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Lo DKH, Muhlebach MS, Smyth AR

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 9
OBJECTIVES 10
METHODS 10
RESULTS 13
Figure 1. 14
Figure 2. 16
DISCUSSION 20
AUTHORS' CONCLUSIONS 21
ACKNOWLEDGEMENTS 21
REFERENCES 22
CHARACTERISTICS OF STUDIES 30
DATA AND ANALYSES 38
Analysis 1.1. Comparison 1: Active treatment versus observation only, Outcome 1: Eradication of MRSA 42
Analysis 1.2. Comparison 1: Active treatment versus observation only, Outcome 2: FEV1 (L) - absolute change from baseline 42
Analysis 1.3. Comparison 1: Active treatment versus observation only, Outcome 3: FEV1 (L) - relative change from baseline 43
Analysis 1.4. Comparison 1: Active treatment versus observation only, Outcome 4: FEV1 (% predicted) - absolute change from baseline 43
Analysis 1.5. Comparison 1: Active treatment versus observation only, Outcome 5: Overall antibiotic use 43
Analysis 1.6. Comparison 1: Active treatment versus observation only, Outcome 6: QoL measured using CFRSD Chronic Respiratory Infection Symptom Score (absolute change from baseline) 44
Analysis 1.7. Comparison 1: Active treatment versus observation only, Outcome 7: QoL measured using CFQ-R Respiratory Symptom Score (absolute change from baseline) 44
Analysis 1.8. Comparison 1: Active treatment versus observation only, Outcome 8: Participants positive for Pseudomonas aeruginosa 44
Analysis 1.9. Comparison 1: Active treatment versus observation only, Outcome 9: Weight (kg) (absolute change from baseline) 45
Analysis 1.10. Comparison 1: Active treatment versus observation only, Outcome 10: BMI (change from baseline) 45
Analysis 1.11. Comparison 1: Active treatment versus observation only, Outcome 11: Adverse effects of treatment 46
Analysis 1.12. Comparison 1: Active treatment versus observation only, Outcome 12: Number of participants with pulmonary exacerbations 47
Analysis 1.13. Comparison 1: Active treatment versus observation only, Outcome 13: Mean number of pulmonary exacerbations 47
Analysis 2.1. Comparison 2: Treatment with oral antibiotics plus nebulised vancomycin versus oral antibiotics plus placebo, Outcome 1: Eradication of MRSA 48
Analysis 2.2. Comparison 2: Treatment with oral antibiotics plus nebulised vancomycin versus oral antibiotics plus placebo, Outcome 2: Adverse effects of treatment 48
Analysis 2.3. Comparison 2: Treatment with oral antibiotics plus nebulised vancomycin versus oral antibiotics plus placebo, Outcome 3: Elimination of MRSA carrier status (number of participants with negative nasal swabs for MRSA) 49
APPENDICES 49
WHAT'S NEW 49
HISTORY 50
CONTRIBUTIONS OF AUTHORS 51
DECLARATIONS OF INTEREST 51
SOURCES OF SUPPORT 52
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 52
INDEX TERMS 52

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[Intervention Review]

Interventions for the eradication of meticillin-resistant Staphylococcus aureus (MRSA) in people with cystic fibrosis

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ABSTRACT

Background

Cystic fibrosis is an inherited recessive disorder of chloride transport that is characterised by recurrent and persistent pulmonary infections from resistant organisms that result in lung function deterioration and early mortality in sufferers.

Meticillin-resistant *Staphylococcus aureus* (MRSA) has emerged not only as an important infection in people who are hospitalised, but also as a potentially harmful pathogen in cystic fibrosis. Chronic pulmonary infection with MRSA is thought to confer on people with cystic fibrosis a worse clinical outcome and result in an increased rate of lung function decline. Clear guidance for MRSA eradication in cystic fibrosis, supported by robust evidence, is urgently needed. This is an update of a previous review.

Objectives

To evaluate the effectiveness of treatment regimens designed to eradicate MRSA and to determine whether the eradication of MRSA confers better clinical and microbiological outcomes for people with cystic fibrosis. To ascertain whether attempts at eradicating MRSA can lead to increased acquisition of other resistant organisms (including *Pseudomonas aeruginosa*), increased adverse effects from drugs, or both.

Search methods

We identified randomised and quasi-randomised controlled trials by searching the Cochrane Cystic Fibrosis and Genetic Disorders (CFGD) Group's Cystic Fibrosis Trials Register, PubMed, MEDLINE and three clinical trials registries; by handsearching article reference lists; and through contact with experts in the field. We last searched the CFGD Group's Cystic Fibrosis Trials Register on 4 October 2021, and the ongoing trials registries on 31 January 2022.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs of any combinations of topical, inhaled, oral or intravenous antimicrobials primarily aimed at eradicating MRSA compared with placebo, standard treatment or no treatment.

Data collection and analysis

We used standard methodological procedures expected by Cochrane and used the GRADE methodology to assess the certainty of the evidence.

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Main results

The review includes three RCTs with 135 participants with MRSA infection. Two trials compared active treatment versus observation only and one trial compared active treatment with placebo.

Active treatment versus observation

In both trials (106 participants), active treatment consisted of oral trimethoprim and sulfamethoxazole combined with rifampicin. One trial administered this combination for two weeks alongside nasal, skin and oral decontamination and a three-week environmental decontamination, while the second trial administered this drug combination for 21 days with five days intranasal mupirocin. Both trials reported successful eradication of MRSA in people with cystic fibrosis, but they used different definitions of eradication.

One trial (45 participants) defined MRSA eradication as negative MRSA respiratory cultures at day 28, and reported that oral trimethoprim and sulfamethoxazole combined with rifampicin may lead to a higher proportion of negative cultures compared to control (odds ratio (OR) 12.6 (95% confidence interval (CI) 2.84 to 55.84; low-certainty evidence). However, by day 168 of follow-up, there was no difference between groups in the proportion of participants who remained MRSA-negative (OR 1.17, 95% CI 0.31 to 4.42; low-certainty evidence).

The second trial defined successful eradication as the absence of MRSA following treatment in at least three cultures over a period of six months. We are uncertain if the intervention led to results favouring the treatment group as the certainty of the evidence was very low (OR 2.74, 95% CI 0.64 to 11.75). There were no differences between groups in the remaining outcomes for this comparison: quality of life, frequency of exacerbations or adverse effects (all low-certainty evidence) or the change from baseline in lung function or weight (both very low-certainty evidence). The time until next positive MRSA isolate was not reported. The included trials found no differences between groups in terms of nasal colonisation with MRSA.

While not a specific outcome of this review, investigators from one study reported that the rate of hospitalisation from screening through day 168 was lower with oral trimethoprim and sulfamethoxazole combined with rifampicin compared to control (rate ratio 0.22, 95% CI 0.05 to 0.72; P = 0.01).

Nebulised vancomycin with oral antibiotics versus nebulised placebo with oral antibiotics

The third trial (29 participants) defined eradication as a negative respiratory sample for MRSA at one month following completion of treatment. No differences were reported in MRSA eradication between treatment arms (OR 1.00, 95% CI 0.14 to 7.39; low-certainty evidence). No differences between groups were seen in lung function or adverse effects (low-certainty evidence), in quality of life (very low-certainty evidence) or nasal colonisation with MRSA. The trial did not report on the change in weight or frequency of exacerbations.

Authors' conclusions

Early eradication of MRSA is possible in people with cystic fibrosis, with one trial demonstrating superiority of active MRSA treatment compared with observation only in terms of the proportion of MRSA-negative respiratory cultures at day 28. However, follow-up at three or six months showed no difference between treatment and control in the proportion of participants remaining MRSA-negative. Moreover, the longer-term clinical consequences – in terms of lung function, mortality and cost of care – remain unclear.

Using GRADE methodology, we judged the certainty of the evidence provided by this review to be very low to low, due to potential biases from the open-label design, high rates of attrition and small sample sizes. Based on the available evidence, we believe that whilst early eradication of respiratory MRSA in people with cystic fibrosis is possible, there is not currently enough evidence regarding the clinical outcomes of eradication to support the use of the interventions studied.

PLAIN LANGUAGE SUMMARY

Treatments to clear the 'superbug' meticillin-resistant *Staphylococcus aureus* (MRSA) from the lungs of people with cystic fibrosis

Review question

We looked for evidence for the effects of different ways of clearing meticillin-resistant *Staphylococcus aureus* (MRSA), a so-called 'superbug', from the lungs of people with cystic fibrosis.

Background

MRSA is a type of bacteria resistant to some types of antibiotics (medicines that kill or inhibit bacteria). Because MRSA is hard to treat, it is sometimes called a 'superbug'. Infection with MRSA is particularly worrying for people with cystic fibrosis, an inherited condition which, amongst other things, causes thick mucus to build up in the lungs. It is very difficult for people with cystic fibrosis to cough up this thick mucus, making it an ideal breeding ground for bacteria, including MRSA, and making these people more prone to chest infections. It is thought that MRSA can cause more damage than other bacteria which are not resistant to antibiotics. We wanted to identify research evidence to support the best way for treating MRSA infections and also to see if this treatment would improve the lives of people with cystic fibrosis. This is an update of a previously published review.

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Search date

The evidence is current to 31 January 2022.

Key results

We found three studies which included 135 people with cystic fibrosis and a diagnosed MRSA infection.

Two studies (106 people) compared treatment given to one group of people versus observation only of a second group of people. In one of these studies, people in the active treatment group were given oral trimethoprim and sulfamethoxazole combined with rifampicin (all three are antibiotic medicines), plus additional decontamination treatment. In the second trial, people in the active treatment group were given two antibiotics orally (co-trimoxazole and rifampicin) and one by nose spray (mupirocin).

The results of these studies showed that clearing MRSA from the airways of people with cystic fibrosis is possible. In both trials, a larger proportion of those who were treated cleared MRSA. However, some people who were untreated also cleared MRSA spontaneously. Also, six months after treatment, the number of individuals who still had MRSA was not different between those who had received treatment and those who had not. We found no differences between treatment groups in quality of life, frequency of exacerbations (that is, flare-ups of the disease), unwanted or harmful effects of treatment, nasal colonisation with MRSA, or in changes in lung function or weight. The studies did not report the length of time until finding the next positive MRSA result in participants. In one of the studies, fewer people who were treated with antibiotics were admitted to hospital in the first 168 days.

The third study compared treatment groups who were given either an inhaled antibiotic or an inhaled placebo (inactive substance). Both groups were also given the same oral antibiotics. In this study, there was no difference between groups in MRSA clearance. There were no differences between groups in lung function, quality of life, unwanted or harmful effects or nasal colonisation with MRSA. The trial did not report on change in weight or frequency of exacerbations.

Treating MRSA early in people with cystic fibrosis has been shown to be possible, but it is not clear what longer-term implications this treatment will have.

Main limitations of the evidence

We had little or no confidence in the evidence we found for the different outcomes. This was due to potential issues from the study designs, where people knew which treatment each participant was receiving (groups were either given medication or just observed), and because there were small numbers of people in each study.

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Summary of findings 1. Active treatment versus observation only for eradicating MRSA in people with cystic fibrosis

Active treatment versus observation only for eradicating MRSA in people with cystic fibrosis

Patient or population: adults or children with positive microbiological isolate of MRSA from a respiratory tract specimen

Settings: outpatient and inpatient

Intervention: any combination of topical, inhaled, oral or intravenous antimicrobials with the primary aim of eradicating MRSA

Comparison: placebo, standard treatment or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Observation only	Oral antibiotics				
Eradication of MRSA: number of participants that were MRSA-negative[a] **Follow-up**: up to 6 months	464 per 1000	552 per 1000	OR 1.72 (0.65 to 4.55)	68 (2)	⊕⊕⊖⊖ **Low**[b,c]	The 2 trials included in this outcome at up to 6 months had different definitions of eradication: Muhlebach 2017 reported participants who were negative at day 28 and remained negative at day 168 (OR 1.17, 95% CI 0.31 to 4.42); Dolce 2019 defined eradication as 3 negative MRSA respiratory cultures over a 6-month period (OR 2.74, 95% CI 0.64 to 11.75). Muhlebach 2017 also reported on the number of participants who were MRSA-negative at day 28 and found that 18/22 (82%) participants on active treatment were MRSA-negative compared to 5/19 (26%) participants in the control group (OR 12.60, 95% CI 2.84 to 55.84; P < 0.001).

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Time until next positive MRSA isolate (from clinically relevant respiratory culture)	This outcome was not reported.				
Quality of life: CFRSD-CRISS symptom score **Follow-up**: up to 6 months	1 study reported quality of life and found no difference between treatment arms: score was 5.14 points higher in the oral antibiotic group than the observation group (5.06 points lower to 15.34 points higher).	NA	45 (1)	⊕⊕⊖⊖ **Low**[b,c]	The same study reported similar results for CFQ-R score at 6 months (MD -3.94, 95% CI -13.96 to 6.08) (Muhlebach 2017).
Lung function: absolute change from baseline in FEV_1 % predicted **Follow-up:** up to 6 months	There was a greater change from baseline in FEV_1 % predicted with active treatment (5.67% higher in the active group (1.43% higher to 9.90% higher).	NA	58 (2)	⊕⊖⊖⊖ **Very low**[c,d]	
Growth: change from baseline in weight (kg) **Follow-up**: up to 6 months	There was no difference in the change in weight between groups: 0.19 kg lower in the active group (1.70 kg lower to 1.32 kg higher).	NA	38 (1)	⊕⊖⊖⊖ **Very low**[c,d]	Additionally, Dolce 2019 reported the change in BMI and found no difference between groups (MD 0.92 kg/m^2, 95% CI -0.12 to 1.96).
Frequency of exacerbations **Follow-up**: up to 6 months	There was no difference in the mean number of pulmonary exacerbations observed in the 2 groups over the 6-month study duration (MD 0.15, 95% CI -0.54 to 0.84).	NA	32 (1)	⊕⊖⊖⊖ **Very low**[c,d]	Muhlebach 2017 reported on the percentage of participants with an exacerbation at 28 days and found no difference between groups (OR 0.29, 95% CI 0.06 to 1.30).
Adverse effects of treatment	There were no differences in the number of adverse events experienced in either study arm.	NA	45 (1)	⊕⊕⊖⊖ **Low**[b,c]	The most frequently occurring adverse events in both treatment arms were gas-

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Follow-up: up to 6 months					trointestinal disorders (OR 2.71, 95% CI 0.75 to 9.79).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BMI: body mass index; **CFQ-R**: Cystic Fibrosis Questionnaire - Revised; **CFRSD**: Cystic Fibrosis Respiratory Symptom Diary; **CI:** confidence interval; **CRISS**: Chronic Respiratory Infection Symptom Score; **FEV_1:** forced expiratory volume in 1 second; **MD**: mean difference; **MRSA:** meticillin-resistant *Staphylococcus aureus*; **OR**: odds ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Both trials included in this outcome defined eradication differently, but both reported at up to 6 months: Dolce 2019 defined eradication as three consecutively negative MRSA samples by three months; and Muhlebach 2017 defined eradication as MRSA-negative at day 168.
[b]Downgraded once due to risk of bias, particularly across the domains of blinding of participants and outcome assessment.
[c]Downgraded once due to imprecision caused by small sample size and low event rates.
[d]Downgraded once due to risk of bias, particularly across the domains of blinding of participants and outcome assessment. There was also risk of attrition bias for this outcome.

Summary of findings 2. Oral plus nebulised antibiotics versus oral antibiotics plus nebulised placebo for eradicating MRSA in people with cystic fibrosis

Oral plus nebulised antibiotics compared with oral antibiotics plus nebulised placebo for eradicating MRSA in people with cystic fibrosis

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

Settings: outpatients

Intervention: oral plus nebulised antibiotics

Comparison: oral antibiotics plus nebulised placebo

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No. of participants (trials)	Certainty of the evidence (GRADE)	Comments

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	Assumed risk	Corresponding risk				
	Oral antibiotics plus placebo	Oral plus nebulised antibiotics				
Eradication of MRSA **Follow-up**: 3 months after treatment	133 per 1000	200 per 1000 (28 to 682)	OR 1.63 (0.19 to 13.93)	25 (1)	⊕⊕⊖⊖ **Low**[a,b]	
Time until next positive MRSA isolate (from clinically relevant respiratory culture)	This outcome was not reported.					
Quality of life: absolute change in CFQ-R respiratory domain score **Follow-up**: up to 3 months after treatment	There was no difference in quality of life scores reported between groups.			25 (1)	⊕⊖⊖⊖ **Very low**[a,b,c]	No numerical results were reported for this outcome and so we have presented the narrative results reported in the paper (Dezube 2019).
Lung function: absolute change from baseline in FEV_1 % predicted **Follow-up**: 3 months after treatment	There was no difference in median (IQR) absolute change from baseline in FEV_1 % predicted: -1.0% (-5.0 to 2.0) in the oral antibiotic plus nebulised vancomycin group compared to 0.0% (-3.0 to 4.0) in the control group.			25 (1)	⊕⊕⊖⊖ **Low**[a,b]	Data were presented as median (IQR) and so we were unable to calculate MD and have reported directly from the paper (Dezube 2019).
Growth	This outcome was not reported.					
Frequency of exacerbations	This outcome was not reported.					
Adverse effects of treatment	933 per 1000	977 per 1000	OR 3.00 (0.11 to 79.91)	29 (1)	⊕⊕⊖⊖ **Low**[a,b]	The most common adverse events were respiratory-related followed by gastrointestinal events.

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Follow-up: up to 3 months after treatment				4 participants were removed from the trial because of respiratory adverse events. There were 6 serious adverse events in 4 participants but none were related to the treatment regimen (Dezube 2019).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: Cystic Fibrosis Questionnaire - Revised; **CI**: confidence interval; **FEV_1**: forced expiratory volume in 1 second; **IQR**: interquartile range; **MD**: mean difference; **MRSA**: meticillin-resistant *Staphylococcus aureus*; **OR**: odds ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to risk of bias caused by unclear blinding of outcome assessment and incomplete outcome data.
[b]Downgraded by one level due to serious imprecision (small sample size and low event rates).
[c]Downgraded once due to selective reporting as the data were not reported.

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BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common autosomal inherited condition in white populations, with a gene carrier rate of 1 in 25 and affecting more than 10,600 people in the United Kingdom (UK) (CF Trust UK 2022). It is a multisystem disorder resulting from a disruption in chloride transport at the cellular level, leading to abnormal, dehydrated secretions within the lungs. This results in impaired mucociliary clearance, leading to recurrent pulmonary infections, bronchiectasis and progressively deteriorating lung function, which is the main cause of the morbidity and mortality seen in CF.

Organism

The abbreviation MRSA stands for meticillin-resistant *Staphylococcus aureus.* Meticillin is an antibiotic no longer in clinical use, but MRSA is resistant to antibiotics within the same class. This includes flucloxacillin, which is prescribed both for prophylaxis and treatment of infection with *S aureus* in people with CF in the UK. Furthermore, MRSA is also resistant to other antibiotics in the beta lactam family, such as cephalosporins (e.g. ceftazidime) and carbapenems (e.g. meropenem). Resistance is not due to production of beta lactamase enzymes, but rather to the production of altered penicillin-binding proteins coded on the *mec*A gene.

Most MRSA infections in both the non-CF and CF populations have been so-called 'healthcare associated' (HA-MRSA), which occur in those who have been hospitalised, had surgery, are on dialysis or who have had invasive procedures. However, in recent years, outbreaks of 'community-acquired' MRSA (CA-MRSA) have occurred in otherwise healthy people with no link to a healthcare facility (Chambers 2009). This distinction by patient location at time of infection is becoming increasingly difficult, given outbreaks of strains of CA-MRSA in hospitals, and the spread of HA-MRSA strains in the community through people with chronic illnesses.

It is possible to further classify MRSA according to the staphylococcal chromosome cassette *mec* (SCC*mec)* type, on which the *mec*A gene is located. Several distinct types have been described to date, of which HA-MRSA is associated with types I to III. These SCC*mec* types also encode for resistance to other classes of antibiotics, thus making HA-MRSA overall more resistant. So-called CA-MRSA carries SCC*mec* types IV and V. Although CA-MRSA usually has the smaller type IV SCC*mec* type, which lacks some of the antibiotic resistance determinants possessed by types I to III, it is also more frequently associated with the production of the virulence factor Panton-Valentine leucocidin (PVL), a cytotoxin which causes leucocyte destruction and tissue necrosis.

Although people with MRSA have been found to require a higher intensity of treatment when compared with their meticillin-sensitive *S aureus* (MSSA) counterparts, this is further complicated by differences observed between different MRSA types (Muhlebach 2011). For instance, the emergence of PVL-positive CA-MRSA within the CF population has been described, and one report suggests this to be associated with a more severe, acute clinical course compared with PVL-negative CA- or HA-MRSA strains (Elizur 2007). This has not been replicated in other reports.

Prevalence

The prevalence of MRSA varies throughout Europe. Though the occurrence of MRSA is stabilising, or even decreasing, in several European countries, the percentage of MRSA among all *S aureus* isolates remains above 25% in six of the 30 reporting countries from the European Union or European Economic Area. In the UK, 6% of isolates of *S aureus* are found to be MRSA compared to 1% in Norway (ECDC 2019). In the USA, approximately 5% of patients in hospitals carry MRSA in their nose or on their skin (CDC 2022).

Amongst people with CF, the prevalence of chronic MSSA (defined as three or more recorded isolates) in the UK has fallen from 20.9% in 2010 to 15.4% in 2020 in adults, but increased in children from 8.1% in 2010 to 11.6% in 2020 (CF Trust 2020). The prevalence of MRSA (defined as any single isolate) has increased gradually in adults from 2.5% in 2009 (CF Trust 2009) to 3.4% in 2020 (CF Trust 2020).

The USA CF registry data report a small decline in respiratory isolates of MSSA from 50.5% in 2010 to 48.9% in 2020, and any isolate of MRSA from 25.8% in 2010 to 19.6% in 2020 (CF Foundation 2020).

Condition

As described above, one of the early key pathogens in CF-lung disease is MSSA, but increasingly, MRSA has been cultured from the lower respiratory tracts of people with CF. The role of MRSA in CF-lung disease remains debated.

A large observational study looking at 1834 participants who had positive respiratory cultures for *S aureus* (MRSA or MSSA) found that presence of MRSA in respiratory cultures was associated with poorer lung function, more courses of antibiotics and longer hospital stays when compared with those colonised with MSSA (Ren 2007). However, the authors were unable to conclude whether their findings were due to cause or effect.

Two studies were published in 2008 addressing this point, but came to differing conclusions (Dasenbrook 2008; Sawicki 2008). Dasenbrook and colleagues suggested that chronic, though not intermittent, detection of MRSA in respiratory tract cultures of people with CF (as defined by reports from the CF Foundation Registry) is associated with poorer survival and reduced lung function (Dasenbrook 2008; Dasenbrook 2010). By contrast, Sawicki and colleagues concluded that although MRSA was a marker for more aggressive therapy and may reflect increased disease severity, MRSA detection was not associated with a significant decline in lung function (Sawicki 2008).

Although both were longitudinal studies, Sawicki and colleagues analysed data from an observational study of people with CF in North America (Epidemiologic Study of Cystic Fibrosis (ESCF) (Morgan 1999)) using multivariate linear regression analysis to study the impact of MRSA on lung function (forced expiratory volume in one second (FEV_1) per cent (%) predicted). Dasenbrook and colleagues used data from the CF Foundation Registry. One of the fundamental differences between the two studies is the inclusion criteria. Sawicki 2008 included participants for analysis who had only one positive culture for MRSA (23% of cohort) whilst Dasenbrook and colleagues studied participants with three or more positive cultures, and excluded those with one or two MRSA cultures.

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Despite these differences, both studies reported an increased rate of decline in FEV_1 % predicted of around 0.5% in their 'before' and 'after' MRSA groups. It is possible that this did not reach statistical significance in the Sawicki 2008 paper secondary to the smaller cohort size (593 versus 1732). An increased rate of decline of 0.8% has more recently been reported by a group in Belgium who conducted a retrospective case-control study based at a single centre (Vanderhelst 2012).

In terms of survival, Dasenbrook and colleagues found that the detection of MRSA from the respiratory tract of people with CF was associated with an increased risk of death when compared with individuals in whom MRSA had never been detected (hazard ratio (HR) 1.27, 95% confidence interval (CI) 1.11 to 1.45) (Dasenbrook 2010). Perhaps of more clinical importance, however, is that they also found that those who clear MRSA within one year have the same risk of death as those who never have a positive culture for MRSA. This emphasises the importance and need for clear guidance on how we manage MRSA infection in CF.

Description of the intervention

Currently in the UK, children are prescribed prophylactic anti-staphylococcal antibiotics (flucloxacillin) from diagnosis until three years of age, with resultant fewer isolates of *S aureus*, though the clinical significance of this finding remains uncertain (Smyth 2017). However, the US Cystic Fibrosis Foundation recommend against the use of prophylaxis in anticipation that this may lead to an increase in colonisation of *Pseudomonas aeruginosa* (Flume 2007).

Some authors suggest a pragmatic approach would be to treat every isolate of MRSA or MSSA with eradication therapy (Solis 2003). However, this approach, with its frequent use of antibiotics, would run the risk of increasing the incidence of multi-resistant organisms that are less susceptible to treatment, whilst potentially adding to the already substantial treatment burden that people with CF face.

Certainly in the case of HA-MRSA infections, there has been encouraging progress since the introduction of stringent MRSA screening and eradication measures in hospitals. A 2010 report by the Centers for Disease Control and Prevention (CDC) showed a 28% decline in invasive MRSA infections originating in hospitals between 2005 and 2008 in the USA (Kallen 2010). In the UK, the Department of Health target to reduce MRSA bloodstream infections by 50% from its peak levels in 2003/2004 was achieved by 2008 (Liebowitz 2009; Pearson 2009).

How the intervention might work

The presence of MRSA in the lower airways of people with CF is thought to be associated with worse clinical outcomes, including poorer lung function and an increased risk of death. Treatment strategies designed to target MRSA when it is first isolated from the respiratory samples of people with CF, if successful at eradicating MRSA from subsequent respiratory cultures, may therefore improve clinical outcomes in people with CF. This includes improved lung function, reduced risk of death, and reduced risk of hospitalisations.

Why it is important to do this review

The clinical significance of MRSA in CF remains unclear and there remains no international consensus for its management. With the increasing prevalence of resistant strains of *S aureus*, it becomes more important for any therapeutic approaches with antibiotics to be justified with the most up-to-date evidence, especially for those with chronic medical conditions.

A previous Cochrane Review could not find sufficient evidence to support the use of any single therapy or combination of therapies for eradicating nasal or extra-nasal colonisation of MRSA over another in the general population (Loeb 2003). Most studies addressing MRSA colonisation have been done in either healthy carriers or people in chronic care facilities, but not in those with chronic lung disease as seen in CF. Such reports include a variety of interventions, often focusing on nasal and skin colonisation, and thus such findings may not be directly applicable to CF. However, a retrospective review of MRSA eradication practice in a single large UK adult CF centre showed some promise (Doe 2010). Doe and colleagues used varying eradication regimens based on sensitivity patterns and individual tolerability, including stringent patient segregation and topical decolonisation, to attempt MRSA eradication from sputum and skin of people with CF. Over a 10-year period they reported an eradication rate of 81% (defined as three consecutive negative sputum and peripheral cultures over six months), though the clinical impact of what successful MRSA eradication meant for patients was not reported.

The 2008 UK CF Trust consensus statement document stated that in the absence of prospective randomised clinical trials looking at the effect on lung function which chronic carriage with MRSA confers, MRSA infection will lead to a reduction in antibiotic treatment options and a likelihood of a deterioration in lung function (CF Trust 2008). It is therefore their recommendation that the eradication of MRSA should be attempted for positive cases (CF Trust 2008).

The rationale for this review is to determine the success of MRSA eradication for people with CF, and to question whether eradication confers improved clinical outcomes. This version of the review is an update of a previously published review (Lo 2013; Lo 2015; Lo 2018).

OBJECTIVES

To evaluate the effectiveness of treatment regimens designed to eradicate MRSA and to determine whether the eradication of MRSA confers better clinical and microbiological outcomes for people with CF.

To ascertain whether attempts at eradicating MRSA can lead to increased acquisition of other resistant organisms (including *Pseudomonas aeruginosa*), increased adverse effects from drugs, or both.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs.

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Types of participants

Children and adults diagnosed with CF clinically and by sweat or genetic testing with a confirmed positive microbiological isolate of MRSA on clinically relevant CF respiratory cultures (bronchoalveolar lavage (BAL), cough or oropharyngeal swab, spontaneous or induced sputum culture) specimen prior to enrolment into the trial.

We included all disease severities. We did not include participants with nasal carriage of MRSA alone in this review.

Types of interventions

Any combinations of topical, inhaled, oral or intravenous antimicrobials with the primary aim of eradicating MRSA once detected on clinically relevant CF respiratory cultures, compared with placebo, standard treatment or no treatment.

Types of outcome measures

We assessed the following outcome measures at up to 14 days, up to one month, up to three months, up to six months and up to 12 months after MRSA therapy.

Primary outcomes

1. Eradication of MRSA (as defined by negative respiratory culture after completion of the eradication protocol)
2. Time until next positive MRSA isolate from clinically relevant respiratory culture

Secondary outcomes

1. Lung function
   a. FEV_1 % predicted
   b. forced vital capacity (FVC) % predicted
   c. other validated measures of lung function
2. Overall antibiotic use
3. Mortality
4. Quality of life (QoL) measured using a validated tool
   a. CF Questionnaire-Revised version (CFQ-R) (Quittner 2009)
   b. CF QoL Questionnaire (CFQoL) (Gee 2000)
5. Isolation of MRSA or other organisms with new antibiotic-resistant phenotypes
   a. *P aeruginosa*
   b. other previously uncultured organism
   c. small colony variants of *S aureus*
6. Growth and nutritional status
   a. weight (kg)
   b. height (cm)
   c. body mass index (BMI) (kg/m^2)
   d. lean body mass (%)
   e. fat body mass (%)
7. Adverse effects of treatment
   a. mild (not requiring treatment)
   b. moderate (requiring treatment or admission or cessation of treatment, or a combination of any of these)
   c. severe (life-threatening)
8. Elimination of carrier status (nasal or skin)
9. Frequency of exacerbations
10. Cost of care

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

We identified relevant studies from the Group's Cystic Fibrosis Trials Register using the terms: (staphylococcus aureus or mixed infections) AND (eradication OR unknown).

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major 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 the latest search: 04 October 2021.

We also searched the following databases and trial registries:

1. MEDLINE Ovid (1946 to 31 January 2022);
2. PubMed (www.ncbi.nlm.nih.gov/pubmed/; 1946 to 31 January 2022);
3. US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov; searched 31 January 2022);
4. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (trialsearch.who.int/; searched 31 January 2022);
5. ISRCTN registry (www.isrctn.com/; searched 31 January 2022).

For details of our search strategies, please see Appendix 1.

Searching other resources

The authors also contacted primary authors and research institutions of ongoing identified trials for unpublished data.

Data collection and analysis

Selection of studies

Two review authors (DL and AS) independently screened trials for inclusion in this review in accordance with methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). Both authors independently examined the title and abstracts to exclude duplicate publications, case reports, review articles and unrelated articles. The two authors (DL and AS) independently examined the full-text publications of the remaining trials to determine if they met the review's eligibility criteria. We planned to resolve any queries on the eligibility of trials by consulting with the third author (MM) for advice and reaching a consensus through discussion between all authors.

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Data extraction and management

Two review authors (DL and AS) extracted data using standardised data acquisition forms, upon which all authors had agreed. We resolved disagreements through discussion between all three authors. Where information was incomplete or unclear, we contacted the lead author of the paper where possible.

We grouped outcome data into those measured at up to 14 days, up to one month, up to three months, up to six months and up to 12 months after MRSA therapy.

Assessment of risk of bias in included studies

Two review authors (DL and AS) assessed the risk of bias using methods described in the *Cochrane Handbook for Systematic Reviews for Interventions* (Higgins 2017). In particular, we examined the methods to determine the adequacy of randomisation and blinding, and also whether any participants lost to follow-up were accounted for and justified. We sought to identify any selective reporting by comparing the full report to the protocol.

In addition, each author independently used the risk of bias assessment tool available in the *Cochrane Handbook for Systematic Reviews for Interventions* in order to judge each of the described seven domains as having low, high or unclear risk of bias (Higgins 2017).

Measures of treatment effect

For dichotomous data (e.g. eradication achieved or not), we analysed the data on an intention-to-treat basis, irrespective of compliance or dropout secondary to adverse effects. We sought data based on each possible outcome event for each treatment arm and calculated the odds ratio (OR) and its 95% confidence interval (CI).

For continuous data, we reported the mean difference (MD) of effect of each variable along with its 95% CI. If two or more trials reported the same outcome but used different scales, we planned to calculate the standardised mean difference (SMD) with its 95% CI.

If the data had allowed, we planned to extract ordinal and count data in all forms in which they were reported. We planned to analyse these as per continuous data for common outcomes; for rare outcomes, we planned to follow the advice in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). If it had been reported, for time-to-event data (e.g. time to next exacerbation), we planned to calculate the hazard ratio (HR) at individual time points (at 14 days, then at one, three, six and 12 months) along with its 95% CI.

Unit of analysis issues

Cross-over trials were not eligible for inclusion within this review since we were reviewing how efficacious the initial attempt at eradication of MRSA was when compared with placebo, usual treatment or no treatment. Consequently, we aimed to evaluate the time until the next positive MRSA culture and number of further courses of antibiotics required following each arm of therapy.

We did not plan to include cluster-RCTs. When randomisation is performed according to participant groups, certain strains of MRSA (which may differ between communities) could potentially be over-represented in either the treatment or placebo arm and hence bias the results.

Dealing with missing data

In cases where data relating to the review's primary or secondary outcomes were missing, we contacted the primary investigator(s) for clarification.

Assessment of heterogeneity

In order to assess heterogeneity between outcomes, we used the I^2 statistic and the Chi^2 test. As stated in the *Cochrane Handbook for Systematic Reviews of Interventions*, the importance of the observed value of I^2 depends, firstly, on the magnitude and direction of effects, and secondly, on the strength of evidence for heterogeneity (e.g. P value for Chi^2) (Deeks 2022). We planned to consider values of 0% to 40% to represent little to no heterogeneity, 30% to 60% as moderate heterogeneity, 60% to 90% as substantial heterogeneity, and values of more than 90% as demonstrating considerable heterogeneity.

Assessment of reporting biases

We assessed selective reporting of results by comparing (where available) the outcomes listed in trials' original protocols to those reported in the final papers. We also searched clinical trials registries for details of the included trials. We contacted the primary investigator(s) of included trials to determine whether they were aware of any relevant unpublished data. We aimed to identify publication bias with the construction of funnel plots. However, insufficient trials were eligible for inclusion in the current version of the review. We plan to undertake this analysis in future if we are able to include more trials.

Data synthesis

We analysed the extracted data using a fixed-effect meta-analysis. If we had found the heterogeneity between the trials to be substantial (more than 60%), we would have performed a random-effects meta-analysis.

Subgroup analysis and investigation of heterogeneity

If we had identified a sufficient number of trials (more than 10) and also found substantial heterogeneity between trials, we would have investigated this with subgroup analysis of the following:

1. eradication therapy commenced at initial acquisition versus following chronic colonisation (three or more positive cultures over a 12-month period);
2. duration of eradication therapy (up to and including six weeks, seven to 12 weeks, over 12 weeks);
3. intravenous versus aerosolised versus oral administration of antibiotics;
4. efficacy of regimens which include methods for skin or nasal eradication, or both, versus those that do not.

Sensitivity analysis

Where we chose outcome measures which use arbitrary numerical endpoints (i.e. number of days, or percentage change), we planned to re-evaluate the effect that alternative endpoints had on our findings, where available data allowed.

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If we had included smaller studies (20 participants or fewer in each group) in the initial meta-analyses, we would have aimed to repeat the analyses without these smaller studies to determine their effect.

Summary of findings and assessment of the certainty of the evidence

In a post hoc change in line with current Cochrane guidance, the authors added a summary of findings table for each comparison presented in the review (Summary of findings 1; Summary of findings 2). We selected the following outcomes to report:

1. eradication of MRSA from respiratory culture;
2. time until next positive MRSA isolate;
3. QoL;
4. lung function (change from baseline in FEV_1 % predicted);
5. growth and nutritional state (change in weight in kg);
6. frequency of exacerbation;
7. adverse effects of treatment.

We determined the certainty of the evidence using the GRADE approach, and rated this with regard to the risk of bias or trial limitations, directness, consistency of results, precision, publication bias and effect size (Schünemann 2022). We downgraded the certainty of the evidence by one level for trial limitations related to bias.

RESULTS

Description of studies

Please see the characteristics tables for further details (Characteristics of included studies; Characteristics of excluded studies).

Results of the search

We identified a total of 66 trials from the Cystic Fibrosis and Genetic Disorders Group's CF Trials Register and 11 additional trials from separate additional searches. We did not identify any new ongoing trials from the ongoing trials registers (www.clinicaltrials.gov; www.isrctn.org; trialsearch.who.int/).

We deemed three trials (135 participants) eligible for inclusion in this review (Dezube 2019; Dolce 2019; Muhlebach 2017). In a previous version of this review, we had listed one of these as ongoing (Dezube 2019). We excluded a total of 74 trials with reasons. There are currently no trials listed as ongoing or awaiting classification.

Please also see the PRISMA study flow diagram (Figure 1).

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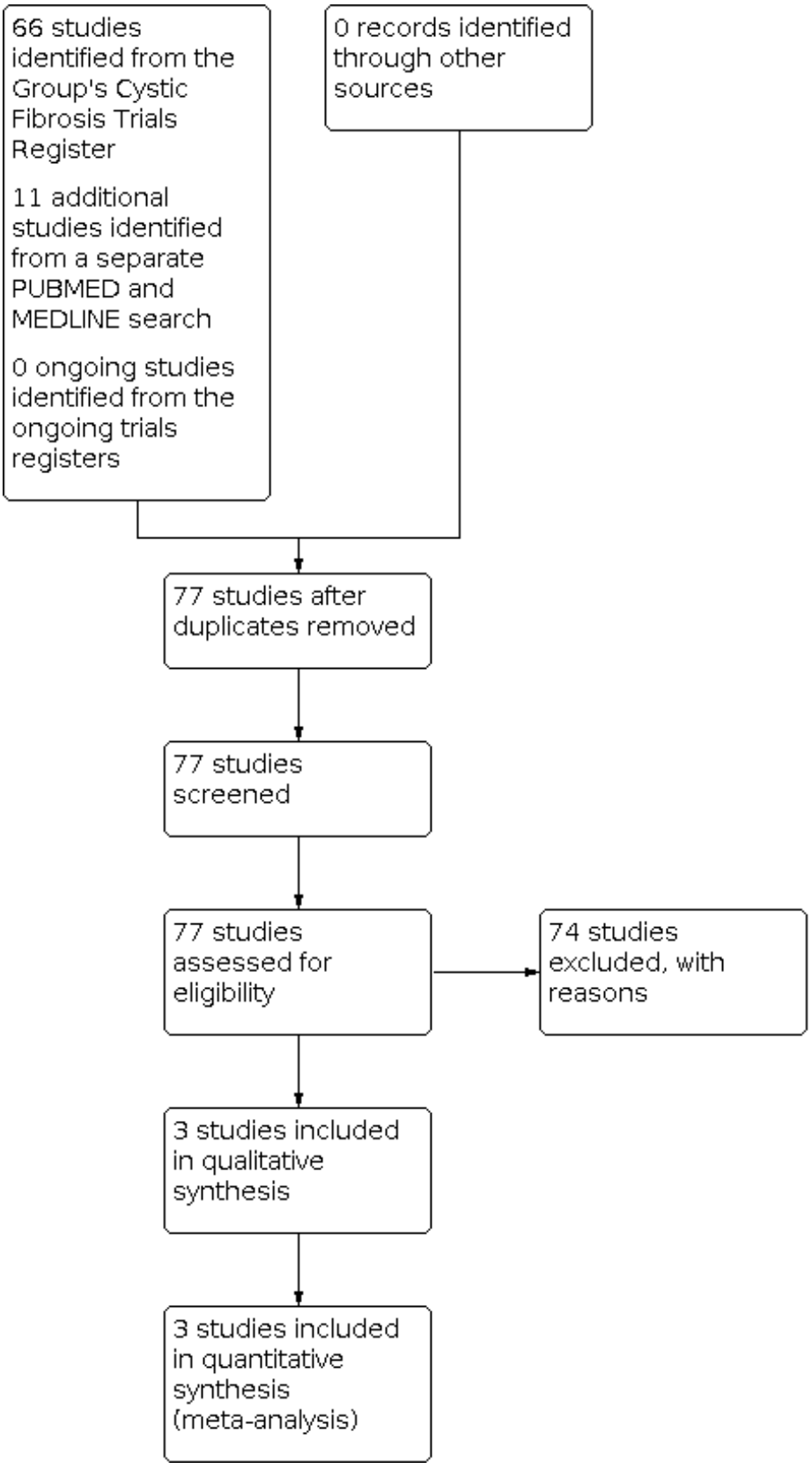
Figure 1. PRISMA study flow diagram



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Included studies

Three trials are eligible for inclusion in the review (Dezube 2019; Dolce 2019; Muhlebach 2017).

Trial design

All three trials were multicentre. Two trials were non-blinded, open-label RCTs, which compared active MRSA eradication treatment to observation only (Dolce 2019; Muhlebach 2017). One trial was a double-blind, placebo-controlled RCT which compared the efficacy of a 28-day eradication strategy of oral and topical antibiotics only (control group) to oral and topical antibiotic plus inhaled vancomycin (intervention) (Dezube 2019).

One trial involved five centres in Italy where participants were followed up for six months (Dolce 2019). The second trial involved 14 centres in the USA where participants were followed up to six months (Muhlebach 2017). The third trial involved two centres in the USA where participants were followed up for three months (Dezube 2019).

Participants

Two trials included people with CF over four years of age with newly-acquired MRSA from respiratory culture. One of these recruited 45 participants (44% female, mean age 11.5 years) (Muhlebach 2017), while the other recruited 61 participants (57% female, mean age 19.1 years) (Dolce 2019).

The third trial only included participants aged 12 years or older with persistent MRSA (defined as two positive MRSA respiratory cultures in the prior two years at least six months apart, plus two positive MRSA respiratory cultures during the screening period) (Dezube 2019). Additionally, at least 50% of the respiratory cultures from the time of the first MRSA culture (in the prior two years) had to have been positive for MRSA. This trial randomised 29 participants (52% female, median age 25 years).

Interventions

Two trials compared active interventions to observation only (Dolce 2019; Muhlebach 2017). In both these trials, the active treatment comprised oral trimethoprim and sulfamethoxazole combined with rifampicin. However, one trial administered this combination for two weeks combined with nasal, skin and oral decontamination and a three-week environmental decontamination (Muhlebach 2017), while the second trial administered this drug combination for 21 days, with five days intranasal mupirocin (Dolce 2019).

In the third trial, all participants received 28 days of oral trimethoprim and sulfamethoxazole combined with rifampicin, and nasal, skin and environmental decontamination (Dezube 2019). Participants randomised to the intervention arm also received 28 days of nebulised vancomycin, whilst the control group received daily nebulised placebo.

Outcome measures

The primary outcome for all three trials was MRSA eradication from the respiratory cultures of participants; however, all three trials used different definitions. One trial defined eradication as an MRSA-negative respiratory culture at day 28 (Muhlebach 2017), the second trial defined successful eradication as the absence of MRSA in at least three respiratory cultures over a period of six months (Dolce 2019), whilst the primary outcome of the third trial was an MRSA-negative respiratory culture one month after treatment was completed at day 58 (Dezube 2019).

All three trials reported change in spirometry (measured by FEV_1). Two trials reported respiratory symptoms as measured by CF-specific outcomes: namely, CFQ-R respiratory domain scores and the emergence of antibiotic-resistant organisms during the follow-up period (Dezube 2019; Muhlebach 2017). Two trials reported nutritional status, number of pulmonary exacerbations and use of antibiotics (Dolce 2019; Muhlebach 2017).

Excluded studies

We excluded a total of 74 trials (Characteristics of excluded studies).

One trial was a tolerability study (Adeboyeku 2001). A total of 19 were pharmacokinetic trials (Coates 2011; Davis 1987; EUCTR2007-005346-20-GB; EUCTR2007-006276-11-GB; EUCTR2009-013660-39-FR; EUCTR2010-023533-34-FR; EUCTR2019-003178-25-HU; Geller 2004; Goldfarb 1986; Griffith 2008; Huls 2000; Keel 2011; NCT03309358; Pai 2006; Roberts 1993; Rosenfeld 2006; Smith 1997; Stutman 1987; Vitti 1975). In 20 trials, the interventions were not relevant to our review (Amelina 2000; Chua 1990; Degg 1996; Dodd 1997; Dodd 1998; Flume 2015; Frederiksen 2006; Gulliver 2003; Hodges 2014; Khorasani 2009; Labiris 2004; Loening-Bauke 1979; NCT03181932; Nolan 1982; Postnikov 2001a; Postnikov 2001b; Ramstrom 2000; Sharma 2016; Wood 1996; NCT02547116). We excluded 22 trials because the participants were not relevant to our review (Carswell 1987; Conway 1996; Cooper 1985; CTRI/2020/06/025699; Di Cicco 2014; EUCTR2016-004033-25-ES; Flume 2016; Heininger 1993; Hjelte 1988; Huang 1979; Junge 2001; Kapranov 1995; Knight 1979; Nathanson 1985; NCT04553419; Postnikov 2000; Romano 1991; Sahl 1992; Shapera 1981; Singh 2013; Van Devanter 2014; Wolter 2004). One trial did not report clinical outcomes relevant for inclusion in this review (Dasenbrook 2015). A further 11 trials had relevant participants, interventions and outcomes but were not RCTs or controlled trials. Of these 11 trials, two were case reports (one of a 10-year old boy (Maiz 1998); one of a 28-year old man (Serisier 2004)), seven were observational studies (Dalbøge 2013; Garske 2004; Hall 2015; Kappler 2016; Macfarlane 2007; Vallières 2016; Vanderhelst 2013), and two were retrospective studies (Bittencourt 2016; Solis 2003).

Risk of bias in included studies

We have summarised the design of the included trials in the Characteristics of included studies table, and present a summary of risk of bias judgements of the included trials in Figure 2.

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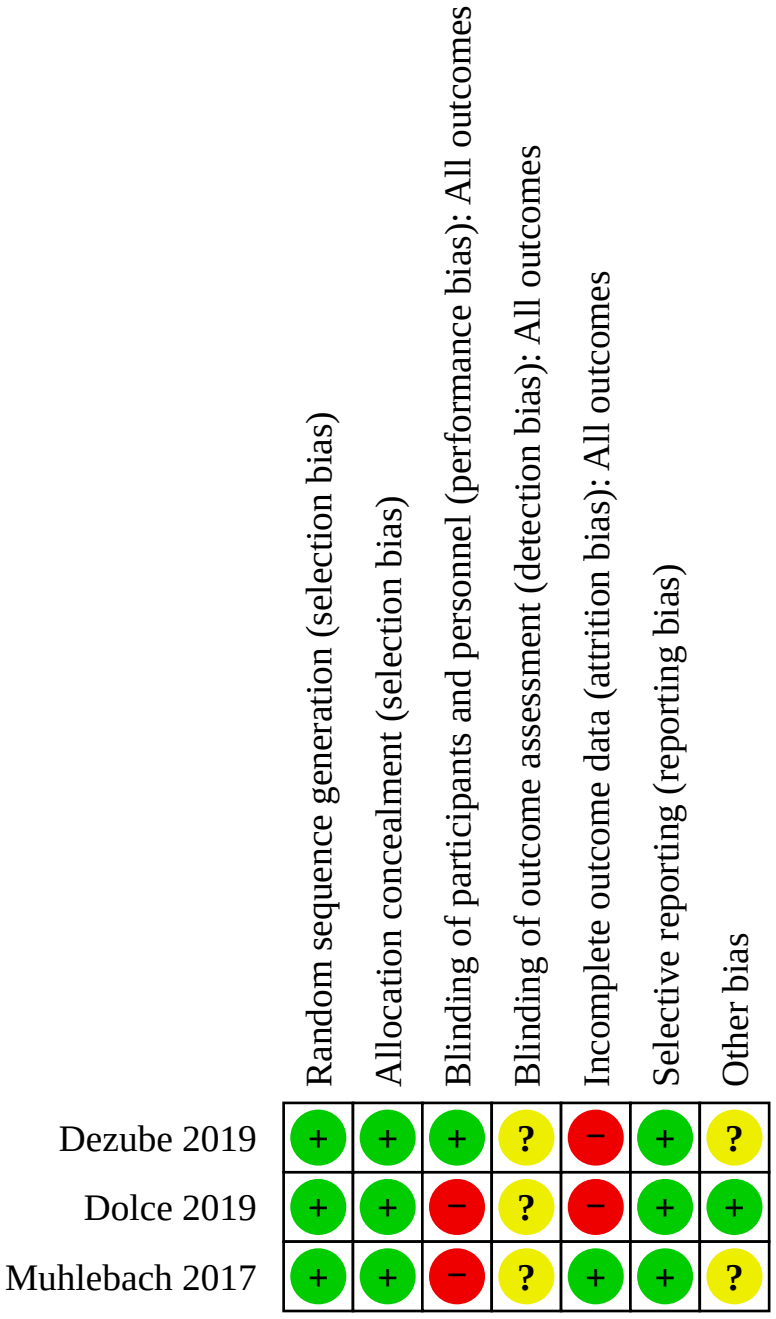
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Using GRADE and incorporating the risk of bias judgements, the certainty of the evidence for outcomes reported ranged from very low to low (Summary of findings 1; Summary of findings 2).

Allocation

Randomisation

Participants in all three trials used randomisation sequences generated by computer or statistical software (Dezube 2019; Dolce

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2019; Muhlebach 2017). We judged the risk of selection bias to be low for all three trials.

Allocation concealment

We judged the risk of bias for all three included trials to be low. Muhlebach 2017 utilised a centralised randomisation system for each enrolled participant, so it was not possible for the investigators to know the allocation sequence in advance (Muhlebach 2017). In the Dolce 2019 trial, randomisation assignment was organised remotely via e-mail. The people involved in randomisation and in treatment assignments were kept separate. In order to ensure allocation concealment and masking in the Dezube 2019 trial, access to the randomisation code was strictly controlled.

Blinding

In two of the trials, neither the participants nor trial personnel were blinded to the treatment regimen (Dolce 2019; Muhlebach 2017). In one trial, this was due to part of the regimen involving enhanced house cleaning, so it would not have been possible to blind participants (Muhlebach 2017). Furthermore, blinding would have been difficult in both trials because rifampicin discolours urine and secretions in a way that would be difficult to mimic with placebo. Thus, we judged the risk of bias from blinding to be high in both these trials (Dolce 2019; Muhlebach 2017).

In the remaining trial, investigators, research staff and participants were all blinded to the identity of intervention and placebo treatments (Dezube 2019). Packaging and labelling of intervention and taste-matched placebo treatments were identical, and the results of vancomycin serum concentrations were not made available to investigators. We judged the risk of bias in this trial to be low.

Incomplete outcome data

We judged one trial to have a low risk of bias due to incomplete outcome data: 41 of the 45 randomised participants were included in the intention-to-treat analysis. The remaining four randomised participants had missing MRSA culture results at day 28 and were all accounted for (two from the observation only group and two from the active treatment group) (Muhlebach 2017).

In the Dezube 2019 trial, 28% of participants in the intervention arm dropped out due to adverse respiratory events related to the treatment drug. The dropout rate in the third trial (Dolce 2019) was 48%. The main cause of dropout was the need for administration of a further antibiotic due to changes in participants' clinical condition during follow-up. We judged the risk of attrition bias in both trials to be high.

Selective reporting

There was no evidence of selective reporting in any of the three included trials (Dezube 2019; Dolce 2019; Muhlebach 2017), where both primary and secondary outcome measures were reported as described on the trials databases. Thus, we judged all three trials to have a low risk of reporting bias.

Other potential sources of bias

We judged there to be an unclear risk for two trials (Dezube 2019; Muhlebach 2017). Difficulties in the Dezube 2019 trial led to recruitment being closed early. In the second trial, the power calculation required the randomisation of 90 participants (Muhlebach 2017). However, the data monitoring committee recommended stopping the trial after 45 participants had been enrolled on the grounds of clinical efficacy.

We did not identify any additional potential sources of bias in the third trial (Dolce 2019).

Effects of interventions

See: **Summary of findings 1** Active treatment versus observation only for eradicating MRSA in people with cystic fibrosis; **Summary of findings 2** Oral plus nebulised antibiotics versus oral antibiotics plus nebulised placebo for eradicating MRSA in people with cystic fibrosis

We have graded the certainty of the evidence for those outcomes included in the summary of findings tables. For the definitions of these gradings, please refer to the summary of findings tables (Summary of findings 1; Summary of findings 2).

Oral antibiotics versus observation only

Primary outcomes

1. Eradication of MRSA

Both included trials reported this outcome (n = 106) but used different definitions of eradication (Dolce 2019; Muhlebach 2017).

One trial reported the number of participants who were MRSA-negative at day 28, and the number who remained MRSA-negative at day 168 (reported at up to six months) (Muhlebach 2017). At day 28, 18 out of 22 (82%) participants on active treatment were MRSA-negative compared to five out of 19 (26%) participants in the control group (OR 12.60, 95% CI 2.84 to 55.84; P < 0.001; low-certainty evidence). However, by six months, 12 out of 21 participants (57%) in the active treatment arm compared to eight out of 15 (53%) participants in the control group remained MRSA-negative (OR 1.17, 95% CI 0.31 to 4.42; low-certainty evidence; Analysis 1.1).

The second trial reported on successful eradication, defined as three negative MRSA respiratory cultures over a six month period (Dolce 2019). In the active treatment arm, 12 out of 19 participants (63%) fulfilled this definition compared to five out of 13 (38%) participants in the control group (OR 2.74, 95% CI 0.64 to 11.75; very low-certainty evidence; Analysis 1.2). Thus, by six months, the second trial had a higher proportion of participants with negative MRSA respiratory cultures in the active treatment arm, but this did not reach statistical significance (Dolce 2019).

Combining the data from both included studies also did not identify a significant difference in eradication rate of MRSA at six months (OR 1.72, 95% CI 0.65 to 4.55).

2. Time until next positive MRSA isolate from clinically relevant respiratory culture

This outcome was not reported by either of the included trials (Dolce 2019; Muhlebach 2017).

Secondary outcomes

1. Lung function

Both trials reported this outcome.

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One trial (n = 35) reported this outcome as FEV_1 measured in L (both absolute and relative change from baseline) and % predicted (absolute change from baseline) at both day 28 and day 168 (reported at up to six months) (Muhlebach 2017). The second trial reported the mean absolute change from baseline in FEV_1 % predicted only at six months (Dolce 2019). No results were statistically significant, although mean values were consistently greater in the active treatment group compared to the observation group at both up to one month and up to six months.

The absolute change from baseline in FEV_1 (L) was greater at up to one month (MD 0.11 L, 95% CI -0.01 to 0.23) than at up to six months (MD 0.06 L, (95% CI -0.06 to 0.18; Analysis 1.2). This was replicated in the data for the relative change from baseline in FEV_1 (L) at up to one month (MD 4.89%, 95% CI -0.61 to 10.39) and at up to six months (MD 3.08%, 95% CI -2.21 to 8.37; Analysis 1.3).

The absolute change in FEV_1 % predicted at up to one month (n = 35) showed no difference between groups in Muhlebach 2017 (MD 4.79%, 95% CI -0.89 to 10.47; Analysis 1.4). However, a meta-analysis of the data from both included trials reporting the absolute change from baseline in FEV_1 % predicted at six months demonstrated a greater change in FEV_1% predicted with active treatment (n = 58) (MD 5.67% predicted, 95% CI 1.43 to 9.90; very low-certainty evidence; Analysis 1.4; Dolce 2019; Muhlebach 2017).

2. Overall antibiotic use

Both trials reported this outcome (n = 77).

In one trial, there was no significant difference between the rate of anti-MRSA antibiotic usage between the two treatment arms (Muhlebach 2017): between day 28 to 168, nine (38%) participants in the treatment arm and nine (43%) in the control arm were treated with anti-MRSA antibiotics (OR 0.80, 95% CI 0.24 to 2.64; Analysis 1.5). This trial also reported that the use of non-MRSA antibiotics (oral, inhaled or intravenous) was similar across groups throughout the trial (Muhlebach 2017).

The second trial reported the number of participants treated with intravenous antibiotics in each arm from baseline to six months (Dolce 2019). Six out of 19 participants (32%) in the treatment arm, and four out of 13 participants (31%) in the placebo arm were treated with intravenous antibiotics (OR 1.04, 95% CI 0.23 to 4.77; Analysis 1.5). Investigators also reported no differences in the number of pulmonary exacerbations, hospitalisations, or total days of antibiotics (oral, inhaled, or intravenous) between treatment arms (Dolce 2019).

3. Mortality

No deaths were reported in either included trial (Dolce 2019; Muhlebach 2017).

4. QoL

Only one trial (n = 45) in this comparison reported on QoL (Muhlebach 2017). No significant differences in participant-reported outcomes were found between treatment arms based on responses to the Cystic Fibrosis Respiratory Symptom Diary Chronic Respiratory Infection Symptom Scale (CFRSD-CRISS) either at day 28 (MD -6.72, 95% CI -14.36 to 0.92) or at day 168 (MD 5.14, 95% CI -5.06 to 15.34; Analysis 1.6). Similarly, there were no differences between groups for the CFQ-R respiratory domain scores at day 28 (MD -0.26, 95% CI -11.32 to 10.80) or at day 168 (MD -3.94, 95% CI -13.96 to 6.08; low-certainty evidence; Analysis 1.7).

5. Isolation of MRSA or other organisms with new antibiotic-resistant phenotypes

One trial (n = 45) reported this outcome (Muhlebach 2017). No emergent MRSA resistances to the antibiotics used or the appearance of small colony variants were identified in either treatment arm (Muhlebach 2017). In particular, investigators found no difference between treatment arms in the proportion of participants testing positive for *P aeruginosa* from screening through to day 168 (OR 0.67, 95% CI 0.11 to 3.87; Analysis 1.8).

6. Growth and nutritional status

Both trials reported on this outcome (Dolce 2019; Muhlebach 2017).

a. Weight (kg)

At day 28, the difference in the change in weight from baseline between treatment arms in Muhlebach 2017 was MD 0.07 kg (95% CI -0.77 to 0.91) and at day 168 it was MD -0.19 kg (95% CI -1.70 to 1.32; very low-certainty evidence; Analysis 1.9). Neither of these were statistically significant.

b. BMI

At six months, the Dolce 2019 trial showed no difference in the mean change in BMI from baseline (MD 0.92 kg/m^2, 95% CI -0.12 to 1.96; Analysis 1.10).

7. Adverse effects of treatment

One trial (n = 45) reported adverse effects (Muhlebach 2017).

There were no statistical differences found between treatment arms for any of the reported adverse event types (all reported adverse events are presented in Analysis 1.11) (low-certainty evidence). None of the adverse events were considered serious or required hospitalisation. The most frequently occurring adverse events in both treatment arms were gastrointestinal disorders, affecting 46% of participants randomised to active treatment and 24% to observation only (OR 2.71, 95% CI 0.75 to 9.79). Two gastrointestinal complaints led to a temporary discontinuation of rifampin, whereas one participant had to discontinue all antibiotics due to urticaria. Two serious adverse events occurred during the first 28 days of the trial, one in the treatment arm (increased cough) and one in the control arm (cellulitis of the eyelid). Three instances of antibiotic discontinuation due to adverse events "probably" related to the trial drug were reported in this trial (Muhlebach 2017) (low-certainty evidence).

8. Elimination of carrier status (nasal)

One trial (n = 45) reported this outcome (Muhlebach 2017).

At screening, 14 of 45 participants had nasal MRSA colonisation with similar distribution across groups: six out of 24 (25%) in the active treatment and eight out of 21 (38%) in the control (P = 0.52) arms. No treatment-related differences emerged during the course of the trial. No other data were available for analysis (Muhlebach 2017).

9. Frequency of exacerbations

Both trials (n = 106) reported this outcome (Dolce 2019; Muhlebach 2017).

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In one trial, 13% of participants in the treatment arm experienced at least one pulmonary exacerbation between screening and day 28 compared to 33% in the observation arm (calculated as the proportion of participants experiencing an event per 28 days of follow-up) (Muhlebach 2017). This was not statistically significant (OR 0.29, 95% CI 0.06 to 1.30; low-certainty evidence; Analysis 1.12). Though not a stated outcome for this review, we feel it is important to present the data that the Muhlebach 2017 trial reported for the rate of hospitalisation of participants from screening through day 168: this was significantly lower in the treatment arm compared to the observation arm (rate ratio 0.22, 95% CI 0.05 to 0.72; P = 0.01).

The Dolce 2019 trial did not report any differences in the mean number of pulmonary exacerbations experienced by either treatment arm over the six months of the study (MD 0.15, 95% CI -0.54 to 0.84; very low-certainty evidence; Analysis 1.13).

10. Cost of care

Although no health economic analysis was performed in any of the included trials, it could be speculated that the lower rate of hospitalisations in the treatment arm of one trial would equate to a lower cost of care (Muhlebach 2017). However, based on the evidence provided, we are unable to comment further.

Oral plus nebulised antibiotics versus oral antibiotics plus placebo

Primary outcomes

1. Eradication of MRSA

In the only trial in this comparison, the primary end point was a negative MRSA respiratory culture at one month following treatment with oral antibiotics plus nebulised vancomycin versus oral antibiotics plus placebo (Dezube 2019). At the one-month follow-up visit, two out of 10 participants (20%) in the intervention arm had a negative MRSA sputum culture, compared to three out of 15 participants (20%) in the comparator arm (OR 1.00, 95% CI 0.14 to 7.39; low-certainty evidence; Analysis 2.1). At three months following completion of treatment, two out of 10 participants (20%) from the intervention arm, and two out of 15 participants (13%) from the control arm remained negative for MRSA on sputum cultures (OR 1.63, 95% CI 0.19 to 13.93; Analysis 2.1).

2. Time until next positive MRSA isolate from clinically relevant respiratory culture

This outcome was not reported by the included trial (Dezube 2019).

Secondary outcomes

1. Lung function

The included trial (n = 25) reported the median (interquartile range (IQR)) absolute change in FEV_1 % predicted from baseline at several different time points. The mean (SD) values were not presented, and therefore it was not possible to calculate the MD of change in FEV_1 % predicted (Dezube 2019). The authors reported that there was no statistically significant difference between the intervention and placebo groups at any time point (low-certainty evidence). The values for the median (IQR) absolute change in FEV_1 % predicted in the intervention group versus placebo group are presented below.

Time point	Oral antibiotics plus nebulised vancomycin		Oral antibiotics plus nebulised vancomycin	
	Median	IQR	Median	IQR
End of 21 days treatment	-0.5	-5.0 to 7.0	1.0	-4.0 to 6.0
1 month post treatment	-2.5	-6.0 to 1.0	1.0	-5.0 to 6.0
3 months post treatment	-1.0	-5.0 to 2.0	0.0	-3.0 to 4.0

2. Overall antibiotic use

The included trial did not report on this outcome (Dezube 2019).

3. Mortality

The included trial did not report on this outcome (Dezube 2019).

4. QoL

The Dezube 2019 trial reported no statistical difference between groups in QoL based on the CFQ-R questionnaires, but no numerical results were presented in the paper (very low-certainty evidence).

5. Isolation of MRSA or other organisms with new antibiotic resistant phenotypes

The included trial did not report on this outcome (Dezube 2019).

6. Growth and nutritional status

The included trial did not report on this outcome (Dezube 2019).

7. Adverse effects of treatment

The most frequently occurring adverse events in both treatment arms were respiratory-related, followed by gastrointestinal events (Dezube 2019). Overall incidence of any adverse events were similar in both groups (OR 3.0, 95% CI 0.11 to 79.91; low-certainty evidence; Analysis 2.2). Four participants, all of whom received inhaled vancomycin, were withdrawn from the trial due to respiratory adverse events. There were also a total of six serious adverse events among four participants, but none of these were thought to be related to the trial drug or treatment regimen (Dezube 2019).

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8. Elimination of carrier status (nasal)

Investigators reported that, at initial screening, 58% of all participants had MRSA positive nasal swabs: 78% randomised to the oral antibiotics plus inhaled vancomycin arm, and 47% randomised to the oral antibiotics plus inhaled placebo arm (Dezube 2019). At the end of the treatment period, 100% of all participants in both arms were negative for MRSA on nasal swabs. However, by one month after treatment, 20% of participants were positive again for MRSA on nasal swabs (40% in the inhaled vancomycin and 7% in the inhaled placebo arm) (OR 0.11, 95% CI 0.01 to 1.17; Analysis 2.3).

9. Frequency of exacerbations

The included trial did not report on this outcome (Dezube 2019).

10. Cost of care

The included trial did not report on this outcome (Dezube 2019).

DISCUSSION

Summary of main results

Although MRSA is an important emerging pathogen in CF respiratory illness, there is no widely accepted consensus for its optimal management. The broad search terms used in this review identified a large number of trials; unfortunately, only three were eligible for inclusion at this time (Dezube 2019; Dolce 2019; Muhlebach 2017). Most of the other trials we identified dealt either with reduction of MRSA bacterial density or were retrospective reports of MRSA treatment.

Oral antibiotics versus observation only

Two of the included trials, which compared active treatment to observation only, demonstrated success in achieving MRSA eradication in people with CF with newly-acquired MRSA on respiratory cultures (Dolce 2019; Muhlebach 2017). One trial showed superiority of active treatment over control at up to one month (Muhlebach 2017). However, by six months, neither trial demonstrated a statistically significant difference in MRSA status between participants in the active treatment and control arms of the trials.

There were no differences observed between treatment arms in terms of QoL, isolation of MRSA or other organisms, weight, adverse events, eliminated carrier status (measured by nasal swabs), or exacerbation rates. One trial reported fewer hospitalisations of participants who received active treatment when compared with controls over the trial period (Muhlebach 2017). Neither trial reported on time until next positive MRSA isolate, mortality or cost of care.

At six months, a meta-analysis of data from both included studies identified a significant improvement in FEV_1% predicted compared to baseline in participants receiving active treatment (low-certainty evidence).

Oral plus nebulised antibiotics versus oral antibiotics plus placebo

One of the included trials (n = 25) compared oral antibiotics with nebulised vancomycin versus oral antibiotics plus nebulised placebo targeted against MRSA, but reported no significant differences in MRSA respiratory clearance at any reported time point. Similar to the other trials in the first comparison, there were no differences observed between treatment arms in terms of lung function, QoL or adverse events. While participants had eliminated carrier status (measured by nasal swabs) at the end of the treatment period, more participants in the oral plus nebulised group were again positive after one month than with oral antibiotics alone; however, this result was not statistically significant. The trial did not report on time until next positive MRSA isolate, overall antibiotic use, mortality, isolation of MRSA or other organisms, growth or nutritional status, frequency of exacerbations or cost of care.

Overall completeness and applicability of evidence

All three trials included relevant participants with positive MRSA cultures obtained from clinically relevant samples; however, two trials excluded children younger than four years of age (Dolce 2019; Muhlebach 2017), and one excluded children younger than 12 years of age (Dezube 2019). One trial also excluded adults over 45 years of age (Muhlebach 2017). Therefore, the generalisability of results to people outside of this age range cannot be assumed.

Certainty of the evidence

We judged all three trials to have an overall low to medium risk of bias and the methodology of the trials was robust (Dezube 2019; Dolce 2019; Muhlebach 2017).

Two trials were terminated earlier than planned, and therefore did not achieve the calculated sample size (Dezube 2019; Muhlebach 2017). The early termination of one trial was recommended by the data monitoring committee following an interim review, which showed a statistically significant microbiological effect (Muhlebach 2017). The second trial was terminated early due to difficulties with recruitment (Dezube 2019).

The design and objectives were set out clearly in all three trials with no evidence of selective reporting of results.

Based on GRADE criteria, we downgraded the certainty of the evidence from two studies by one point because both were open-label studies and thus introduced performance bias (Dolce 2019; Muhlebach 2017). We downgraded two studies by one point for attrition bias (Dezube 2019; Dolce 2019). We downgraded all three studies by a further point due to imprecision (small sample sizes and wide CIs) (Summary of findings 1; Summary of findings 2).

Potential biases in the review process

One of the co-authors of this review (MM) was the lead investigator for one of the included trials (Muhlebach 2017). However, MM was not involved in data extraction or risk of bias assessment in this review for her own trial. We identified no other potential biases in the review process.

Agreements and disagreements with other studies or reviews

Various strategies have been proposed for the eradication of MRSA when isolated from CF respiratory samples. It has become apparent from this review that these are based on anecdotal evidence or, at best, a small number of observational studies involving small numbers of participants as detailed below.

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We identified 11 non-randomised and non-controlled studies. Four of these were in children (age range one to 16 years), four in adults and three in mixed children and adult groups. With the exception of a case report on one 10-year old boy (Maiz 1998), and a cohort study which reported on efficacy of *S aureus* eradication, where only 0.3% of participants were MRSA-positive (Dalbøge 2013), the remaining nine studies reported successful eradication of MRSA in at least a proportion of their participants (Bittencourt 2016; Garske 2004; Hall 2015; Kappler 2016; Macfarlane 2007; Serisier 2004; Solis 2003; Vallières 2016; Vanderhelst 2013).

In the case report, MRSA was not eradicated after the 17-month treatment with daily continuous inhaled vancomycin; however, the authors did report improvements in lung function and symptom score in the child (Maiz 1998). One study (n = 11) reported that, after successful eradication of MRSA, there was a non-statistically significant trend in improvement of FEV_1 % predicted (Vanderhelst 2013). The largest cohort study (n = 65) successfully eradicated *S aureus* from the sputum samples of participants and reported a statistically significant median (range) improvement in FEV_1 % predicted of 3.3% (−25% to 36%; P < 0.0001) (Dalbøge 2013). However, they did not differentiate between those individuals who grew MSSA or those who grew MRSA from their sputum (Dalbøge 2013). This finding is contradictory to three other studies, which reported no significant differences in lung function between participants where MRSA was successfully eradicated when compared to those in whom it failed (Garske 2004; Hall 2015; Solis 2003). However, this may be because the numbers were too small to detect a difference.

With regards to long-term microbiological outcome, one study followed their cohort for three years after initial eradication (dual intravenous antibiotic treatment over three weeks, accompanied by hygenic directives and topical therapy for five days, followed by a six-week period with dual oral antibiotic therapy and inhalation with vancomycin) (Kappler 2016). Long-term success of eradication following a therapy per protocol was 84% (n = 31) but MRSA was still detectable in the third year of observation in six participants (16%).

The final four studies reported successful eradication of MRSA in 94% of participants (Macfarlane 2007), in 80% of participants (Bittencourt 2016), in 79% of participants (Vallières 2016) and in one 28-year old (Serisier 2004), but did not report on lung function or clinical status during or following eradication.

AUTHORS' CONCLUSIONS

Implications for practice

We have included the only reported randomised control trials to date in this review (Dezube 2019; Dolce 2019; Muhlebach 2017). Only one trial reported meticillin-resistant *Staphylococcus aureus* (MRSA) eradication favouring the treatment arm compared to controls (observation only) at up to one month (Muhlebach 2017), but results from all three trials failed to show differences between treatment arms during follow-up at either three months (Dezube 2019) or six months (Dolce 2019; Muhlebach 2017). Fewer hospital admissions during follow-up were seen in participants in the active treatment arm of one trial (Muhlebach 2017). The included trials were unable to demonstrate differences in other clinically relevant outcomes. The currently available evidence does not demonstrate that routine treatment of respiratory MRSA in people with cystic fibrosis (CF) is effective.

Implications for research

This review has highlighted the lack of evidence supporting the present management of MRSA respiratory infections in CF and emphasises the need for well-designed, adequately-powered trials with long-term follow-up in order to address this issue.

Such trials will need to address these questions.

1. Does eradication of MRSA confer a favourable long-term prognosis (see Types of outcome measures) for people with CF?
2. What is the optimal duration of treatment?
3. Should there be recurrent treatment cycles to avoid recurrence?
4. What is the most effective method of providing treatment (oral or intravenous or inhaled)?
5. Are there any pitfalls to treating MRSA aggressively (i.e. selection for other resistant pathogens, reduced tolerability, increased adverse effects)?
6. When should treatment be initiated?

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Dezube 2019

Study characteristics	
Methods	RCT (placebo-controlled and double-blinded) - participants were assigned in a 1:1 ratio to either the intervention or control group Design: parallel Location: dual centre in the USA Duration: 28 days with additional 3-month follow-up
Participants	Participants with persistent respiratory tract MRSA infection were randomised in this trial. Inclusion criteria: • male or female ≥ 12 years of age; • confirmed diagnosis of CF; • written informed consent (and assent when applicable) obtained from participant or participant's legal representative and ability for participant to comply with the requirements of the trial;

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Dezube 2019 *(Continued)*

- 2 positive MRSA respiratory cultures in the last 2 years at least 6 months apart, plus 2 positive MRSA respiratory cultures during the screening period;
- at least 50% of respiratory cultures from the time of the first MRSA culture (in the last 2 years) have been positive for MRSA;
- FEV_1 > 30% of predicted normal for age, gender and height at screening.

Between October 2012 to March 2017, 29 participants were randomised 1:1 to treatment or control (14 in the treatment group, 15 in the control group). 25 were included for analysis.

Age (median): 25.5 years in treatment group, 25.0 years in control group (age range 12 to 46 years)

Sex: female 52%

No significant differences in age, sex or disease severity between treatment arms

Interventions	**Treatment group**: 28-day course of vancomycin for inhalation (250 mg 2x daily) plus oral rifampicin and oral TMP-SMX **Control group**: taste-matched inhaled placebo (sterile water) plus oral rifampicin and oral TMP-SMX In addition, both groups received oral rifampin, a second oral antibiotic (TMP-SMX or doxycycline, protocol-determined), mupirocin intranasal cream and chlorhexidine body washes.
Outcomes	**Primary outcome measure** 1. Difference in MRSA eradication rates between intervention and placebo groups 1 month after completion of treatment **Secondary outcome measures** 1. Difference in MRSA eradication rates at the end of treatment and 3 months after treatment 2. Absolute change in FEV_1 from baseline to follow-up 3. Absolute change in participant-reported CFQ-R respiratory domain score from baseline to follow-up 4. Absolute change in CFU density (CFU/g) of MRSA isolates from baseline to follow-up 5. MRSA positivity of nasal swabs at baseline, at the end of treatment, and at 1 month follow-up 6. Number of participants with newly developed MRSA resistance to vancomycin, TMP/SMX, doxycycline, and/or rifampin 7. Serum vancomycin concentrations 8. Vancomycin MICs for MRSA isolates 9. Emergence of new gram-negative bacteria in respiratory cultures
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible participants were assigned to either intervention or placebo in a 1:1 ratio using a computer-generated randomization scheme".
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed in blocks of random sizes and stratified by FEV1 percent predicted and center". "In order to ensure allocation concealment and masking, access to the randomization code was strictly controlled, packaging and labeling of intervention and taste-matched placebo

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Dezube 2019 *(Continued)*

		treatments were identical, and results of vancomycin serum concentrations were not made available to investigators."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators, research staff, and subjects were masked to the identity of intervention and placebo treatments".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of blinding of outcome assessors given.
Incomplete outcome data (attrition bias) All outcomes	High risk	29 participants were randomised. 25 participants were included for analysis. 4/14 (29%) participants were withdrawn from the intervention arm due to bronchospasm, before obtaining any outcome data. All missing participants accounted for.
Selective reporting (reporting bias)	Low risk	No selective reporting identified. Reported outcomes matched stated outcomes on clinical trials registry.
Other bias	Unclear risk	Trial closed to further enrolment prior to meeting the sample size goal of 40 due to challenges associated with recruitment and enrolment of eligible participants at both study sites.

Dolce 2019

Study characteristics	
Methods	RCT (open-label) Design: parallel Location: multicentre (5 centres) in Italy Duration: 21 days of treatment with follow-up to 6 months
Participants	People with CF over 4 years of age with either a first isolation of MRSA from the airways or a new MRSA isolation after a clearance period of 12 months (after performance of 4 negative cultures). Between 18 July 2013 to 12 April 2016, 61 participants were randomised 1:1 to treatment or control (29 in the treatment group, 32 in the control group). Mean age 17.0 years in treatment arm, 17.2 years in control arm (range 2.4 to 50.7 years)
Interventions	**Treatment group**: oral rifampicin and oral TMP-SMX for 21 days, combined with 2% nasal mupirocin – each nostril 3 times daily for 5 days **Control group**: observation only
Outcomes	**Primary outcome measure** 1. MRSA eradication, defined as the participant having 3 successive negative cultures in 6 months **Secondary outcome measures** 1. Change in FEV_1 2. Change in nutritional status (BMI)

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Dolce 2019 *(Continued)*

	3. Pulmonary exacerbations 4. Antibiotic use
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a balanced randomization sequence with permuted blocks of size 4 was created using statistical software".
Allocation concealment (selection bias)	Low risk	Quote: "Randomization assignment, performed at the coordinator Center (Meyer Hospital), was organized by e-mail. Patients, allocated 1:1, were enrolled at their own CF Center. The people involved in randomization and in the treatment assignments were kept completely separate".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of blinding of outcome assessors given.
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition rate: 29 (47.5%) out of 61 randomised participants (10 from the treatment arm and 19 from the observation arm) dropped out of the study.
Selective reporting (reporting bias)	Low risk	No selective reporting identified. Reported outcomes matched stated outcomes on clinical trials registry.
Other bias	Low risk	No other biases identified.

Muhlebach 2017

Study characteristics

Methods	RCT (open-label) Design: parallel Location: multicentre (14 centres) in USA Duration: 14 days of treatment, follow-up to 6 months
Participants	People with first or early (≤ 2 positive cultures within 3 years) MRSA-positive culture without MRSA active antibiotics within 4 weeks. Between 01 April 2011 to September 2014, 45 participants were randomised 1:1 to treatment or control (24 in the treatment group, 21 in the control group). Age (mean): 11.5 years (6.1) (ages 4 to 45 years were eligible for inclusion) Sex: 44% female

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Muhlebach 2017 *(Continued)*

	No significant differences in lung function, weight or *Pseudomonas aeruginosa* status between treatment arms
Interventions	**Treatment group**: 14-day oral rifampicin plus TMP-SMX or minocycline in people with contraindications to TMP-SMX; chlorhexidine mouthwash for 2 weeks; nasal mupirocin and chlorhexidine body wipes for 5 days and, in addition, environmental decontamination (wipe down high-touch surfaces and medical equipment with surface disinfecting wipes daily for the first 21 days. Wash all linens and towels in hot water 1x weekly for 3 weeks). Drug: rifampin (adult dose: 300 mg 2x daily for 14 days; paediatric dose: < 40 kg: 15 mg/kg daily for 14 days divided every 12 hours). Drug: TMP-SMX (adult dose: 320/1600 orally 2x daily for 14 days; paediatric dose: < 40 kg: 8 mg/kg trimethoprim, > 40 mg/kg sulfamethoxazole twice daily for 14 days). Drug: minocycline (only for participants ≥ 8 years of age, who can not tolerate TMP-SMX or whose screening MRSA is resistant to TMP/SMX. Adult dose: 100 mg orally 2x daily for 14 days. Paediatric dose: < 50 kg: 2 mg/kg orally twice daily for 14 days not to exceed 200 mg/day). Drug: mupirocin (1 g 2% nasal ointment generously applied to each nostril using a cotton swab twice daily for 14 days). Drug: chlorhexidine gluconate oral rinse (0.12% chlorhexidine gluconate oral rinse twice daily for 14 days). Drug: 2% chlorhexidine solution wipes (whole body wash solution wipes once daily for the first 5 days). **Control group**: observation with current standard of care, i.e. treatment for MRSA only with pulmonary exacerbations.
Outcomes	**Primary outcome measure** 1. Proportion of participants in each arm with MRSA-negative respiratory cultures at day 28 **Secondary outcome measures** 1. Safety and tolerability of treatment regimen 2. Protocol adherence 3. Duration of microbiological effect 4. Number of pulmonary exacerbations 5. Use of antibiotics 6. Change in spirometry (FEV_1) 7. Respiratory symptoms as measured by the CF-specific patient outcomes: CFQ-R respiratory domain scores and Cystic Fibrosis Respiratory Symptom Diary, Chronic Respiratory Infection Symptom Scale 8. Weight
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomised (1:1) to an MRSA eradication protocol...or to no treatment" using a secure web-based randomisation system.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation assignments were generated via a centralised, secure web based randomisation system for each enrolled subject".

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Muhlebach 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Study personnel and participants were not blinded to the treatment regimen".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Clinical evaluations, physical examination and spirometry were performed on day 1 (randomisation), day 15, day 28, day 84 and day 168; but no details of blinding of outcome assessors given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	47 participants were randomised. 2 withdrew immediately post randomisation. Of the remaining 45 participants, 4 had "missing" MRSA culture results at day 28 (2 from each arm) and so not included in ITT-Efficacy (ITT - E) analysis. All missing participants accounted for.
Selective reporting (reporting bias)	Low risk	No selective reporting identified. Reported outcomes matched stated outcomes on clinical trials registry.
Other bias	Unclear risk	Trial stopped early based on recommendations of data monitoring committee due to treatment efficacy, so did not reach planned recruitment target.

BMI: body mass index
CF: cystic fibrosis
CFU: colony-forming unit
CFQ-R: Cystic Fibrosis Questionnaire-Revised
FEV_1: forced expiratory volume in 1 second
ITT-E: Intention-to-treat - efficacy
IV: intravenous
MIC: minimum inhibitory concentration
MRSA: meticillin-resistant *Staphyloccocus aureus*
RCT: randomised controlled trial
TMP-SMX: trimethoprim-sulfamethoxazole

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

Study	Reason for exclusion
Adeboyeku 2001	Ineligible intervention: tolerability study of differing dosages of nebulised colistin
Amelina 2000	Ineligible intervention: difference in quality of life between home versus hospital IV treatment
Bittencourt 2016	Ineligible design: non-randomised, retrospective cohort study
Carswell 1987	Ineligible participants: trial of *P aeruginosa* treatment
Chua 1990	Ineligible intervention: trial used differing tonicities of inhaled antibiotics to assess airway responsiveness
Coates 2011	Ineligible outcomes: pharmacokinetic study
Conway 1996	Ineligible participants: did not differentiate between organisms causing exacerbation leading to inclusion into the trial
Cooper 1985	Ineligible participants: trial of *P aeruginosa* treatment
CTRI/2020/06/025699	Ineligible participants

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Study	Reason for exclusion
Dalbøge 2013	Ineligible design: non-randomised observational study
Dasenbrook 2015	No relevant outcomes reported
Davis 1987	Ineligible outcomes: pharmacokinetic study
Degg 1996	Ineligible intervention: study on long-term effects of gentamicin on hearing. Participants not selected on basis of microbial colonisation
Di Cicco 2014	Ineligible participants
Dodd 1997	Ineligible intervention: tested differences in lung function relating to tonicity of nebulised colistin
Dodd 1998	Ineligible intervention: a compliance study. No suitable control
EUCTR2007-005346-20-GB	Ineligible outcomes: pharmacokinetic study
EUCTR2007-006276-11-GB	Ineligible outcomes: pharmacokinetic study
EUCTR2009-013660-39-FR	Ineligible outcomes: pharmacokinetic study
EUCTR2010-023533-34-FR	Ineligible outcomes: pharmacokinetic study
EUCTR2016-004033-25-ES	Ineligible participants
EUCTR2019-003178-25-HU	Ineligible outcomes: pharmacokinetic study
Flume 2015	Ineligible intervention: safety evaluation of levofloxacin inhalation solution
Flume 2016	Ineligible participants: trial of *P aeruginosa* treatment
Frederiksen 2006	Ineligible intervention: not an eradication study
Garske 2004	Ineligible design: an observational study
Geller 2004	Ineligible outcomes: pharmacokinetic study
Goldfarb 1986	Ineligible outcomes: pharmacokinetic study
Griffith 2008	Ineligible outcomes: pharmacokinetic / tolerability study
Gulliver 2003	Ineligible intervention: tested whether nebulised IV tobramycin solution induced cough, bronchoconstriction or both
Hall 2015	Ineligible design: non-randomised, observational study
Heininger 1993	Ineligible participants: trial of *P aeruginosa* treatment
Hjelte 1988	Ineligible participants: investigated effect of home IV antibiotics for *P aeruginosa* on quality of life
Hodges 2014	Ineligible intervention
Huang 1979	Ineligible participants: did not differentiate between organisms causing exacerbation leading to inclusion into trial

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Study	Reason for exclusion
Huls 2000	Ineligible outcomes: pharmacokinetic study
Junge 2001	Ineligible participants: investigated risk of ototoxicity or cochlea damage in once daily versus thrice daily IV tobramycin
Kappler 2016	Ineligible design: non-randomised, observational study
Kapranov 1995	Ineligible participants: trial of *P aeruginosa* treatment
Keel 2011	Ineligible outcomes: pharmacokinetic study
Khorasani 2009	Ineligible intervention: primary objective was not to eradicate MRSA
Knight 1979	Ineligible participants: trial of *P aeruginosa* treatment
Labiris 2004	Ineligible intervention: objective was to determine whether preservative containing inhaled tobramycin causes airway inflammation
Loening-Bauke 1979	Ineligible intervention: used cephalexin as prophylaxis
Macfarlane 2007	Ineligible design: an observational study
Maiz 1998	Ineligible design: a case report of one 10-year old boy
Nathanson 1985	Ineligible participants: trial of *P aeruginosa* treatment
NCT02547116	Ineligible interventions
NCT03181932	Ineligible intervention: did not aim for eradication and primary outcome was change in lung function
NCT03309358	Ineligible outcomes: pharmacokinetic study
NCT04553419	Ineligible participants: children with MSSA not MRSA
Nolan 1982	Ineligible intervention: prophylaxis rather than eradication
Pai 2006	Ineligible outcomes: pharmacokinetic study
Postnikov 2000	Ineligible participants: compared children with CF and aplastic anaemia
Postnikov 2001a	Ineligible intervention: described risk of quinolone arthropathy in children
Postnikov 2001b	Ineligible intervention: investigated the effect on growth with the addition of ciprofloxacin to the treatment of children with CF
Ramstrom 2000	Ineligible intervention: compared quality of life scores in participants who received pre-made infusion devices compared to those who reconstituted drugs themselves
Roberts 1993	Ineligible outcomes: pharmacokinetic study
Romano 1991	Ineligible participants: trial of *P aeruginosa* treatment
Rosenfeld 2006	Ineligible outcomes: pharmacokinetic study

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Study	Reason for exclusion
Sahl 1992	Ineligible participants: MRSA not required for entry into study
Serisier 2004	Ineligible design: a case report of one 28-year old man
Shapera 1981	Ineligible participants: did not differentiate between MRSA and MSSA in inclusion criteria. Unclear how randomisation was achieved
Sharma 2016	Ineligible intervention
Singh 2013	Ineligible participants: study of efficacy of interventions for pre-pseudomonal pathogens
Smith 1997	Ineligible outcomes: pharmacokinetic study
Solis 2003	Ineligible design: retrospective study
Stutman 1987	Ineligible outcomes: pharmacokinetic study
Vallières 2016	Ineligible design: non-randomised, observational study
Vanderhelst 2013	Ineligible design: non-randomised, observational study
Van Devanter 2014	Ineligible participants: trial of *P aeruginosa* treatment
Vitti 1975	Ineligible outcomes: pharmacokinetic study
Wolter 2004	Ineligible participants
Wood 1996	Ineligible intervention: compared aminoglycoside toxicity in twice and thrice daily dosing regimens

CF: cystic fibrosis
IV: intravenous
MRSA: meticillin-resistant *Staphylococcus aureus*
MSSA: meticillin-sensitive *Staphylococcus aureus*
P aeruginosa: Pseudomonas aeruginosa

DATA AND ANALYSES

Comparison 1. Active treatment versus observation only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Eradication of MRSA	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1.1 At up to 1 month	1	41	Odds Ratio (M-H, Fixed, 95% CI)	12.60 [2.84, 55.84]
1.1.2 At up to 6 months	2	68	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [0.65, 4.55]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 FEV_1 (L) - absolute change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 At up to 1 month	1	35	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.01, 0.23]
1.2.2 At up to 6 months	1	31	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.06, 0.18]
1.3 FEV_1 (L) - relative change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3.1 At up to 1 month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3.2 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 FEV_1 (% predicted) - absolute change from baseline	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 At up to 1 month	1	35	Mean Difference (IV, Fixed, 95% CI)	4.79 [-0.89, 10.47]
1.4.2 At up to 6 months	2	58	Mean Difference (IV, Fixed, 95% CI)	5.67 [1.43, 9.90]
1.5 Overall antibiotic use	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5.1 Anti-MRSA antibiotics from day 28 until day 168	1	45	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.24, 2.64]
1.5.2 Intravenous antibiotics use from baseline until 6 months	1	32	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.23, 4.77]
1.6 QoL measured using CFRSD Chronic Respiratory Infection Symptom Score (absolute change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.1 At up to 1 month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.2 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7 QoL measured using CFQ-R Respiratory Symptom Score (absolute change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.1 At up to 1 month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.2 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8 Participants positive for *Pseudomonas aeruginosa*	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8.1 At screening	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8.2 At up to 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8.3 At up to 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8.4 At up to 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.9 Weight (kg) (absolute change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.1 At up to 1 month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.2 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10 BMI (change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10.1 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.11 Adverse effects of treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.1 Gastrointestinal disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.2 Skin and subcutaneous tissue disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.3 Injury, poisoning and procedural complications	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.4 Nervous system disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.5 General disorders and administration site conditions	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.6 Renal and urinary disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11.7 Musculoskeletal and connective tissue disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.8 Immune system disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.9 Eye disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.10 Ear and labyrinth disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.11 Infections and infestations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.12 Psychiatric disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.13 Blood and lymphatic system disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.14 Metabolism and nutrition disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.15 Investigations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11.16 Congenital, familial and genetic disorders	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.12 Number of participants with pulmonary exacerbations	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.12.1 At up to 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.13 Mean number of pulmonary exacerbations	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13.1 At up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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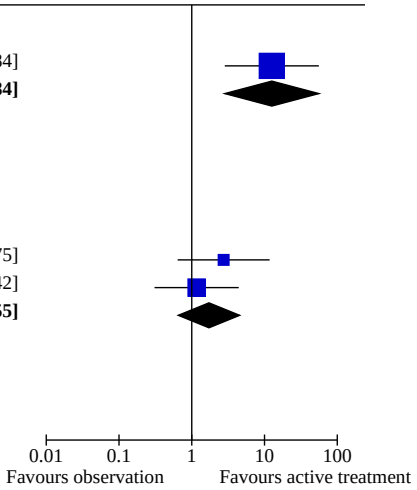
Analysis 1.1. Comparison 1: Active treatment versus observation only, Outcome 1: Eradication of MRSA

Study or Subgroup	Active treatment Events	Total	Observation only Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 At up to 1 month						
Muhlebach 2017	18	22	5	19	100.0%	12.60 [2.84 , 55.84]
Subtotal (95% CI)		**22**		**19**	**100.0%**	**12.60 [2.84 , 55.84]**
Total events:	18		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.34 (P = 0.0009)						
1.1.2 At up to 6 months						
Dolce 2019 (1)	12	19	5	13	35.4%	2.74 [0.64 , 11.75]
Muhlebach 2017 (2)	12	21	8	15	64.6%	1.17 [0.31 , 4.42]
Subtotal (95% CI)		**40**		**28**	**100.0%**	**1.72 [0.65 , 4.55]**
Total events:	24		13			
Heterogeneity: Chi² = 0.72, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 1.10 (P = 0.27)						



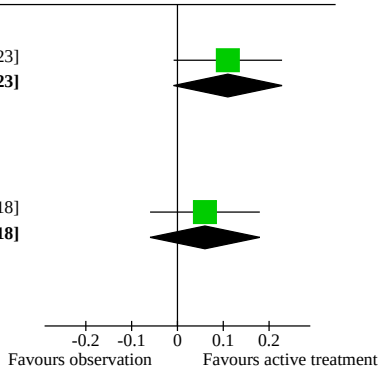
Footnotes

(1) Eradication defined as 3 consecutively negative MRSA samples by 3 months

(2) Eradication defined as MRSA negative at Day 168

Analysis 1.2. Comparison 1: Active treatment versus observation only, Outcome 2: FEV_1 (L) - absolute change from baseline

Study or Subgroup	Active treatment Mean	SD	Total	Observation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 At up to 1 month								
Muhlebach 2017	0.06	0.13	19	-0.05	0.21	16	100.0%	0.11 [-0.01 , 0.23]
Subtotal (95% CI)			**19**			**16**	**100.0%**	**0.11 [-0.01 , 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.82 (P = 0.07)								
1.2.2 At up to 6 months								
Muhlebach 2017 (1)	0.06	0.18	17	0	0.16	14	100.0%	0.06 [-0.06 , 0.18]
Subtotal (95% CI)			**17**			**14**	**100.0%**	**0.06 [-0.06 , 0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.33)								



Footnotes

(1) At Day 168

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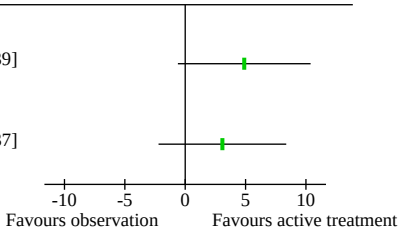
Analysis 1.3. Comparison 1: Active treatment versus observation only, Outcome 3: FEV_1 (L) - relative change from baseline

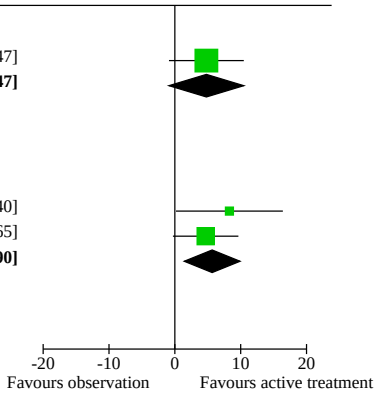
Study or Subgroup	Active treatment Mean	SD	Total	Observation Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.3.1 At up to 1 month							
Muhlebach 2017	2.45	6.5	19	-2.44	9.5	16	4.89 [-0.61 , 10.39]
1.3.2 At up to 6 months							
Muhlebach 2017 (1)	3.35	7.72	17	0.27	7.27	14	3.08 [-2.21 , 8.37]



Footnotes
(1) At day 168

Analysis 1.4. Comparison 1: Active treatment versus observation only, Outcome 4: FEV_1 (% predicted) - absolute change from baseline

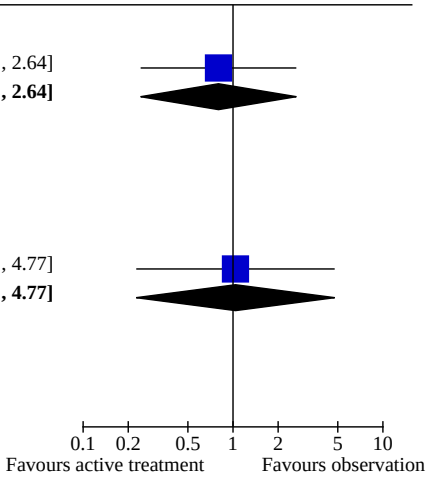
Study or Subgroup	Active treatment Mean	SD	Total	Observation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 At up to 1 month								
Muhlebach 2017	0.74	6.89	19	-4.05	9.72	16	100.0%	4.79 [-0.89 , 10.47]
Subtotal (95% CI)			**19**			**16**	**100.0%**	**4.79 [-0.89 , 10.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.65 (P = 0.10)								
1.4.2 At up to 6 months								
Dolce 2019	7.13	14.92	15	-1.16	5.25	12	27.3%	8.29 [0.18 , 16.40]
Muhlebach 2017 (1)	-0.56	6.45	17	-5.24	7.47	14	72.7%	4.68 [-0.29 , 9.65]
Subtotal (95% CI)			**32**			**26**	**100.0%**	**5.67 [1.43 , 9.90]**
Heterogeneity: Chi^2 = 0.55, df = 1 (P = 0.46); I^2 = 0%								
Test for overall effect: Z = 2.62 (P = 0.009)								



Footnotes
(1) At day 168

Analysis 1.5. Comparison 1: Active treatment versus observation only, Outcome 5: Overall antibiotic use

Study or Subgroup	Active treatment Events	Total	Observation only Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Anti-MRSA antibiotics from day 28 until day 168						
Muhlebach 2017	9	24	9	21	100.0%	0.80 [0.24 , 2.64]
Subtotal (95% CI)		**24**		**21**	**100.0%**	**0.80 [0.24 , 2.64]**
Total events:	9		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
1.5.2 Intravenous antibiotics use from baseline until 6 months						
Dolce 2019	6	19	4	13	100.0%	1.04 [0.23 , 4.77]
Subtotal (95% CI)		**19**		**13**	**100.0%**	**1.04 [0.23 , 4.77]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						



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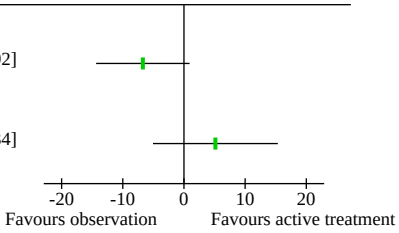
Analysis 1.6. Comparison 1: Active treatment versus observation only, Outcome 6: QoL measured using CFRSD Chronic Respiratory Infection Symptom Score (absolute change from baseline)

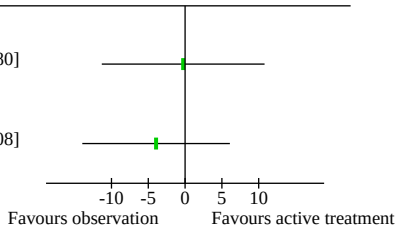
Study or Subgroup	Active treatment Mean	SD	Total	Observation only Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.6.1 At up to 1 month							
Muhlebach 2017	-3.77	9.78	22	2.95	14.35	19	-6.72 [-14.36 , 0.92]
1.6.2 At up to 6 months							
Muhlebach 2017 (1)	-0.05	11.07	21	-5.19	18.44	16	5.14 [-5.06 , 15.34]



Footnotes
(1) At day 168

Analysis 1.7. Comparison 1: Active treatment versus observation only, Outcome 7: QoL measured using CFQ-R Respiratory Symptom Score (absolute change from baseline)

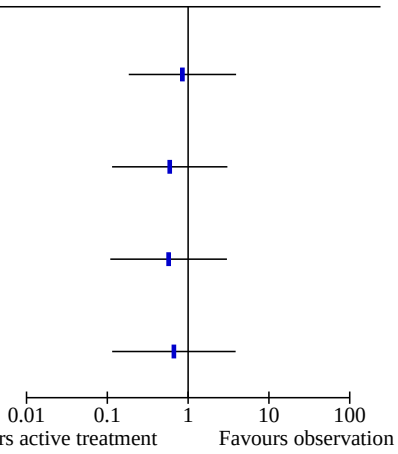
Study or Subgroup	Active treatment Mean	SD	Total	Observation only Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.7.1 At up to 1 month							
Muhlebach 2017	-2.73	16.29	22	-2.47	18.86	18	-0.26 [-11.32 , 10.80]
1.7.2 At up to 6 months							
Muhlebach 2017 (1)	-5.5	14.73	21	-1.56	15.91	16	-3.94 [-13.96 , 6.08]



Footnotes
(1) At day 168

Analysis 1.8. Comparison 1: Active treatment versus observation only, Outcome 8: Participants positive for *Pseudomonas aeruginosa*

Study or Subgroup	Active treatment Events	Total	Observation only Events	Total	Odds Ratio M-H, Fixed, 95% CI
1.8.1 At screening					
Muhlebach 2017	4	24	4	21	0.85 [0.18 , 3.92]
1.8.2 At up to 1 month					
Muhlebach 2017	3	22	4	19	0.59 [0.11 , 3.06]
1.8.3 At up to 3 months					
Muhlebach 2017 (1)	3	20	4	17	0.57 [0.11 , 3.02]
1.8.4 At up to 6 months					
Muhlebach 2017 (2)	3	21	3	15	0.67 [0.11 , 3.87]



Footnotes
(1) At day 84
(2) At day 168

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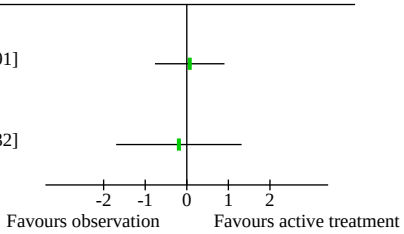
Analysis 1.9. Comparison 1: Active treatment versus observation only, Outcome 9: Weight (kg) (absolute change from baseline)

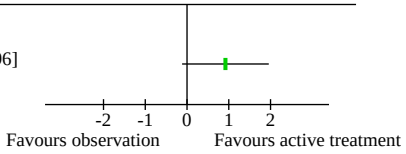
Study or Subgroup	Active treatment Mean	SD	Total	Observation only Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.9.1 At up to 1 month							
Muhlebach 2017	0.44	1.29	23	0.37	1.48	20	0.07 [-0.77 , 0.91]
1.9.2 At up to 6 months							
Muhlebach 2017 (1)	1.78	1.76	21	1.97	2.75	17	-0.19 [-1.70 , 1.32]



Footnotes
(1) At day 168

Analysis 1.10. Comparison 1: Active treatment versus observation only, Outcome 10: BMI (change from baseline)

Study or Subgroup	Active treatment Mean	SD	Total	Observation only Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.10.1 At 6 months							
Dolce 2019	0.54	1.33	19	-0.38	1.56	13	0.92 [-0.12 , 1.96]



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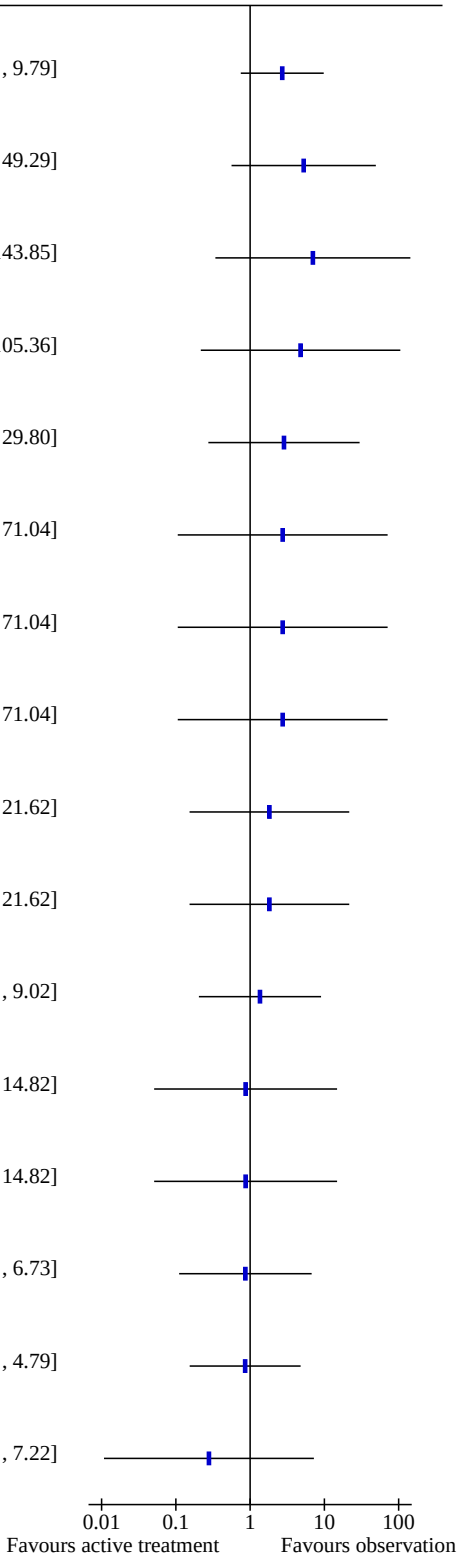
Analysis 1.11. Comparison 1: Active treatment versus observation only, Outcome 11: Adverse effects of treatment

Study or Subgroup	Active treatment Events	Total	Observation only Events	Total	Odds Ratio M-H, Fixed, 95% CI
1.11.1 Gastrointestinal disorders					
Muhlebach 2017	11	24	5	21	2.71 [0.75 , 9.79]
1.11.2 Skin and subcutaneous tissue disorders					
Muhlebach 2017	5	24	1	21	5.26 [0.56 , 49.29]
1.11.3 Injury, poisoning and procedural complications					
Muhlebach 2017	3	24	0	21	7.00 [0.34 , 143.85]
1.11.4 Nervous system disorders					
Muhlebach 2017	2	24	0	21	4.78 [0.22 , 105.36]
1.11.5 General disorders and administration site conditions					
Muhlebach 2017	3	24	1	21	2.86 [0.27 , 29.80]
1.11.6 Renal and urinary disorders					
Muhlebach 2017	1	24	0	21	2.74 [0.11 , 71.04]
1.11.7 Musculoskeletal and connective tissue disorders					
Muhlebach 2017	1	24	0	21	2.74 [0.11 , 71.04]
1.11.8 Immune system disorders					
Muhlebach 2017	1	24	0	21	2.74 [0.11 , 71.04]
1.11.9 Eye disorders					
Muhlebach 2017	2	24	1	21	1.82 [0.15 , 21.62]
1.11.10 Ear and labyrinth disorders					
Muhlebach 2017	2	24	1	21	1.82 [0.15 , 21.62]
1.11.11 Infections and infestations					
Muhlebach 2017	3	24	2	21	1.36 [0.20 , 9.02]
1.11.12 Psychiatric disorders					
Muhlebach 2017	1	24	1	21	0.87 [0.05 , 14.82]
1.11.13 Blood and lymphatic system disorders					
Muhlebach 2017	1	24	1	21	0.87 [0.05 , 14.82]
1.11.14 Metabolism and nutrition disorders					
Muhlebach 2017	2	24	2	21	0.86 [0.11 , 6.73]
1.11.15 Investigations					
Muhlebach 2017	3	24	3	21	0.86 [0.15 , 4.79]
1.11.16 Congenital, familial and genetic disorders					
Muhlebach 2017	0	24	1	21	0.28 [0.01 , 7.22]



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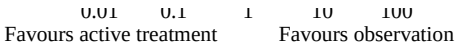
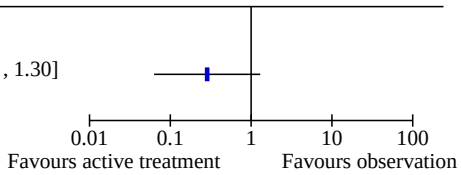
Analysis 1.11. (Continued)



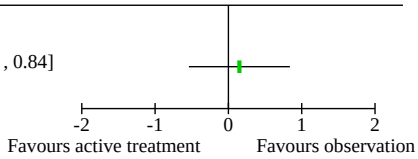
Analysis 1.12. Comparison 1: Active treatment versus observation only, Outcome 12: Number of participants with pulmonary exacerbations

Study or Subgroup	Active treatment Events	Total	Observation only Events	Total	Odds Ratio M-H, Fixed, 95% CI
1.12.1 At up to 1 month					
Muhlebach 2017	3	24	7	21	0.29 [0.06 , 1.30]



Analysis 1.13. Comparison 1: Active treatment versus observation only, Outcome 13: Mean number of pulmonary exacerbations

Study or Subgroup	Active treatment Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.13.1 At up to 6 months							
Dolce 2019	1	0.82	19	0.85	1.07	13	0.15 [-0.54 , 0.84]



Comparison 2. Treatment with oral antibiotics plus nebulised vancomycin versus oral antibiotics plus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Eradication of MRSA	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1.1 At up to 1 month	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1.2 At up to 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.2 Adverse effects of treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.2.1 Any adverse event	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.3 Elimination of MRSA carrier status (number of participants with negative nasal swabs for MRSA)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

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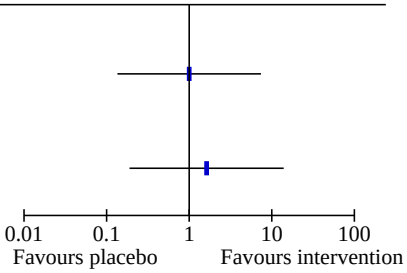
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3.1 At baseline	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.3.2 At end of 1 month treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.3.3 1 month after completion of treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Treatment with oral antibiotics plus nebulised vancomycin versus oral antibiotics plus placebo, Outcome 1: Eradication of MRSA

	Intervention		Placebo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.1.1 At up to 1 month						
Dezube 2019 (1)	2	10	3	15	1.00 [0.14 , 7.39]	
2.1.2 At up to 3 months						
Dezube 2019 (1)	2	10	2	15	1.63 [0.19 , 13.93]	

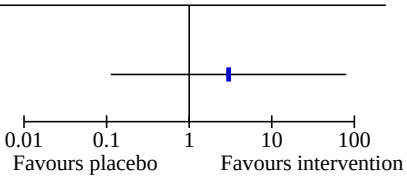


Footnotes

(1) Eradication defined as negative respiratory culture 1 month following treatment

Analysis 2.2. Comparison 2: Treatment with oral antibiotics plus nebulised vancomycin versus oral antibiotics plus placebo, Outcome 2: Adverse effects of treatment

	Intervention		Placebo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.2.1 Any adverse event						
Dezube 2019	14	14	14	15	3.00 [0.11 , 79.91]	



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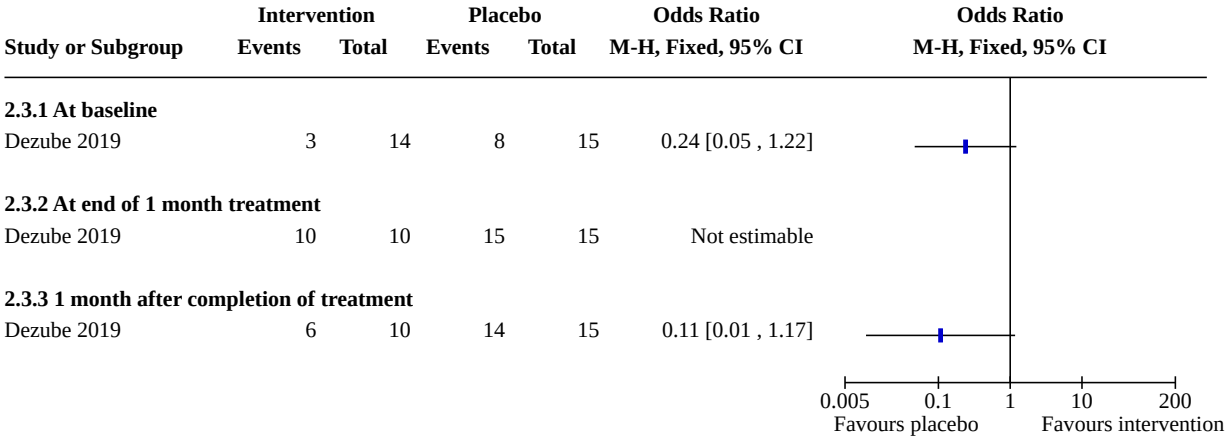
Analysis 2.3. Comparison 2: Treatment with oral antibiotics plus nebulised vancomycin versus oral antibiotics plus placebo, Outcome 3: Elimination of MRSA carrier status (number of participants with negative nasal swabs for MRSA)



APPENDICES

Appendix 1. Electronic searches

Database/Resource	Strategy
Medline Ovid (1946 onwards)	1 cystic fibrosis or CF 2 methicillin resistant staphylococcus aureus OR meticillin resistant staphylococcus aureus OR MRSA 3 1 OR 2
PubMed (1946 onwards)	*[PubMed Advanced Search Builder]* #1 (cystic fibrosis[Title]) OR CF[Title] #2 ((methicillin resistant staphylococcus aureus[Title]) OR meticillin resistant staphylococcus aureus[Title]) OR MRSA[Title] #3 1 AND 2
Clinicaltrials.gov	Condition/Disease: cystic fibrosis Other terms: mrsa
WHO ICTRP	cystic fibrosis AND mrsa
ISRCTN registry	cystic fibrosis AND mrsa

WHAT'S NEW

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Date	Event	Description
11 January 2023	Amended	Data entered for eradication of MRSA at six months in comparison 'Active treatment versus observation only' has been corrected. The result is still not statistically significant and does not change our conclusions.

HISTORY

Protocol first published: Issue 2, 2012
Review first published: Issue 2, 2013

Date	Event	Description
3 August 2022	New citation required but conclusions have not changed	Despite the addition of a single study, our conclusions have not changed.
3 August 2022	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified 18 new references potentially eligible for inclusion in this review. Two references were added to two included studies (four references in total) (Dolce 2019; Muhlebach 2017). Two references were added to one study previously listed as ongoing and which has now been included in this review (Dezube 2019). 14 references were not eligible for inclusion and excluded with reasons (Excluded studies). A search of the ongoing trials registries identified no new trials eligible for inclusion.
28 June 2018	New search has been performed	A search of the Group's Cystic Fibrosis Register identified nine new references (Frederiksen 2006, Singh 2013, Sharma 2016, Khorasani 2009, Flume 2015, Hodges 2014; Muhlebach 2017; Dolce 2019). Two trials were eligible for inclusion (Dolce 2019; Muhlebach 2017). One article reports the data from a recently completed study identified in a previous version of this review (Muhlebach 2017). A search of PubMed and MEDLINE identified a further four trials, none of which were not eligible and are listed under 'Excluded studies' (Bittencourt 2016; Hall 2015; Kappler 2016; Vallières 2016). A search of two ongoing trials registers (www.clinicaltrials.gov; www.isrctn.org) identified one new trial, which is not eligible for inclusion in the review (NCT03181932). Two of the ongoing trials identified in the previous version of this review are now listed as completed - NCT01349192 (Muhlebach 2017) and NCT01746095 (Dasenbrook 2015a). Data from one of these are included in this review (Muhlebach 2017), but currently the only published data identified from the Dasenbrook trial has been in abstract form only and does not provide sufficient information to assess eligibility for inclusion (Dasenbrook 2015a). Therefore this trial is currently listed under "Studies awaiting

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Date	Event	Description
		classification". The third previously identified ongoing trial is still ongoing but no longer recruiting participants (Dasenbrook 2012a). At this update a summary of findings table has been added to the review.
28 June 2018	New citation required and conclusions have changed	The inclusion of two trials in a previously empty review has enabled us to revise our earlier conclusions.
18 February 2015	New citation required but conclusions have not changed	Given that no new data have been added to this review, our conclusions remain the same.
18 February 2015	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified no new studies to be included in this review. A search of PUBMED, Embase and MEDLINE identified a further three studies, none of which were eligible for inclusion in the analysis (Dalbøge 2013; Serisier 2004; Vanderhelst 2013). A search of the ongoing trials registers (www.clinicaltrials.gov; www.isrctn.org) identified one further ongoing study, which has been listed in the review (Dasenbrook 2015a).

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	WHO UNDERTOOK THE TASK?
Protocol stage: draft the protocol	David Lo
Review stage: selected which trials to include (2 + 1 arbiter)	David Lo, Marianne Muhlebach, Alan Smyth
Review stage: extracted data from trials (2 people)	David Lo, Alan Smyth
Review stage: entered data into RevMan	David Lo
Review stage: carried out the analysis	David Lo
Review stage: interpreted the analysis	David Lo, Marianne Muhlebach, Alan Smyth
Review stage: drafted the final review	David Lo
Update stage: updated the review	David Lo, Marianne Muhlebach, Alan Smyth

DECLARATIONS OF INTEREST

David Lo: none known.

Marianne Muhlebach is one of the principle investigators for a randomised controlled trial evaluating early treatment of meticillin-resistant *Staphylococcus aureus* (MRSA) (Muhlebach 2017). She has acted as a consultant for Nabriva Therapeutics (who produce an antibiotic for use

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in community-acquired pneumonia) and participated in an advisory group meeting in 2021. This included a preview of material provided by the company and participation in a three-hour online meeting.

Alan Smyth is the Co-ordinating Editor of the Cochrane Cystic Fibrosis and Genetic Disorders Group and declares holding a patent for alkyl quinolones as biomarkers of *Pseudomonas aeruginosa* infection and uses thereof; however, he has not benefited from this financially.

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Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2015 update, we changed the spelling of 'methicillin' to 'meticillin' in line with the change in the international non-proprietary name (although we are aware that, in some parts of the world, the drug is still known as methicillin).

In the 2018 update, we reported the rate of hospitalisations of participants (from screening through to end of trial) under the existing outcome of 'Frequency of exacerbations'. Even though the rate of hospitalisation was not a stated outcome within the original protocol, we felt that hospital admissions represent a significant morbidity and important health outcome for people with CF.

In the 2018 update, we reported data at day 28, day 168 and six months as per the original included studies. For the 2022 update, we have reverted to the original reporting plan set out in the protocol, with time points of 14 days, up to one month, up to three months, up to six months and up to 12 months after MRSA therapy.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [therapeutic use]; *Cystic Fibrosis [drug therapy]; *Methicillin-Resistant Staphylococcus aureus; Pseudomonas aeruginosa; Rifampin [therapeutic use]

MeSH check words

Humans

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