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Antibiotic adjuvant therapy for pulmonary infection in cystic fibrosis (Review)

Hurley MN, Smith S, Forrester DL, Smyth AR

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[Intervention Review]

Antibiotic adjuvant therapy for pulmonary infection in cystic fibrosis

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ABSTRACT

Background

Cystic fibrosis is a multi-system disease characterised by the production of thick secretions causing recurrent pulmonary infection, often with unusual bacteria. This leads to lung destruction and eventually death through respiratory failure. There are no antibiotics in development that exert a new mode of action and many of the current antibiotics are ineffective in eradicating the bacteria once chronic infection is established. Antibiotic adjuvants - therapies that act by rendering the organism more susceptible to attack by antibiotics or the host immune system, by rendering it less virulent or killing it by other means, would be a significant therapeutic advance. This is an update of a previously published review.

Objectives

To determine if antibiotic adjuvants improve clinical and microbiological outcome of pulmonary infection in people with cystic fibrosis.

Search methods

We searched the Cystic Fibrosis Trials Register which is compiled from database searches, hand searches of appropriate journals and conference proceedings.

Date of most recent search: 16 January 2020.

We also searched MEDLINE (all years) on 14 February 2019 and ongoing trials registers on 06 April 2020.

Selection criteria

Randomised controlled trials and quasi-randomised controlled trials of a therapy exerting an antibiotic adjuvant mechanism of action compared to placebo or no therapy for people with cystic fibrosis.

Data collection and analysis

Two of the authors independently assessed and extracted data from identified trials.

Main results

We identified 42 trials of which eight (350 participants) that examined antibiotic adjuvant therapies are included. Two further trials are ongoing and five are awaiting classification. The included trials assessed β-carotene (one trial, 24 participants), garlic (one trial, 34 participants), KB001-A (a monoclonal antibody) (two trials, 196 participants), nitric oxide (two trials, 30 participants) and zinc supplementation (two trials, 66 participants). The zinc trials recruited children only, whereas the remaining trials recruited both adults and children. Three trials were located in Europe, one in Asia and four in the USA.

Three of the interventions measured our primary outcome of pulmonary exacerbations (β-carotene, mean difference (MD) -8.00 (95% confidence interval (CI) -18.78 to 2.78); KB001-A, risk ratio (RR) 0.25 (95% CI 0.03 to 2.40); zinc supplementation, RR 1.85 (95% CI 0.65 to 5.26). β-carotene and KB001-A may make little or no difference to the number of exacerbations experienced (low-quality evidence); whereas, given the moderate-quality evidence we found that zinc probably makes no difference to this outcome.

Respiratory function was measured in all of the included trials. β-carotene and nitric oxide may make little or no difference to forced expiratory volume in one second (FEV_1) (low-quality evidence), whilst garlic probably makes little or no difference to FEV_1 (moderate-quality evidence). It is uncertain whether zinc or KB001-A improve FEV_1 as the certainty of this evidence is very low.

Few adverse events were seen across all of the different interventions and the adverse events that were reported were mild or not treatment-related (quality of the evidence ranged from very low to moderate).

One of the trials (169 participants) comparing KB001-A and placebo, reported on the time to the next course of antibiotics; results showed there is probably no difference between groups, HR 1.00 (95% CI 0.69 to 1.45) (moderate-quality evidence). Quality of life was only reported in the two KB001-A trials, which demonstrated that there may be little or no difference between KB001-A and placebo (low-quality evidence). Sputum microbiology was measured and reported for the trials of KB001-A and nitric oxide (four trials). There was very low-quality evidence of a numerical reduction in *Pseudomonas aeruginosa* density with KB001-A, but it was not significant. The two trials looking at the effects of nitric oxide reported significant reductions in *Staphylococcus aureus* and near-significant reductions in *Pseudomonas aeruginosa*, but the quality of this evidence is again very low.

Authors' conclusions

We could not identify an antibiotic adjuvant therapy that we could recommend for treating of lung infection in people with cystic fibrosis. The emergence of increasingly resistant bacteria makes the reliance on antibiotics alone challenging for cystic fibrosis teams. There is a need to explore alternative strategies, such as the use of adjuvant therapies. Further research is required to provide future therapeutic options.

PLAIN LANGUAGE SUMMARY

Antibiotic enhancing treatment for lung infections in cystic fibrosis

Review question

We reviewed the evidence about the use of agents to help antibiotics in treating lung infections in people with cystic fibrosis.

Background

People with cystic fibrosis suffer from infections in their lungs as they produce thick secretions which allow bacteria to grow in them. Often the infections are caused by unusual bacteria, including *Pseudomonas aeruginosa,* and these bacteria become resistant to treatment with antibiotics. Long-term infection reduces a person's quality of life and their lung function. There are no new antibiotics currently being developed which use a new type of action. New agents - antibiotic adjuvants - are needed to work alongside antibiotics to make bacteria more sensitive to either antibiotics or to the body's own immune system, and to interfere with the formation of colonies of bacteria in the lungs.

Search date

The evidence is current to: 16 January 2020.

Trial characteristics

The review includes eight trials with 350 people with cystic fibrosis aged between five and 54 years of age. Trials compared different antibiotic adjuvants (beta-carotene (one trial), garlic (one trial), a biological agent (two trials), nitric oxide (two trials) and zinc (two trials)) with placebo (a substance that contains no medication) and people were selected for one treatment or the other randomly. The trials lasted from two days to one year.

Key results

None of the treatments led to a longer time until the next flare up of lung disease compared to the people who received placebo. For the other measures we looked at (lung function, side effects, quality of life or number of infections) there were also no differences between the people given the adjuvant and the people given the placebo. All of the trials measured side effects of the treatment but these were mostly mild and happened in both the people receiving the treatment and those that did not.

None of the therapies for enhancing the actions of antibiotics which we found, showed a significant benefit for either lung function, rate of infection or quality of life. More randomised controlled trials are needed before we can recommend the routine use of any of these therapies.

Quality of the evidence

The quality of the evidence ranges from very low to moderate, but we judged it to be low overall. We made these judgements because of the small number of trials that looked at each of the different adjuvant treatments meaning we were unable to combine results. The quality was also affected by the small number of people who were included.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings: β-carotene compared with placebo for chronic pulmonary infection in cystic fibrosis

β-carotene compared with placebo for chronic pulmonary infection in cystic fibrosis

Patient or population: children and adults with cystic fibrosis

Settings: outpatients

Intervention: oral β-carotene supplementation

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	β-carotene				
Pulmonary exacerbations Days of antibiotic use Follow-up: 3 months	The mean number of days of antibiotics was 18.5 days in the control group.	The mean number of days of antibiotics in the intervention group was **8 days lower** (18.8 days lower to 2.78 days higher).	**MD -8.00** (-18.78 to 2.78)	24 (1)	⊕⊕⊖⊖ **low**[a,b]	The authors of this paper defined pulmonary exacerbations by the number of days of antibiotics. Pulmonary exacerbations were less frequent in the intervention group but this was not statistically significant (P = 0.15).
Respiratory function absolute FEV_1 % predicted Follow-up: 3 months	The mean FEV_1 % predicted was 80.9% in the control group.	The mean FEV_1 % predicted in the intervention group was **10.9% lower** (32.2% lower to 10.4% higher).	**MD -10.90** (-32.23 to 10.43)	24 (1)	⊕⊕⊖⊖ **low**[a,b]	The results favour the placebo for effect on FEV_1 but this was not significant (P = 0.32).
Adverse events Follow-up: 6 months	See comments.			24 (1)	⊕⊕⊖⊖ **low**[a,b]	There were no adverse events reported during the trial. Some participants reported better tanning after exposure to sunlight. No further data were provided for adverse events.
Need for antibiotics	See comments.					This outcome was reported by the authors as their definition of pulmonary exacerbations. The number of days of antibiotics was less in

see pulmonary exacerbations		the β-carotene group but not significantly so (P = 0.15).
QoL	This outcome was not measured.	
Sputum microbiology	This outcome was not measured.	
Inflammatory markers	This outcome was not measured.	

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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 1 second; **MD**: mean difference; **QoL**: quality of life.

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.

[a] Downgraded once due to risk of bias within the included trial, particularly from uncertainty of randomisation method and allocation concealment.
[b] Downgraded once due to imprecision. The trial had a small number of participants which is well below the optimal information size and low event rates.

Summary of findings 2. Summary of findings: garlic supplementation compared with placebo for chronic pulmonary infection in cystic fibrosis

Garlic supplementation compared with placebo for chronic pulmonary infection in cystic fibrosis

Patient or population: children aged over eight and adults with cystic fibrosis and chronic pulmonary infection with *P aeruginosa*

Settings: outpatients

Intervention: garlic capsule once daily

Comparison: placebo capsule once daily

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	Placebo	Garlic supplement				
Pulmonary exacerbations	This outcome was not measured in this trial.					
Respiratory function change from baseline in % predicted FEV_1 Follow-up: 8 weeks	The mean change in FEV_1 % predicted was -3.6 % in the control group.	The mean change in FEV_1 % predicted in the intervention group was **1.59% higher** (7.49% lower to 10.67% higher).	**MD 1.59** (-7.49 to 10.67)	26 (1)	⊕⊕⊕⊖ **moderate**[a]	There was no significant difference between the groups after 8 weeks of treatment (P = 0.73).
Adverse events mild adverse events Follow-up: 8 weeks	See comments.			26 (1)	⊕⊕⊕⊖ **moderate**[a]	5 participants in the garlic group reported minor adverse effects: diarrhoea: OR 5.87 (95% CI 0.25 to 135.15; P = 0.27); halitosis: OR 5.87 (95% CI 0.25 to 135.15; P = 0.27); abdominal pain: OR 3.24 (95% CI 0.12 to 87.13; P = 0.48); dysuria: OR 3.24 (95% CI 0.12 to 87.13; P = 0.48). 1 participant in each group reported minor haemoptysis, OR 1.00 (95% CI 0.06 to 17.90; P = 1.0). Overall there was no significant difference between garlic and placebo for any of the adverse effects.
Need for antibiotics days of antibiotic use Follow-up: 8 weeks	This outcome was not measured in this trial.					Days of antibiotic use was not reported but 7 participants in the garlic group received intravenous antibiotics compared to 5 in the placebo group.
QoL	This outcome was not measured in this trial.					
Sputum microbiology	This outcome was not measured in this trial					
Inflammatory markers	This outcome was not measured in this trial					

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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 1 second; **MD:** mean difference; **QoL**: quality of life.

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.

[a] Downgraded once due to imprecision from low number of participants which does not reach the optimal information size.

Summary of findings 3. Summary of findings: monoclonal antibody KB001-A compared with placebo for chronic pulmonary infection in cystic fibrosis

Monoclonal antibody KB001-A compared with placebo for chronic pulmonary infection in cystic fibrosis

Patient or population: children (12 or over) and adults with cystic fibrosis and lung infection

Settings: outpatients

Intervention: monoclonal antibody KB001-A

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	KB001-A				
Pulmonary exacerbations Follow-up: 8 to 16 weeks	Of the 2 trials reporting this outcome, the small trial reported no pulmonary exacerbations in the low-dose group (10 mg/kg), 1 pulmonary exacerbation in the 3 mg/kg group and 2 pulmonary exacerbations in the placebo group (RR 0.25 (95% CI 0.03 to 2.40)). This showed a slight difference in favour of KB001-A but this was non-significant (Milla 2013). The larger Jain trial, did not report exacerbations as an outcome, but did report that exacerbations were the most commonly reported adverse event in both the KB001-A and placebo group (57.8% of KB001-A participants and 67.4% of placebo participants) (Jain 2018).			196 (2)	⊕⊕⊖⊖ **low[a]**	The data from the 2 trials could not be combined as 1 was a single-dose trial whilst the other trial administered KB001-A via infusion every 4 weeks over 16 weeks in total.

Respiratory function number of episodes of a drop in FEV_1 (unit of measurement not given) Follow-up: 8 to 16 weeks	Six participants who received a single 3 mg/kg dose of KB001-A experienced a decrease in FEV_1, RR 4.74 (95% CI 0.28 to 79.44) compared to no drop in FEV_1 in the placebo group (Milla 2013). At the end of the 16-week trial of KB001-A, the authors reported a 3 percentage point increase from baseline in % predicted FEV_1, MD 3.2% (95% CI 1.12% predicted to 5.30% predicted; P = 0.003) in the KB001-A arm versus placebo (Jain 2018).	196 (2)	⊕⊖⊖⊖ **very low[a,b]**	
Adverse events number of participants experiencing adverse events Follow up: 56 days	Milla (single-dose trial) reported a slight non-significant difference in how many participants experienced any adverse event favouring placebo, RR 1.30 (95% CI 0.90 to 1.87) and no significant difference between intervention and placebo for serious adverse events: bronchitis (1 participant in the KB001-A group) RR 1.58 (95% CI 0.07 to 35.32); sinusitis (1 participant in the placebo group) RR 0.18 (95% CI 0.01 to 3.92) (Milla 2013). Jain reported no treatment-emergent adverse events and similar numbers of participants with infusion reactions between intervention and placebo groups.	196 (2)	⊕⊖⊖⊖ **very low[a,c]**	Neither of the trials reported significant differences in any adverse events, but event rates were very low.
Need for antibiotics time to need for antibiotics Follow-up: 16 weeks	Jain found no difference in the time to need for antibiotics in the KB001-A group versus placebo over the 16-week trial period, HR 1.00 (95% CI 0.69 to 1.45).	169 (1)	⊕⊕⊕⊖ **moderate[d]**	
QoL change in CFQ-R score Follow-up: 56 days	Milla reported no difference in the change in CFQ-R from baseline between the KB001-A and placebo groups.	27 (1)	⊕⊕⊖⊖ **low[e,f]**	Only the Milla study reported CFQ-R (Milla 2013). Jain (n = 169) did not measure CFQ-R, but did measure change in respiratory symptom scores from baseline using the CFRSD-CRISS symptom severity score. There was no difference found between

				treatment groups (Jain 2018).
Sputum microbiology Follow-up: 28 days	We were not able to enter the data into the analysis and have reported results narratively (Milla 2013). At day 28 there was a numerical reduction from baseline in median mucoid *P aeruginosa* density in the KB001-A 10 mg/kg group (-0.4 log_{10}) compared to placebo (0.8 log_{10}), but the changes were not significant.	27 (1)	⊕⊕⊖⊖ **low**[e,f]	
Inflammatory markers Follow-up: 28 to 56 days	Milla reported no significant change from baseline in any biomarkers but there was a trend towards a KB001-A dose-dependent reduction in sputum MPO, IL-8, IL-1β and NE (Milla 2013). Jain reported a -0.24 log_{10} reduction in IL-8 in the KB001-A group compared to placebo at week 16 (P = 0.04) (Jain 2018).	196 (2)	⊕⊖⊖⊖ **very low**[a,c]	The Jain trial also reported a non-significant decrease in sputum NE, MD -0.27 (95% CI -0.58 to 0.04; P = 0.084) (Jain 2018).

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CFQ-R: CF Questionnaire-Revised; **CFRSD-CRISS**: Cystic Fibrosis Respiratory Symptom Diary-Chronic Respiratory Infection Symptom Score; **CI:** confidence interval; **FEV_1**: forced expiratory volume in 1 second; **HR**: hazard ratio; **IL-1β**: interleukin-1β ;**IL-8**: interleukin 8; **MD**: mean difference; **MPO**: myeloperoxidase; **NE**: neutrophil elastase; ***P aeruginosa*** *: Pseudomonas aeruginosa*; **QoL**: quality of life; **RR**: risk ratio.

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

a. Dowgraded twice due to risk of bias within the trials contributing to this outcome. There was concern around randomisation and allocation concealment in 1 trial and a risk from attrition bias in the other included trial.
b. Downgraded due to inconsistency caused by heterogeneity between the 2 studies for his outcome.
c. Downgraded due to imprecision from low event rates.
d. Downgraded once because there was unclear risk of bias from attrition in the 1 included trial. Although an intention-to-treat analysis was used, there was a 27% drop-out rate
e. Downgraded once due to risk of bias within the 1 included trial for this outcome. There was concern around randomisation and allocation concealment as this was not clearly stated.
f. Downgraded once due to imprecision caused by low participant numbers and low event rates.

Summary of findings 4. Summary of findings: nitric oxide compared with placebo for chronic pulmonary infection in cystic fibrosis

Nitric oxide compared with placebo for chronic pulmonary infection in cystic fibrosis
Patient or population: children (12 or over) and young adults with cystic fibrosis

Settings: unclear if inpatient or outpatient

Intervention: inhaled NO (10 ppm inhaled overnight for 5 - 7 days; 20 ppm or 40 ppm inhaled continuously for 44 hours)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	NO				
Pulmonary exacerbations	This outcome was not measured in this trial.					
Respiratory function mean change in FEV_1 % predicted from baseline Follow-up: 20 days	The mean change in FEV_1 % predicted in the control group is 6.17%.	The mean FEV_1 % predicted in the intervention group was **2% lower** (10% lower to 6% higher).	**MD -1.95** (-9.94 to 6.04)	12 (1)	⊕⊕⊖⊖ **low**[a,b]	There was no significant difference between the NO group and placebo (P = 0.63).
Adverse events Follow-up: 48 hours to 20 days	In one trial 4 participants reported adverse events including epistaxis, cough and cold, increased cough and haemoptysis but all were considered mild and only possibly related to the trial treatment. In the placebo group only one adverse event was reported, which was epistaxis (Howlin 2017). Sagel reported no serious adverse events in either NO or placebo group at either the low dose or high dose of NO (Sagel 2009).			30 (2)	⊕⊖⊖⊖ **very low**[a,b]	
Need for antibiotics	This outcome was not measured.					
QoL	This outcome was not measured.					
Sputum microbiology Follow-up: 48 hours to 20 days	One trial showed a significant reduction in *S aureus* colony counts in the high-dose NO group relative to placebo (P = 0.03) and a near significant reduction in *P aeruginosa* colony counts in the high-dose group relative to placebo (P = 0.06) (Sagel 2009). The second trial found a significant reduction in *P aeruginosa* biofilm aggregates compared with those receiving placebo with antibiotics over the 7-day treatment period (P = 0.029) and there was less *P aeruginosa* biofilm in the NO group compared with placebo (Howlin 2017).			30 (2)	⊕⊖⊖⊖ **very low**[b,c]	

Inflammatory markers	This outcome was not measured.

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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 1 second; **NO**: nitric oxide; ***P aeruginosa***: *Pseudomonas aeruginosa*; **RR**: risk ratio; ***S aureus***: *Staphylococcus aureus*.

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.

[a] Downgraded once from risk of bias because of uncertainty around selective reporting of outcomes.
[b] Downgraded once due to imprecision from very low number of participants and low event rates.
[c] Downgraded twice for risk of bias within the included trials. There were concerns around randomisation, allocation concealment, selective reporting and attrition bias.

Summary of findings 5. Summary of findings: Zinc supplementation compared with placebo for chronic pulmonary infection in cystic fibrosis

Zinc supplementation compared with placebo for chronic pulmonary infection in cystic fibrosis

Patient or population: children with cystic fibrosis

Settings: outpatients

Intervention: zinc supplementation (30 mg orally once daily)

Comparison: placebo (orally once daily)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Zinc supplement				
Pulmonary exacerbations number of participants requiring IV antibiotics Follow-up: 12 months	**211 per 1000.**	**390 per 1000** (137 to 1000).	**RR 1.85** (0.65 to 5.26)	37 (1)	⊕⊕⊕⊖ **moderate**[a]	Results favour placebo, but not significantly (P = 0.25) (Sharma 2016).

Respiratory function mean FEV_1 % predicted Follow-up: 24 months	One trial showed no difference between groups, MD -5.46 (95% CI -19.44 to 8.52) (Abdulhamid 2008). A further paper reported that the median (IQR) FEV_1 % predicted value was 8.97% (-18.23% to 0.33%) lower than baseline in the zinc group and 9.55% (-9.59% to 12.88%) higher in the placebo group (P = 0.08) (Sharma 2016).			62 (2)	⊕⊖⊖⊖ **very low**[b,c,d]	Results have been reported narratively as the outcome was reported differently in the 2 trials.
Adverse events number of participants hospitalised during the trial Follow-up: 12 months	**316 per 1000**.	**389 per 1000** (161 to 939).	**RR 1.23** (0.51 to 2.97)	37 (1)	⊕⊕⊕⊖ **moderate**[a]	All of the serious adverse events were related to exacerbations. Although no data were reported, the Abdulhamid trial reported there were no adverse events (Abdulhamid 2008).
Need for antibiotics number of days on IV or oral antibiotics Follow-up: 24 months	Abdulhamid reported that significantly fewer oral antibiotics alone were needed by participants in the zinc group, MD -17.74 (95% CI -26.98 to -8.50); but there was no significant difference between groups in the need for IV antibiotics alone, MD 0.52 (95% CI -3.07 to 4.11) (Abdulhamid 2008). The Sharma trial found no significant difference in the number of days on IV or oral antibiotics (P = 0.76) (Sharma 2016).			62 (2)	⊕⊖⊖⊖ **very low**[b,c]	
QoL	This outcome was not reported.					
Sputum microbiology	This outcome was not reported.					
Inflammatory markers	This outcome was not reported.					

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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 1 second; **IV**: intravenous; **IQR**: interquartile range; **RR**: risk ratio; **MD**: mean difference.

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.

[a] Downgraded once due to imprecision caused by low event rates and a small participant numbers (n = 37).
[b] Downgraded once due to risk of bias within 1 of the included trials; there were concerns across 5 out of the 6 domains for assessing risk of bias.
[c] Downgraded once due to imprecision from small number of participants.

[d] Downgraded once due to inconsistency caused by heterogeneity between the 2 trial results.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a multi-system disease characterised by the production of thick secretions causing recurrent pulmonary infection and pancreatic malabsorption. The altered lung environment in people with CF provides an ideal niche for bacteria such as *Pseudomonas aeruginosa* to flourish and chronic infection to develop. This results in damage to the airways leading to a decline in lung function that is largely responsible for the morbidity and mortality in CF. Over the last two decades more efficient treatment of pulmonary infections has contributed to a large increase in life-expectancy (Dodge 2007). The mean life expectancy for a baby born in 2003 was 42 years for a boy and 36 years for a girl (Dodge 2007). However, the adaptive behaviour of *P aeruginosa* enables it to rapidly evolve in response to selective pressures exerted by the host environment and the use of bactericidal antibiotics. Thus, the increased use of broad spectrum antimicrobials has resulted in a reduction in their efficacy and an increase in bacterial resistance. In addition to *P aeruginosa*, other important, antibiotic-resistant pathogens can be found in the lungs of people with CF such as *Burkholderia cepacia* and methicillin-resistant *Staphylococcus aureus* (MRSA).

Description of the intervention

Novel agents are urgently needed, which act differently to antibiotics and can eradicate the organism without selecting for resistance and whilst re-sensitising them to readily available antibiotics. Antibiotics commonly act by killing the organism or stopping its growth. Antibiotic adjuvants may exert their effect on the organism without killing it. Antibiotic adjuvant therapies are a diverse group of novel agents that are similar in that they act by interfering with a mechanism the organism uses to decrease its susceptibility to antibiotics; by reducing the organism's virulence; or by rendering the organism more susceptible to the host immune system. Such agents include: quorum sensing inhibitors (see below); agents that interfere with biofilm construction (the sugars fucose and galactose, and novel dendrimers acting on lectin blockade); efflux pump inhibitors that stop bacteria removing antibiotics from within the bacterial cell; glutamine as an amino acid supplement; and biological agents (such as bacteriophages) that infect bacteria causing their break-down and demise. In the case of bacteriophages that may cause the death of the organism, they act by 'infecting' the bacteria and therefore act differently to, but alongside, conventional antibiotics.

Some of the agents that may be considered in the review are available direct to the consumer (e.g. garlic, zinc). It is therefore conceivable that the results of the trial may alter an individual's behaviour directly.

How the intervention might work

Antibiotic adjuvants are varied in their design. Many of the bacteria causing infections in CF communicate via quorum sensing, such that the bacteria only produce virulence factors when the population of bacteria has reached a critical size. The organism can therefore remain invisible to the host immune system until the population is in a position to withstand such host attack. Some antibiotic adjuvant therapies interfere with this bacterial communication, thus potentiating the efficacy of conventional antibiotics (von Bodman 2008). Some approaches attach to the genetic material of the organism, preventing the bacteria from becoming more resistant to antibiotics and some therapies target other mechanisms exploited by bacteria, such as the ability to form biofilms. Other antibiotic adjuvant therapies include bacteriophages or their products, viruses that directly target the bacterial cell, invade it and kill it (Borysowski 2006).

Why it is important to do this review

Worldwide, there is a burgeoning interest in agents that may potentiate, refine or replace the action of antibiotics without exerting selective pressure for antibiotic resistance. It is suggested that many of these agents are less susceptible to becoming inactive (due to the organism developing resistance toward them) because in many cases they do not *directly* influence the organisms' ability to reproduce. Currently both chronic pulmonary infections and acute infective exacerbations are difficult to treat and eradication of infection may be only temporary (Langton-Hewer 2017; Lo 2018; Regan 2019). With research proceeding along diverse paths and individuals making decisions regarding supplementing conventional treatment with high-street products, there is a need to evaluate current evidence to advise people with CF and their clinicians and to direct research targets.

This is an update of previous reviews (Hurley 2010; Hurley 2013).

OBJECTIVES

To determine if antibiotic adjuvant therapies improve clinical and microbiological outcome of pulmonary infection in people with CF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs.

Types of participants

Adults and children with CF, diagnosed using the Cystic Fibrosis Foundation consensus statement (Rosenstein 1998). Therefore, a diagnosis of CF should be based on:

- presence of one or more characteristic phenotypic features;
- or a positive newborn screening test result;
- or a history of CF in a sibling and laboratory evidence of an abnormality in the cystic fibrosis transmembrane regulator (CFTR) as documented by an elevated sweat chloride concentration or the identification of mutations in each CFTR gene known to cause CF or in vivo demonstration of characteristic abnormalities in ion transport across the nasal epithelium.

As no standardised, validated definitions of acute exacerbation or chronic infection exists, we have employed the definitions employed by the CF Trust Antibiotic Working Group (UK Cystic Fibrosis Trust Antibiotic Working Group) alongside those identified by Rosenfeld (Rosenfeld 2001). An acute exacerbation will be defined as at least four of the following (UK Cystic Fibrosis Trust Antibiotic Working Group):

- increased productive cough or breathlessness;
- changes in the appearance or volume of sputum;

- new signs on auscultation;
- new chest radiograph signs;
- loss of appetite;
- fall in respiratory function;
- fever requiring treatment with intravenous antibiotics.

Alternatively, an acute exacerbation was defined by the following score meeting or exceeding 2.6 (Rosenfeld 2001).

Feature	Score
Decreased exercise tolerance	1.8
Increased cough	1.5
Increased sputum or cough congestion	1.5
School or work absenteeism	1.6
Increased adventitial sounds on lung examination	1.2
Decreased appetite	1.1

The bacterium targeted by such an approach will not be limited by species. A chronic *P aeruginosa* infection will be defined by more than 50% of months in a year when samples had been taken being *P aeruginosa* culture-positive (Lee 2004). We previously had used the UK Cystic Fibrosis Trust definition of two or more occasions of *P aeruginosa* isolation over six months (UK Cystic Fibrosis Trust 2004); however, the definition cited above more closely replicates current clinical practice. A similar approach will be used for other infections, except for non-tuberculous mycobacteria which will be considered chronic is infection persists despite a year of intensive eradication treatment.

In the case of trials including both clinical scenarios or less defined criteria, we shall aim to manage these separately using a pragmatic approach.

Types of interventions

Antibiotic adjuvant agents compared to conventional antibiotics (either alone or in combination), placebo or no therapy via any route of administration.

Antibiotic adjuvant agents are those which augment the host immune response or potentiate antibiotic action. The adjuvants themselves may exert a direct killing or bacteriostatic effect on the organism but their primary role is to augment the effect of the co-administered antibiotics. Such adjuvants include those that exert an effect on bacterial susceptibility to antibiotics and include efflux pump inhibitors (agents that block the action of efflux pumps - pumps on the cell membrane that remove toxic substances from within the bacterium) or quorum sensing inhibitors. Other adjuvants change the physical resistance of an infection (e.g. lectin inhibitors) or those that act at the genetic level of the organism to prevent the acquisition of antibiotic resistance (e.g. anti-sense strategies).

Biological agents (such as bacteriophages) were eligible for inclusion in this review. Agents were considered which are intended to treat bacteria, fungi and viruses.

We excluded trials of agents that physically alter the host environment (e.g. gene therapy, immunotherapy); anti-inflammatory agents (e.g. steroids, ibuprofen); agents that alter mucociliary clearance (e.g. mannitol, hypertonic saline and dornase alfa); physical interventions (such as physiotherapy and exercise); and environmental changes (such as an infection control policy).

Types of outcome measures

Primary outcomes

1. Pulmonary exacerbations (protocol defined)
2. Respiratory function
   a. per cent (%) predicted forced expiratory volume in one second (FEV_1) values for age, sex and height
   b. % predicted forced vital capacity (FVC) values for age, sex and height
   c. other validated measures of respiratory function
3. Adverse events (AEs)
   a. mild (not requiring treatment)
   b. moderate (requiring treatment or admission)
   c. severe (life-threatening)

Secondary outcomes

1. Need for antibiotics (oral, inhaled or intravenous (IV))
   a. Time to next course of antibiotics (oral or IV)
   b. Antibiotic consumption (days of antibiotic use)
2. Quality of life (QoL) using standardised and validated QoL scores (e.g. CFQ-R (Quittner 2009)) and symptom scores (e.g. Respiratory and Systemic Symptoms Questionnaire (RSSQ), Respiratory Symptom Score (RSS) (Goss 2007))
   a. time of work or school
   b. treatment burden (e.g. challenges of living with CF evaluation)

3. Change in sputum microbiology:
   a. emergence of new CF pathogens, including development of allergic bronchopulmonary aspergillosis (ABPA) (increase in serum IgE with clinical or radiological features)
   b. quantitative microbiology (change in numbers of pathogens isolated from respiratory tract secretion culture)
4. Change in inflammatory markers
   a. serum (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR))
   b. sputum (IL-8, leukotrienes, cytokines)
5. Mortality

We assessed these outcomes for both chronic infection and acute infective exacerbations where data allowed. We assessed and analysed results separately for the two clinical scenarios at the time-points detailed below (Data extraction and management).

Search methods for identification of studies

There are no restrictions regarding language or publication status.

Electronic searches

We searched for relevant trials from the Group's Cystic Fibrosis Trials Register using the terms 'pulmonary infection' AND 'non-antibiotic'.

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 hand-searching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis 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 register, please see the relevant sections of the Cochrane Cystic Fibrosis and Genetic Disorders Group website.

Date of last search of the Cystic Fibrosis Trials Register: 16 January 2020.

We also searched MEDLINE separately; the search strategy is given in the appendices (Appendix 1; Appendix 2).

Date of last search of MEDLINE: 14 February 2019.

We also searched the ongoing trials registries as detailed in the appendices (Appendix 3); date of last search: 06 April 2020

Searching other resources

We hand-searched reference lists of identified trials. We also contacted primary authors of identified trials and research institutions or biotech companies for unpublished trials for the original review. We have contacted authors for clarification and extra data for this update.

Data collection and analysis

We used methods described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). We aimed to analyse acute infective exacerbations and chronic infection separately as defined previously in the section Types of participants. There were no interventions with outcomes in both acute and chronic conditions. We would aim to make this comparison in future updates of this review if there are suitable new trials.

Selection of studies

Originally two authors (MH and DF) independently reviewed all potential trials for inclusion in the original review. For the 2020 update MH and SS reviewed the potential trials. These two authors examined the title and abstract of potential publications to remove those that did not meet inclusion criteria (e.g. single case reports, reviews etc.). We then examined the full text publications of the remaining trials to determine if they met the eligibility criteria. In the case that we were unable to reach agreement regarding the determination of eligibility by discussion, we would have sought the opinion of the third independent author (AS); however, there were no such occurrences. Authors examined publications potentially eligible for inclusion for duplication by comparing author, institution, trial detail (intervention, dosing, timing etc.) and participant demographics.

Data extraction and management

For the 2020 update, two authors (MH and SS) independently extracted information from the eligible trials using a data collection form. We discussed the results from each data extraction form to ensure agreement of interpretation; if there had been an absence of agreement, we planned to seek the opinion from a third author (AS).

It is possible that during a trial a participant may experience more than one exacerbation; in this event the shortest time between exacerbations would have been used.

Where trials, particularly with regard to chronic infection, take multiple assessments of individuals over a protracted time period, we would have defined time-frames of follow-up to represent short-, medium- and long-term follow-up. For the acute exacerbation trials we would have assessed data at time points of up to two weeks (standard duration of exacerbation therapy), over two weeks and up to six weeks (to assess efficacy of sustaining an effect). As previously discussed we would have assessed the outcome measure, time to next exacerbation as an indicator of long-term effectiveness of antibiotic therapy. For the chronic infection trials, we would have taken assessment time points at one month, over one month and up to three months, over three months and up to six months, over six months and up to 12 months and annually thereafter. For future updates, if outcome data are recorded at other time points, we shall consider examining these as well.

Assessment of risk of bias in included studies

The authors assessed the risk of bias using the 'Risk of bias' assessment tool as documented in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In particular, authors considered generation of allocation sequence and allocation concealment, blinding and incomplete outcome data. We also sought to identify selective outcome reporting by comparing those outcomes reported in the published paper to those considered in the protocol. For the 2020 update, MH and SS assessed the risk of bias for any new trials identified. We did not

reassess the risk of bias for those trials already included in the review.

Measures of treatment effect

In identifying any treatment effect, we had planned to analyse the results of intervention measures separately for acute exacerbation and chronic infection. For dichotomous data we planned to analyse these by calculating the relative risk (RR) and its 95% confidence intervals (CIs) on an intention-to-treat basis (ITT). No trials reported mortality as an outcome measure, although we had planned to combine data in order to calculate the hazard ratio (HR) with 95% CIs, or if it is more appropriate, to describe the outcomes of mortality and adverse events descriptively.

For continuous outcome variables, we documented the mean difference (MD) of effect and standard deviation (SD) of each variable. We did not use a standardised scoring system; if trials had documented scores using the same scoring system, we had planned to calculate the MD and 95% CIs. If trials had used different validated scoring systems, we would have calculated the standardised mean difference (SMD) and 95% CIs.

No trial reported data for 'time to next exacerbation'. If in future updates, such data become available, we plan to calculate the HR and its 95% CIs (appropriate as the risk of an exacerbation is not dependent upon other variables and should be uniform throughout the time period).

We describe count data narratively.

Unit of analysis issues

Cross-over trials are difficult to include as in many cases the duration of action of individual treatments may be prolonged. As a result we planned to only consider the first treatment phase of a cross-over trial and would not include such trials in full until such time that duration of action detail is understood, a washout period provided, measures of treatment effect are available and the data are available from each treatment phase. When considering trials of long duration (and measures of number of exacerbations or requirement of antibiotics) repeated values should be available for each participant.

Dealing with missing data

In the case where it was obvious that any of the included publications missed important data from the review's primary or secondary outcomes, the authors approached the primary investigator for clarification or more detail. This was the case for the trial by Abdulhamid, who kindly provided the additional data (Abdulhamid 2008). If, in future, we do not receive any reply from primary investigators to possible enquires, we shall seek to account for all missing data by contact with the co-investigators.

Assessment of heterogeneity

If we had identified data from multiple trials of a common therapy, we would have performed a meta-analysis of these trials. To assess heterogeneity between trials in the meta-analysis, we planned to use the I^2 statistic (Higgins 2003). We would have based our interpretation of this statistic on the guide given in the *Cochrane Handbook of Systematic Reviews of Interventions* such that we would regard an I^2 statistic below 40% as not important, between 30% and 60% as representing moderate heterogeneity, between 50% and 90% representing substantial and over 75% representing considerable heterogeneity (Higgins 2011). We would have interpreted this within the context of magnitude and direction of any effect and the strength of evidence for any heterogeneity, including a CI if possible for the I^2 result.

Assessment of reporting biases

We contacted the primary author of each included trial for the original iteration of the review to determine if they knew of other trials which have been completed but may not have been published. This process might have identified some small older trials and in this instance we could have determined the effects of these along with any reporting biases with the construction of funnel plots, accepting the multiple causes of asymmetry. When available, we made efforts to identify selective reporting of results by comparing the trial protocol (as published on a clinical trials register) with the final published results and by comparing the methods and results as detailed in the publication for any inconsistency in reporting.

Data synthesis

In the event of multiple trials we planned to analyse data using a fixed-effects model unless the measures of heterogeneity were at least substantial (as defined above) in which case a random-effects model would be most appropriate (RevMan 2011).

Subgroup analysis and investigation of heterogeneity

If we had identified a sufficient number of trials, we planned to undertake the following subgroup analyses for each class of agent:

1. adults (aged 18 years and over) versus children;
2. presence or absence of chronic infection (defined as three or more isolates in one year) with:
   a. *P aeruginosa;*
   b. *B cepacia;*
   c. MRSA.

Sensitivity analysis

In the case that we had multiple analyses, we would have determined the effect our decisions made relating to arbitrary categorisations by repeating these analyses with different categorisations; for example, repeating the analyses of treatment effect with different measures of short, medium and long term. With regard to determining the effect of small trials on the end result, we would repeat the analyses without these small trials (e.g. participant numbers less than 20 in each group) to determine their effect.

Summary of findings tables

We have presented a summary of findings table for each separate comparison in the review:

- β-carotene versus placebo;
- garlic versus placebo;
- monoclonal antibody KB001-A versus placebo;
- inhaled nitric oxide versus placebo;
- zinc versus placebo.

Within each table we present the following outcomes which we selected based on their clinical relevance and importance to the CF community:

- pulmonary exacerbations;
- respiratory function;
- adverse events
- need for antibiotics;
- QoL;
- sputum microbiology; and
- inflammatory markers.

We determined the quality of the evidence using the GRADE approach and starting from a judgement of high quality, downgraded evidence in the presence of a high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if we considered the limitation to be serious and by two levels if very serious.

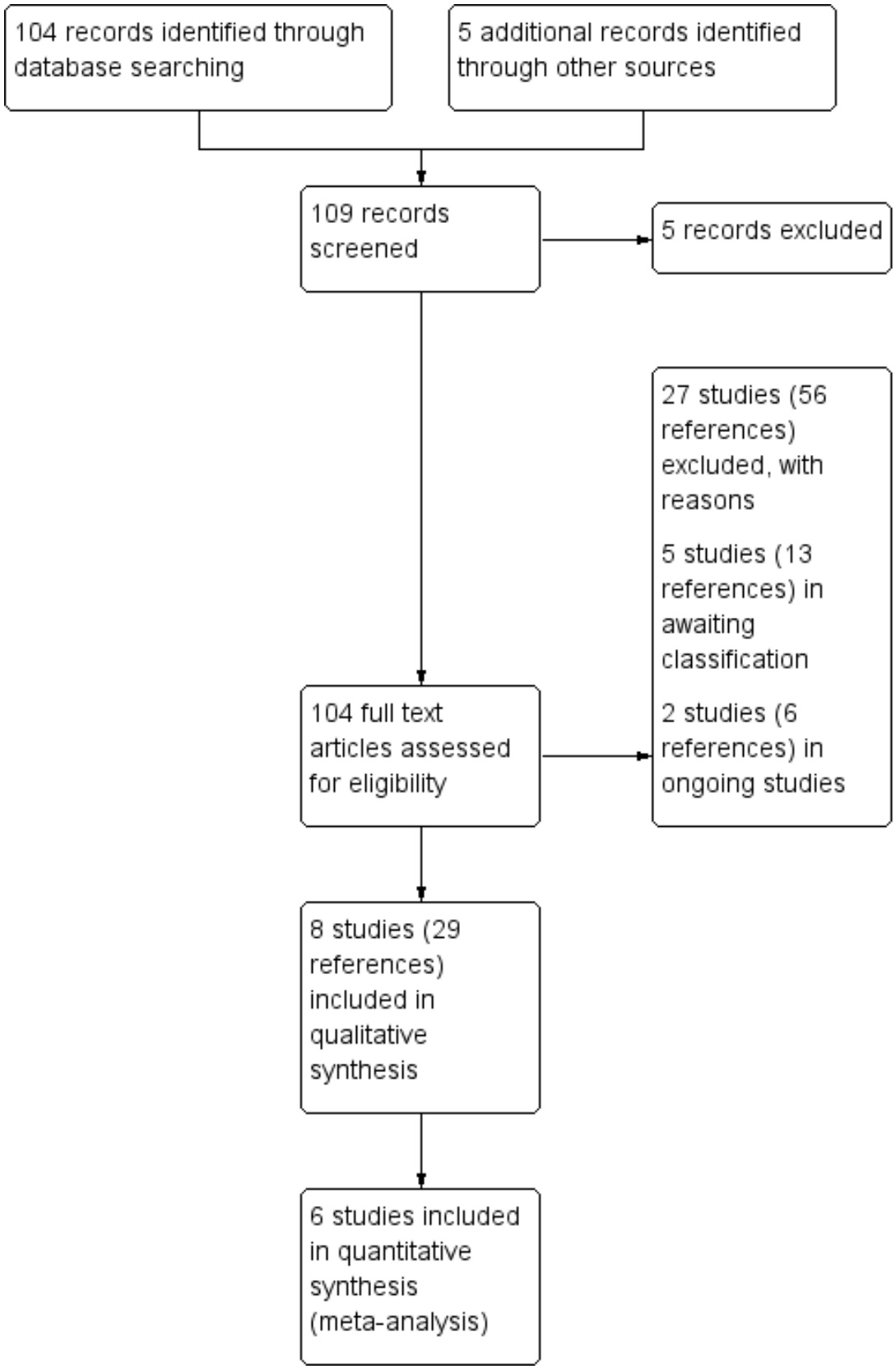
RESULTS

Description of studies

Results of the search

We have presented the results of the searches in a PRISMA chart (Figure 1).

Figure 1. Study flow diagram.



The search strategy identified a total of 42 trials. Of these trials, eight investigating the use of antibiotic adjuvant therapies for chronic infection are included in the review (Abdulhamid 2008; Howlin 2017; Jain 2018; Milla 2013; Renner 2001; Sagel 2009; Sharma 2016; Smyth 2010) and 27 trials were excluded. Two trials are still ongoing and will be assessed for inclusion in the review when they are completed and results available (Pressler 2017; Zabner 2009a). Five trials are currently awaiting classification (CARE-CF-1; Khorasani 2009; Puvvadi 2019 Rye 2015; Walshaw 2014). Two are cross-over trials and we are awaiting first-arm data (Rye 2015; Walshaw 2014); it is unclear at this stage whether one of the trials is randomised as it is only presented as an abstract (Khorasani 2009). The remaining two trials are only presented as conference abstracts (CARE-CF-1; Puvvadi 2019).

Included studies

Acute respiratory exacerbations

None of the included trials involved the treatment of acute infectious exacerbations.

Chronic infection

Eight trials with a total of 350 participants with chronic infection are included.

Trial design

All eight trials were randomised, double-blind, placebo-controlled trials of parallel design. Two of the trials were three-armed trials, one comparing two different doses of KB001-A to placebo (Milla 2013) and the other comparing high- and low-dose nitric oxide (NO) with placebo (Sagel 2009). Two of the trials were multicentre and both were carried out in the USA (Jain 2018; Milla 2013). The remaining six trials were single centre; two were carried out in the USA (Abdulhamid 2008; Sagel 2009), two in the UK (Howlin 2017; Smyth 2010), one in Austria (Renner 2001) and one in Northern India (Sharma 2016). The duration of the trials ranged from a 48-hour single-dose trial (Sagel 2009) to one year (Abdulhamid 2008; Sharma 2016).

Participants

The number of participants in the included trials ranged from 12 (Howlin 2017) to 169 (Jain 2018). Six of the trials included both adults and children (age range 6.8 to 54 years) (Howlin 2017; Jain 2018; Milla 2013; Renner 2001; Sagel 2009; Smyth 2010) and the remaining two trials recruited children only (age range 5 to 18 years) (Abdulhamid 2008; Sharma 2016). Most of the trials required a confirmed diagnosis of CF for inclusion, but two of the trials did not make this explicit (Abdulhamid 2008; Howlin 2017).

Interventions

All eight trials compared the intervention to a placebo.

One trial (n = 24) reported on a high-dose of β-carotene supplementation at 1 mg/kg/day for three months followed by low-dose regimen of 10 mg/day for three months (Renner 2001). One trial (n = 34) compared a garlic capsule once daily (656 mg of garlic oil macerate and 10 mg cardamom oil) to placebo (Smyth 2010). Two trials (n = 196) reported on a monoclonal antibody preparation KB001-A, but at different doses and for different durations (Jain 2018; Milla 2013). Jain (n = 169) looked at the effect of up to five IV infusions of 10 mg/kg of KB001-A once every four weeks during the 16-week treatment period (Jain 2018), whilst Milla (n = 27) looked at the effect of a single IV infusion of either 3 mg/kg or 10 mg/kg given over one hour (Milla 2013). Two trials (n = 30) assessed inhaled NO, but again at different doses and duration (Howlin 2017; Sagel 2009). The Howlin trial (n = 12) administered 10 ppm NO delivered via nasal cannula for eight hours overnight for five to seven days of therapy (Howlin 2017). The second trial (n = 18) of inhaled NO studied a 'low' dose of 20 ppm via nasal cannula for 44 hours in one arm and a 'high' dose of 40 ppm via nasal cannula for 44 hours (Sagel 2009). The remaining two trials (n = 66) reported on zinc supplementation at a dose of 30 mg per day, both for a duration of 12 months (Abdulhamid 2008; Sharma 2016).

The dose regimens for each supplement are detailed in the tables (Characteristics of included studies).

Outcomes

Three trials reported our primary outcome of pulmonary exacerbations (Abdulhamid 2008; Renner 2001; Sharma 2016). Renner looked at the number of pulmonary exacerbations over six months during supplementation with β-carotene (Renner 2001), whilst the two 12-month zinc trials looked at respiratory tract infections against a defined criteria (Abdulhamid 2008) or the number of pulmonary exacerbations requiring antibiotics (Sharma 2016).

All eight trials reported some measure of respiratory function over different time periods; six of these specifically measured FEV_1 (Howlin 2017; Jain 2018; Milla 2013; Sagel 2009; Sharma 2016; Smyth 2010), whilst Howlin and Milla also measured FVC (Howlin 2017; Milla 2013) and Milla also measured FEF_{25-75} (Milla 2013). Both of the trials looking at the effects of NO reported adverse events (Howlin 2017; Sagel 2009), as did one of the KB001-A trials (Milla 2013) and one of the zinc trials (Sharma 2016).

Four trials reported on the first of our secondary outcomes, need for antibiotics (Abdulhamid 2008; Jain 2018; Sharma 2016; Smyth 2010). Only Jain reported on the time to a need for antibiotics (Jain 2018), whilst the remaining three trials reported the number of days or courses of antibiotics needed (Abdulhamid 2008; Sharma 2016; Smyth 2010). The two trials of KB001-A measured QoL; one trial used the CFQ-R (Milla 2013) and one trial measured the change in respiratory symptoms (Jain 2018). None of the trials looked at the emergence of new pathogens, but four trials looked at changes in quantitative microbiology (Howlin 2017; Jain 2018; Sagel 2009; Sharma 2016) and three trials reported on inflammatory markers (Abdulhamid 2008; Jain 2018; Milla 2013).

Excluded studies

Publications that were obviously not relevant to the review after interrogation of the abstracts were excluded and are not listed in the review; we have listed a total of 27 trials as excluded.

Nine trials were excluded for methodological reasons: seven trials were not RCTs or quasi-RCTs (Durairaj 2007; Homnick 1995; Kollberg 2003; Lands 2010; Sagel 2011; Winklhofer-Roob 1995); one was a single case report (Kutateladze 2008); and two were cross-over trials which had no data from the first phase of the trial available for analysis; one assessed edetate sodium (EDTA) aerosolisation (Brown 1985) and one zinc supplementation (Safai-Kutti 1991).

A further 16 trials were excluded as the interventions were not considered to be antibiotic adjuvant therapies. We excluded one trial investigating the effect of polyunsaturated fats (Panchaud 2006) and another trial of fatty acid supplements (Olveira 2010); these interventions appear to exert an independent anti-inflammatory effect and so were considered not to meet our definition of an antibiotic adjuvant (as described in our exclusion criteria). A phase 2 trial of a CXCR2 antagonist was excluded as the mechanism of action is anti-inflammatory (Moss 2013). One trial of magnesium (Gontijo-Amaral 2012) and another of L-arginine (Grasemann 2013) were excluded as an adjuvant effect does not appear to have been demonstrated in either trial. Two trials of immunotherapy agents for chronic infection were also excluded (Kollberg 2010; NCT01455675). Two trials of miglustat were excluded as this agent acts at the host genetic level and is not an adjuvant (NCT00742092; Leonard 2012). Two trials examined the effect of vitamin D supplementation, but not as an antibiotic adjuvant (Alvarez 2017; Tangpricha 2017) and one looked at a multivitamin with antioxidants but again, not as an antibiotic adjuvant (Sagel 2018). One trial looked at the distribution of nebulised solutions in the lungs, but not as an adjuvant therapy (Hodges 2014) and a further trial reported the effect of proton pump inhibition to prevent acid aspiration, not as an antibiotic adjuvant (DiMango 2014). One trial of glutamine supplementation ws excluded since direct bactericidal activity was expected (Forrester 2015). One trial was excluded because it looked at inhaled dry powder mannitol, but we deemed it to be an adjunct to airway clearance rather than as an antibiotic adjuvant (Middleton 2015).

Two trials in participants with an acute respiratory exacerbation were excluded (Hauber 2008; Winnie 1989). One trial randomised participants to receive either inhaled sugars (inhaled fucose and galactose) for treating their pulmonary exacerbation or inhaled sugars accompanied by IV antibiotics (Hauber 2008). While these agents are specific substrates for the galactophilic and fucophilic lectins (cell surface proteins involved in bacterial aggregation) which are known in vitro to inhibit aggregation and promote dispersal of *P aeruginosa* biofilms (Johansson 2008), these agents have a novel non-osmotic mechanism of action. While the trial was not immediately excluded, further assessment ascertained that there was no true control group and it was therefore excluded (Hauber 2008). The second trial examined the effect of immunoglobulin on the treatment of pulmonary exacerbations and was excluded since it was a trial of immunotherapy (Winnie 1989).

Trials awaiting classification

Six trials are listed as 'Awaiting classification' (CARE-CF-1; Khorasani 2009; Puvvadi 2019; Rye 2015; Walshaw 2014; Zabner 2009).

Two cross-over RCTs of OligoG have been completed but we are awaiting first-arm data (Rye 2015; Walshaw 2014). OligoG is an oligosaccharide derived from alginate polysaccharide. It is suggested that this disrupts bacterial biofilm formation (a mode of bacterial growth associated with antibiotic tolerance and resistance). One RCT includes 12 participants with CF who also have chronic *Burkholderia sp.* infection; inhaled OligoG is given for 28 days to look at the effect on lung function, QoL, sputum rheology and microbiological outcomes (Rye 2015). The second RCT includes 26 participants aged 18 or over who have *P aeruginosa* in expectorated sputum. Inhaled OligoG was compared to saline to look at safety and tolerability (Walshaw 2014).

The third trial awaiting classification is looking at the effect of zinc on lung function, the rate of respiratory infections and the need for antibiotics; it is unclear at this stage whether it is randomised as it is only presented as an abstract. It includes 20 children with CF between seven and 18 years (Khorasani 2009).

A further trial awaiting assessment has six arms comparing five different doses of oral cysteamine (Lynovex®) to placebo over 14 days (CARE-CF-1). It is multicentre and double-blind and has recruited 89 adults with CF experiencing an acute exacerbation. Investigators are assessing the change in sputum bacterial load, QoL, blood leukocyte count, adverse events and serious adverse events, the change from baseline in sputum neutrophil elastase and IL-8 levels, in FEV_1, in weight and in BMI. To date some information has been published in abstract form and we are awaiting the publication of the full trial before including or excluding the trial (CARE-CF-1).

One trial compared calcium ethylene diamine tetra-acetate to saline in 24 people with CF with chronic *P aeruginosa* infection (Puvvadi 2019). For the initial two weeks, treatment was administered four times daily in conjunction with antibiotics; following this treatment was administered twice daily for a further two weeks and finally a four-week safety follow-up period. Investigators planned to assess the mean *P aeruginosa* sputum count, FEV_1 % predicted and adverse events. Again, this trial has only been published in abstract form and we are awaiting the publication of the full trial before including or excluding the trial (Puvvadi 2019).

The final trial listed as 'Awaiting classification' is a double-blind, parallel RCT in people with CF aged 16 or older (Zabner 2009). It compares hypertonic xylitol with hypertonic saline in terms of lung function, adverse events, respiratory symptoms, density of colonisation and time to exacerbations. The putative mechanism of action is a reduction in airway surface liquid salt concentration, thus facilitating lysozyme and β-defensins' protective action. One of the trials excluded on the basis of non-randomisation (Durairaj 2007) is a pre-cursor to this trial; the trial has now been completed but the results are not yet available (Zabner 2009).

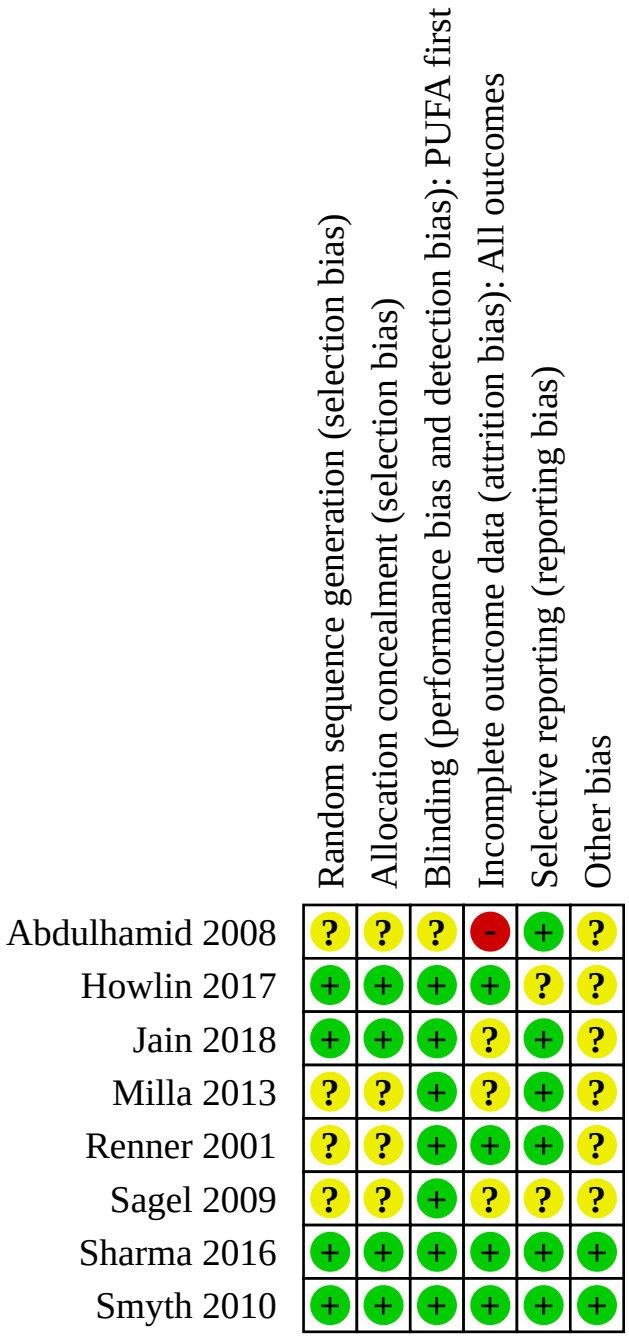
Ongoing trials

We will assess the ongoing trial for inclusion in the review when it is completed and results available (Pressler 2017). It is a double-blind, cross-over RCT looking at the effects of OligoG in 76 adults with CF and *P aeruginosa* in expectorated sputum. OligoG is given via inhalation compared to placebo and the outcomes include FEV_1, mucociliary clearance, rheology, microbiology and QoL (Pressler 2017).

Risk of bias in included studies

We did not identify any trials undertaken during acute respiratory exacerbations; all the following information relates to trials in participants with chronic infection. The risk of bias summary figure summarises these judgements (Figure 2).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Generation of sequence

We deemed four trials to be at low risk of bias for this domain (Howlin 2017; Jain 2018; Sharma 2016; Smyth 2010). In one of the NO trials the sequence was generated by an online randomisation service (Howlin 2017). One of the KB001-A trials used an interactive web response system (Jain 2018) and one of the zinc trials used computer-generated randomisation carried out by a person not involved in the trial (Sharma 2016). The garlic trial used a web-

based random allocation system provided by an external agency (Smyth 2010).

We judged four trials to have an unclear risk of bias (Abdulhamid 2008; Milla 2013; Renner 2001; Sagel 2009). The β-carotene trial was described as 'randomised', unfortunately the randomisation method is not described (Renner 2001). In the second zinc trial, the assignment of participants to the treatment group was reported to have occurred 'randomly', but no methods are described (Abdulhamid 2008); this is also the case with the remaining KB001-A trial (Milla 2013). The second NO trial claimed to be randomised but no description of the randomisation process was given (Sagel 2009).

Allocation concealment

We deemed four trials to be at low risk of bias for allocation concealment (Howlin 2017; Jain 2018; Sharma 2016; Smyth 2010). The Howlin NO trial stated that randomisation was undertaken via an online randomisation service to ensure concealment of treatment allocation (Howlin 2017). The Jain KB001-A trial stated that the drug assignment was conducted via an interactive web response system (Jain 2018). In the Sharma zinc trial, the drugs were labelled sequentially and put into sealed opaque envelopes by a person not involved in the trial (Sharma 2016). The authors of the garlic trial confirmed that the garlic supplements were dispensed in coded opaque sealed containers (Smyth 2010).

The remaining four trials did not provide details on allocation concealment so we judged the risk of bias to be unclear; the β-carotene trial (Renner 2001); one of the zinc trials (Abdulhamid 2008); one of the KB001-A trials (Milla 2013); and one of the NO trials (Sagel 2009).

Blinding

We judged seven of our eight included trials to have a low risk of bias due to blinding (Howlin 2017; Jain 2018; Milla 2013; Renner 2001; Sagel 2009; Sharma 2016; Smyth 2010). Both NO trials were described as double-blinded with NO and placebo being given via nasal cannulae so that participants were not able to differentiate between treatments (Howlin 2017; Sagel 2009). Similarly, both KB001-A trials reported that they were double-blind and IV infusion bags were labelled to maintain blinding (Jain 2018; Milla 2013). In the β-carotene trial, the supplement was reported as being identical to a starch-containing placebo (Renner 2001). The garlic trial detailed the flavour masking agent, described both active and placebo agents as identical and reported participant guesses of which treatment they thought they had received (no significant difference) (Smyth 2010). One of the zinc trials administered similar looking zinc or placebo tablets to the children (Sharma 2016).

The remaining zinc supplement trial detailed that the two groups were given either zinc gluconate or placebo preparations in capsules. The appearance of these capsules was unreported and so we judge the risk of bias to be unclear (Abdulhamid 2008).

Incomplete outcome data

We judged four trials to have a low risk of bias due to incomplete outcome data (Howlin 2017; Renner 2001; Sharma 2016; Smyth 2010). One NO trial reported that all 12 participants completed the trial and were included in the analysis (Howlin 2017). The β-carotene trial reports end results for all 24 participants identified in the methods section (Renner 2001). One zinc trial carried out a ITT analysis as well as a per protocol analysis and only three participants withdrew consent (Sharma 2016). The garlic trial randomised 34 participants of whom eight withdrew: four in the garlic group (one received lung transplant, one forgot to take capsules, one withdrew due to indigestion and one could not attend the second visit); and four in the placebo group (two forgot to take capsules, one withdrew due to halitosis and one could not attend the second visit). Furthermore, data for the primary outcome (lung function) were missing for one participant in the placebo arm; analysis was per protocol (Smyth 2010).

We judged three trials to have an unclear risk of attrition bias (both KB001-A trials and one NO trial) (Jain 2018; Milla 2013; Sagel 2009). Jain used a modified ITT analysis where any participant who had received three doses of the trial drug were included in the analysis; however, from the original 182 participants randomised, five withdrew from the placebo group before the start of treatment and eight from the KB001-A group. A further 15 participants from the placebo group and 21 from the KB001-A group withdrew before the end of the trial but no reasons were given (Jain 2018). Of the 27 participants randomised in the Milla trial, two participants discontinued the trial due to infusion-related AEs (one from each of the KB001-A groups) and a further three participants were excluded from the analysis as they received prohibited medications (two from the KB001-A 3 mg/kg group and one from the placebo group). As the number of participants dropping out is more than 15%, we judged the risk of attrition bias to be unclear (Milla 2013). Although all 18 participants remained in the Sagel inhaled NO trial, one participant was given both NO and nitrogen and the authors state that they removed these data from their analysis. However, the data reported in the clinical trials registration document is for 18 participants, therefore it is not clear whether the data were removed for this participant or not; for this reason we judged the risk of attrition bias to be unclear (Sagel 2009).

The second zinc trial randomised 13 children to each group, but one participant in the treatment group withdrew from the trial and it is unclear whether this person was included in the final analysis (Abdulhamid 2008). We therefore judged there to be a high risk of bias since the incomplete outcome data were not addressed.

Selective reporting

Six trials were judged to have a low risk of selective reporting bias (Abdulhamid 2008; Jain 2018; Milla 2013; Renner 2001; Sharma 2016; Smyth 2010). We did not identify any evidence of selective outcome reporting in the Jain trial after comparing the protocol and the trial report (Jain 2018). We compared the published protocols of one of the KB001-A trials and the garlic trial to the trial publications and no issues of selective reporting were identified (Milla 2013; Smyth 2010). In the Sharma trial, all outcomes stated in the methods section of the trial report are reported in the results section (Sharma 2016). The β-carotene trial does not have a registration on a clinical trials registry making it difficult to determine the primary outcome measures; however, the impact of any bias due to this is likely to be minimal (Renner 2001). When considered in isolation, the individual publications of the β-carotene trial each suffer from selective reporting as a result of duplicate publications with differing emphasis. The post hoc analysis describing an effect upon FEV_1 in the 'younger' participants suffers from selective reporting as only data for the treatment group are described. However, with the post hoc analysis

issue aside, when the individual reports are considered together, the results appear to not suffer from selective reporting (Renner 2001).

One of the zinc trials suffers considerably from selective reporting in the original paper (Abdulhamid 2008). The groups were originally assigned to one of the two trial arms 'randomly' without respect to their prior zinc status; however, the outcomes of these participants are reported in terms of prior zinc status. Investigators reported zinc status using a threshold of normal far below what is considered by their institutions' laboratory to be normal. Indeed, they later state that their groups had normal zinc levels within the clinically acceptable normal range and justify their use of a higher range of 'normal' zinc level by citing their own previous work which reports that those with lower zinc levels are more susceptible to infections. The protocol lists lung function as an outcome measure, but this is not reported in the original paper (Abdulhamid 2008). We therefore initially judged the risk of selective outcome reporting bias to be high; however, the authors have provided the raw data without reference to prior zinc status, which has reduced our interpretation of the bias introduced to low.

We deemed the remaining two trials of NO to have an unclear risk of bias for selective outcome reporting (Howlin 2017; Sagel 2009). In the Howlin trial, not all of the outcomes specified in the trial registration document and methods section of the paper were reported in the paper's results (Howlin 2017). In the second NO trial not all of the outcomes listed in the methods section of the paper were reported in the results (Sagel 2009).

Other potential sources of bias

We considered compliance to treatment, but in three trials we judged compliance not to be an issue (Howlin 2017; Milla 2013; Sagel 2009). In the safety trial of KB001-A compliance is not an issue as this was a trial of a one-dose infusion; this trial was sponsored by the pharmaceutical company developing KB001-A (Milla 2013). Compliance was also not identified as a potential risk of bias in the NO trials as the intervention was administered in hospital (Howlin 2017; Sagel 2009).

We judged there to be a low risk of bias with regards to compliance in three trials (Jain 2018; Sharma 2016; Smyth 2010). We found no source of bias relating to compliance in the Jain trial (Jain 2018). One of the zinc trials measured adherence by capsule counting of returned medication and was deemed to be at a low risk of other potential bias (Sharma 2016). In the Smyth trial, compliance to the garlic protocol was assessed by participant report and capsule counting; this was reported as equal and so we judged the risk of bias to be low (Smyth 2010).

In the remaining two trials the risk of bias from compliance was judged to be unclear (Abdulhamid 2008; Renner 2001). Compliance to the zinc trial protocol for the was reported only in terms of prior zinc status and the per protocol analysis of compliance is not provided (Abdulhamid 2008). Compliance to the β-carotene protocol was assessed by participant report and capsule counting; however, the result was not reported (Renner 2001).

Effects of interventions

See: **Summary of findings 1** Summary of findings: β-carotene compared with placebo for chronic pulmonary infection in cystic fibrosis; **Summary of findings 2** Summary of findings: garlic supplementation compared with placebo for chronic pulmonary infection in cystic fibrosis; **Summary of findings 3** Summary of findings: monoclonal antibody KB001-A compared with placebo for chronic pulmonary infection in cystic fibrosis; **Summary of findings 4** Summary of findings: nitric oxide compared with placebo for chronic pulmonary infection in cystic fibrosis; **Summary of findings 5** Summary of findings: Zinc supplementation compared with placebo for chronic pulmonary infection in cystic fibrosis

The effects of interventions are summarised in the summary of findings tables, the quality of the evidence has been graded for pre-defined outcomes (see above) and definitions of these gradings provided (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).

Acute respiratory exacerbations

There were no trials included which considered acute respiratory exacerbations.

Chronic infection

All eight included trials investigated antibiotic adjuvant therapies for chronic pulmonary infection (Abdulhamid 2008; Howlin 2017; Jain 2018; Milla 2013; Renner 2001; Sagel 2009; Sharma 2016; Smyth 2010). For simplicity we have reported below only the review's outcome measures that have been reported in the selected trials.

β-carotene supplementation

One trial (n = 24) compared β-carotene supplementation to placebo (Renner 2001).

Primary outcomes

1. Pulmonary exacerbations (protocol defined)

Investigators report a reduced rate of pulmonary exacerbations in the treatment arm, defined as the number of days of antibiotic consumption, although this is not statistically significant, MD -8.00 (95% CI -18.78 to 2.78) (Analysis 1.1). We judged the quality of evidence for this outcome to be low.

2. Respiratory function

a. FEV_1 % predicted

There appeared to be no effect upon lung function (FEV_1 % predicted) between the two groups, MD -10.90% (95% CI -32.23% to 10.43%) (Analysis 1.2). The authors describe an apparently post hoc analysis of the 'younger patients' (undefined) and suggest their FEV_1 'clearly improved'. Unfortunately only data for the treatment group are presented. We judged the quality of evidence for this outcome to be low.

b. FVC % predicted

This outcome was measured but not reported per protocol. The authors state that mean (SD) FVC did not change during the treatment (baseline 87.6% predicted (21.2%), week 12 85.1% predicted (24.6%) and week 24 85.6% predicted (25.1%)) (Renner 2001).

3. Adverse events

There were no adverse events reported during the trial, but some participants reported better tanning after exposure to sunlight (Renner 2001). We judged the quality of evidence for this outcome to be low.

Secondary outcomes

1. Antibiotic consumption

b. As above, the protocol definition of pulmonary exacerbation was the antibiotic consumption rate in days (Analysis 1.1) (low-quality evidence).

5. Mortality

There were no dropouts during the trial and so we assume that no deaths occurred, although this was not explicitly discussed (Analysis 1.3).

Garlic supplementation

One included trial (n = 34) investigated garlic supplementation (Smyth 2010). There were no statistically significant changes in clinical score and lung function. It was also not possible to detect a difference in quorum sensing molecules in plasma or sputum.

Primary outcomes

2. Respiratory function

a. FEV_1 % predicted

The percentage change in % predicted FEV_1 between the treated and control groups did not reach significance, MD 1.59% predicted (95% CI -7.49% to 10.67%) (Analysis 2.1). We judged the quality of evidence to be moderate.

3. Adverse events

a. mild (not requiring treatment)

Five participants in each group had abnormal liver function or triglyceride levels. Five participants in the garlic group reported minor adverse effects (diarrhoea (two participants), halitosis (two participants), abdominal pain (one participant), dysuria (one participant), minor haemoptysis (one participant)). One participant from the placebo group reported a minor haemoptysis (Analysis 2.3). We again judged the quality of evidence to be moderate.

Secondary outcomes

2. Antibiotic consumption (days of antibiotic use)

Seven participants in the garlic group received intravenous antibiotics compared to five in the placebo group; however, days of antibiotic use was not reported (Smyth 2010).

5. Mortality

There were no deaths during the trial period (Analysis 2.2).

KB001-A

Two trials compared KB001-A to placebo (n = 196) (Jain 2018; Milla 2013). One trial was single-dose trial (n = 27) with participants followed up for eight weeks (Milla 2013), whilst the second trial (n = 169) administered KB001-A via infusion once every four weeks over a 16-week period (Jain 2018). For this reason we could not combine the results in a meta-analysis.

Primary outcomes

1. Pulmonary exacerbations (protocol defined)

In the single-dose trial investigators reported the number of CF exacerbations (Milla 2013). No participants experienced a CF exacerbation after the 10 mg/kg dose of KB001-A, one participant who received a 3 mg/kg dose of KB001-A experienced a pulmonary exacerbation and there were two reports of pulmonary exacerbations in the placebo group, RR 0.25 (95 % CI 0.03 to 2.40) (Analysis 3.1).

Jain did not report pulmonary exacerbations as a primary outcome, but found that an infective pulmonary exacerbation was the most common adverse event in both groups (57.8% of KB001-A participants and 67.4% of placebo participants) (Jain 2018).

The GRADE assessment for this outcome was judged to be low.

2. Respiratory function

a. FEV_1 % predicted

Milla reports the number of episodes of a drop in lung function (FEV_1, unit of measurement not given); however, the lung function data in terms of the size of decrease in FEV_1 are not reported (Milla 2013). Six participants who received a 3 mg/kg dose of KB001-A experienced a decrease in FEV_1, RR 4.74 (95% CI 0.28 to 79.44) (Analysis 3.2).

In the trial of KB001-A given over a longer period, the authors reported a 3% increase in the absolute change from baseline in % predicted FEV_1 at week 16 for the KB001-A arm versus placebo, MD 3.2% (95% CI 1.12% to 5.30%) (P = 0.003) (Jain 2018).

We judged the GRADE assessment for this outcome to be very low.

b. FVC % predicted

Milla found no significant differences between active treatment and placebo groups for FVC (unit not stated) at any time point (Milla 2013).

c. Other validated measures of respiratory function

Milla also found no significant differences between active treatment and placebo groups for any other spirometry parameters (FEF_{25-75}) at any time point (Milla 2013).

3. Adverse events

The primary outcome of the Milla trial was the number of participants experiencing adverse events. Seven of those who received placebo and all (n = 18) of those who received KB001-A experienced an adverse event, RR 1.30 (95% CI 0.90 to 1.87) (Analysis 3.3).

There is insufficient information to determine the severity of the events according to our classification of mild, moderate and severe, we have therefore used the classification reported in the trial - 'serious' and 'other'. The trial reports the following serious adverse effects: a participant receiving a 3 mg/kg dose of KB001-A developed bronchitis, RR 1.58 (95% CI 0.07 to 35.32); and a

participant who received placebo developed sinusitis, RR 0.18 (95% CI 0.01 to 3.92) (Analysis 3.4). The 'other' events are described under group headings and presented in the analyses (Analysis 3.5; Analysis 3.6; Analysis 3.7; Analysis 3.8; Analysis 3.9; Analysis 3.10; Analysis 3.11; Analysis 3.12; Analysis 3.13; Analysis 3.14; Analysis 3.15).

Jain reported no treatment-emergent adverse events and similar numbers of participants with infusion reactions between intervention and placebo. The number of hospitalised participants was higher in the KB001-A group compared to placebo (28.9% versus 16.3%) (Jain 2018).

Again, we judged the GRADE assessment of quality to be very low.

Secondary outcomes

1. Need for antibiotics

a. Time to next course of antibiotics (oral, inhaled or IV)

The Jain trial found no difference in the time to need for antibiotics in the KB001-A group versus placebo over the 16-week period, HR 1.00 (95% CI 0.69 to 1.45) (result taken directly from the paper) (Jain 2018). We deemed the quality of this evidence to be moderate.

2. QoL

b. Treatment burden

Milla looked at change in CFQ-R scores but found no significant differences between groups at any time point (data not given) (Milla 2013). Similarly, Jain measured change in respiratory symptom scores from baseline using the CFRSD-CRISS symptom severity score, but found no difference between treatment groups (Jain 2018). We rated the quality of evidence as low for this outcome.

3. Change in sputum microbiology

b. Quantitative microbiology

At day 28 there was a numerical reduction from baseline in median mucoid *P aeruginosa* density in the KB001-A 10 mg/kg group (-0.4 $\log_{10}$) compared to placebo (0.8 $\log_{10}$) but the changes were not significant (Milla 2013). We deemed the quality of this evidence to be low.

4. Change in inflammatory markers

Milla reported no significant changes in biomarkers from baseline, but there was a trend towards a KB001-A dose-dependent reduction in sputum myeloperoxidase, IL-8, IL-1β and neutrophil elastase (Milla 2013). Jain reported a -0.24 $\log_{10}$ reduction in IL-8 in the KB001-A group compared to placebo at week 16 (P = 0.04), but the decrease in sputum neutrophil elastase (NE) was not significant, MD -0.27 (95% CI -0.58 to 0.04; P = 0.084) (Jain 2018). The quality of this evidence was found to be very low.

5. Mortality

Milla reported no deaths during the trial (Milla 2013).

Nitric oxide

Two trials (n = 30) reported on the effect of inhaled NO as an antibiotic adjuvant, but the data cannot be combined in a meta analysis because one trial administered NO at 10 ppm for eight hours overnight for five to seven days (Howlin 2017), whilst the second trial administered NO continuously for 44 hours at doses of either 20 or 40 ppm (Sagel 2009).

Primary outcomes

2. Respiratory function

a. FEV_1 % predicted

Howlin reported a greater increase in FEV_1 % predicted in the placebo group compared to the inhaled NO group but this was not significant after 20 days (Howlin 2017), MD -1.95 (95% CI -9.94 to 6.04) (P = 0.63) (Analysis 4.1). The Sagel trial only reported a value for baseline FEV_1 (L) for each group and a value after 48 hours, but no statistics were given (Sagel 2009). We graded the quality of evidence as low.

b. FVC % predicted

This was only reported in the Howlin trial which found that after five to seven days of inhaled NO or placebo gas, there was a greater (non-significant) change from baseline in FVC % predicted in the placebo group compared to the NO group, MD -8.03 (95 % CI -18.50 to 2.44) (P = 0.13) (Howlin 2017).

3. Adverse events

Both trials reported adverse events but numbers were low. Howlin reported that in the NO group four participants reported adverse events including epistaxis, cough and cold, increased cough and haemoptysis, but all events were considered mild and only possibly related to the trial treatment. In the placebo group only one adverse event was reported, which was epistaxis (Howlin 2017). Sagel reported no serious adverse events in either the NO group or the placebo group at either the low or high dose of NO (Sagel 2009). We rated the quality of evidence as very low for this outcome.

Secondary outcomes

3. Change in sputum microbiology

b. Quantitative microbiology

Howlin found that there was a significant reduction in *P aeruginosa* biofilm aggregates compared with those receiving placebo with antibiotics over the seven-day treatment period (P = 0.029) and there was less *P aeruginosa* biofilm in the NO group compared with placebo (Howlin 2017). Sagel reported that there was a significant reduction in *S aureus* colony counts in the high-dose NO group compared to placebo (P = 0.03) and a near significant reduction in *P aeruginosa* colony counts in the high-dose group compared to placebo (P = 0.06) (Sagel 2009). Again, we rated the quality of this evidence as very low.

Zinc supplementation

Two trials (n = 66) compared zinc supplementation to placebo (Abdulhamid 2008; Sharma 2016).

Primary outcomes

1. Pulmonary exacerbations (protocol-defined)

Investigators in the Abdulhamid trial do not report on their protocol definition of an exacerbation; they only report the number of episodes requiring IV and oral antibiotics (see results below) (Abdulhamid 2008). In the Sharma trial, the authors report on the number of participants requiring IV antibiotics during the

treatment phase. Seven participants (38.9%) in the zinc group and four participants (20.1%) in the placebo group experienced exacerbations requiring IV antibiotics during the 12-month trial, RR 1.85 (95% CI 0.65 to 5.26) (Analysis 5.1); this result is not statistically significant (Sharma 2016). We graded the quality of evidence as moderate.

2. Respiratory function

a. FEV_1 % predicted

Abdulhamid presents this measure in the baseline characteristics, but the outcome is not reported post-treatment in the published paper (Abdulhamid 2008). After contacting the authors, we received the data to allow us to analyse this outcome in the graphs and these showed no difference between groups, MD -5.46 (95% CI -19.44 to 8.52) (Analysis 5.6).

Sharma measured the change in FEV_1 % predicted and reported the median and interquartile range (IQR); thus we were not able to combine the results of the two trials. Sharma found that the median (IQR) FEV_1 % predicted was 8.97% (-18.23 to 0.33) lower than baseline in the zinc group and 9.55% (-9.59 to 12.88) higher in the placebo group (P = 0.08).

We judged the quality of this evidence to be very low.

b. FVC % predicted

Only the Abdulhamid trial reported this outcome; again, the measure was presented in the baseline characteristics, but not reported in the published paper (Abdulhamid 2008). Dr Abdulhamid supplied data for analysis and these showed a statistically non-significant difference between groups, MD -1.75 (95% CI -13.09 to 9.59) (Analysis 5.2).

3. Adverse events

Abdulhamid reported no adverse events (Abdulhamid 2008). Sharma reported 15 serious adverse events or hospitalisations in 13 participants; all of the serious adverse events were related to exacerbations (Sharma 2016). Seven children were hospitalised in the zinc group compared to six in the placebo group, RR 1.23 (95% CI 0.51 to 2.97) (P = 0.64) (Analysis 5.7). We judged to quality of evidence for this outcome to be moderate.

Secondary outcomes

2. Antibiotic consumption (days of antibiotic use)

Additional data for one trial (provided by the investigators) showed that zinc supplementation resulted in a statistically significant reduction in the number of days of oral antibiotics alone, MD -17.74 (95% CI -26.98 to -8.50) (P = 0.05) (Analysis 5.3) (Abdulhamid 2008). However, the difference between groups was not statistically significant for duration of IV antibiotics, MD 0.52 (95% CI -3.07 to 4.11) (Analysis 5.4). When the data for both oral and IV antibiotics combined, as supplied by Dr Abdulhamid, were analysed these showed a statistically significant difference between treatment and control groups, MD -17.22 (95% CI -27.06 to -7.38) (Analysis 5.5).

The Sharma trial reported the median (range) number of days of oral or IV antibiotics, but found no significant difference between groups. The median (range) in the zinc group was 42 days (0 to 238) and in the placebo group 38 days (0 to 224) (P = 0.76) (Sharma 2016).

We judged the quality of this outcome to be very low.

5. Mortality

Sharma reported that none of the participants died during the trial (Sharma 2016).

DISCUSSION

Summary of main results

We identified eight RCTs with 350 participants from our systematic search of the literature (Abdulhamid 2008; Howlin 2017; Jain 2018; Milla 2013; Renner 2001; Sagel 2009; Sharma 2016; Smyth 2010). The trials looked at the effects of five different interventions compared with placebo: β-carotene; garlic; monoclonal antibody KB001-A; NO; and zinc supplementation. Neither the trial of β-carotene supplementation or the trial of garlic supplementation detected a statistically significant difference between those in the treatment and control groups for any outcome measure (Renner 2001; Smyth 2010). Similarly, the trials of KB001-A found no significant difference in exacerbations and we are uncertain as to the effect on FEV_1; there is also probably no difference in time to need for antibiotics between KB001-A and placebo (Jain 2018; Milla 2013). The earlier trial of KB001-A was a safety trial with limited data published online (Milla 2013), but this led to the repeat-dose RCT where therapeutic efficacy was the primary outcome (measured by time-to-next antibiotic treatment) with safety and tolerability being secondary outcome measures (Jain 2018). The NO trials did not report on exacerbations and there may be little or no difference between NO and placebo in the effect on FEV_1 (Howlin 2017; Sagel 2009). The addition of two further trials of zinc supplementation since the last update offers no further evidence of a difference between zinc and placebo for our primary outcomes (Abdulhamid 2008; Sharma 2016). One of these trials found a reduction in the number of days of oral or IV antibiotics needed during the trial period, but the quality of evidence was very low and so we are uncertain if this is a genuine effect (Abdulhamid 2008). It is notable that the need for IV antibiotics did not differ between the two groups, an inconsistency that is difficult to explain.

Respiratory function was measured in all of the included trials and no difference between intervention and placebo was found for β-carotene, garlic, NO or zinc (Abdulhamid 2008; Howlin 2017; Renner 2001; Sagel 2009; Sharma 2016; Smyth 2010). The earlier trial of single-dose KB001-A reported a non-significant drop in FEV_1 in the intervention group compared to placebo, where a slight increase in FEV_1 was seen, RR 4.74 (95% CI 0.28 to 79.44) (Milla 2013). However, in the 16-week trial of KB001-A there was a 3% absolute increase from baseline in % predicted FEV_1 at week 16 for the KB001-A arm versus placebo, MD 3.2% (95% CI 1.12 % to 5.30 %) (P = 0.003) (Jain 2018). The quality of this evidence, however, was deemed to be very low.

Few adverse events were seen across all of the different interventions and the adverse events that were reported were mild or not treatment related. QoL was only reported in the trials of KB001-A where no difference in CFQ-R was seen between KB001-A and placebo (Jain 2018; Milla 2013). Sputum microbiology was measured and reported for the trials of KB001-A and NO. There was very low-quality evidence of a numerical reduction in *P aeruginosa* density after KB001-A, but it was non-significant (Milla 2013). The trials looking at the effects of NO reported significant reductions in *S aureus* and near significant reductions in *P aeruginosa* but the quality of this evidence is very low (Howlin 2017; Sagel 2009).

Overall completeness and applicability of evidence

We are confident that we have identified all the trials that meet our inclusion criteria as our searches were thorough and we contacted authors for extra information where necessary. One of the trials included in the 2013 update was only in abstract form, but the full paper has now been published and included in the 2020 update (Jain 2018). Not all of the included trials measure our primary outcome (pulmonary exacerbations) and some of those that did used surrogate measures such as days on antibiotics. There is a preponderance to include participants in the younger age group - children and adolescents. Potentially this group of younger individuals, prior to chronic colonisation with multi-resistant bacteria, could have most to gain from an intervention that might act to reduce infection and hence spare lung function and QoL at an earlier age. However, the generalisability of this approach to the more unwell individuals, who tend not to be included in such trials, is questionable.

It should also be noted that since the β-carotene trial was conducted, larger randomised trials with subsequent analyses have demonstrated an increased risk of development of certain malignancies (lung and stomach) in individuals with lung disease when given a daily 20 mg to 30 mg β-carotene supplement (Druesne-Pecollo 2010). The authors believe this precludes further investigation of the high-dose supplementation regimen investigated in this review.

One trial is yet to be completed and published and we await the results of this (Pressler 2017). There are six trials which have been completed but which are listed as 'Awaiting assessment' until we have the results we can include and analyse (CARE-CF-1; Khorasani 2009; Puvvadi 2019; Rye 2015; Walshaw 2014; Zabner 2009a).

Quality of the evidence

The gradings for the quality of the evidence for each comparison are presented in the summary of findings tables (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).

The quality of the evidence for this review is limited by the size and quality of the underlying trials and the fact that there were no data to combine in a meta-analysis. Two of our five comparisons included only one trial (β-carotene (Renner 2001); garlic (Smyth 2010)), the remaining three comparisons include two trials each (KB001-A (Jain 2018; Milla 2013); NO (Howlin 2017; Sagel 2009); and zinc (Abdulhamid 2008; Sharma 2016)).

The quality of the evidence for β-carotene was low because of concerns around randomisation and allocation concealment as well as the trial having a small sample size and low event rates. We are uncertain whether β-carotene improves our primary outcomes (Renner 2001).

Although there was only one trial included in the comparison of garlic with placebo the quality of the trial was deemed to be moderate and only downgraded because of small sample size. However, the trial did not report on our primary outcome of pulmonary exacerbations and there is probably little or or no difference in respiratory function or adverse events (Smyth 2010).

There were two trials looking at the effect of KB001-A, but they were heterogeneous in design, intervention and in the outcomes they reported (Jain 2018; Milla 2013). The quality of evidence for our primary outcomes was deemed to be very low and we are very uncertain as to whether KB001-A improves pulmonary exacerbation rates (Milla 2013). The evidence for one of our secondary outcomes (need for antibiotics) was deemed to be moderate because the trial reporting on this outcome had a larger sample size and fewer concerns around trial design (Jain 2018).

The quality of evidence for NO was deemed to be low or very low due again to small sample sizes, low event rates and risk of bias within the two included trials. We are very uncertain as to the effect of NO on our primary and secondary outcomes (Howlin 2017; Sagel 2009).

The evidence for zinc supplementation was deemed moderate for pulmonary exacerbations and adverse events, but very low for the remaining outcomes reported. This is because we were unable to combine the data and so the quality reflects the underlying quality of the trials (Abdulhamid 2008; Sharma 2016).

Potential biases in the review process

One of the co-authors of this review is lead investigator of one of the included trials (Smyth 2010).

Agreements and disagreements with other studies or reviews

There have been no previous systematic reviews of antibiotic adjuvant therapies for pulmonary infection in individuals with CF. Reviews of strategies in development stress the pre-clinical nature of much of these approaches and unfortunately biotechnology companies developing new therapies may defer publication of commercially sensitive results.

AUTHORS' CONCLUSIONS

Implications for practice

Various strategies have been investigated in an attempt to improve the current position where individuals are infected with resistant bacteria for which no successful treatment is available. Unfortunately, however, trials of these strategies have been of poor quality and often limited to observational or limited cohort studies. The more rigorous trials have suffered from either a lack of statistical power or robust outcome measures.

There continues to be no alternative to conventional antibiotics alone in the treatment of pulmonary infection in those with cystic fibrosis (CF).

Implications for research

Antibiotics remain the mainstay of treatment for pulmonary infection in CF. The emergence of increasingly-resistant bacteria makes the reliance on antibiotics alone challenging for CF teams. There is a need to explore alternative strategies, such as the use of adjuvant therapies, that may prove a beneficial alternative. Novel strategies should aim to be founded on robust in vitro pre-clinical development work that includes clinical isolates of mixed phenotypes of bacteria in models of infection that include both planktonic and biofilm modes of growth. Well-designed placebo-controlled double-blind randomised trials of sufficient power and duration are required to determine the efficacy of any new strategy in both children and adults with CF. Such trials need to use outcome

measures that are both objective and important to people with CF, specifically lung function, pulmonary exacerbation frequency, hospital attendance and measures of quality of life.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abdulhamid 2008

Study characteristics	
Methods	Double-blind placebo-controlled RCT. Parallel design. Location: Michigan, USA. Duration: 12 months.
Participants	26 children (aged 7 - 18 years) with CF and mild to moderate lung disease without a concurrent acute severe infection were recruited.
Interventions	**Intervention**: zinc gluconate supplementation (30 mg daily dose). **Control**: placebo.
Outcomes	Outcomes not stratified. At each visit, the participant's interval medical history, height and weight, number of hospitalizations, the use of oral and intravenous antibiotics, pulmonary function test, and physical examination findings were recorded. Respiratory tract infections were also recorded at each visit based on reported criteria. **Primary outcome**: number of days of oral antibiotics during active infection per year. **Secondary outcomes**: production of inflammatory cytokines and IL-2.
Notes	Dr Abdulhamid has kindly provided a per-protocol analysis of the data with analysis limited to results of the treatment group compared to that of the placebo group.

Abdulhamid 2008 *(Continued)*

	No specific comment on *P aeruginosa* infection.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but method not described.
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding (performance bias and detection bias) PUFA first	Unclear risk	Both groups (treatment and placebo) were given capsules although these were not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	1 child withdrew (no reason provided) and does not contribute to the data analysis
Selective reporting (reporting bias)	Low risk	In the published trial, there is considerable selective reporting with the outcomes reported as per a subgroup analysis comparing those that were previously 'zinc adequate' or 'zinc inadequate'. The thresholds used to define zinc adequacy varied considerably to the 'clinically acceptable normal range'. Dr Abdulhamid has kindly provided the per-protocol data with groups defined by their treatment group (placebo or zinc supplementation). After the provision of this additional information we therefore judge the risk of selective reporting to be low.
Other bias	Unclear risk	The compliance with treatment is reported as per the subgroup analysis and not as per protocol which further introduces uncertainty.

Howlin 2017

Study characteristics

Methods	Double-blind, placebo-controlled RCT. Parallel design. Location: single centre in the UK. Duration: 20 days.
Participants	12 adolescents and young adults with CF. Age, mean (SD): NO group 30 (13.99) years; placebo group 29.3 (15.6) years. Gender split: not stated Baseline disease status: FEV_1 % predicted, mean (SD): NO group 40.2% (20.14); placebo group 45.7% (18.28). FVC % predicted, mean (SD): NO group 54.4% (17.6); placebo group: 71.5 (21.11).

Howlin 2017 *(Continued)*

Interventions	**Intervention group**: NO gas (10 ppm; INOmax, 400 ppm mol/mol inhalation gas; INO Therapeutics) delivered via INOvent (Ikaria, supplied by INO Therapeutics), inhaled via nasal cannula for 8 h overnight for 5 – 7 days of therapy. **Placebo group**: air or air and oxygen mix, inhaled via nasal cannula for 8 h overnight for 5 – 7 days of therapy. Participants were followed up for the 7 days of therapy and at day 20.
Outcomes	Change from baseline in Ln CFU, FEV_1 (% predicted), FVC (% predicted). Adverse events. Change in *P aerugoinosa* biofilm aggregates.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with block lengths 2 and 4 was undertaken via an online randomisation service in a 1:1 ratio.
Allocation concealment (selection bias)	Low risk	Randomisation was undertaken via an online randomisation service to ensure concealment of treatment allocation.
Blinding (performance bias and detection bias) PUFA first	Low risk	Double-blind trial; participants and outcome assessors were blinded to allocation. The placebo was administered via nasal cannula in the same way as the NO so that participants did not know whether they were getting NO or placebo. They also used sham weaning procedures.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 participants were randomised and all completed the trial and were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Not all of the outcomes specified in the trial registration document and methods were reported in the results. In the methods the authors state they will measure QoL via CFQ-UK but there is no mention of this in the results or in any of the tables. Authors state that it is presented in the supplementary tables but we have not been able to locate these.
Other bias	Unclear risk	None identified.

Jain 2018

Study characteristics

Methods	Double-blind, placebo-controlled, repeat-dose clinical RCT. Parallel design. Location: multicentre in USA (58 centres), Australia (3 centres), Israel (4 centres), New Zealand (2 centres). Duration: 16 weeks.

Jain 2018 *(Continued)*

Participants	169 children and adults with a confirmed diagnosis of CF based on a sweat chloride > 60 mEq or 2 identifiable mutations consistent with CF (or both) and 1 or more clinical feature of CF. Infected with *P aeruginosa*. Age, mean (SD), median: KB001-A group 29.1 (9.7) years, 28 years; placebo group: 29.8 (11.1) years, 28.5 years. Gender males/females (%): KB001-A group 41 males (49.4%) and 42 females (50.6%); placebo group 42 males (48.8%) and 44 females (51.2%). Baseline FEV_1 % predicted, mean (SD): KB001-A group: 60.7% (15); placebo group: 61.4% (13.5). Antibiotic regimen, n (%): KB001-A group 33 (39.8%) continuous and 50 (60.2%) intermittent; placebo group38 (44.2%) continuous and 48 (55.8%) intermittent. Baseline CFRSD-CRISS, mean (SD): KB001-A group 36.5 (9.7); placebo group: 37.2 (10.3).
Interventions	**Intervention group**: KB001-A up to 5 IV infusions of 10 mg/kg once every 4 weeks during the 16-week treatment period with an additional loading dose at week 2. **Placebo group**: up to 5 IV infusions of once every 4 weeks during the 16-week treatment period with an additional loading dose at week 2. Details of placebo not given. Trial duration included a 2-week screening period, 16-week treatment period and 4-week follow-up period.
Outcomes	**Primary outcome**: time to need for antibiotics. **Secondary outcomes**: change from baseline in respiratory symptoms, BMI, weight, % predicted FEV_1, change from baseline in inflammatory markers, change in bacterial density. Adverse events: treatment adverse events and other adverse events.
Notes	All participants continued their regularly scheduled inhaled antibiotic regimen (concurrently with the trial drug) for the first 4 weeks of treatment. After 4 weeks this scheduled maintenance therapy was discontinued.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drug assignment was conducted via interactive web response system. Randomised 1:1.
Allocation concealment (selection bias)	Low risk	Drug assignment was conducted via interactive web response system.
Blinding (performance bias and detection bias) PUFA first	Low risk	This is a double-blind trial in which participants, trial personnel and outcome assessors were blinded. No information given on blinding of the trial drug.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A modified ITT analysis was used where any participant who had received 3 doses of the trial drug were included in the analysis. However, from the original 182 randomised, 5 withdrew from the placebo group before the start of treatment and 8 from the KB001-A group. A further 15 from the placebo group and 21 from the KB001-A group withdrew before the end of the trial. No reasons were given.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias found.

Jain 2018 *(Continued)*

Other bias	Unclear risk	None identified.

Milla 2013

Study characteristics	
Methods	Double-blind, placebo-controlled single-dose RCT. Parallel design (3-armed). Location: 10 CF centres in the USA. Duration: single-dose given on day 0 and followed up until day 56.
Participants	27 participants (aged over 12 years) with *P aeruginosa* infection. KB001-A 3 mg/kg n = 10; KB001-A 10 mg/kg n = 8; placebo n = 9. Age, mean (range): 3 mg/kg 29.9 (17 – 58) years; 10 mg/kg group 27.8 (20 – 37) years; placebo 33.4 (19 – 55) years. Gender split, n (%): 3 mg/kg group 5 males (50%); 10 mg/kg group 6 males (75%); placebo 7 males (78%). Baseline FEV_1 % predicted, mean (SD): 3 mg/kg group 75.2% (21.4); 10 mg/kg group 69.6% (19.7); placebo 67.8% (13.0). Baseline CFQ-R respiratory symptom score, mean (SD): 3 mg/kg group 66.7 (7.4); 10 mg/kg group 75.0 (14.6); placebo 71.6 (15.3). Baseline sputum *P aeruginosa* density $\log_{10}$ CFU/g, mean (SD): 3 mg/kg group 8.00 (1.20); 10 mg/kg group 7.80 (0.73); placebo 7.33 (2.07).
Interventions	KB001-A is a monoclonal antibody that works by inactivating the infection mechanism of *P aeruginosa.* **Intervention 1**: KB001-A (3 mg/kg), single IV infusion given over 1 hour. **Intervention 2**: KB001-A (10 mg/kg), single IV infusion given over 1 hour. **Control**: placebo (0.9 % sodium chloride), single IV infusion given over 1 hour.
Outcomes	Safety outcomes, adverse events, inflammatory markers, CFQ-R respiratory domain scores, spirometry (FEV_1, FEF_{25-75}, FVC) Outcomes were reported at baseline and day 28 and day 56.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as "randomized" but no detail provided.
Allocation concealment (selection bias)	Unclear risk	No detail provided.

Milla 2013 *(Continued)*

Blinding (performance bias and detection bias) PUFA first	Low risk	Research teams and participants were blinded. Unblinded pharmacists prepared the infusion bags but labelled bags to maintain blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	27 participants randomised. 2 participants discontinued the trial, 1 from each of the KB001-A groups (due to infusion related AE). A further 2 from the KB001-A 3 mg/kg group were excluded from the analysis (received prohibited medications) and 1 from the placebo group for the same reason. All participants were included in the safety analysis.
Selective reporting (reporting bias)	Low risk	Protocol deposited on clinicaltrials.gov. Primary outcomes are safety and tolerability which are reported.
Other bias	Unclear risk	The trial was sponsored by the pharmaceutical company developing KB001-A.

Renner 2001

Study characteristics	
Methods	Double-blind placebo-controlled RCT. Parallel design. Location: single centre in Vienna, Austria. Duration: 6 months.
Participants	24 participants with CF from 1 unit in Vienna; 13 randomised to supplementation group and 11 to placebo group. Age, mean (range): supplementation group 12.8 years (6.8 to 27.7); placebo group 10.5 years (6.7 to 17.3). Gender split: 18/24 female, 9 in supplementation group and 9 in placebo group.
Interventions	**Intervention**: 'high dose supplementation' of β-carotene at 1 mg/kg/day for 3 months followed by low-dose regimen of 10 mg/day for 3 months. **Control**: starch-containing placebo.
Outcomes	**Primary outcomes**: normalised plasma concentration of β-carotene; number of pulmonary exacerbations, lung function.
Notes	No specific data regarding bacteria presented - author contacted for more information 26 Jan 2010. The control group was on average 2.3 years younger than the intervention group.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but method of randomisation not described.
Allocation concealment (selection bias)	Unclear risk	Capsules were of identical appearance. Procedure for dispensing preparation unclear.

Renner 2001 *(Continued)*

Blinding (performance bias and detection bias) PUFA first	Low risk	Described as 'double-blind' but method not described. Capsules were of identical appearance. Rust 2000: Described as double blind but no further detail.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts. Two publications for this trial appear to report separate outcome data.
Selective reporting (reporting bias)	Low risk	Selective reporting not identified other than the separate reporting of different outcome data.
Other bias	Unclear risk	Participant compliance not reported.

Sagel 2009

Study characteristics	
Methods	Double-blind, placebo-controlled RCT. Parallel 3-arm trial. Location: single centre, USA. Duration: 48 hours.
Participants	18 participants aged 12 or over. Clinically stable with confirmed CF diagnosis Age, mean (SD): total cohort 16.7 years (3.40); low-dose NO 16.9 years (2.14); high-dose NO 15.6 years (2.33); placebo 17.7 years (5.14). Gender split: total cohort 13 males and 5 females; low-dose NO 4 males and 2 females; high-dose NO 4 males and 2 females; placebo 5 males and 1 female.
Interventions	**Low-dose group**: inhaled NO at 20 ppm via nasal cannula for 44 hours. **High-dose group**: inhaled NO at 40 ppm via nasal cannula for 44 hours. **Placebo**: nitrogen at 20 ppm or 40 ppm via nasal cannula.
Outcomes	Respiratory function (FEV_1), quantitative microbiology, adverse events.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised trial but method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Allocation method not described.
Blinding (performance bias and detection bias) PUFA first	Low risk	The trial was quadruple blinded i.e. participants, care providers, investigator, outcome assessor. NO and placebo were administered via nasal cannulae.

Sagel 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Although all participants remained in the trial, 1 participant was given both NO and nitrogen and the authors state that they removed the data from their analysis. The data reported in the clinical trials registration document is for 18 participants therefore it is not clear whether the data were removed for this participant or not.
Selective reporting (reporting bias)	Unclear risk	The sputum inflammatory markers were not reported, but all other outcomes listed were reported.
Other bias	Unclear risk	None identified.

Sharma 2016

Study characteristics	
Methods	Double-blind, placebo-controlled RCT. Parallel design. Location: single centre, Northern India. Duration: 12 months.
Participants	40 children aged 5 – 15 years. CF diagnosed by 2 abnormal sweat chloride values in the presence of physical symptoms. Age, median (IQR): zinc group 127.5 (100 – 150.5) months; placebo group 147.5 (126.5 – 162) months; P = 0.34. Gender split, n (%): zinc group 13 boys (65%); placebo group 11 boys (55%); P = 0.52. FEV_1 % predicted at baseline, median (IQR): zinc group 58.4% (37.5% – 81.75%); placebo group 48.1% (41.1% – 72.5%); P = 0.84. FVC % predicted at baseline, median (IQR): zinc group 65.4% (52.5% – 80.05%); placebo group 65.05% (53.33% – 73.75%); P = 0.84. BMI Z score at baseline, median (IQR): zinc group -2.4 (-2.75 to -1.37); placebo group -1.75 (-2.74 to -0.53). Participants with zinc deficiency at baseline n (%): zinc group 15 (75); placebo group 18 (90).
Interventions	**Intervention**: 1.5x 20 mg zinc tablet (giving 30 mg zinc) in 5 – 10 mL of water given orally once a day for 12 months. **Control**: placebo tablet given in the same way as active intervention for 12 months. Zinc tablets supplied by Bharat Immunologicals and Biologicals (Bulandshahr, India) a Government of India undertaking.
Outcomes	**Primary outcome**: reduction in the average days of systemic antibiotics. **Secondary outcomes**: change in FEV_1, rate of colonisation with PA, mortality, adverse events, pulmonary exacerbations requiring antibiotics. Timepoints: baseline, 3, 6, 9 and 12 months.

Sharma 2016 *(Continued)*

Notes	Children who received zinc in the month prior to enrolment and those not willing to attend for regular follow-up were excluded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomisation described and was carried out by a person not involved in the trial. Computer-generated randomisation. Block randomisation.
Allocation concealment (selection bias)	Low risk	The drugs were labelled by a person not involved in the trial. Strips were labelled as per the randomisation list. Sequentially numbered, sealed, opaque envelopes.
Blinding (performance bias and detection bias) PUFA first	Low risk	Double-blind trial. Similar looking zinc or placebo tablets were administered to the children.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data analysed as ITT and per protocol. 3 participants withdrew consent (1 from the placebo group and 2 from the zinc group).
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods were reported in the results.
Other bias	Low risk	No other risk of bias found.

Smyth 2010

Study characteristics

Methods	Pilot double-blinded, placebo-controlled RCT. Parallel design. Location: Nottingham, UK. Duration: 8 weeks.
Participants	34 participants over 8 years of age with CF (definition given) and chronic pulmonary infection with *P aeruginosa* and at the time of randomisation. Age, median (range): 18 years (11– 54 years). Adult/child split: garlic group 8 adults (62%) and 5 children (38%); placebo group 9 adults (69%) and 4 children (31%). Gender split: 14/26 (54%) were male. Baseline FEV_1 (L), mean (SD): garlic group 1.84 L (0.79); placebo group 1.91 L (1.05) Baseline FEV_1 % predicted, mean (SD): garlic group 62.0% (18.4); placebo group 57.4% (26.1). Weight (kg), mean (SD): garlic group 46.7 kg (14.6); placebo group 54.2 kg (14.1). Baseline clinical score, median (range): garlic group 2 (0 to 6) 3 (0 to 6); placebo group: 4 (0 to 6).
Interventions	**Intervention**: garlic capsule once daily (656 mg of garlic oil macerate and 10 mg cardamom oil).

Smyth 2010 *(Continued)*

	Control: placebo capsule once daily (656 mg of olive oil and 10 mg cardamom oil).
Outcomes	**Primary outcome**: FEV_1. **Secondary outcomes**: weight, clinical score, quorum sensing signal molecule level, number of courses of IV antibiotics over the 8-week trial period. Measured at baseline and 8 weeks.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web-based randomisation sequence.
Allocation concealment (selection bias)	Low risk	Procedure for dispensing preparation unclear - unpublished details demonstrate the supplements were dispensed in coded sealed opaque containers.
Blinding (performance bias and detection bias) PUFA first	Low risk	Double-blind, identical placebo. The cardamom oil was present as an odour control agent.
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 participants withdrew - four in each group: Garlic - 1 received lung transplant, 1 forgot to take capsules, 1 side effect of indigestion, 1 could not attend second visit; Placebo - 2 forgot to take capsules, 1 side effect of halitosis, 1 could not attend visit 2. Analysis was per protocol.
Selective reporting (reporting bias)	Low risk	No selective reporting identified.
Other bias	Low risk	No other bias identified.

BMI: body mass index
CF: cystic fibrosis
CFQ-R: cystic fibrosis questionnaire revised
CFU: colony forming units
FEF_{25-75}: mid peak expiratory volume
FEV_1: forced expiratory volume at 1 second
FVC: forced vital capacity
ITT: intention-to-treat
IV: intravenous
Ln: natural logarithm
NO: nitric oxide
P aeruginosa: Pseudomonas aeruginosa
QoL: quality of life
SD: standard deviation

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

Study	Reason for exclusion
Alvarez 2017	Not an antibiotic adjuvant - vitamin D supplementation.
Brown 1985	Cross-over RCT but authors have confirmed that data from 1st phase are unavailable.
DiMango 2014	Effect of proton pump inhibition to prevent acid aspiration - not a trial of an adjuvant.
Durairaj 2007	Safety study therefore not blinded, randomised or controlled.
Forrester 2015	Not an antibiotic adjuvant - direct bactericidal activity expected.
Gontijo-Amaral 2012	Examination of the effect of magnesium on respiratory muscle strength was the objective of the trial and so not an adjuvant.
Grasemann 2013	Effect of arginine on smooth muscle tone (via nitric oxide) is the target of the trial and so not an adjuvant.
Hauber 2008	Lacked a control group that did not receive examined intervention.
Hodges 2014	Trial of the distribution of nebulised solutions in the lungs not as an adjuvant therapy.
Homnick 1995	Non-randomised study.
Kollberg 2003	Non-randomised study, immunotherapy.
Kollberg 2010	Immunotherapy not an antibiotic adjuvant therapy.
Kutateladze 2008	Single patient experience described.
Lands 2010	Non-randomised study.
Leonard 2012	Trial of oral miglustat - not an antibiotic adjuvant therapy.
Middleton 2015	Trial of airway clearance adjunct, not an antibiotic adjuvant therapy.
Moss 2013	Immunotherapy not an antibiotic adjuvant therapy.
NCT00742092	Trial of nasal miglustat - not an antibiotic adjuvant therapy.
NCT01455675	Immunotherapy not an antibiotic adjuvant therapy.
Olveira 2010	The fatty acid supplement exerts an anti-inflammatory effect and does not meet the definition of antibiotic adjuvant.
Panchaud 2006	Independent anti-inflammatory effect - does not meet the definition of antibiotic adjuvant.
Safai-Kutti 1991	Placebo-controlled, double-blind, cross-over RCT of zinc supplementation, but no 1st arm data available.
Sagel 2011	Non-randomised, open-label study.
Sagel 2018	Not an antibiotic adjuvant - multivitamin with antioxidant for antioxidant concentrations, inflammation and oxidative stress.
Tangpricha 2017	Not an antibiotic adjuvant - vitamin D for improving immune response.

Study	Reason for exclusion
Winklhofer-Roob 1995	Non-randomised, healthy controls.
Winnie 1989	Immunotherapy not an antibiotic adjuvant therapy.

RCT: randomised controlled trial

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

CARE-CF-1

Methods	Multicentre, double-blind, placebo-controlled RCT. 6-arm.
Participants	89 adults with CF experiencing acute exacerbations. Age, mean (SD): 29.8 years (9.6). Gender split: 48% female. FEV_1 % predicted, mean (SD): 43.3% (18.3) predicted.
Interventions	Oral cysteamine (Lynovex®) as an adjunct to conventional treatment over 14 days. Intervention arm 1: 450 mg 4x daily. Intervention arm 2: 150 mg 3x daily. Intervention arm 3: 450 mg 2x daily. Intervention arm 4: 300 mg 3x daily. Intervention arm 5: 450 mg 3x daily. Intervention arm 6: placebo.
Outcomes	Change from baseline in sputum gram-negative bacterial load. Changes in patient-reported outcome measures from baseline: assessment using the CF respiratory symptom diary; chronic respiratory infection symptom score (CFRSD-CRSS); CFQ-R; and Jarad and Sequeiros Symptom Score Questionnaire. Blood leukocyte count. Change from baseline in sputum neutrophil elastase and IL-8 levels. Change in FEV_1, weight and BMI. Adverse events and serious adverse events.
Notes	The trial looks at the safety and efficacy of oral cysteamine in addition to finding the most important patient-reported outcomes. Awaiting full publication of efficacy trial.

Khorasani 2009

Methods	Double-blind placebo-controlled trial. Unclear if participants were randomised.

Khorasani 2009 *(Continued)*

Participants	20 children aged between 7 and 18 years with CF.
Interventions	Daily 5 mg/kg (max 30 mg) elemental zinc for 1 year.
Outcomes	Plasma zinc, pulmonary function tests, rate of respiratory infections and use of antibiotics measured at baseline and end of the trial.
Notes	Unclear whether this trial was randomised as it is only an abstract and no detail is given.

Puvvadi 2019

Methods	Placebo-controlled RCT.
Participants	24 people with CF with chronic *P aeruginosa* infection.
Interventions	Standard IV antibiotic treatment. **Intervention**: 5 mg CaEDTA (n = 12). **Placebo**: saline (n = 12). Both interventions given 4x daily for 2 weeks (while on IV antibiotics) and 2x daily for the following 4 weeks, with a 4-week safety follow-up period subsequently.
Outcomes	Mean *P aeruginosa* sputum count ($\log_{10}$ CFU/g). Lung function (FEV_1 % predicted). Adverse events.
Notes	Randomisation process is unclear - abstract only.

Rye 2015

Methods	A double-blind, placebo-controlled cross-over RCT.
Participants	12 participants with CF with chronic *Burkholderia sp*. infection.
Interventions	28 days treatment with OligoG as dry powder for inhalation.
Outcomes	Lung function, quality of life, sputum rheology and other microbiological outcome measures.
Notes	Presented in abstract form as a placeholder abstract without data. Cross-over trial and so we had planned to only consider the first treatment phase of a cross-over trial and did not include such trials in full until such time that duration of action detail is understood, a washout period is provided, measures of treatment effect are available and the data are available from each treatment phase - awaiting classification until such time as individual-patient data and measure of duration of treatment effect are provided. Email sent to AlgiPharma and PI 17/05/2017.

Walshaw 2014

Methods	Double-blind (participant, caregiver, investigator, outcomes assessor), randomised, placebo-controlled, cross-over trial.
Participants	26 participants aged 18 years and older with a positive microbiological finding of *P aeruginosa* in expectorated sputum or cough swab documented within 24 months prior to screening. The FEV_1 at screening was between 35% - 80% of the predicted normal value following adjustment for age, gender, and height according to the Knudson equation. Those with ABPA, an isolate of *Burkholderia species*, in the last year, or those who had, or were considering transplantation were excluded. Also those who had commenced inhaled TOBI in the previous 4 months were excluded.
Interventions	**Intervention**: inhaled 6% OligoG. **Control**: 0.9% saline.
Outcomes	**Primary outcome**: safety and local tolerability of multiple dose administration of inhaled OligoG in people with CF. **Secondary outcome**: effect of multiple dose administration of inhaled OligoG on various efficacy variables.
Notes	Primary completion date: July 2012. Cross-over trial and so we had planned to only consider the 1st treatment phase of a cross-over trial and did not include such trials in full until such time that duration of action detail is understood, a washout period is provided, measures of treatment effect are available and the data are available from each treatment phase - awaiting classification until such time as IPD and measure of duration of treatment effect are provided. Email sent to AlgiPharma and primary investigator July 2019.

Zabner 2009

Methods	Double-blind (participant, caregiver, investigator), parallel assignment, safety/efficacy RCT.
Participants	People with CF aged 16 years or older.
Interventions	**Intervention**: hypertonic xylitol. **Control**: hypertonic saline.
Outcomes	**Primary outcome measures**: FEV_1 change from baseline, adverse events and respiratory symptom score at 14 days. **Secondary outcome measures**: density of colonization/g of sputum, time to next exacerbation, sputum cytokines and revised CF QoL questionnaire at 14 days.
Notes	Marked as completed on clinicaltrials.gov.

CaEDTA: calcium ethylene diamine tetra-acetate
CF: cystic fibrosis
IPD: individual patient data
QoL: quality of life
RCT: randomised controlled trial

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

Pressler 2017

Study name	A Phase IIb Study of OligoG in Subjects With Cystic Fibrosis (SMR-2984).
Methods	Double-blind, placebo-controlled cross-over RCT.
Participants	76 adults with CF and *P aeruginosa* in expectorated sputum or cough swab within 24 months prior to screening. FEV_1 between 40% - 100% and no clinical or laboratory findings suggestive of significant pulmonary illness, other than CF.
Interventions	**Intervention 1**: inhalation of a dry powder OligoG in the 1st treatment period, and of placebo in the 2nd period. **Intervention 2**: inhalation of placebo in the 1st treatment period, and of a dry powder OligoG in the 2nd period.
Outcomes	FEV_1; mucociliary clearance, rheology, microbiology and QoL.
Starting date	October 2014.
Contact information	
Notes	Estimated trial completion date: April 2017.

CF: cystic fibrosis
FEV_1: forced expiratory volume at 1 second
P aeruginosa: *Pseudomonas aeruginosa*
QoL: quality of life
RCT: randomised controlled trial

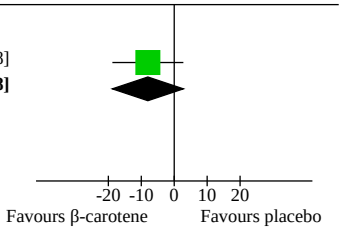
DATA AND ANALYSES

Comparison 1. Chronic infection: β-carotene supplementation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Days of antibiotic consumption	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 Over 1 month and up to 3 months	1	24	Mean Difference (IV, Fixed, 95% CI)	-8.00 [-18.78, 2.78]
1.2 Respiratory function absolute FEV_1 % predicted up to 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Over 1 month and up to 3 months	1	24	Mean Difference (IV, Fixed, 95% CI)	-10.90 [-32.23, 10.43]
1.3 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3.1 Over 1 month and up to 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

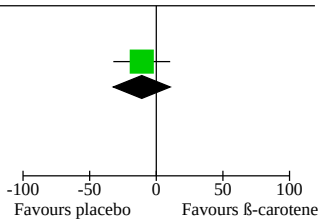
Analysis 1.1. Comparison 1: Chronic infection: β-carotene supplementation versus placebo, Outcome 1: Days of antibiotic consumption

Study or Subgroup	ß-carotene supplement Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Over 1 month and up to 3 months								
Renner 2001	10.5	9.9	13	18.5	15.8	11	100.0%	-8.00 [-18.78 , 2.78]
Subtotal (95% CI)			**13**			**11**	**100.0%**	**-8.00 [-18.78 , 2.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.45 (P = 0.15)								



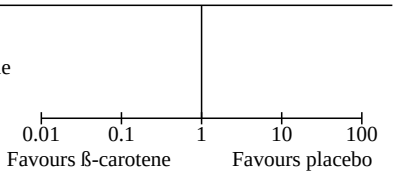
Analysis 1.2. Comparison 1: Chronic infection: β-carotene supplementation versus placebo, Outcome 2: Respiratory function absolute FEV_1 % predicted up to 3 months

Study or Subgroup	ß-carotene supplement Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Over 1 month and up to 3 months								
Renner 2001	70	33.3	13	80.9	19.1	11	100.0%	-10.90 [-32.23 , 10.43]
Subtotal (95% CI)			**13**			**11**	**100.0%**	**-10.90 [-32.23 , 10.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.00 (P = 0.32)								



Analysis 1.3. Comparison 1: Chronic infection: β-carotene supplementation versus placebo, Outcome 3: Mortality

Study or Subgroup	ß-carotene supplement Events	Total	Placebo Events	Total	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Over 1 month and up to 3 months					
Renner 2001	0	11	0	13	Not estimable



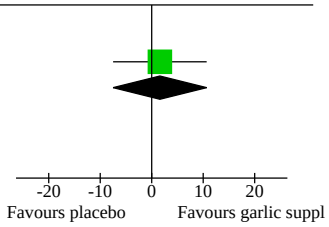
Comparison 2. Chronic infection: garlic supplementation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Respiratory function (% change FEV_1)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1.1 Over 1 month and up to 3 months	1	26	Mean Difference (IV, Fixed, 95% CI)	1.59 [-7.49, 10.67]
2.2 Mortality	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
2.2.1 Over 1 month and up to 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.3 Mild adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.3.1 Diarrhoea	1	26	Odds Ratio (M-H, Fixed, 95% CI)	5.87 [0.25, 135.15]
2.3.2 Halitosis	1	26	Odds Ratio (M-H, Fixed, 95% CI)	5.87 [0.25, 135.15]
2.3.3 Abdominal pain	1	26	Odds Ratio (M-H, Fixed, 95% CI)	3.24 [0.12, 87.13]
2.3.4 Dysuria	1	26	Odds Ratio (M-H, Fixed, 95% CI)	3.24 [0.12, 87.13]
2.3.5 Minor haemoptysis	1	26	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 17.90]

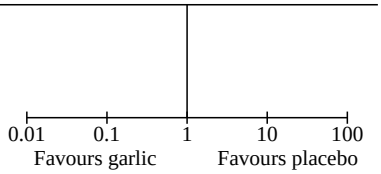
Analysis 2.1. Comparison 2: Chronic infection: garlic supplementation versus placebo, Outcome 1: Respiratory function (% change FEV_1)

Study or Subgroup	Garlic supplementation Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 Over 1 month and up to 3 months								
Smyth 2010	-2.01	12.3	13	-3.6	11.31	13	100.0%	1.59 [-7.49 , 10.67]
Subtotal (95% CI)			**13**			**13**	**100.0%**	**1.59 [-7.49 , 10.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.73)								

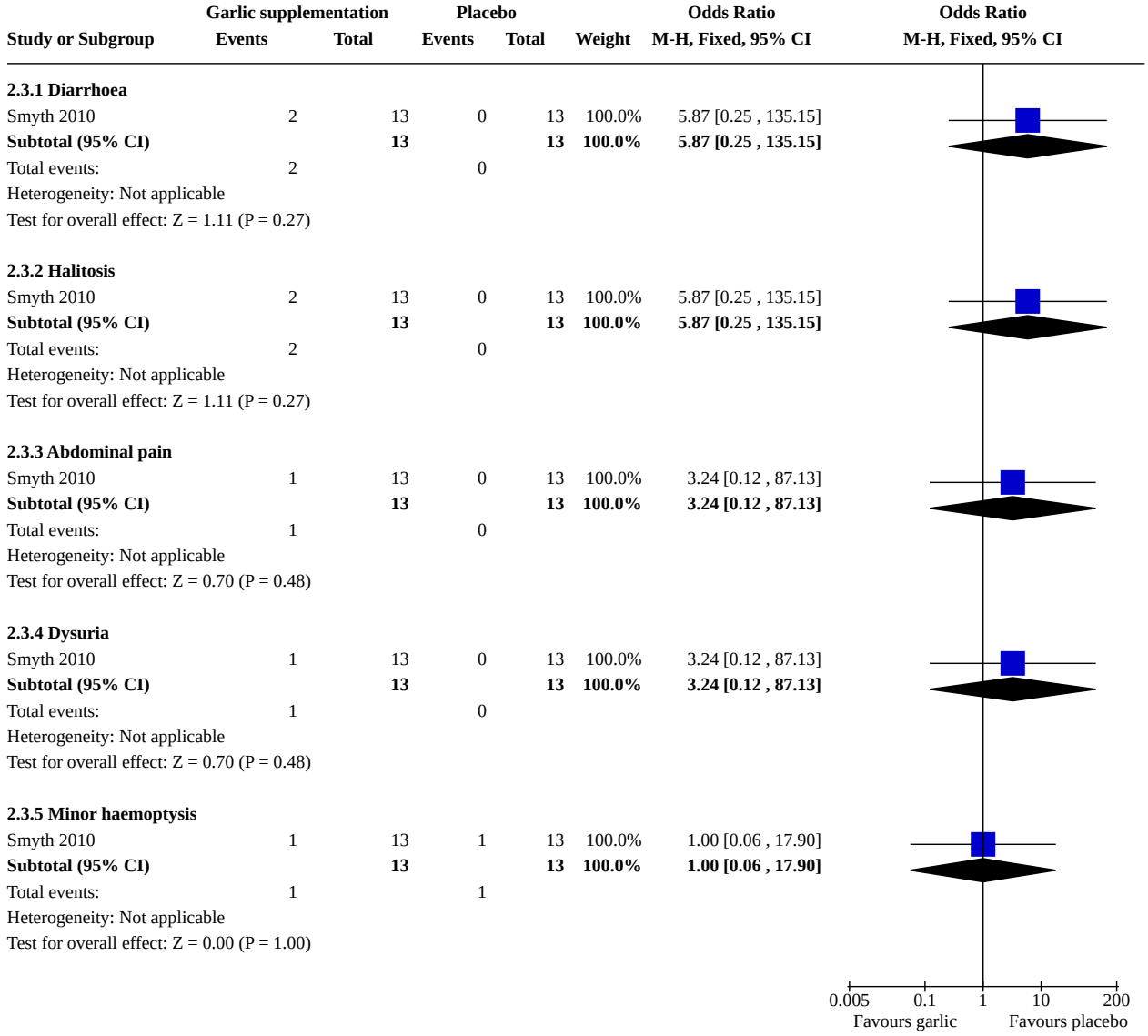


Analysis 2.2. Comparison 2: Chronic infection: garlic supplementation versus placebo, Outcome 2: Mortality

Study or Subgroup	Garlic supplementation Events	Total	Placebo Events	Total	Odds Ratio M-H, Fixed, 95% CI
2.2.1 Over 1 month and up to 3 months					
Smyth 2010	0	13	0	13	Not estimable



Analysis 2.3. Comparison 2: Chronic infection: garlic supplementation versus placebo, Outcome 3: Mild adverse events



Comparison 3. Chronic infection: KB001-A versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Pulmonary exacerbations	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.40]
3.2 Decrease in respiratory function (FEV_1)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.3 Number of participants experiencing an adverse event	1	27	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.90, 1.87]

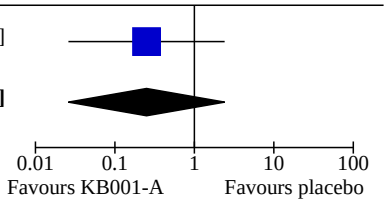
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.4.1 Bronchitis	1	27	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.07, 35.32]
3.4.2 Sinusitis	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.92]
3.5 Ear and labyrinth adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.5.1 Tinnitus	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6 Gastrointestinal adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6.1 Abdominal pain upper	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6.2 Cheilitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6.3 Pancreatitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6.4 Vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7 General adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7.1 Chest discomfort	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7.2 Chills	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7.3 Crepitations	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7.4 Fatigue	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7.5 Infusion-related reaction	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7.6 Infusion site discolouration	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7.7 Infusion site rash	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7.8 Irritability	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7.9 Pyrexia (fever)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.8 Infections and infestations	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.8.1 Sinusitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.9 Injury, poisoning and procedural complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.9.1 Procedural pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.9.2 Sunburn	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.10 Investigative adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.10.1 Blood pressure increased	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.10.2 Abnormal breath sounds	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.10.3 Increased heart rate	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.11 Nervous system adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.11.1 Dizziness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.11.2 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.11.3 Sinus headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.12 Psychiatric adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.12.1 Anxiety	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.12.2 Depression	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.12.3 Stress	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13 Respiratory, thoracic and mediastinal adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.1 Asthma	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.2 Cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.3 Dysphonia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.4 Dyspnoea	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.5 Haemoptysis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.6 Nasal congestion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.7 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.8 Pharyngolaryngeal pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.9 Productive cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.13.10 Rales	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.11 Respiratory tract congestion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.12 Rhinorrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.13 Sinus congestion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.14 Throat irritation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.15 Wheezing	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.14 Skin and subcutaneous tissue adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.14.1 Oral pruritus	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.14.2 Pruritus	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.14.3 Urticaria	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.15 Vascular adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.15.1 Flushing	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

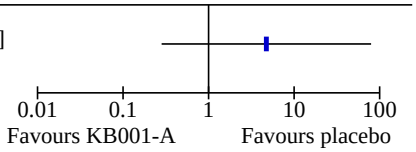
Analysis 3.1. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 1: Pulmonary exacerbations

	KB001-A		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Milla 2013	1	18	2	9	100.0%	0.25 [0.03 , 2.40]	
Total (95% CI)		**18**		**9**	**100.0%**	**0.25 [0.03 , 2.40]**	
Total events:	1		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.20 (P = 0.23)							
Test for subgroup differences: Not applicable							



Analysis 3.2. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 2: Decrease in respiratory function (FEV_1)

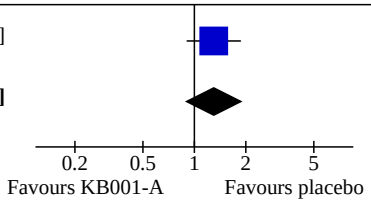
Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Milla 2013	4	18	0	9	4.74 [0.28 , 79.44]



Analysis 3.3. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 3: Number of participants experiencing an adverse event

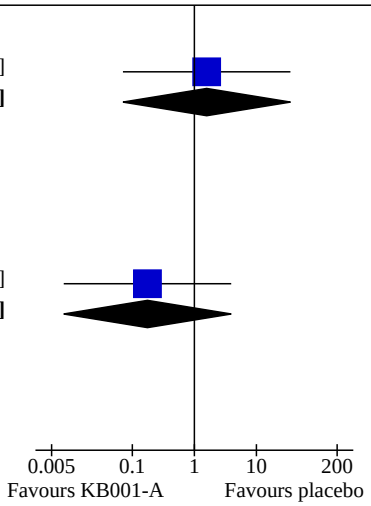
Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Milla 2013	18	18	7	9	100.0%	1.30 [0.90 , 1.87]
Total (95% CI)		**18**		**9**	**100.0%**	**1.30 [0.90 , 1.87]**
Total events:	18		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



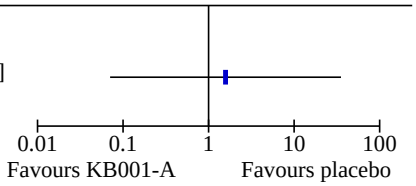
Analysis 3.4. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 4: Serious adverse events

Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Bronchitis						
Milla 2013	1	18	0	9	100.0%	1.58 [0.07 , 35.32]
Subtotal (95% CI)		**18**		**9**	**100.0%**	**1.58 [0.07 , 35.32]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
3.4.2 Sinusitis						
Milla 2013	0	18	1	9	100.0%	0.18 [0.01 , 3.92]
Subtotal (95% CI)		**18**		**9**	**100.0%**	**0.18 [0.01 , 3.92]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						



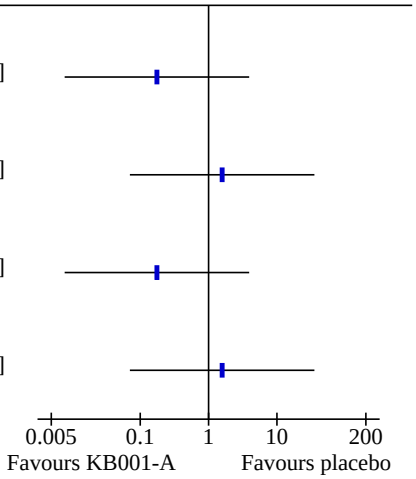
Analysis 3.5. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 5: Ear and labyrinth adverse effects

Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Tinnitus					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]



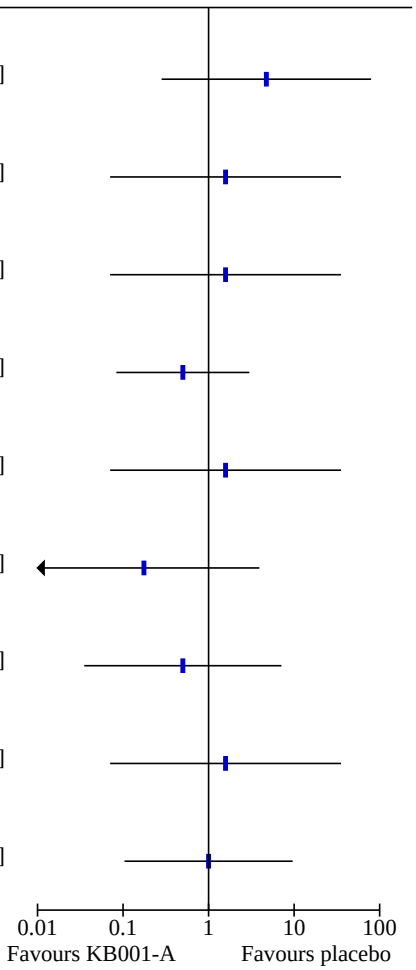
Analysis 3.6. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 6: Gastrointestinal adverse events

Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
3.6.1 Abdominal pain upper					
Milla 2013	0	18	1	9	0.18 [0.01 , 3.92]
3.6.2 Cheilitis					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.6.3 Pancreatitis					
Milla 2013	0	18	1	9	0.18 [0.01 , 3.92]
3.6.4 Vomiting					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]



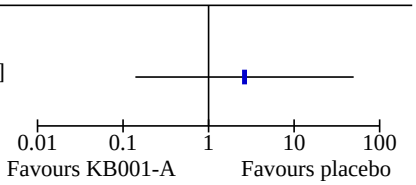
Analysis 3.7. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 7: General adverse events

Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
3.7.1 Chest discomfort					
Milla 2013	4	18	0	9	4.74 [0.28 , 79.44]
3.7.2 Chills					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.7.3 Crepitations					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.7.4 Fatigue					
Milla 2013	2	18	2	9	0.50 [0.08 , 2.99]
3.7.5 Infusion-related reaction					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.7.6 Infusion site discolouration					
Milla 2013	0	18	1	9	0.18 [0.01 , 3.92]
3.7.7 Infusion site rash					
Milla 2013	1	18	1	9	0.50 [0.04 , 7.10]
3.7.8 Irritability					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.7.9 Pyrexia (fever)					
Milla 2013	2	18	1	9	1.00 [0.10 , 9.61]



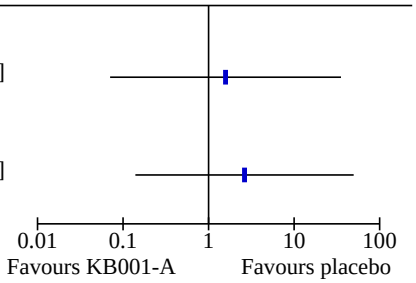
Analysis 3.8. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 8: Infections and infestations

Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
3.8.1 Sinusitis					
Milla 2013	2	18	0	9	2.63 [0.14 , 49.69]



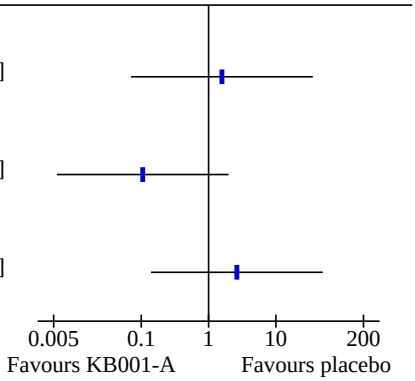
Analysis 3.9. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 9: Injury, poisoning and procedural complications

Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
3.9.1 Procedural pain					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.9.2 Sunburn					
Milla 2013	2	18	0	9	2.63 [0.14 , 49.69]



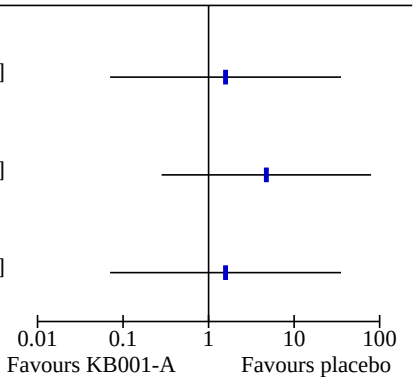
Analysis 3.10. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 10: Investigative adverse events

Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
3.10.1 Blood pressure increased					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.10.2 Abnormal breath sounds					
Milla 2013	0	18	2	9	0.11 [0.01 , 1.99]
3.10.3 Increased heart rate					
Milla 2013	2	18	0	9	2.63 [0.14 , 49.69]



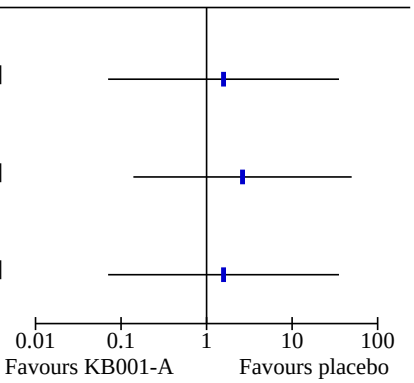
Analysis 3.11. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 11: Nervous system adverse events

Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
3.11.1 Dizziness					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.11.2 Headache					
Milla 2013	4	18	0	9	4.74 [0.28 , 79.44]
3.11.3 Sinus headache					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]



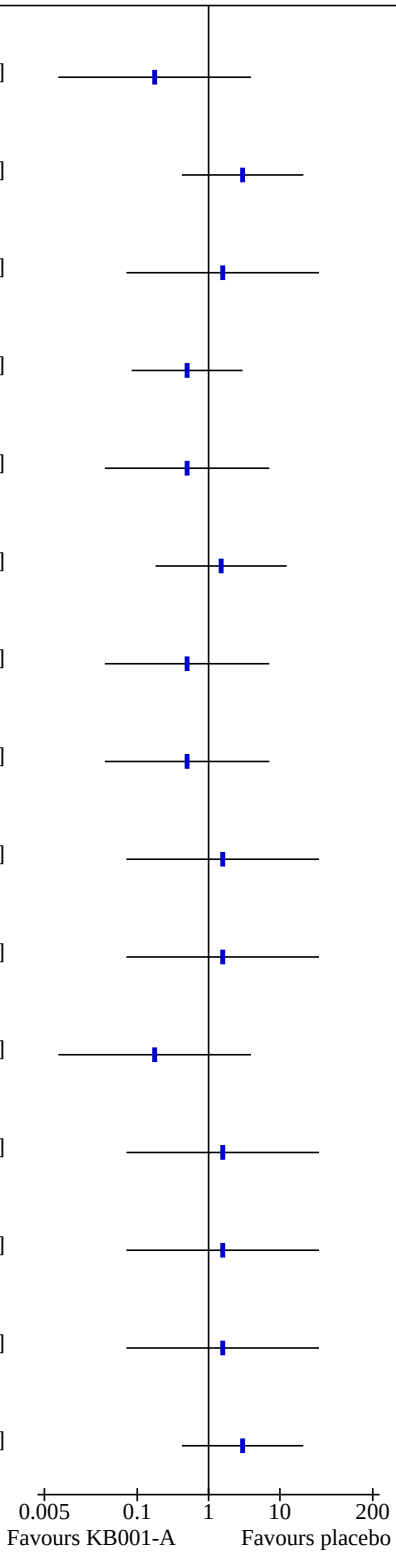
Analysis 3.12. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 12: Psychiatric adverse events

Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
3.12.1 Anxiety					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.12.2 Depression					
Milla 2013	2	18	0	9	2.63 [0.14 , 49.69]
3.12.3 Stress					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]



Analysis 3.13. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 13: Respiratory, thoracic and mediastinal adverse events

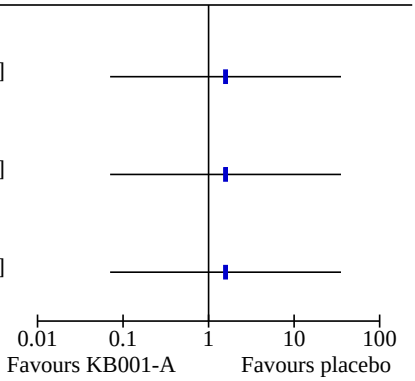
Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
3.13.1 Asthma					
Milla 2013	0	18	1	9	0.18 [0.01 , 3.92]
3.13.2 Cough					
Milla 2013	6	18	1	9	3.00 [0.42 , 21.30]
3.13.3 Dysphonia					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.13.4 Dyspnoea					
Milla 2013	2	18	2	9	0.50 [0.08 , 2.99]
3.13.5 Haemoptysis					
Milla 2013	1	18	1	9	0.50 [0.04 , 7.10]
3.13.6 Nasal congestion					
Milla 2013	3	18	1	9	1.50 [0.18 , 12.46]
3.13.7 Nausea					
Milla 2013	1	18	1	9	0.50 [0.04 , 7.10]
3.13.8 Pharyngolaryngeal pain					
Milla 2013	1	18	1	9	0.50 [0.04 , 7.10]
3.13.9 Productive cough					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.13.10 Rales					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.13.11 Respiratory tract congestion					
Milla 2013	0	18	1	9	0.18 [0.01 , 3.92]
3.13.12 Rhinorrhoea					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.13.13 Sinus congestion					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.13.14 Throat irritation					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.13.15 Wheezing					
Milla 2013	6	18	1	9	3.00 [0.42 , 21.30]



Analysis 3.13. (Continued)

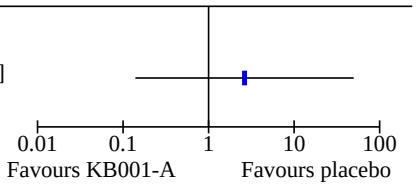
Analysis 3.14. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 14: Skin and subcutaneous tissue adverse events

Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
3.14.1 Oral pruritus					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.14.2 Pruritus					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]
3.14.3 Urticaria					
Milla 2013	1	18	0	9	1.58 [0.07 , 35.32]



Analysis 3.15. Comparison 3: Chronic infection: KB001-A versus placebo, Outcome 15: Vascular adverse events

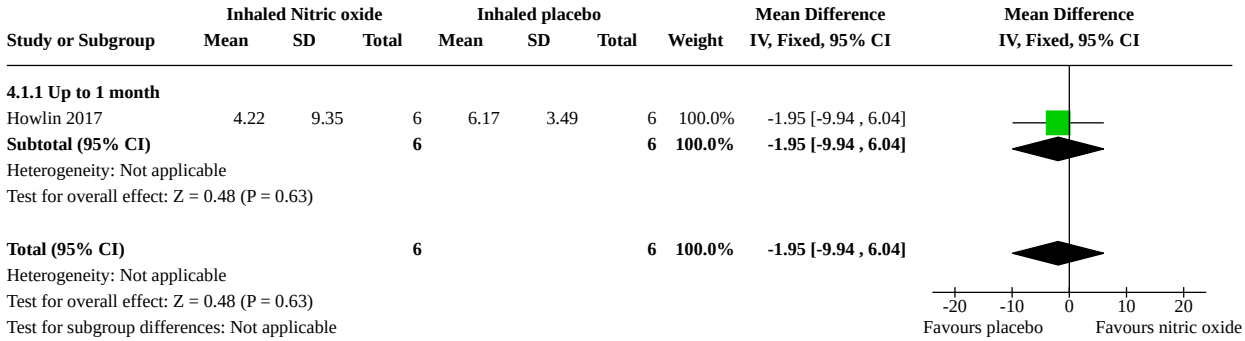
Study or Subgroup	KB001-A Events	KB001-A Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
3.15.1 Flushing					
Milla 2013	2	18	0	9	2.63 [0.14 , 49.69]



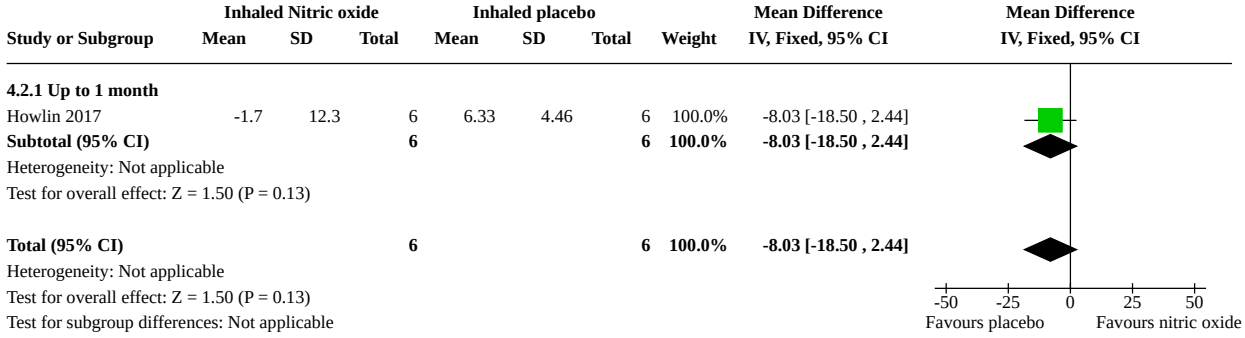
Comparison 4. Chronic infection: nitric oxide versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Change from baseline in FEV_1 % predicted	1	12	Mean Difference (IV, Fixed, 95% CI)	-1.95 [-9.94, 6.04]
4.1.1 Up to 1 month	1	12	Mean Difference (IV, Fixed, 95% CI)	-1.95 [-9.94, 6.04]
4.2 Change from baseline in FVC % predicted	1	12	Mean Difference (IV, Fixed, 95% CI)	-8.03 [-18.50, 2.44]
4.2.1 Up to 1 month	1	12	Mean Difference (IV, Fixed, 95% CI)	-8.03 [-18.50, 2.44]

Analysis 4.1. Comparison 4: Chronic infection: nitric oxide versus placebo, Outcome 1: Change from baseline in FEV_1 % predicted



Analysis 4.2. Comparison 4: Chronic infection: nitric oxide versus placebo, Outcome 2: Change from baseline in FVC % predicted



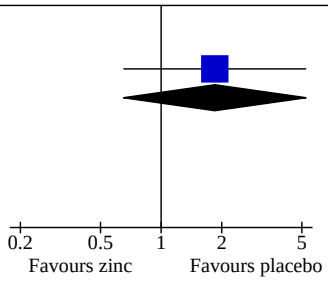
Comparison 5. Chronic infection: zinc supplementation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Pulmonary exacerbations (number of participants requiring IV antibiotics)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1.1 Up to 12 months	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.65, 5.26]
5.2 Respiratory function (FVC %predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.2.1 Up to 24 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.3 Antibiotic consumption (days oral antibiotics)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.3.1 Up to 24 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4 Antibiotic consumption (days IV antibiotics)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.4.1 Up to 24 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.5 Antibiotic consumption (days of oral and IV antibiotics)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.5.1 Up to 24 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.6 Respiratory function (FEV_1 % predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.6.1 Up to 24 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.7 Adverse events (number of participants hospitalised in the study period)	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.51, 2.97]
5.7.1 Up to 12 months	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.51, 2.97]

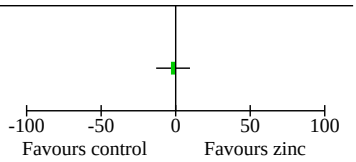
Analysis 5.1. Comparison 5: Chronic infection: zinc supplementation versus placebo, Outcome 1: Pulmonary exacerbations (number of participants requiring IV antibiotics)

Study or Subgroup	Zinc supplementation Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Up to 12 months						
Sharma 2016	7	18	4	19	100.0%	1.85 [0.65 , 5.26]
Subtotal (95% CI)		**18**		**19**	**100.0%**	**1.85 [0.65 , 5.26]**
Total events:	7		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
Test for subgroup differences: Not applicable						



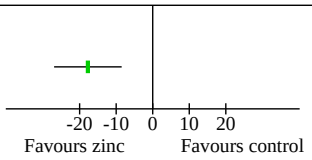
Analysis 5.2. Comparison 5: Chronic infection: zinc supplementation versus placebo, Outcome 2: Respiratory function (FVC %predicted)

Study or Subgroup	Zinc supplementation Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.2.1 Up to 24 months							
Abdulhamid 2008	82.95	15.14	12	84.7	13.67	13	-1.75 [-13.09 , 9.59]



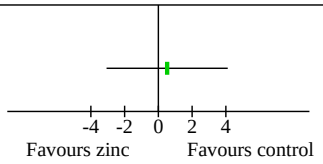
Analysis 5.3. Comparison 5: Chronic infection: zinc supplementation versus placebo, Outcome 3: Antibiotic consumption (days oral antibiotics)

Study or Subgroup	Zinc supplementation Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
5.3.1 Up to 24 months								
Abdulhamid 2008	30.8	9.71	12	48.54	13.67	13	-17.74 [-26.98 , -8.50]	



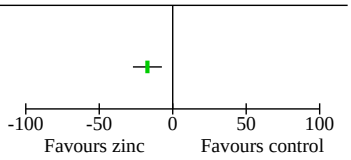
Analysis 5.4. Comparison 5: Chronic infection: zinc supplementation versus placebo, Outcome 4: Antibiotic consumption (days IV antibiotics)

Study or Subgroup	Zinc supplementation Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
5.4.1 Up to 24 months								
Abdulhamid 2008	5.32	4.96	12	4.8	4.12	13	0.52 [-3.07 , 4.11]	



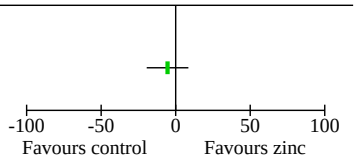
Analysis 5.5. Comparison 5: Chronic infection: zinc supplementation versus placebo, Outcome 5: Antibiotic consumption (days of oral and IV antibiotics)

Study or Subgroup	Zinc supplementation Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
5.5.1 Up to 24 months								
Abdulhamid 2008	36.08	11.81	12	53.3	13.3	13	-17.22 [-27.06 , -7.38]	

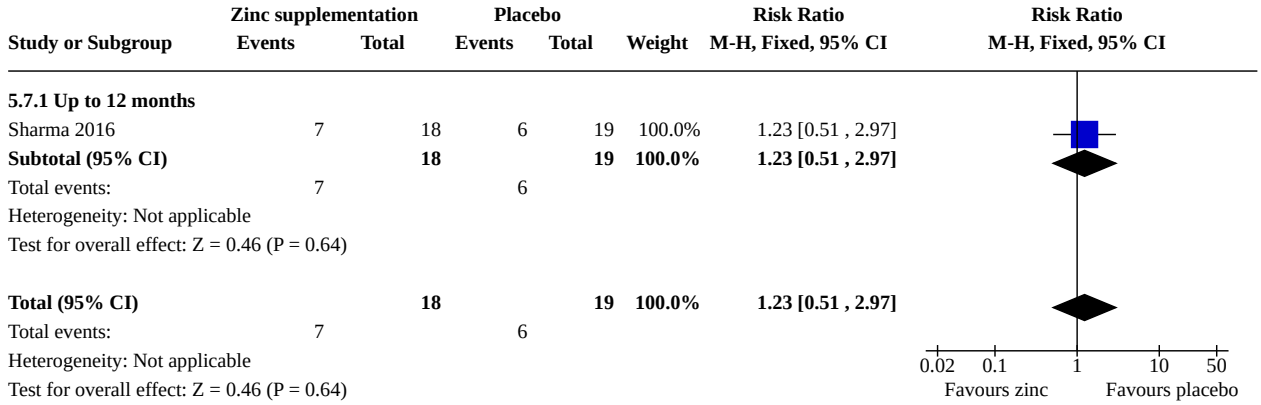


Analysis 5.6. Comparison 5: Chronic infection: zinc supplementation versus placebo, Outcome 6: Respiratory function (FEV_1 % predicted)

Study or Subgroup	Zinc supplementation Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
5.6.1 Up to 24 months								
Abdulhamid 2008	66.85	18.32	12	72.31	17.25	13	-5.46 [-19.44 , 8.52]	



Analysis 5.7. Comparison 5: Chronic infection: zinc supplementation versus placebo, Outcome 7: Adverse events (number of participants hospitalised in the study period)



APPENDICES

Appendix 1. MEDLINE search strategy (1950 to present) searched 11January 2010

1.	exp Cystic Fibrosis/
2.	cystic fibrosis.tw.
3.	fibrocystic near disease near pancreas.tw.
4.	mucoviscidos$.tw.
5.	(cystic$ adj10 fibros$).tw.
6.	1 or 2 or 3 or 4 or 5
7.	(immune adj4 (stimulant$ or augment$ or activat$ or potentiat$ or modulat$)).tw.
8.	exp Adjuvants, Immunologic/
9.	exp quorum sensing/
10.	Plant Extracts/ or Dietary Supplements/ or Vitamins/ or Phytotherapy/ or nutriceutical.mp. or Antioxidants/ or Nutritional Physiological Phenomena/
11.	(quorum and (sensing or quenching$)).tw.
12.	(garlic or ajoene).tw.
13.	exp Glutamine/
14.	glutamine.tw.
15.	exp Bacteriophages/

(Continued)

16.	bacteriophage$.tw.
17.	alginate lyase.tw.
18.	exp endolysin/
19.	endolysin$.tw.
20.	(IgY or immunoglobulin Y).tw.
21.	((efflux pump or lectin) adj inhibitor$).tw.
22.	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23.	6 and 22
24.	limit 23 to (humans and clinical trial, all)

Appendix 2. Ovid MEDLINE search strategy (1946 to present) searched 16 February 2019

1. Cystic Fibrosis/

2. cystic fibrosis.tw.

3. (fibrocystic adj10 disease adj10 pancreas).tw.

4. mucoviscidos$.tw.

5. (cystic$ adj10 fibros$).tw.

6. or/1-5

7. exp Adjuvants, Immunologic/

8. adjuvant$.tw.

9. (immune adj4 (stimulant$ or augment$ or activat$ or potentiat$ or modulat$)).tw.

10. exp Quorum Sensing/

11. (quorum and (sensing or quenching$)).tw.

12. Garlic/

13. (garlic or ajoene).tw.

14. glutamine.mp. or exp Glutamine/

15. exp Bacteriophages/

16. bacteriophage$.tw.

17. alginate lyase.tw.

18. (IgY or immunoglobin Y).tw.

19. ((efflux pump or lectin) adj inhibitor$).tw.

20. or/7-19

21. 6 and 20

22. randomized controlled trial.pt.

23. controlled clinical trial.pt.

24. randomized.ab.

25. placebo.ab.

26. drug therapy.fs.

27. randomly.ab.

28. trial.ab.

29. groups.ab.

30. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29

31. exp animals/ not humans.sh.

32. 30 not 31

33. 21 and 32

Lines 22 – 32 are the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format

Appendix 3. Online trial registry searches

Database	Search terms	Date last searched
ClinicalTrials.gov (www.clinicaltrials.gov)	'cystic fibrosis' and limited to phase III and IV clinical trials	06 April 2020
International Standard Randomised Controlled Trial Number Registry (isrctn.orgctn.org/)	'cystic fibrosis' and limited to phase III and IV clinical trials	06 April 2020
WHO clinical trials platform (ICTRP) (apps.who.int/trialsearch/)	'cystic fibrosis' and limited to phase III and IV clinical trials	06 April 2020

Appendix 4. Glossary

Medical term	Explanation
antibiotic adjuvant	an agent that acts alongside an antibiotic, but itself has little or no bactericidal activity; it acts by increasing the organisms' susceptibility to the co-administered antibiotic
bacteriophage	a virus that infects bacteria
biofilm	a thin layer of micro-organisms (e.g. bacteria) that form on and coat various surfaces. Various substances coat the biofilm and provide protection to those organisms living within the biofilm
dendrimer	a large and complex molecule with a very well-defined chemical structure

(Continued)

dysuria	painful urination
efflux pump	a mechanism located in the cell wall allowing substances toxic to the cell to be removed
efflux pump inhibitor	a molecule that interferes with the process of removing toxic substances and antibiotics from the cell
haemoptysis	coughing up of blood or of blood-stained sputum
halitosis	bad breath
lectin	a sugar-binding protein located on the surface off cells to allow cells to link to each other
quorum sensing inhibitors	molecules that interrupt the pathway of communication bacteria use to regulate expression of virulence factors
resistance	refers to the pathogens ability to withstand exposure to toxic substances, including antibiotics.
virulence factor	a substance produced by a pathogen that promotes its ability to cause disease

WHAT'S NEW

Date	Event	Description
8 September 2020	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2009
Review first published: Issue 10, 2010

Date	Event	Description
7 July 2020	New citation required but conclusions have not changed	Despite the inclusion of three new studies in this review, our conclusions have not changed. A new author, Sherie Smith, has joined the team.
7 July 2020	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified 60 new references potentially eligible for inclusion in the review. Five references were identified from trial registry searches. Extra Medline searches carried out January 2016 (n = 142), December 2016 (n = 182) and February 2019 (n = 16) did not identify any trials that had not already been identified. Eight references were found to three newly included trials (Howlin 2017; Sagel 2009; Sharma 2016). Two additional references to a trial previously listed as ongoing (Molfino 2012 unpublished) were identified and the trial has now been included (Jain 2018). There were seven additional references to three already included trials (Abdulhamid 2008; Milla 2013; Smyth 2010).

Date	Event	Description
		24 references to seven new trials were excluded (Alvarez 2017; DiMango 2014; Forrester 2015; Hodges 2014; Middleton 2015; Sagel 2018; Tangpricha 2017). There were eight additional references to six already excluded trials (Grasemann 2013; Hauber 2008; Kollberg 2010; Leonard 2012; Moss 2013; Panchaud 2006). 11 new references were identified to four trials listed as 'Awaiting classification' (CARE-CF-1; Khorasani 2009; Puvvadi 2019; Rye 2015;). One additional reference was identified to a trial previously listed as ongoing and now listed as 'Awaiting classification' (Walshaw 2014). A further trial previously listed as ongoing has been marked as completed on clinicaltrials.gov and moved to 'Awaiting assessment' pending publication of the trial results (Zabner 2009). Five references were identified to a new trial listed as ongoing (Pressler 2017). The outcome measures have been updated in line with current MECIR guidelines and summary of findings tables added.
7 May 2013	New citation required but conclusions have not changed	No new studies were identified for inclusion in the review; limited results from a safety study previously listed as ongoing have been presented, but our conclusions have not changed.
7 May 2013	New search has been performed	A search of the Cystic Fibrosis Trials Register identified three references to two separate studies which were potentially eligible for inclusion in the review. Two of these references relate to the ongoing study identified for the initial version of the review (NCT00633191) now listed as (Kollberg 2010) which we have excluded as it refers to an immunotherapy. The remaining reference was excluded for the same reason (Winnie 1989). A renewed search of MEDLINE revealed six more studies. Two of these were excluded due to adjuvant activity being unclear (Gontijo-Amaral 2012; Grasemann 2013). One study of immunotherapy (NCT01455675) and one of anti-inflammatory therapy (Moss 2013) were also excluded. Two studies were excluded as they were not randomised (Lands 2010; Sagel 2011). A search of ongoing trials registers identified two studies which are listed as ongoing and which will be assessed for inclusion when completed (Molfino 2012; Walshaw 2014a). Four studies, which were listed as ongoing in the previous version of the review, have now been excluded. Two studies of miglustat were excluded as this is not an adjuvant (NCT00742092; Leonard 2012); the full publication of one of these studies was identified in the MEDLINE search (Leonard 2012). A safety study of a biological agent is now included (Milla 2013). The remaining cross-over study was excluded after the study investigators confirmed that there were no first-arm data available for analysis (Brown 1985). A study previously listed as 'Awaiting classification' has been excluded as the order of treatment was not randomised (Safai-Kuti 1991).

CONTRIBUTIONS OF AUTHORS

For the original review

MH, DF and AS conceived the title. MH wrote the protocol, completed a search of the literature, was an independent assessor of the trials identified and drafted the review. DF was the second independent assessor of the trials identified from the literature search and commented upon the drafts of the protocol and the substantive review. AS supervised, gave comments and advised on the protocol and review.

MH acts as guarantor of the review.

For the 2020 update

Selection of trials and data extraction were performed by MH and SS for newly identified references. SS created summary of findings tables, added in the extra data from the new trials and updated the text of the review.

MH acts as guarantor of the review.

DECLARATIONS OF INTEREST

Dr Matthew Hurley
Dr Hurley has no conflicts of interest to declare.

Sherie Smith
Sherie Smith has no conflicts of interest to declare.

Dr Doug Forrester
Dr Doug Forrester declares he has received support from Wellcome Trust as a Wellcome Trust Clinical Research Training Fellow, travel support from Vertex Pharmaceuticals and GSK and consultancy fees from Mologic.

Professor Alan Smyth
Professor Smyth is lead investigator on one of the trials included in the review (Smyth 2010). He further declares relevant activities of lectures paid for by Teva and Novartis. He is affiliated to a research group which holds a patent: "ALKYL QUINOLONES AS BIOMARKERS OF PSEUDOMONAS AERUGINOSA INFECTION AND USES THEREOF".

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External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We altered the title of the review to be more informative - changing 'non-antibiotic' terminology to a new term - antibiotic adjuvants.

We have altered the definition of chronic infection to a definition that is most commonly used in routine clinical practice (Lee 2004) and have added requirement of antibiotics (days) as a secondary outcome measure.

We restated the outcome measures in line with current MECIR guidelines.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*administration & dosage]; Antibodies, Monoclonal [therapeutic use]; Bacterial Infections [*drug therapy] [microbiology]; beta Carotene [therapeutic use]; Chemotherapy, Adjuvant; Cystic Fibrosis [*complications]; Disease Progression; Garlic; Immunoglobulin Fab Fragments [therapeutic use]; Lung Diseases [*drug therapy] [microbiology]; Nitric Oxide [therapeutic

use]; Pseudomonas aeruginosa; Pseudomonas Infections [drug therapy]; Randomized Controlled Trials as Topic; Vitamins [therapeutic use]; Zinc [administration & dosage]

MeSH check words

Adolescent; Adult; Child; Humans; Young Adult