias)	Unclear risk	Did not report how allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Reported as double blind. Participants were blinded by providing a placebo inhalation with a similar taste to the treatment inhalation, but it is not clear whether the clinicians administering the treatment were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 out of 11 participants withdrew from treatment group; 5 out of 11 participants withdrew from placebo group. The trial was analysed on an available case basis.
Selective reporting (reporting bias)	High risk	Reported there was no change in spirometric pulmonary function during or after the treatment period, but no data were given
Other bias	Low risk	No evidence of other bias identified.

A xylosoxidans: Achromobacter xylosoxidans
B cepacia: *Burkholderia cepacia*
BAL: bronchoalveolar lavage
BMI: body mass index
FEF_{25-75}: mid-forced expiratory flow
FEV_1: forced expiratory volume at one second
FVC: forced vital capacity
IgG: immunoglobulin G
IV: intravenous
MU: million units
P aeruginosa: *Pseudomonas aeruginosa*
RCT: randomised controlled trial
S maltophilia: Stenotrophomonas maltophilia
TSI: tobramycin solution for inhalation

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

Study	Reason for exclusion
Alothman 2002	Drug tolerability trial, not eradication therapy.

Study	Reason for exclusion
Alothman 2005	Drug tolerability trial, not eradication therapy.
Ballman 1998	Eradication treatment not used. Observational study.
Brett 1992	Participants allocated to treatment by minimisation on the basis of IgG levels and clinical indications compared to therapy based on clinical indications alone.
Church 1997	Symptomatic treatment not eradication.
Clancy 2013	Participants chronically infected with *P aeruginosa.*
Coates 2011	Participants chronically infected with *P aeruginosa.*
Elborn 2015	Participants chronically infected with *P aeruginosa.*
Flume 2015a	Participants chronically infected with *P aeruginosa.*
Flume 2015b	Participants chronically infected with *P aeruginosa.*
Flume 2016	Participants chronically infected with *P aeruginosa.*
Frederiksen 1997	Historical control group.
Geller 2007	Pharmacokinetic and drug tolerability trial, not eradication therapy.
Geller 2011	Participants chronically infected with *P aeruginosa.*
Gibson 2007	Not randomised and with no allocation concealment.
Goss 2009	Participants chronically infected with *P aeruginosa.*
Griese 2002	Case-control study.
Heinzl 2002	No control group.
Kenny 2009	Retrospective cohort study.
Konstan 2010	Participants chronically infected with *P aeruginosa.*
Konstan 2011	Participants chronically infected with *P aeruginosa.*
Konstan 2015	Participants chronically infected with *P aeruginosa.*
Latzin 2008	The primary aim of this trial was not to evaluate eradication regimens for *P aeruginosa* and 112 of 118 participants were treated for an acute exacerbation or suppression of chronic infection with *P aeruginosa*.
Lenoir 2007	Trial not designed to look at eradication of *P aeruginosa*. At baseline, 47 of 59 participants had chronic infection with *P aeruginosa*.
Littlewood 1985	No control group.
Mainz 2014	Sinonasal nebulisation of antibiotic aiming to eradicate from the sinuses only.
Mazurek 2012	Participants chronically infected with *P aeruginosa.*

Study	Reason for exclusion
Oermann 2009	Participants chronically infected with *P aeruginosa,* not an eradication trial, no randomisation.
Postnikov 2000	No control group and no randomisation.
Postnikov 2007	Not an eradication trial, participants chronically infected with *P. aeruginosa.*
Prayle 2013	Participants chronically infected with *P aeruginosa.*
Ramsey 1999	Participants chronically infected with *P aeruginosa.*
Ratjen 2001a	No control group.
Retsch-Bogart 2008	Participants chronically infected with *P aeruginosa.*
Retsch-Bogart 2009	Participants chronically infected with *P aeruginosa.*
Rietschel 2009	Pharmacokinetic trial of inhaled tobramycin, not eradication therapy.
Ruddy 2013	Pharmacokinetic trial.
Schaad 1997	Symptomatic treatment not eradication.
Schelstraete 2010	No randomisation or eradication therapy.
Schuster 2013	Drug tolerability trial in chronic *P aeruginosa* infection, not eradication therapy.
Stass 2013	Pharmacokinetic trial.
Steinkamp 1989	No control group.
Steinkamp 2007	Participants chronically infected with *P aeruginosa.*
Stockmann 2015	Participants with chronic *P aeruginosa*.
Taccetti 2005	Primary outcome did not have a control group. Historical controls utilised for other outcomes. No randomisation.
Tramper-Stranders 2009	Trial of prophylaxis against future infection with *P aeruginosa*, not of eradication.
Trapnell 2012	Participants chronically infected with *P aeruginosa.*
Vazquez 1993	Historical control group.
Wainwright 2011a	Randomised to therapy directed by the results of bronchoalveolar lavage compared to therapy based on clinical indications or upper respiratory samples.
Wainwright 2011b	Participants chronically infected with *P aeruginosa.*

P aeruginosa: Pseudomonas aeruginosa

Characteristics of studies awaiting assessment *[ordered by study ID]*

Noah 2010

Methods	Single-centre, randomised, prospective trial.
Participants	Stable children with CF and positive surveillance cultures for *P aeruginosa.*
Interventions	Nebulised tobramycin 300 mg 2x daily for 4 weeks or intravenous ceftazidime with tobramycin for 2 weeks at standard weight-adjusted doses.
Outcomes	Primary efficacy endpoint was change in BAL fluid percentage neutrophils from the most affected lobe at bronchoscopy. Secondary outcomes included change in BAL fluid differential cell counts, cytokines and bacterial quantity.
Notes	8 participants from a total of 15 had first ever isolate of *P aeruginosa* and can be included in this review. Outcome data for these 8 participants not published, author contacted for them.

BAL: bronchoalveolar lavage
CF: cystic fibrosis
P. aeruginosa: Pseudomonas aeruginosa

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

Ratjen 2016

Trial name or title	A Randomized, Double-Blind, Placebo-Controlled, Crossover Multi-Center Study to Assess the Efficacy and Safety of Inhaled Tobramycin Nebuliser Solution (TOBI®) for the Treatment of Early Infections of P. Aeruginosa in Cystic Fibrosis Subjects Aged From 3 Months to Less Than 7 Years
Methods	Randomised, double-blind trial. Multicentre in Europe and Canada.
Participants	Aim to enrol 50 participants aged 3 months to 6 years, both males and females. Inclusion criteria • Diagnosis of CF • Early lower respiratory tract infection with *P aeruginosa* Exclusion Criteria: • Known local or systemic hypersensitivity to aminoglycosides or inhaled antibiotics. • Administration of loop diuretics within 7 days prior to study drug administration. • Other protocol-defined inclusion/exclusion criteria may apply
Interventions	**Experimental**: TOBI (tobramycin inhaled solution)/placebo Participants randomized to TOBI received the investigational treatment for 28 days 2x daily in the 1st treatment cycle. At the end of 1st treatment cycle, participants who were positive for *P aeruginosa* entered the open-label phase of the trial and received TOBI for 28 days 2x daily. Participants who were negative for *P aeruginosa* at the end of 1st treatment cycle and agreed to participate in the cross-over treatment period received placebo for 28 days 2x daily (2nd treatment cycle). **Comparator**: placebo/TOBI Participants randomized to placebo group received 0.9 % saline (NaCl) for 28 days 2x daily in the 1st treatment cycle. At the end of 1st treatment cycle, participants who were positive for *P aeruginosa* entered the open-label phase of the study and received TOBI for 28 days 2x daily. Participants

Ratjen 2016 *(Continued)*

	who were negative for *P aeruginosa* at the end of 1st treatment cycle and agreed to participate in the cross-over treatment period received TOBI for 28 days 2x daily (2nd treatment cycle).
Outcomes	Primary Outcome Percentage of participants *P aeruginosa*-free after completion of the first treatment cycle (Day 29) as assessed by sputum/throat swab cultures Secondary Outcomes Percentage of participants free from *P aeruginosa* 28 days after termination of the second treatment cycle (Day 91) as assessed by sputum/throat swab cultures Percentage of participants *P aeruginosa*-free at termination of the double blind period (Day 91) as assessed by sputum/throat swab cultures
Starting date	April 2010
Contact information	Prof Felix Ratjen, The Hospital for Sick Children, Toronto, Canada.
Notes	Completion date: June 2015 (final data collection date for primary outcome measure). Sponsors: Novartis Pharmaceuticals

TORPEDO Trial

Trial name or title	TORPEDO-CF (Trial of Optimal Therapy for Pseudomonas Eradication in Cystic Fibrosis)
Methods	Multi-centre, parallel group, RCT.
Participants	**Inclusion criteria** 1. Diagnosis of CF 2. Children over the age of 28 days, older children and adult CF participants are all eligible with no upper age limitation 3. Competent adults should provide fully informed written consent to participate in the trial 4. Minors should have proxy consent by the parent or legal guardian and should provide assent where applicable to participate in the trial 5. The participant should have isolated *P.aeruginosa* and should be either: a. *P aeruginosa*-naïve (i.e. has never previously isolated *P aeruginosa*) or b. *P aeruginosa*-free (i.e. a minimum of 4 consecutive cough or sputum samples should be *P aeruginosa*-free within a 12-month period) 6. The participant should be able to commence treatment no later than 21 days from the date of a *P aeruginosa* positive microbiology report
Interventions	Objective: this trial will assess whether 10 days IV ceftazidime with tobramycin is superior to 3 months oral ciprofloxacin. Both treatment regimens will be in conjunction with 3 months nebulised colistin. **Arm A**: 14 days IV ceftazidime 50 mg/kg/dose, to a maximum of 3 g 3x daily and IV tobramycin 10 mg/kg/day either 1x daily or in divided doses (maximum 660 mg/day). **Arm B**: 3 months oral ciprofloxacin 2x daily (ciprofloxacin dose will be 15 - 20 mg/kg/dose 2x daily for children aged < 5 years and 20 mg/kg/dose 2x daily (maximum 750 mg 2x daily) for those aged ≥ 5 years). Both treatment arms will receive 3 months of nebulised colistin in conjunction to the randomised treatment. Colistin dose will be as recommended by the UK CF Trust: 1,000,000 units 2x daily for children aged ≤ 2 years and 2,000,000 units 2x daily for children aged > 2 years and adults.
Outcomes	**Primary outcome**

TORPEDO Trial *(Continued)*

	1. Successful eradication of *P aeruginosa* infection 3 months after allocated treatment has started, remaining infection-free through to 15 months after the start of allocated treatment **Secondary outcomes** 1. Time to reoccurrence of original *P aeruginosa* infection 2. Re-infection with a different genotype of *P aeruginosa* 3. Lung function (FEV_1 , FVC, FEF_{25-75}) 4. Oxygen saturation 5. Growth and nutritional status – height, weight and BMI 6. Number of pulmonary exacerbations 7. Admission to hospital 8. Number of days spent as inpatient in hospital over the 3-month period after allocated treatment has finished, and between 3 months and 15 months after eradication treatment has finished (other than 14 days spent on initial IV treatment) 9. Quality of life (CFQ) 10. Utility (EQ-5D) 11. Adverse events 12. Other sputum/cough microbiology (MRSA, *B cepacia* complex, Aspergillus, candida infection) 13. Cost per patient (from NHS perspective) 14. Incremental cost effectiveness ratio (cost per successfully treated patient, cost per QALY) 15. Carer burden (absenteeism from school or work) 16. Participant burden (absenteeism from education or work)
Starting date	24/05/2010.
Contact information	Dr Simon Langton Hewer Bristol Royal Hospital for Children Paul O'Gorman Building Upper Maudlin Street Bristol BS2 8BJ UK
Notes	Anticipated end date: 01/11/2014 HTA 07/51/01

A xylosoxidans: *Alcaligenes xylosoxidans*
B cepacia: *Burkholderia cepacia*
BMI: body mass index
CF: cystic fibrosis
FEF_{25-75}: mid-forced expiratory flow
FEV_1: forced expiratory volume at 1 second
FVC: forced vital capacity
IV: intravenous
MRSA: Methicillin-resistant *Staphylococcus aureus*
NHS: National Health Service
P aeruginosa: Pseudomonas aeruginosa
QALY: quality-adjusted life year
RCT: randomised controlled trial
S maltophilia: *Stenotrophomonous maltophilia*

DATA AND ANALYSES

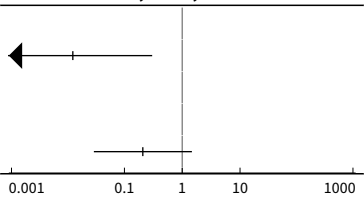
Comparison 1. Inhaled tobramycin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Positive respiratory culture for *P aeruginosa* (300 mg 2x daily)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 At 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At 2 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Positive respiratory culture for *P aeruginosa* (80 mg 2x daily)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 At 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 At 2 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 At 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 At 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 At 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Positive respiratory culture for *P aeruginosa* (combined available case analysis)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 At 1 month	2	38	Odds Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.33]
3.2 At 2 months	2	38	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.03, 0.65]
4 Positive respiratory culture for *P aeruginosa* (combined) - best case	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 At 1 month	2	39	Odds Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.30]
4.2 At 2 months	2	39	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.03, 0.60]
4.3 At 3 months	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.16]
4.4 At 6 months	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.48]
4.5 At 12 months	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.01 [0.00, 0.26]
5 Positive respiratory culture for *P aeruginosa* (combined) - worst case	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 At 1 month	2	39	Odds Ratio (M-H, Fixed, 95% CI)	0.08 [0.02, 0.38]
5.2 At 2 months	2	39	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.04, 0.73]
5.3 At 3 months	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.05, 2.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4 At 6 months	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 1.83]
5.5 At 12 months	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.05, 2.77]
6 Weight (kg) - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 At 1 month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 At 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Cough	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Modified Shwachmann score - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 At 1 month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 At 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

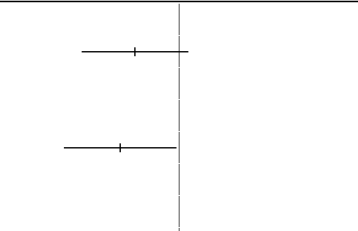
Analysis 1.1. Comparison 1 Inhaled tobramycin versus placebo, Outcome 1 Positive respiratory culture for *P aeruginosa* (300 mg 2x daily).

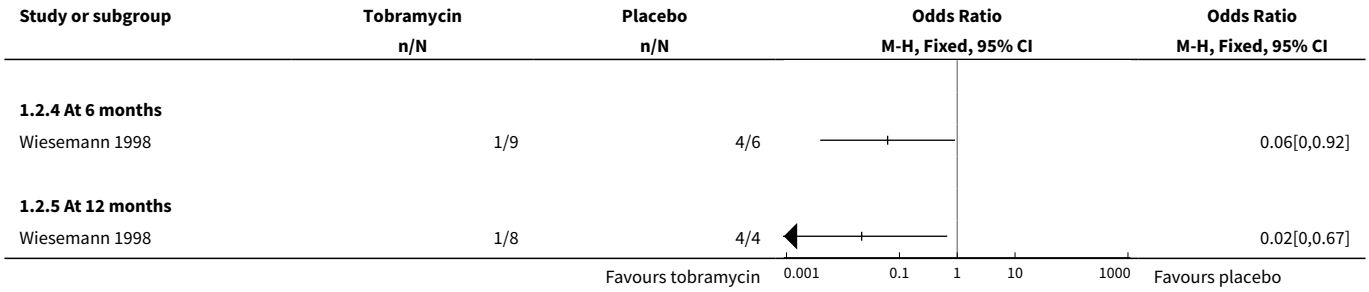
Study or subgroup	Tobramycin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.1.1 At 1 month				
Gibson 2003	0/8	11/13		0.01[0,0.3]
1.1.2 At 2 months				
Gibson 2003	2/8	8/13		0.21[0.03,1.47]



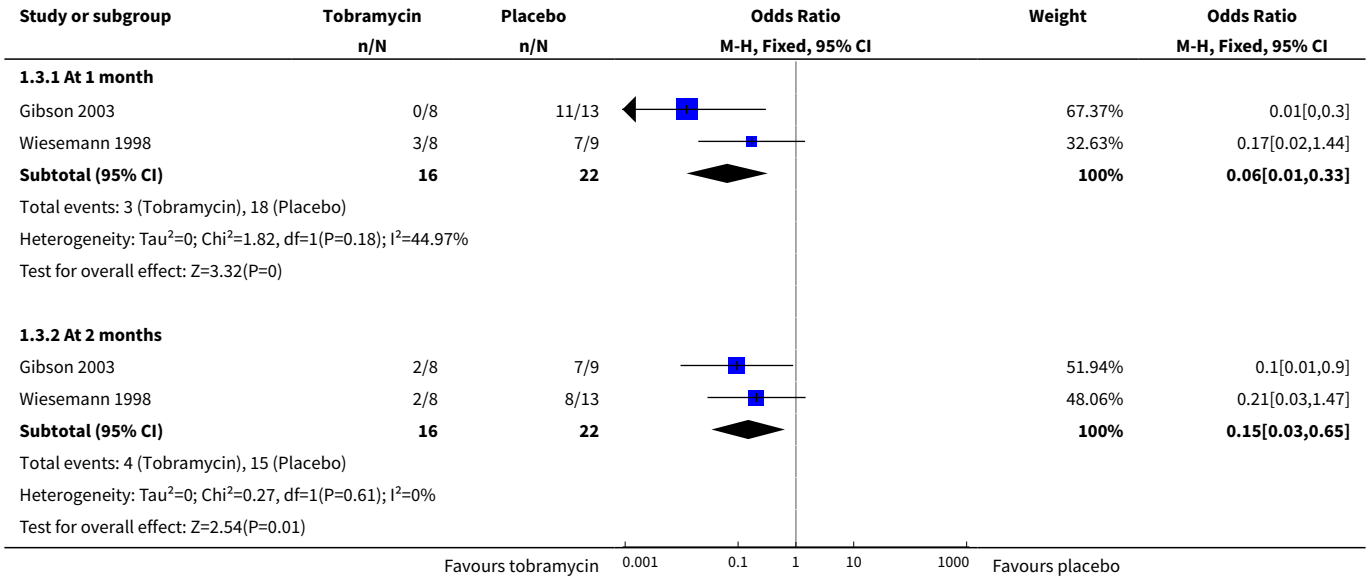
Analysis 1.2. Comparison 1 Inhaled tobramycin versus placebo, Outcome 2 Positive respiratory culture for *P aeruginosa* (80 mg 2x daily).

Study or subgroup	Tobramycin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.2.1 At 1 month				
Wiesemann 1998	3/8	7/9		0.17[0.02,1.44]
1.2.2 At 2 months				
Wiesemann 1998	2/8	7/9		0.1[0.01,0.9]
1.2.3 At 3 months				
Wiesemann 1998	2/8	4/7		0.25[0.03,2.24]

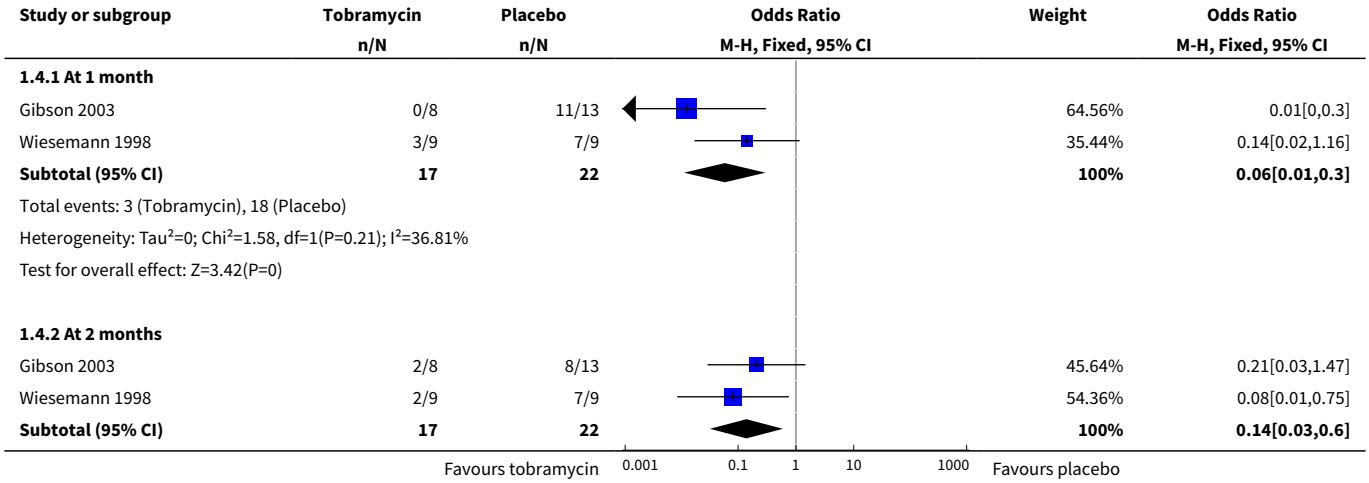


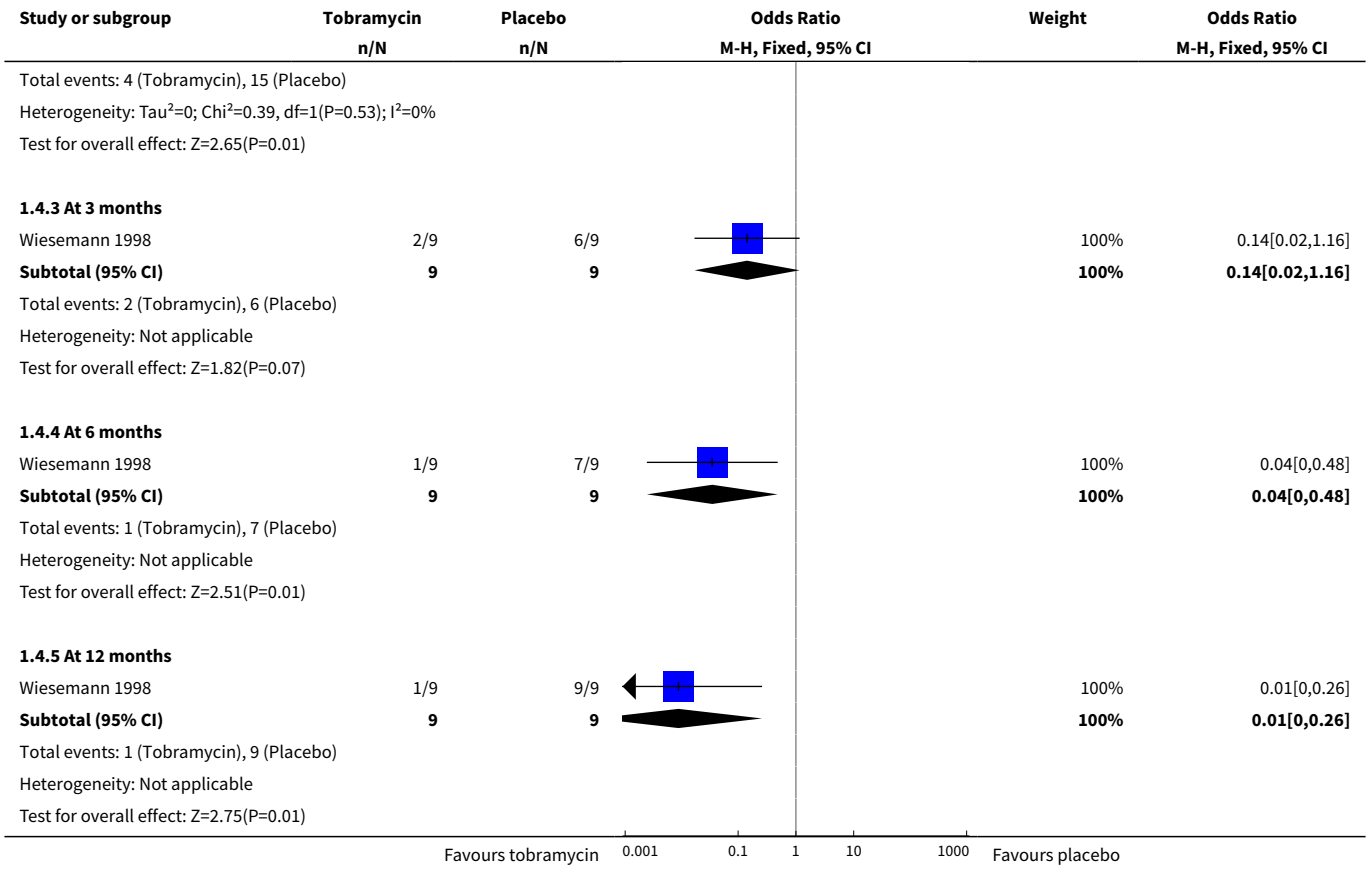


Analysis 1.3. Comparison 1 Inhaled tobramycin versus placebo, Outcome 3 Positive respiratory culture for *P aeruginosa* (combined available case analysis).

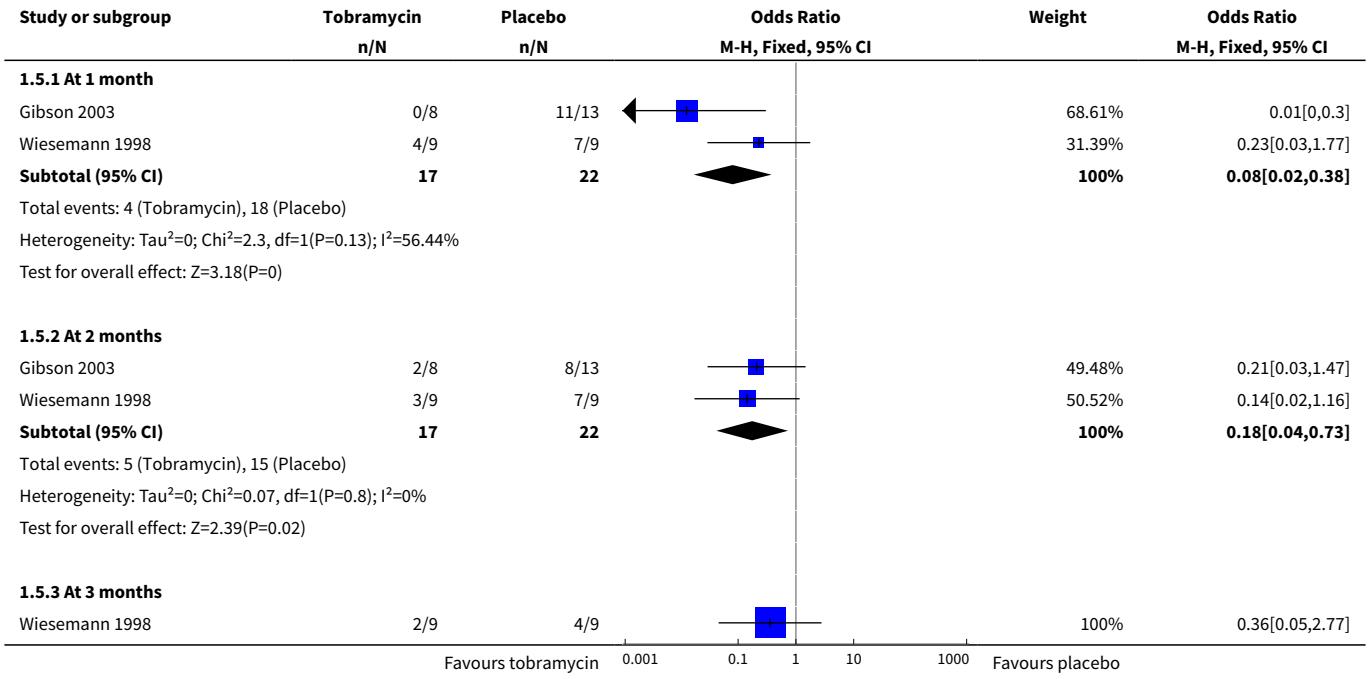


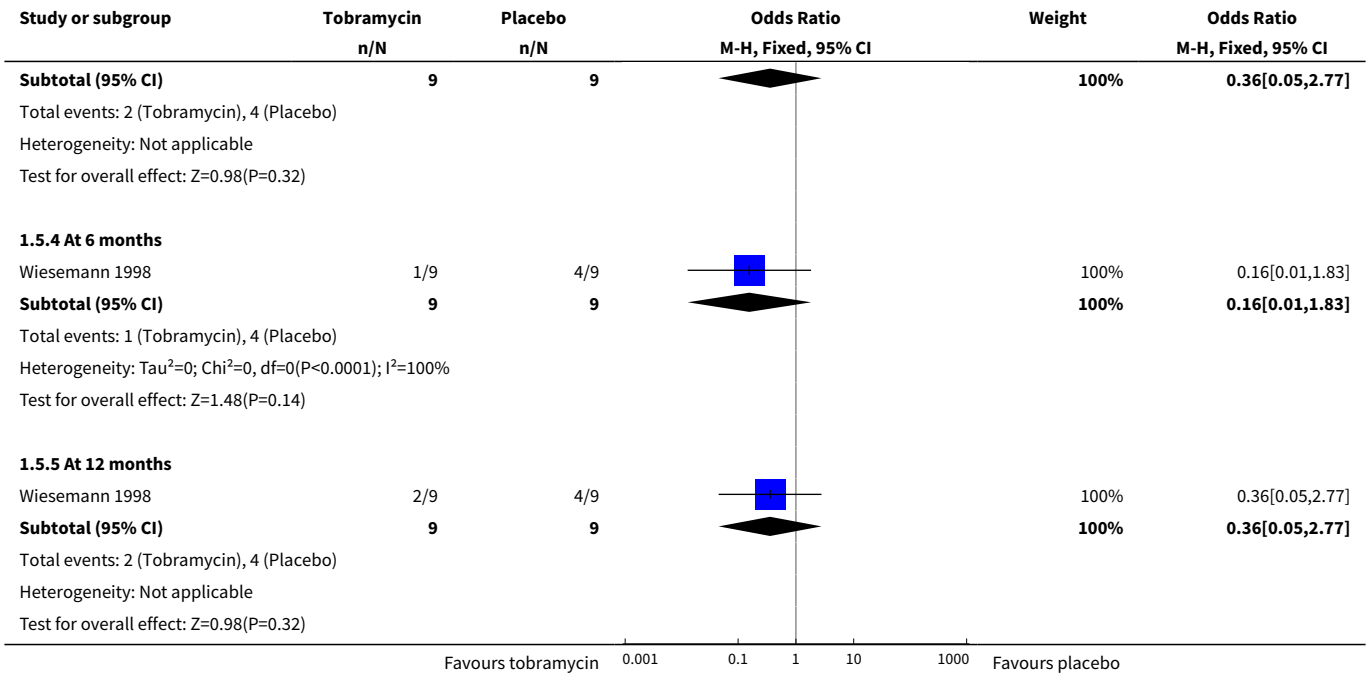
Analysis 1.4. Comparison 1 Inhaled tobramycin versus placebo, Outcome 4 Positive respiratory culture for *P aeruginosa* (combined) - best case.



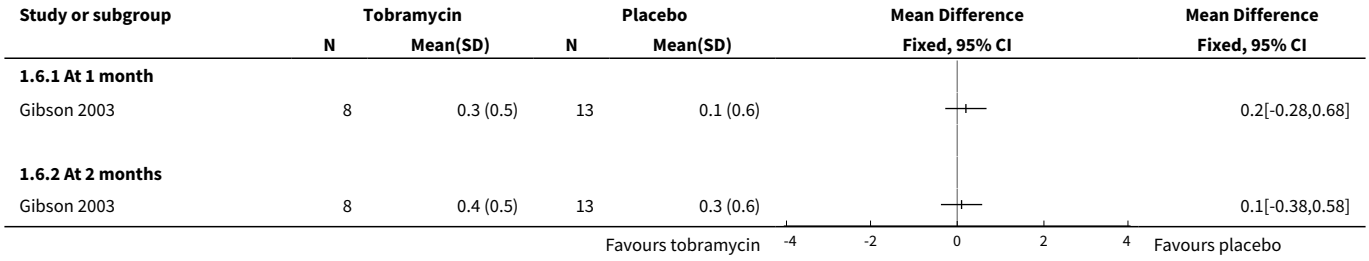


Analysis 1.5. Comparison 1 Inhaled tobramycin versus placebo, Outcome 5 Positive respiratory culture for *P aeruginosa* (combined) - worst case.

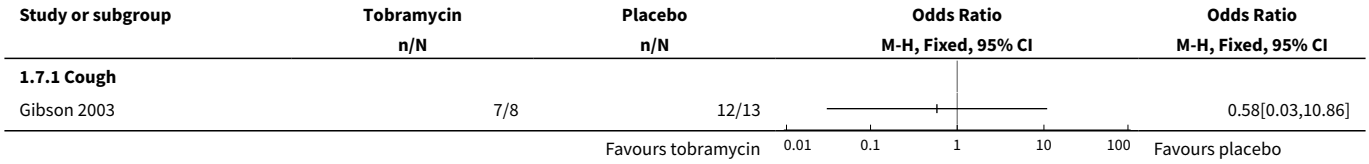




Analysis 1.6. Comparison 1 Inhaled tobramycin versus placebo, Outcome 6 Weight (kg) - change from baseline.

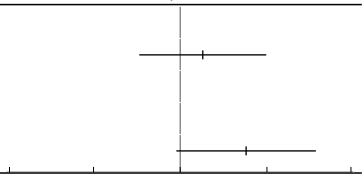


Analysis 1.7. Comparison 1 Inhaled tobramycin versus placebo, Outcome 7 Adverse events.



Analysis 1.8. Comparison 1 Inhaled tobramycin versus placebo, Outcome 8 Modified Shwachmann score - change from baseline.

Study or subgroup	Tobramycin N	Tobramycin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.8.1 At 1 month						
Gibson 2003	8	0.5 (2.4)	13	-0.8 (6)		1.3[-2.36,4.96]
1.8.2 At 2 months						
Gibson 2003	8	2.4 (3.4)	13	-1.4 (6)		3.8[-0.22,7.82]

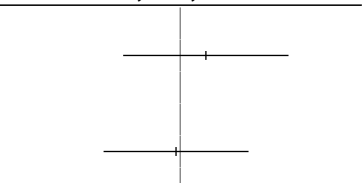


Comparison 2. Oral ciprofloxacin and inhaled colistin versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion colonised with *P aeruginosa*	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 At 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 At 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 At 24 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Oral ciprofloxacin and inhaled colistin versus no treatment, Outcome 1 Proportion colonised with *P aeruginosa*.

Study or subgroup	Antibiotics n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.1.1 At 3 months				
Valerius 1991	1/14	0/12		2.78[0.1,74.7]
2.1.2 At 6 months				
Valerius 1991	1/14	1/12		0.85[0.05,15.16]
2.1.3 At 12 months				
Valerius 1991	2/14	6/12		0.17[0.03,1.09]
2.1.4 At 24 months				
Valerius 1991	2/14	7/12		0.12[0.02,0.79]

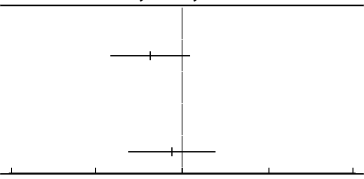


Comparison 3. Oral ciprofloxacin and inhaled colistin versus inhaled tobramycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Positive respiratory culture for *P aeruginosa*	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 In first 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At 24 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Severe cough	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

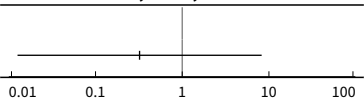
Analysis 3.1. Comparison 3 Oral ciprofloxacin and inhaled colistin versus inhaled tobramycin, Outcome 1 Positive respiratory culture for *P aeruginosa*.

Study or subgroup	Ciprofloxacin & Inhaled colistin n/N	Inhaled tobramycin n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
3.1.1 In first 6 months				
Proesmans 2013	10/29	16/29		0.43[0.15,1.23]
3.1.2 At 24 months				
Proesmans 2013	9/23	11/24		0.76[0.24,2.42]



Analysis 3.2. Comparison 3 Oral ciprofloxacin and inhaled colistin versus inhaled tobramycin, Outcome 2 Adverse events.

Study or subgroup	Ciprofloxacin & Inhaled colistin n/N	Inhaled tobramycin n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
3.2.1 Severe cough				
Proesmans 2013	0/29	1/29		0.32[0.01,8.24]



Comparison 4. Nebulised tobramycin 28 days versus 56 days

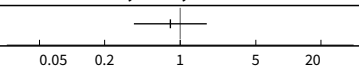
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to next isolation of *P aeruginosa* from BAL, sputum or oropharyngeal cultures	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of respiratory exacerbations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Until recurrence of *P. aeruginosa*	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse events (up to 3 months)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Cough	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Productive cough	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Haemoptysis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Rhinitis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 Sinusitis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.6 Nasopharyngitis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.7 Tonsilitis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.8 Oropharyngeal pain	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.9 Dysphonia	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.10 Headache	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.11 URTI	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.12 Lung disorder	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.13 Bronchitis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.14 *P. aeruginosa* infection	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.15 Influenza	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.16 Otitis media	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.17 Deafness	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.18 Drug level increased	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.19 Pyrexia	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.20 Vomiting	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.21 Varicella	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Adverse events (over 3 months)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Cough	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Productive cough	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Haemoptysis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 Rhinitis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 Sinusitis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 Nasopharyngitis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 Tonsilitis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.8 Oropharyngeal pain	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.9 Dysphonia	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.10 Headache	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.11 URTI	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.12 Lung disorder	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.13 Bronchitis	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.14 *P. aeruginosa* infection	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.15 Influenza	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.16 Otitis media	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.17 Deafness	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.18 Drug level increased	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.19 Pyrexia	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.20 Vomiting	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.21 Varicella	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

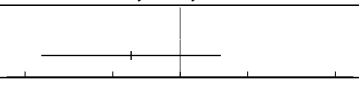
Analysis 4.1. Comparison 4 Nebulised tobramycin 28 days versus 56 days, Outcome 1 Time to next isolation of *P aeruginosa* from BAL, sputum or oropharyngeal cultures.

Study or subgroup	TIS 56 days N	TIS 28 days N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Ratjen 2010	31	34	-0.2 (0.396)		0.81[0.37,1.76]



Analysis 4.2. Comparison 4 Nebulised tobramycin 28 days versus 56 days, Outcome 2 Number of respiratory exacerbations.

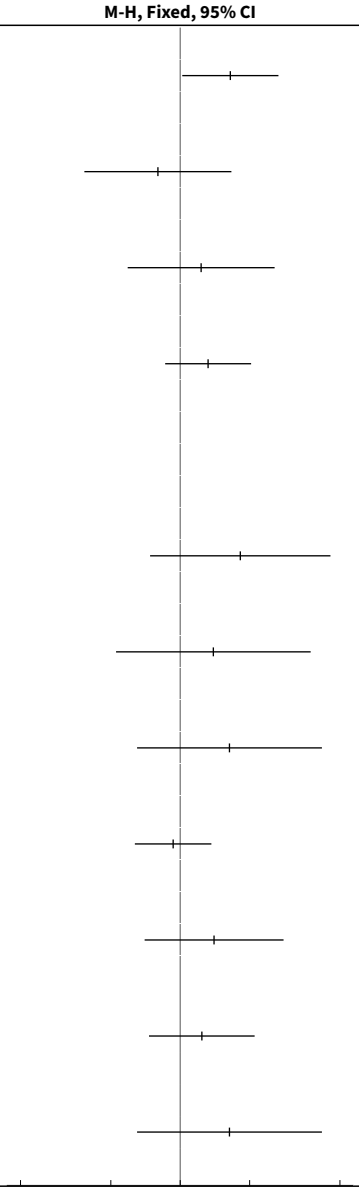
Study or subgroup	TIS 28-day n/N	TIS 56-day n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
4.2.1 Until recurrence of P. aeruginosa				
Ratjen 2010	0/44	2/43		0.19[0.01,4]



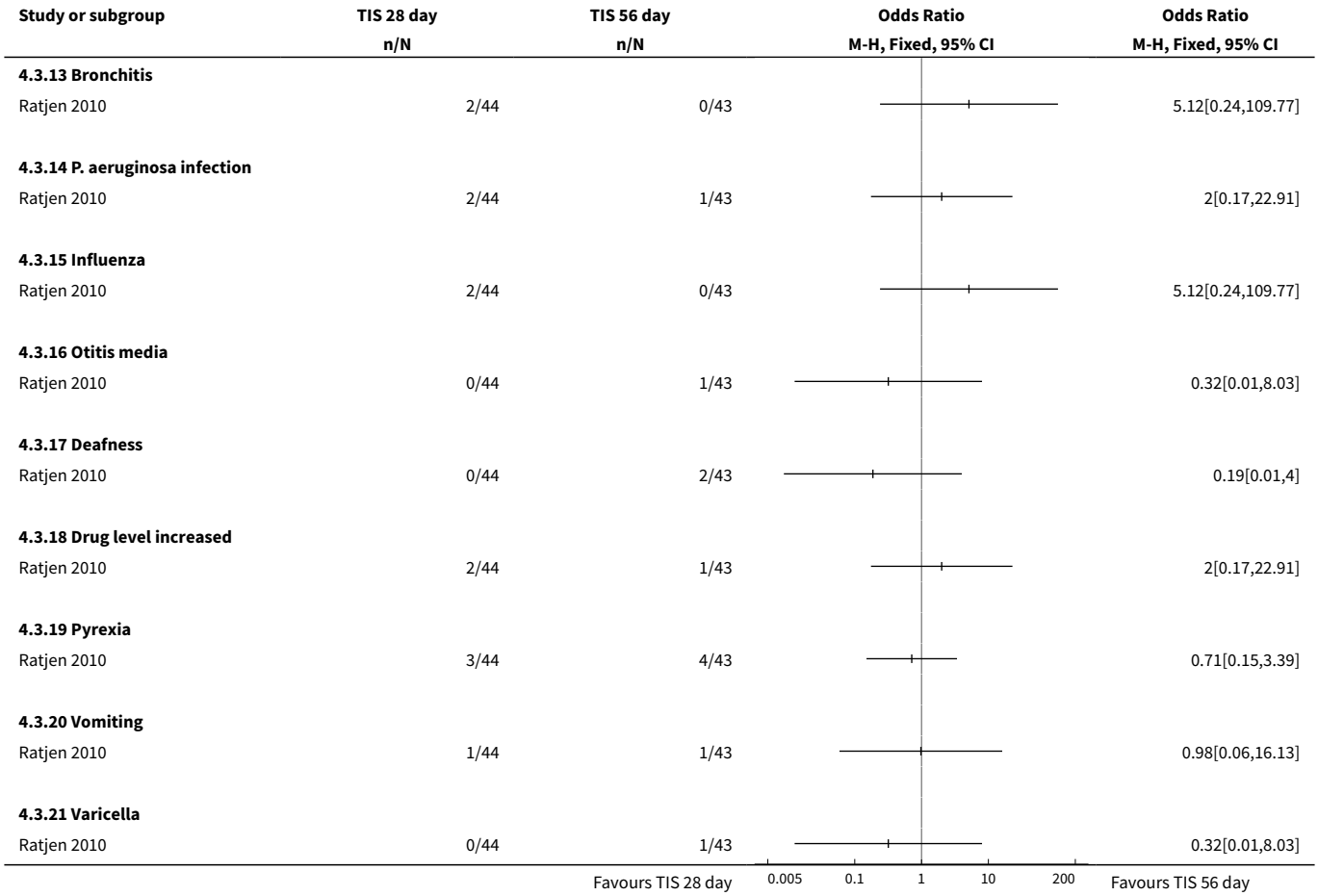
Favours TIS 28-day — Favours TIS 56-day

Analysis 4.3. Comparison 4 Nebulised tobramycin 28 days versus 56 days, Outcome 3 Adverse events (up to 3 months).

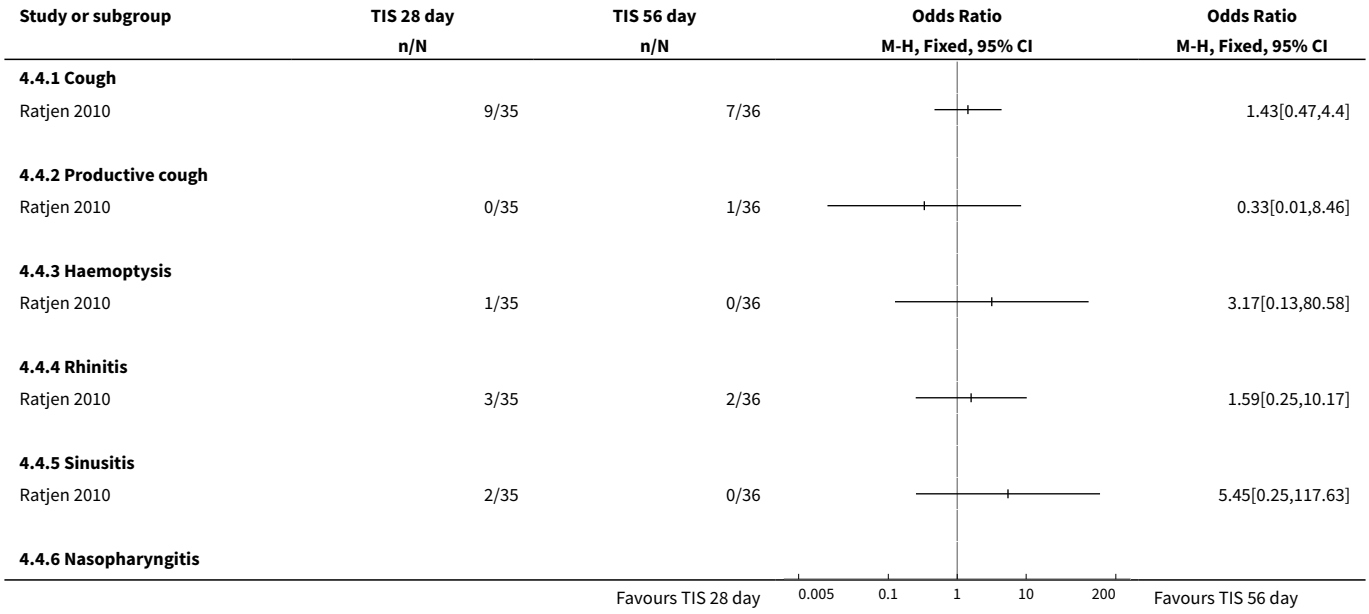
Study or subgroup	TIS 28 day n/N	TIS 56 day n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
4.3.1 Cough				
Ratjen 2010	9/44	2/43		5.27[1.07,26.04]
4.3.2 Productive cough				
Ratjen 2010	1/44	2/43		0.48[0.04,5.46]
4.3.3 Haemoptysis				
Ratjen 2010	2/44	1/43		2[0.17,22.91]
4.3.4 Rhinitis				
Ratjen 2010	7/44	3/43		2.52[0.61,10.48]
4.3.5 Sinusitis				
Ratjen 2010	0/44	0/43		Not estimable
4.3.6 Nasopharyngitis				
Ratjen 2010	3/44	0/43		7.34[0.37,146.43]
4.3.7 Tonsilitis				
Ratjen 2010	1/44	0/43		3[0.12,75.69]
4.3.8 Oropharyngeal pain				
Ratjen 2010	2/44	0/43		5.12[0.24,109.77]
4.3.9 Dysphonia				
Ratjen 2010	5/44	6/43		0.79[0.22,2.81]
4.3.10 Headache				
Ratjen 2010	3/44	1/43		3.07[0.31,30.77]
4.3.11 URTI				
Ratjen 2010	4/44	2/43		2.05[0.36,11.83]
4.3.12 Lung disorder				
Ratjen 2010	2/44	0/43		5.12[0.24,109.77]

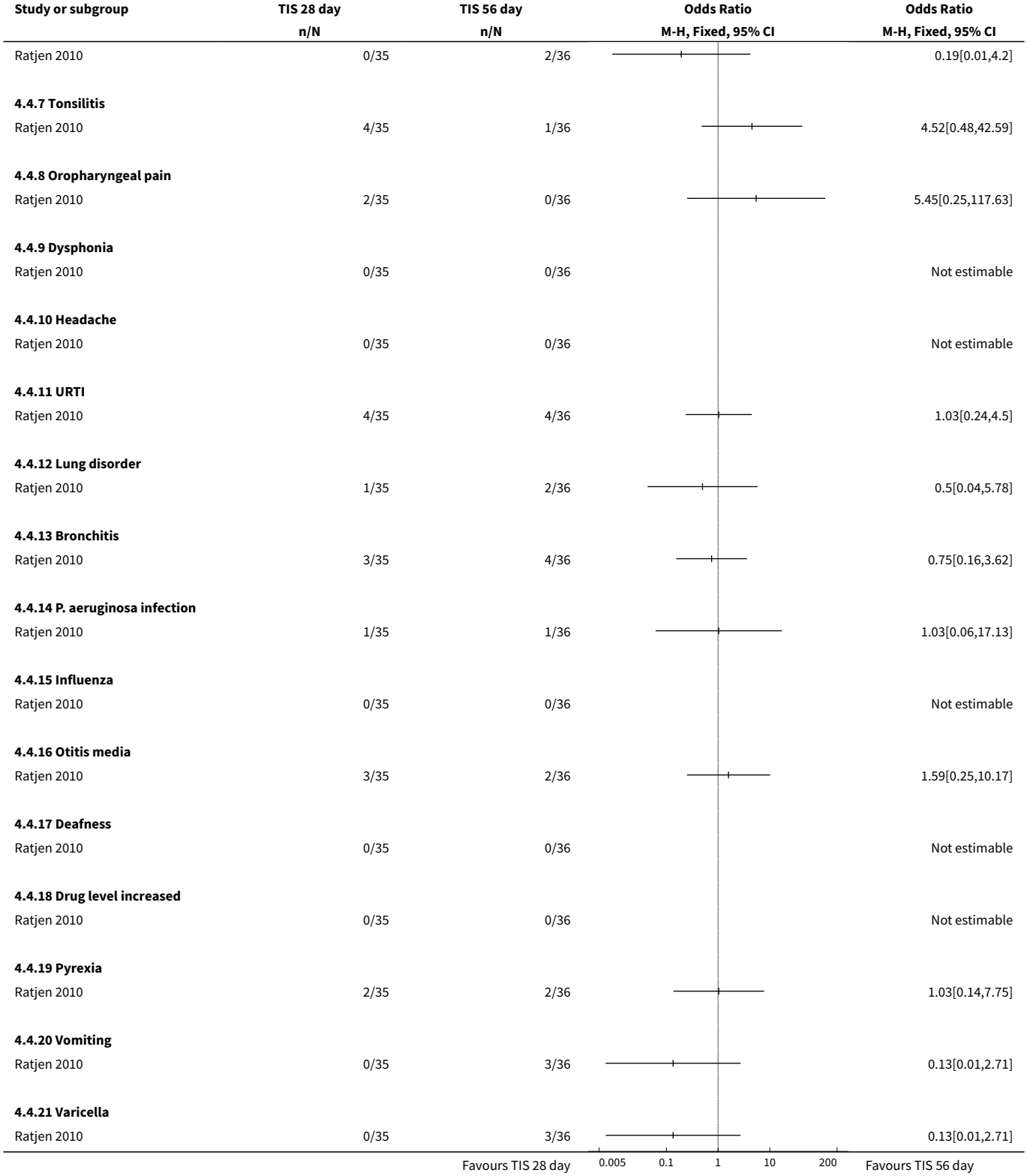


Favours TIS 28 day — Favours TIS 56 day



Analysis 4.4. Comparison 4 Nebulised tobramycin 28 days versus 56 days, Outcome 4 Adverse events (over 3 months).





Comparison 5. Inhaled colistin/oral ciprofloxacin versus inhaled tobramycin/oral ciprofloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Positive respiratory culture for *P aeruginosa*	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 In first 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 At end of follow up (median 16 months)	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 FEV_1 % predicted (relative change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 At mean 54 days	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Microbiology status (post-trial)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 *Stenotrophomonas maltophilia*	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 *Achromobacter xylosoxidans*	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 *Aspergillus* species	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Adverse events leading to trial discontinuation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Vomiting	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Photosensitivity	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Wheeze	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 Pulmonary exacerbation during early eradication treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 Lack of compliance	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Inhaled colistin/oral ciprofloxacin versus inhaled tobramycin/oral ciprofloxacin, Outcome 1 Positive respiratory culture for *P aeruginosa*.

Study or subgroup	Colistin/ciprofloxacin n/N	Tobramycin/ciprofloxacin n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
5.1.1 In first 6 months				
Taccetti 2012	39/105	41/118		1.11[0.64,1.92]
5.1.2 At end of follow up (median 16 months)				
Taccetti 2012	36/97	34/108		1.28[0.72,2.29]
		Favours colistin/cipro	0.5 0.7 1 1.5 2	Favours tobramycin/cipro

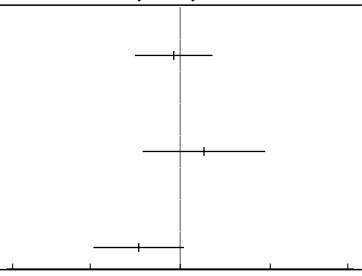
Analysis 5.2. Comparison 5 Inhaled colistin/oral ciprofloxacin versus inhaled tobramycin/oral ciprofloxacin, Outcome 2 FEV_1 % predicted (relative change from baseline).

Study or subgroup	Colistin/ciprofloxacin		To-bramycin/ciprofloxacin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
5.2.1 At mean 54 days						
Taccetti 2012	60	2.2 (8.5)	68	4.6 (11.5)		-2.4[-5.89,1.09]

Favours tobramycin/cipro | Favours colistin/cipro

Analysis 5.3. Comparison 5 Inhaled colistin/oral ciprofloxacin versus inhaled tobramycin/oral ciprofloxacin, Outcome 3 Microbiology status (post-trial).

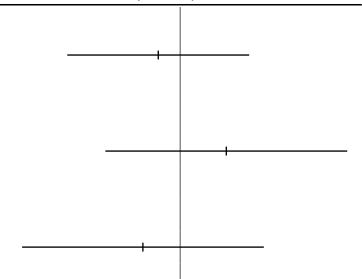
Study or subgroup	Colistin/ciprofloxacin	To-bramycin/ciprofloxacin	Odds Ratio	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
5.3.1 Stenotrophomonas maltophilia				
Taccetti 2012	18/97	22/108		0.89[0.45,1.78]
5.3.2 Achromobacter xylosoxidans				
Taccetti 2012	8/97	6/108		1.53[0.51,4.57]
5.3.3 Aspergillus species				
Taccetti 2012	10/97	21/108		0.48[0.21,1.07]



Favours colistin/cipro | Favours to-bramycin/cipro

Analysis 5.4. Comparison 5 Inhaled colistin/oral ciprofloxacin versus inhaled tobramycin/oral ciprofloxacin, Outcome 4 Adverse events leading to trial discontinuation.

Study or subgroup	Colistin/ciprofloxacin	To-bramycin/ciprofloxacin	Odds Ratio	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
5.4.1 Vomiting				
Taccetti 2012	1/105	2/118		0.56[0.05,6.24]
5.4.2 Photosensitivity				
Taccetti 2012	1/105	0/118		3.4[0.14,84.41]
5.4.3 Wheeze				
Taccetti 2012	0/105	1/118		0.37[0.01,9.21]
5.4.4 Pulmonary exacerbation during early eradication treatment				
Taccetti 2012	4/105	5/118		0.9[0.23,3.42]
5.4.5 Lack of compliance				
Taccetti 2012	11/105	13/118		0.95[0.4,2.21]



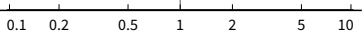
Favours colistin/cipro | Favours to-bramycin/cipro

Comparison 6. Cycled inhaled tobramycin versus culture-based inhaled tobramycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with one or more isolates of *P aeruginosa* from respiratory tract	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected
2 FEV_1 % predicted - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Mean duration of 70 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Weight (kg) - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Mean duration of 70 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Height (cm) - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Mean duration of 70 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Time to severe pulmonary exacerbation	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected
6 Participants with one or more severe pulmonary exacerbations	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected
7 Time to pulmonary exacerbation (any severity)	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected
8 Participants with one or more pulmonary exacerbations (any severity)	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected
9 Participants with new isolates of *Stenotrophomonas maltophilia*	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected
10 Participants with one or more serious adverse event	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected

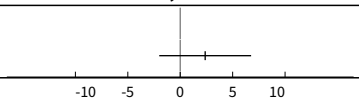
Analysis 6.1. Comparison 6 Cycled inhaled tobramycin versus culture-based inhaled tobramycin, Outcome 1 Participants with one or more isolates of *P aeruginosa* from respiratory tract.

Study or subgroup	Cycled n/N	Culture-based n/N	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Treggiari 2011	43/148	67/150		0.51[0.31,0.82]



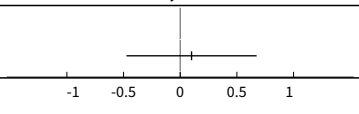
Analysis 6.2. Comparison 6 Cycled inhaled tobramycin versus culture-based inhaled tobramycin, Outcome 2 FEV_1 % predicted - change from baseline.

Study or subgroup	Cycled N	Cycled Mean(SD)	Culture-based N	Culture-based Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.2.1 Mean duration of 70 weeks						
Treggiari 2011	73	0.8 (12.7)	70	-1.6 (14)		2.38[-2,6.76]



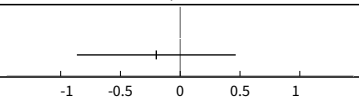
Analysis 6.3. Comparison 6 Cycled inhaled tobramycin versus culture-based inhaled tobramycin, Outcome 3 Weight (kg) - change from baseline.

Study or subgroup	Cycled N	Cycled Mean(SD)	Culture-based N	Culture-based Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.3.1 Mean duration of 70 weeks						
Treggiari 2011	152	4 (2.7)	152	3.9 (2.4)		0.1[-0.47,0.67]



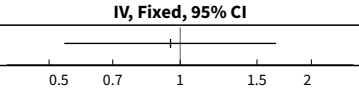
Analysis 6.4. Comparison 6 Cycled inhaled tobramycin versus culture-based inhaled tobramycin, Outcome 4 Height (cm) - change from baseline.

Study or subgroup	Cycled N	Cycled Mean(SD)	Culture-based N	Culture-based Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.4.1 Mean duration of 70 weeks						
Treggiari 2011	152	9.2 (2.8)	152	9.4 (3.1)		-0.2[-0.86,0.46]



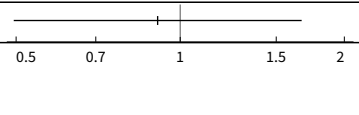
Analysis 6.5. Comparison 6 Cycled inhaled tobramycin versus culture-based inhaled tobramycin, Outcome 5 Time to severe pulmonary exacerbation.

Study or subgroup	Cycled N	Culture-based N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Treggiari 2011	152	152	-0.1 (0.286)		0.95[0.54,1.66]



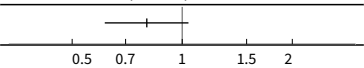
Analysis 6.6. Comparison 6 Cycled inhaled tobramycin versus culture-based inhaled tobramycin, Outcome 6 Participants with one or more severe pulmonary exacerbations.

Study or subgroup	Cycled n/N	Culture-based n/N	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Treggiari 2011	24/152	26/152		0.91[0.5,1.67]



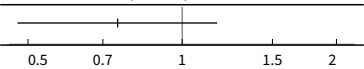
Analysis 6.7. Comparison 6 Cycled inhaled tobramycin versus culture-based inhaled tobramycin, Outcome 7 Time to pulmonary exacerbation (any severity).

Study or subgroup	Cycled	Culture-based	log[Hazard Ratio]	Hazard Ratio	Hazard Ratio
	N	N	(SE)	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Treggiari 2011	152	152	-0.2 (0.135)		0.8[0.61,1.04]



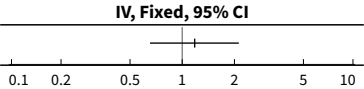
Analysis 6.8. Comparison 6 Cycled inhaled tobramycin versus culture-based inhaled tobramycin, Outcome 8 Participants with one or more pulmonary exacerbations (any severity).

Study or subgroup	Cycled	Culture-based	Odds Ratio	Odds Ratio
	n/N	n/N	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Treggiari 2011	70/152	81/152		0.75[0.48,1.17]



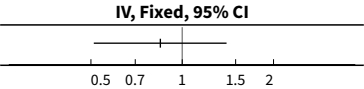
Analysis 6.9. Comparison 6 Cycled inhaled tobramycin versus culture-based inhaled tobramycin, Outcome 9 Participants with new isolates of *Stenotrophomonas maltophilia*.

Study or subgroup	Cycled	Culture-based	Odds Ratio	Odds Ratio
	n/N	n/N	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Treggiari 2011	29/138	26/141		1.18[0.65,2.12]



Analysis 6.10. Comparison 6 Cycled inhaled tobramycin versus culture-based inhaled tobramycin, Outcome 10 Participants with one or more serious adverse event.

Study or subgroup	Cycled	Culture-based	Odds Ratio	Odds Ratio
	n/N	n/N	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Treggiari 2011	39/152	44/152		0.85[0.51,1.4]



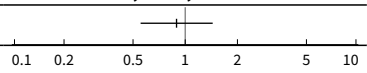
Comparison 7. Ciprofloxacin versus placebo added to cycled and culture-based inhaled tobramycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with one or more isolates of *P aeruginosa* from respiratory tract	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected
2 FEV_1 % predicted - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Mean duration of 70 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Weight (kg) - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Mean duration of 70 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Height (cm) - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Mean duration of 70 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Time to severe pulmonary exacerbation	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected
6 Participants with one or more severe pulmonary exacerbations	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected
7 Time to pulmonary exacerbation (any severity)	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected
8 Participants with one of more pulmonary exacerbation (any severity)	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected
9 Participants with new isolates of *Stenotrophomonas maltophilia*	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected
10 Participants with one or more serious adverse event	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected

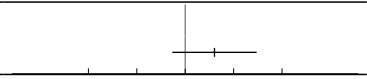
Analysis 7.1. Comparison 7 Ciprofloxacin versus placebo added to cycled and culture-based inhaled tobramycin, Outcome 1 Participants with one or more isolates of *P aeruginosa* from respiratory tract.

Study or subgroup	Ciprofloxacin n/N	Placebo n/N	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Treggiari 2011	49/146	55/152		0.89[0.55,1.44]



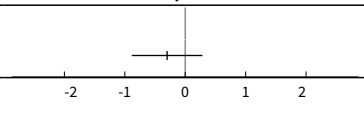
Analysis 7.2. Comparison 7 Ciprofloxacin versus placebo added to cycled and culture-based inhaled tobramycin, Outcome 2 FEV_1 % predicted - change from baseline.

Study or subgroup	Ciprofloxacin N	Ciprofloxacin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
7.2.1 Mean duration of 70 weeks						
Treggiari 2011	67	1.2 (13.6)	76	-1.8 (12.9)		3.02[-1.33,7.37]



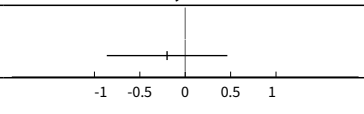
Analysis 7.3. Comparison 7 Ciprofloxacin versus placebo added to cycled and culture-based inhaled tobramycin, Outcome 3 Weight (kg) - change from baseline.

Study or subgroup	Ciprofloxacin		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
7.3.1 Mean duration of 70 weeks						
Treggiari 2011	152	3.8 (2.5)	152	4.1 (2.7)		-0.3[-0.88,0.28]



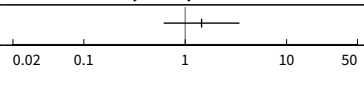
Analysis 7.4. Comparison 7 Ciprofloxacin versus placebo added to cycled and culture-based inhaled tobramycin, Outcome 4 Height (cm) - change from baseline.

Study or subgroup	Ciprofloxacin		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
7.4.1 Mean duration of 70 weeks						
Treggiari 2011	152	9.2 (2.8)	152	9.4 (3.1)		-0.2[-0.86,0.46]



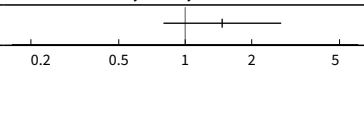
Analysis 7.5. Comparison 7 Ciprofloxacin versus placebo added to cycled and culture-based inhaled tobramycin, Outcome 5 Time to severe pulmonary exacerbation.

Study or subgroup	Ciprofloxacin	Placebo	log[Hazard Ratio]	Hazard Ratio	Hazard Ratio
	N	N	(SE)	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Treggiari 2011	152	152	0.4 (0.439)		1.45[0.61,3.43]



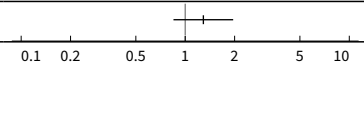
Analysis 7.6. Comparison 7 Ciprofloxacin versus placebo added to cycled and culture-based inhaled tobramycin, Outcome 6 Participants with one or more severe pulmonary exacerbations.

Study or subgroup	Ciprofloxacin	Placebo	Odds Ratio	Odds Ratio
	n/N	n/N	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Treggiari 2011	29/152	21/152		1.47[0.8,2.72]



Analysis 7.7. Comparison 7 Ciprofloxacin versus placebo added to cycled and culture-based inhaled tobramycin, Outcome 7 Time to pulmonary exacerbation (any severity).

Study or subgroup	Ciprofloxacin	Placebo	log[Hazard Ratio]	Hazard Ratio	Hazard Ratio
	N	N	(SE)	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Treggiari 2011	152	152	0.3 (0.214)		1.29[0.85,1.96]



Analysis 7.8. Comparison 7 Ciprofloxacin versus placebo added to cycled and culture-based inhaled tobramycin, Outcome 8 Participants with one of more pulmonary exacerbation (any severity).

Study or subgroup	Ciprofloxacin n/N	Placebo n/N	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Treggiari 2011	83/152	68/152		1.49[0.95,2.33]
		Favours ciprofloxacin	0.5 0.7 1 1.5 2	Favours placebo

Analysis 7.9. Comparison 7 Ciprofloxacin versus placebo added to cycled and culture-based inhaled tobramycin, Outcome 9 Participants with new isolates of *Stenotrophomonas maltophilia*.

Study or subgroup	Ciprofloxacin n/N	Placebo n/N	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Treggiari 2011	29/137	26/142		1.2[0.66,2.16]
		Favours ciprofloxacin	0.5 0.7 1 1.5 2	Favours placebo

Analysis 7.10. Comparison 7 Ciprofloxacin versus placebo added to cycled and culture-based inhaled tobramycin, Outcome 10 Participants with one or more serious adverse event.

Study or subgroup	Ciprofloxacin n/N	Placebo n/N	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Treggiari 2011	48/152	35/152		1.54[0.93,2.57]
		Favours ciprofloxacin	0.2 0.5 1 2 5	Favours placebo

WHAT'S NEW

Date	Event	Description
27 February 2020	Amended	Clarification statement added from Kevin Southern, Cystic Fibrosis Editor on 27 February 2020: This review was found by the Cochrane Funding Arbiters, post-publication, to be noncompliant with the Cochrane conflict of interest policy, which includes the relevant parts of the Cochrane Commercial Sponsorship Policy. The review will be updated by February 2021; the update will have a majority of authors and lead author free of conflicts. Current version (post-publication): Simon Langton Hewer is the lead investigator on the ongoing trial Torpedo-CF: Trial of Optimal Therapy for Pseudomonas Eradication in Cystic Fibrosis, he has no financial conflicts of interest. Alan Smyth declares relevant activities of membership of a Raptor steering committee, consultancies for Raptor, Gilead, Vertex, Roche and PTC. Actavis provide support for CF team educational activities.

HISTORY

Protocol first published: Issue 2, 2003
Review first published: Issue 1, 2006

Date	Event	Description
19 April 2017	New citation required but conclusions have not changed	We have not been able to include data from any new trials at this update and our conclusions remain the same.
18 April 2017	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified 56 unique references possibly eligible for inclusion in the review. One reference (conference abstract) was a new ongoing trial (Ratjen 2016). Four references were added to an already included trial (Treggiari 2011). Eight references were added to four already excluded trials: four references (Goss 2009); one reference (Mainz 2014); two references (Wainwright 2011a); and one reference (Wainwright 2011b). Ten new trials (47 references) were excluded (Elborn 2015; Flume 2015a; Flume 2015b; Flume 2016; Geller 2011; Konstan 2011; Konstan 2015; Ruddy 2013; Stass 2013; Stockmann 2015). Two references described two of the trials and one reference described three of the trials - these references are linked multiple times, once to each of the trials they describe. Summary of findings tables have been included in the review at this update.
29 October 2014	New search has been performed	A search of the Group's CF Register identified 117 references for possible inclusion in the review. Three references have been added to an already included trial (Proesmans 2013). One trial, known as the ELITE trial, has been moved from 'Ongoing studies' to 'Included studies' and the reference to the full publication added; this trial has provided a comparison of duration of intervention not previously available for inclusion (Ratjen 2010). A further trial also previously listed as ongoing with the study ID Ramsey 2005 (also known as the EPIC trial) has been included with 11 new references (Treggiari 2011). One new trial, with nine references has been included (Taccetti 2012). A total of 22 new trials (97 references) have been excluded: one reference each (Alothman 2005; Goss 2009; Prayle 2013; Postnikov 2007; Wainwright 2011b); two references each (Alothman 2002; Kenny 2009; Mainz 2014; Schelstraete 2010; Tramper-Stranders 2009); three references each (Coates 2011; Geller 2007; Mazurek 2012; Rietschel 2009); four references each (Retsch-Bogart 2008; Trapnell 2012); five references each (Clancy 2013; Konstan 2010); six references each (Oermann 2009; Schuster 2013); 10 references (Retsch-Bogart 2009); and 32 references (Ramsey 1999). Two trials previously listed as 'Awaiting classification' have now been excluded (Latzin 2008; Lenoir 2007). One additional refer-

Date	Event	Description
		ence has been added to a previously excluded study (Wainwright 2011a) The full paper to an abstract already listed as 'Awaiting Classification' has now been published and added to the existing study ID while we await clarification regarding participants from the authors (Noah 2010). One new trial (with a single reference) has been added to 'Ongoing studies' (TORPEDO Trial). There have been three *post hoc* changes to the review at this update: • we now include participants who have received treatment within six months of the first isolation of *P. aeruginosa* (previously not more than two months); • we now allow trials where all patients receive some eradication therapy before randomisation which reflects current recommended 'standard of care' and consequent trial design; • we have added cost as an outcome measure, as cost-effectiveness has become increasingly important in CF care.
29 October 2014	New citation required but conclusions have not changed	This review has been updated, but the conclusions remain the same.
10 June 2009	New search has been performed	A new search of the Group's CF Register identified 14 new references. We have included one new study with one reference (Proesmans 2013) and excluded two new studies with three new references (Postnikov 2000; Steinkamp 2007). Three studies with a total of five references are listed as 'Awaiting classification' until we are able to obtain further details (Latzin 2008a; Lenoir 2007a; Noah 2007). We have added five references to the two ongoing studies: one reference to Ramsey 2005a and four references to Ratjen 2006a.
10 June 2009	New citation required but conclusions have not changed	From the 2009 update of this review, the lead author Dr Damian Wood has stepped down and is no longer involved in the review. The new lead author is Dr Simon Langton Hewer.
12 November 2008	Amended	Converted to new review format.
13 November 2007	Amended	The review authors have addressed some comments from the CFGD Group's medical statistician within this update.
13 November 2007	New search has been performed	The search identified four new trials; two of which have been excluded (Gibson 2007; Griese 2002); and two of which are still ongoing (Ramsey 2005a; Ratjen 2006a).
15 November 2006	Feedback has been incorporated	The review now contains the response from the authors to feedback regarding the necessity of further trials received through The Cochrane Library Feedback system.

CONTRIBUTIONS OF AUTHORS

Damian Wood wrote the first draft of the review and both Damian Wood and Alan Smyth edited it to produce the final original review version. Both Damian Wood and Alan Smyth have worked on updated versions of the review up until 2007. As from Issue 2, 2009 the new lead author is Simon Langton Hewer. The most recent version of the review was jointly written by Simon Langton Hewer and Alan Smyth.

Simon Langton Hewer acts as guarantor of the review.

DECLARATIONS OF INTEREST

Dr Langton Hewer is the lead investigator on the ongoing trial Torpedo-CF: Trial of Optimal Therapy for Pseudomonas Eradication in Cystic Fibrosis.

Prof Smyth declares relevant activities of membership of a Raptor steering committee, consultancies for Raptor, Gilead, Vertex, Roche and PTC. Actavis provide support for CF team educational activities.

Clarification statement added from Kevin Southern, Cystic Fibrosis Editor on 27 February 2020: This review was found by the Cochrane Funding Arbiters, post-publication, to be noncompliant with the Cochrane conflict of interest policy, which includes the relevant parts of the Cochrane Commercial Sponsorship Policy. The review will be updated by February 2021; the update will have a majority of authors and lead author free of conflicts.

Current version (post-publication): Dr Langton Hewer is the lead investigator on the ongoing trial Torpedo-CF: Trial of Optimal Therapy for Pseudomonas Eradication in Cystic Fibrosis, he has no financial conflicts of interest.

Prof Smyth declares relevant activities of membership of a Raptor steering committee, consultancies for Raptor, Gilead, Vertex, Roche and PTC. Actavis provide support for CF team educational activities.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

  This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2014

The inclusion criteria have been changed to include participants who have received study treatment within six months of the first isolation of *P aeruginosa* (previously not more than two months). This is to reflect differences in clinical practice between Europe and North America and to allow trials from earlier decades (where early treatment of *P aeruginosa* was not established clinical practice) to be included. A large trial (306 participants), published in 2011, is therefore now eligible for inclusion (Treggiari 2011). However, it is possible that, where infection has been present for as long as six months, it may have become more difficult to eradicate.

In recent years 28 days of inhaled tobramycin has been recommended as 'standard of care' for eradication of *P aeruginosa* in guidelines (Döring 2012). This has been reflected in trial design, where investigators have designed their trials to ensure that all participants receive an initial 28-day course of inhaled tobramycin before randomisation to the next stage of therapy. We have therefore altered our eligibility criteria to allow trials where all participants receive some eradication therapy before randomisation (Treggiari 2011).

We have added cost as an outcome measure, as cost-effectiveness has become increasingly important in CF care. None of the trials included to date have reported this outcome but future trials may do so.

2009

After the new lead reviewer re-assessed the review, the section 'Objectives' was expanded to include the sentence:

'To investigate whether there is evidence of superiority or improved cost-effectiveness between antibiotic strategies.'

Currently, we have included both *P aeruginosa*-free and *P aeruginosa*-naive individuals according to the definition by Lee (Lee 2003). At the update in 2009 we have added plans to analyse these subgroups separately if sufficient data become available from included studies in the future.

2005

Two clinically relevant additional outcomes were added at review stage to the ones we had originally listed:

1. Time to chronic infection (defined as the presence of *P aeruginosa* in each monthly sputum sample for six consecutive months or the presence of precipitating antibodies to *P aeruginosa* or both)
2. Clinical and radiological scores

INDEX TERMS

Medical Subject Headings (MeSH)

*Pseudomonas aeruginosa; Administration, Inhalation; Administration, Oral; Anti-Bacterial Agents [administration & dosage] [*therapeutic use]; Ciprofloxacin [administration & dosage] [therapeutic use]; Colistin [administration & dosage] [therapeutic use]; Cystic Fibrosis [*complications] [microbiology]; Pseudomonas Infections [*drug therapy]; Randomized Controlled Trials as Topic; Respiratory System [microbiology]; Tobramycin [administration & dosage] [therapeutic use]

MeSH check words

Adult; Child; Humans