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[Intervention Review]

Vaccines for preventing infection with Pseudomonas aeruginosa in cystic fibrosis

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ABSTRACT

Background

Chronic pulmonary infection in cystic fibrosis results in progressive lung damage. Once colonisation of the lungs with *Pseudomonas aeruginosa* occurs, it is almost impossible to eradicate. Vaccines, aimed at reducing infection with *Pseudomonas aeruginosa*, have been developed. This is an update of a previously published review.

Objectives

To assess the effectiveness of vaccination against *Pseudomonas aeruginosa* in cystic fibrosis.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register using the terms vaccines AND pseudomonas (last search 30 March 2015). We previously searched PubMed using the terms vaccin* AND cystic fibrosis (last search 30 May 2013).

Selection criteria

Randomised trials (published or unpublished) comparing *Pseudomonas aeruginosa* vaccines (oral, parenteral or intranasal) with control vaccines or no intervention in cystic fibrosis.

Data collection and analysis

The authors independently selected trials, assessed them and extracted data.

Main results

Six trials were identified. Two trials were excluded since they were not randomised and one old, small trial because it was not possible to assess whether is was randomised. The three included trials comprised 483, 476 and 37 patients, respectively. No data have been published from one of the large trials, but the company stated in a press release that the trial failed to confirm the results from an earlier study and that further clinical development was suspended. In the other large trial, relative risk for chronic infection was 0.91 (95% confidence interval 0.55 to 1.49), and in the small trial, the risk was also close to one. In the large trial, one patient was reported to have died in the observation period. In that trial, 227 adverse events (4 severe) were registered in the vaccine group and 91 (1 severe) in the control group. In this large trial of a vaccine developed against flagella antigens, antibody titres against the epitopes contained in the vaccine were higher in the vaccine group compared to the placebo group ($P < 0.0001$).

Authors' conclusions

Vaccines against *Pseudomonas aeruginosa* cannot be recommended.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing infection with *Pseudomonas aeruginosa* in cystic fibrosis

Review question

We reviewed the evidence about the effect of vaccinating people with cystic fibrosis to prevent infection with *Pseudomonas aeruginosa*.

Background

Cystic fibrosis is a hereditary disease where thick mucus is produced in the lungs. This can stop the lungs clearing bacteria such as *Pseudomonas aeruginosa* and other bacteria. This causes long-lasting lung infections in approximately 80% of adult patients; these infections result in permanent lung damage.

Vaccines have been developed which aim to reduce infection with *Pseudomonas aeruginosa* and it is important to know whether using these vaccines can prevent lung infection.

Search date

The evidence is current to: 30 March 2015.

Study characteristics

We searched for vaccine trials where cystic fibrosis patients were selected at random to receive either an active vaccine or no vaccine (or a placebo, which is a dummy vaccine with no active medication). We also looked for trials comparing different types of vaccine or different schedules or doses of the same vaccine. We included three trials; two compared a *Pseudomonas aeruginosa* vaccine to a placebo and the third compared a vaccine to no vaccine. The two trials comparing a vaccine to placebo had 959 cystic fibrosis patients (483 in one and 476 in the other); the third trial recruited 37 patients with cystic fibrosis. The average age of the patients was about seven years in all three trials. All of the patients were free of infection with *Pseudomonas aeruginosa* at the start of the trials and had a lung function of at least 50% of predicted for age. The two large trials followed the patients for two and four years, respectively; the small trial followed the patients for between 10 and 12 years.

Key results

We were only able to present the results from one of the large trials (483 cystic fibrosis patients) comparing an active vaccine to a placebo and the small trial (37 cystic fibrosis patients) with a no vaccination comparison group. Results for the second large trial have not been published, but the manufacturers stated that results did not confirm the findings from an earlier trial and that further clinical development had been suspended. The results we have from the two trials show that after vaccination the risk of getting a chronic infection did not decrease and lung function was similar in both groups of cystic fibrosis patients. One of the patients from the large trial died during the two year follow-up period; in the small trial, one patient from each group had died after seven to eight years and by the end of the trial (10 to 12 years) six patients in each group had died. Those who died were all chronically infected with *Pseudomonas aeruginosa*. Investigators in the large trial, recorded 227 adverse events (four of which were classed as severe) in the vaccine group and 91 (one of which was classed as severe) in the placebo group. The large trial also reported a rise in antibodies against *Pseudomonas aeruginosa* with no change in the placebo group.

On the basis of these results, we cannot recommend the use of vaccines against *Pseudomonas aeruginosa* in patients with cystic fibrosis.

Quality of the evidence

We did have some concerns that in the large trial which provided data for this review, the participants in the vaccine group were apparently older, taller and heavier than those in the placebo group. This may be due to pure chance, but the paper did not acknowledge this fact. We also had some concerns about how the cystic fibrosis patients in the small trial were randomised to the different treatments.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is an autosomal recessive genetic disease in Caucasians affecting approximately 1 in 2500 to 4700 live births (Lewis 1995). The gene that is abnormal encodes a protein called the cystic fibrosis transmembrane regulator protein (CFTR) which is a membrane bound chloride channel important in the transport of salt and water in and out of the cells that line the airways (Sheppard 1995). This in turn leads to the production of thick mucus, which causes plugging of the airways and impairs the clearance of bacteria from the lungs (Döring 1995). Recurrent episodes of infection and inflammation lead to progressive damage to the lung tissue, characterised by bronchiolitis and bronchiectasis and eventually to respiratory failure.

Recurrent and chronic lung infections are caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* (*P. aeruginosa*) and in some patients with CF also *Burkholderia cepacia* complex (Høiby 2000). Virtually all patients with CF will eventually become infected with *P. aeruginosa*. The presence of *P. aeruginosa* is associated with a pronounced antibody response and a marked neutrophil inflammation (intense acute inflammation), which is ineffective in clearing the bacteria from the lungs (Sheppard 1995). The main reasons are that *P. aeruginosa* produces alginate (carbohydrate), which surrounds the bacteria growing in small colonies within the lungs (biofilm). This biofilm mode of growth protects the bacteria from the host defence mechanisms and antibiotics (Høiby 1995).

The immune response can be divided into the antibody-mediated response, and the cellular-mediated response. When bacteria infect the airways, an antibody response usually ensues in immunocompetent individuals. As a result, antibodies which can hinder the attachment of further bacteria and neutralise toxic products are produced. Additionally, the antibodies activate the complement system, and increase the ability of some white blood cells, neutrophil leukocytes, to ingest and kill bacteria. Most patients with CF produce large quantities of antibodies directed against various components of *P. aeruginosa*. However, the naturally occurring immune response is generally ineffective in clearing the infection, and the antibodies may even be detrimental, e.g. because of immune complex formation. Wheeler and colleagues (Wheeler 1994) found that CF children with low antibody levels (total IgG) had better respiratory status than those with a normal or high IgG level. The ability of antibodies to fight infection is limited, as neutrophil elastase and other enzymes digest them. *P. aeruginosa* also produce large quantities of alginate that may mask targets for antibodies on the surface of the bacteria. Additionally, *P. aeruginosa* growing in microcolonies are too large to be ingested and killed by neutrophils, which allows the bacteria to effectively evade the immune system. The constant attempts of the immune system to clear the large microcolonies of *P. aeruginosa* results in leakage of toxic enzymes from neutrophils (frustrated phagocytosis), causing further lung damage (Döring 1995; Sheppard 1995).

Description of the intervention

Vaccination aims to elicit a long-term protective immune response by the administration of a safe preparation of an organism or a purified or recombinant component. Vaccination may be effective:

1. by preventing an organism entering the body (usually by generation of neutralising antibodies);
2. by eliciting a strong immune response that clears infection rapidly, should it occur; or
3. by neutralising toxic products of the infecting organism during the course of the infection.

Once an immune response has been induced, it cannot be readily reversed, even if it subsequently proves to be detrimental.

How the intervention might work

The role of the cellular immune system involving T lymphocytes and their products in protection against bacterial infections is unclear in patients with CF. However, in a rat model of chronic *P. aeruginosa* lung infection, a vaccine containing depolymerised alginate conjugated to toxin A produced a cellular response (Th1 response) that was protective (Johansen 1995). It is possible, although by no means clear, that such a response could be beneficial in CF.

It has generally been accepted that the immune function is normal in patients with CF. However, it has been demonstrated that the CF gene product, CFTR, is expressed on T lymphocytes, and that production of chemical messengers that co-ordinate the immune response (cytokines) by these T lymphocytes may be altered in CF (Moss 1996). Thus, the response to vaccination may be altered in patients with CF.

Why it is important to do this review

We aimed to study whether vaccination against *P. aeruginosa* is beneficial in CF, and to compare the effects of different vaccines. There are two potential groups of patients with CF in whom vaccination against *P. aeruginosa* is of interest:

1. patients who are not yet colonised by *P. aeruginosa*;
2. patients who are intermittently colonised by *P. aeruginosa*.

This review is an update of previously published versions (Johansen 2008; Johansen 2013; Keogan 1999).

OBJECTIVES

To study the immunogenicity and clinical effectiveness of vaccination against *P. aeruginosa* in CF, and to compare the effects of different anti-pseudomonal vaccines. Specifically, we wished to test the following hypotheses that vaccination against *P. aeruginosa*:

1. delays or prevents chronic *P. aeruginosa* lung infection;
2. prevents deterioration in respiratory function;
3. decreases the frequency of pulmonary exacerbations;
4. increases the levels of anti-pseudomonas antibodies in serum or secretions;
5. enhances T cell reactivity to *P. aeruginosa*.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials, in any language, published or unpublished.

Types of participants

Patients with CF, diagnosed on the basis of abnormal sweat test or genotype, or both, of all ages and degrees of disease severity, regardless of the *P. aeruginosa* colonisation status.

Types of interventions

Experimental intervention: vaccination with oral, parenteral or intranasal *P. aeruginosa* vaccines.
Control interventions: placebo, no intervention, other vaccines, or different schedules or doses of the same vaccine as in the experimental group.

Types of outcome measures

Clinical and laboratory outcomes were considered for the review. Changes in certain laboratory outcomes may demonstrate that a vaccine provokes an immune response. However, this does not necessarily imply a protection, since immune responses to vaccines can also be neutral (providing neither protection nor damage) or harmful.

We defined chronic infection as either presence of *P. aeruginosa* in the lungs for at least six months, based on at least three positive cultures with at least one month intervals with direct (e.g. inflammation or fever) or indirect (specific antibody response) signs of infection and tissue damage; or a positive antibody response in at least two examinations for participants who do not expectorate and present negative bacterial cultures (Döring 2000; Döring 2004).

Primary outcomes

1. Time to chronic *P. aeruginosa* infection
2. Pulmonary function
   a. forced expiratory volume in one second (FEV_1) as per cent of predicted for age, sex and height
   b. forced vital capacity (FVC) as per cent of predicted for age, sex and height
3. Mortality

Secondary outcomes

1. Frequency of infective pulmonary exacerbations (per patient-year)
2. Days of antibiotic usage (per patient-year)
3. Body mass index (BMI)
4. Shwachman score (a score which includes clinical and x-ray measures of disease severity)
5. Days unable to carry out normal daily activities (days per patient-year)
6. Adverse events
7. Antibody levels to *P. aeruginosa* in serum, saliva or bronchoalveolar lavage (BAL)
8. T cell proliferation to *P. aeruginosa* antigens in cells recovered from serum, sputum or BAL
9. T cell cytokine production in response to *P. aeruginosa* antigens in cells recovered from serum, sputum or BAL

Search methods for identification of studies

Electronic searches

Relevant trials were identified from the Group's Cystic Fibrosis Trials register using the terms: vaccines AND pseudomonas.

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 through the abstract books of two major cystic fibrosis conferences - 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 Module. Date of last search: 30 March 2015.

We also previously searched PubMed (*see* Appendix 1), but this search was not re-run for the 2015 update of the review. Date of last search: 30 May 2013.

Searching other resources

The register held by the Cochrane Vaccine Field (comprising handsearching of *Vaccine* and the *Journal of Medical Virology*) was also searched; reference lists of identified papers were checked; and research institutes and companies involved in the development or marketing of relevant vaccines were contacted.

We accepted letters, abstracts and unpublished trials.

Data collection and analysis

For each step below, we resolved any disagreements by discussion.

Selection of studies

The two authors independently selected the trials to be included in the review.

Data extraction and management

The two authors independently extracted data using a data collection form.

Assessment of risk of bias in included studies

The two authors independently assessed the risk of bias. In particular, we recorded generation of the randomisation sequence, concealment of treatment allocation, any blinding, and exclusions of patients from the analysis.

Measures of treatment effect

We sought data on on all randomised patients, i.e. including patients the investigators might have excluded because of poor compliance, ineligibility or loss to follow-up (intention-to-treat analysis).

For dichotomous data, we used the risk ratio. For continuous outcomes, we preferred post-treatment values when available rather than changes. For time-to-event data, we preferred to use the hazard ratio, but accepted the relative risk if that was the only statistic available.

Dealing with missing data

When trial reports provided insufficient information, we contacted the corresponding author.

Assessment of heterogeneity

If there are enough trials in future updates of this review, we will assess statistical heterogeneity visually and by use of the I^2 statistic (Higgins 2003).

Assessment of reporting biases

We accepted letters, abstracts and unpublished trials in an attempt to minimize the impact of publication bias. In future updates of this review, we will attempt to assess publication bias using a funnel plot.

We also attempt to identify any outcome reporting bias.

Data synthesis

If it should be possible to perform meta-analyses in the future, we will calculate the weighted mean difference or standardised mean difference, as appropriate, for continuous outcomes. We plan to use a random-effects model, as the vaccines will be different.

Subgroup analysis and investigation of heterogeneity

We will try to explain any heterogeneity by comparing the characteristics of participants, interventions and outcomes measured in the included trials.

Sensitivity analysis

If possible in future, we will perform a sensitivity analysis where only trials with adequate allocation concealment are included (Schulz 1995).

RESULTS

Description of studies

Results of the search

We identified six trials and excluded three of these (Day 1984; Gibbs 1970; Lang 2004a).

Included studies

A total of 996 patients had been randomised into one of the three included trials: 483 patients (Döring 2007); 476 patients (Lang 2004b); and 37 patients (Langford 1983). The mean age at enrolment was 7.5 years in one trial (Döring 2007) and 7 years in another trial (Langford 1983); the mean age was not reported in the third trial (Lang 2004b). In all cases, the patients were free of *P. aeruginosa* at enrolment.

The experimental intervention was a vaccine consisting of flagella proteins of subtypes $a_0a_1a_2$ and b from strains 1210 and 5142, respectively, that had showed a protective effect in animal studies (Döring 2007), and a polysaccharide vaccine of 16 international serotypes of *P. aeruginosa* (Lot PEV01, Wellcome) (Langford 1983). Details of the vaccine were not reported in the third trial other than reference to it by its commercial name (Aerugen) (Lang 2004b). The control group received placebo (Döring 2007; Lang 2004b) or no intervention (Langford 1983).

The follow up in one trial was two years (Döring 2007); it was not stated in the second trial (Lang 2004b); and follow up was 10 to 12 years in the third trial (Langford 1983).

For further details, please see the table Characteristics of included studies.

Excluded studies

Three trials were excluded; two trials were not randomised (Gibbs 1970; Lang 2004a) and it was not possible to assess whether the third was randomised, as it is old and has only been published as an abstract (Day 1984). This trial included only 21 children and did not report any clinical outcomes.

Risk of bias in included studies

Allocation

In one of the large trials, the allocation was described as randomised (random numbers algorithm of Wichmann and Hill) and appeared to have been adequately concealed (Döring 2007). The second large trial was described as randomised, but we have no details of the generation or concealment of the allocation sequence (Lang 2004b). Two conference abstracts stated that the small trial was randomised, which one of the investigators has confirmed (Hiller 2005), but we have no details of the randomisation process and regard the allocation concealment as unclear (Langford 1983).

Blinding

In one of the large trials, the treatments were blinded; the placebo contained the same ingredients as the intervention, apart from the vaccine, but there was no information about appearance (Döring 2007). The other large trial was stated to be double-blind, with no further information (Lang 2004b). The small trial was not blinded as it compared vaccination with no intervention (Langford 1983).

Incomplete outcome data

In one of the large trials, intention-to-treat analyses were performed (Döring 2007). In the smaller trial, it is unclear whether the analysis was by intention-to-treat, and reported numbers are inconsistent (Langford 1983). Most reports describe 34 patients, with 17 in each group, but the most recent report describes 37 patients, with 16 and 18 in the analysis.

Selective reporting

There is very little information about one of the large trials and most of it comes from slides presented at congresses (Lang 2004b). It was stated in a press release that the trial failed to confirm the results in an earlier study and that the company had suspended further clinical development (Lang 2004b).

Other potential sources of bias

In the Döring trial, the authors noted that there were no significant differences between the groups in sex, age, height, weight, body mass index and FEV_1 at baseline (Döring 2007). However, as there were rather obvious differences in a table, we checked this statement. There were no data for body mass index, but we calculated significant differences for age (P = 0.01), height (P = 0.008) and weight (P = 0.04), with higher numbers in the vaccine group. Differences of such magnitudes do occasionally happen in adequately randomised trials, e.g. in 8 out of 1000 trials, if height

is considered, and they are not necessarily important, but as the statement in the paper was incorrect, it raises the question whether other analyses were also incorrectly reported.

In the small trial, the patients were "divided into two groups, matched for age and sex" "with no knowledge of clinical details" (Langford 1983). However, "several patients allocated to a group developed *pseudomonas* infection after the study commenced but before they could be entered and vaccinated", and the authors reported that "this led to some slight imbalance in sex distribution" despite the matching for sex. This suggests that some patients (no numbers are given in any of the publications) with a poor prognosis who were allocated to the vaccine group were either excluded from the trial or later changed status and were referred to the control group.

Effects of interventions

As noted above, data were available for only one of the large trials, involving 483 patients (Döring 2007), and for the small trial of 37 patients (Langford 1983). We have only included outcomes for which we have been able to obtain data.

Primary outcomes

1. Time to chronic P. aeruginosa infection

Kaplan-Maier plots or hazard ratios were not available. In the large trial, it is reported that the risk ratio for chronic infection was 0.91 (95% confidence interval (CI) 0.55 to 1.49) (Döring 2007).

In the small trial, 6 out of 17 of the vaccinated patients had become chronically infected compared to 7 out of 17 of the controls after three years; and nine patients in both groups after seven years (Langford 1983). After 10 to 12 years follow up, 6 out of 10 surviving patients in the vaccine group and 7 out of 12 in the control group were infected.

2. Pulmonary function

a. FEV_1 as per cent of predicted for age, sex and height

FEV_1 was measured in the large trial, but no data were provided, only a statement that there was no difference between the groups in the rate of decline during the trial period (Döring 2007). In the smaller trial, in the *P. aeruginosa* infected subgroup, FEV_1 was 50% of predicted in the vaccinees and 57% in the control group. After 10 to 12 years the mean FEV_1 was 62% of predicted for the 10 vaccine group survivors, and 58% of predicted for the 12 controls (Langford 1983).

b. FVC as per cent of predicted for age, sex and height

After 10 to 12 years the mean FVC in the small trial was 73% of predicted for the 10 vaccine group survivors, and 69% of predicted for the 12 controls (Langford 1983).

3. Mortality

In the large trial, one patient died from acute lymphatic leukaemia (described in an adverse effects table) (Döring 2007). In the small trial, one patient had died in each group after seven to eight years follow up (Langford 1983). After 10 to 12 years, six patients in each group had died, at a median age of 17 years in both groups. All those who died were chronically infected with *P. aeruginosa*.

Secondary outcomes

4. Shwachman score

This outcome was not measured in the large trial (Döring 2007). In the small trial, the one to three years follow-up data showed no significant difference in Shwachman score with a mean score of 71 (range 36 to 92) in the vaccinees and 73 (range 51 to 90) in the controls (Langford 1983). At seven years of follow-up, the authors stated that the two groups had similar scores. The *P. aeruginosa* infected vaccinees demonstrated a mean fall in Shwachman score from 80 to 58, whereas the controls fell from 80 to 62.

6. Adverse events

In the large trial, 227 adverse events (four severe) were registered in the vaccine group and 91 (one severe) in the control group (Döring 2007). All but one patient recovered. This patient developed acute lymphatic leukaemia, which was not considered related to the vaccine, and died. The numbers of patients who had one or more events were not stated. In the small trial, 1 out of 17 vaccinees had a mild local reaction (Langford 1983).

7. Antibody levels to P. aeruginosa in serum, saliva or bronchoalveolar lavage (BAL)

In the large trial of a vaccine developed against flagella antigens, antibody titres against the epitopes contained in the vaccine were higher in the vaccine group compared to the placebo group ($P < 0.0001$, reciprocal IgG titres were below 1500 at baseline and increased to about 7000) (Döring 2007). In this trial, the authors' primary outcome was number of patients with at least one positive throat culture or at least one positive antibody titre against antigens not represented in the vaccine, risk ratio 0.80 (95% CI 0.64 to 1.00).

In the small trial, the antibody response to some of the 16 serotypes of *P. aeruginosa* in the vaccine was measured by an enzyme-linked immunosorbent assay (ELISA) (Langford 1983). Antibody responses were discussed, but no data were provided. The authors noted that vaccination did not produce a protective immune response.

None of the other secondary outcomes were reported.

DISCUSSION

The trial data we reviewed did not suggest that the vaccines tested for preventing infection against *P. aeruginosa* were effective. Two large trials have been performed, but no data have been made public from one of them (Lang 2004a). The press release announcing that the company had suspended further clinical development stated that the trial failed to confirm the results from an earlier study but did not contain any data (Lang 2004b. We contacted the company and were initially informed that we would be able to obtain the unpublished data. However, we have not received any information, not even when we only asked for an abstract. The press release was distributed in July 2006, and we believe it is an obligation towards the patients who volunteered for the trial that the results of their efforts and altruism become publicly available. Other researchers may develop vaccines and it is important to know about past successes and failures to proceed as rationally as possible.

In the other large trial, the patients were recruited over a three-year period, until February 2000 (Döring 2007). An additional seven

years passed before the trial was published in 2007. The analyses could therefore have been more powerful if the authors had used survival analysis and followed the patients up for longer, rather than reporting a relative risk after only two years.

In the small trial, there were no meaningful data on lung function. A significantly larger fall in PEFR was observed in the vaccinated group during follow up, but a significantly higher mean PEFR on entry was also observed (Langford 1983). Furthermore, this was a subgroup result among those 13 out of 34 patients who developed chronic infection, and after ten years, there was no difference in survival, lung function or proportion with chronic *P. aeruginosa* infection.

Effective vaccines have been developed against other bacteria, e.g. *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae*, and there is clearly a need for additional basic research to further increase our understanding of those elements of the immune response to *P. aeruginosa* that could potentially have a protective effect in patients with CF. Beneficial alterations in immune responses have been seen in animal experiments (Johansen 1995) and should be further evaluated (Moser 2000).

AUTHORS' CONCLUSIONS

Implications for practice

Vaccines against *P. aeruginosa* cannot be recommended.

Implications for research

Additional basic research is needed to further increase our understanding of those elements of the immune response to *P. aeruginosa* that could potentially have a protective effect. The risk of inducing immunologically mediated damage following vaccination must be considered in all trials, and long-term follow up of all trial patients will be necessary to adequately address this issue when new vaccines have been developed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Döring 2007

Study characteristics	
Methods	Randomised 1:1 in blocks of 12 stratified by centre. Double-blinding. Public funding.
Participants	483 randomised, all in intention-to-treat analyses, and 381 in per protocol analyses. Method of diagnosis of cystic fibrosis not stated ("conventional criteria"). Age: 1 or 2 years (both limits stated) to 18 years, free of *P. aeruginosa*. 239 children received vaccine and 244 placebo.
Interventions	4 doses of vaccine consisting of pseudomonas flagella proteins of subtypes a0a1a2 and b from strains 1210 and 5142, respectively, every 4 weeks (first 3 doses) and last dose after 1 year, or placebo.
Outcomes	Primary: infection with *P. aeruginosa*, diagnosed by a positive throat swab or positive antibody titre towards other antigens (exotoxin A, alkaline protease, or elastase) than the flagella proteins in the vaccine.

Döring 2007 *(Continued)*

	Another outcome was added during the trial: chronic infection, diagnosed by 3 positive swabs or titres during 1 year. Other outcomes were: specific antibodies against vaccine components and flagella subtypes; adverse events. FEV_1 was measured but no data were provided.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random numbers algorithm of Wichmann and Hill".
Allocation concealment (selection bias)	Unclear risk	"Syringes numbered with the randomisation code". "Patients...assigned...in ascending numerical order as they were enrolled consecutively".
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo contained same ingredients, apart from vaccine; no information about appearance. Statistical analysis plan finalised before unblinding, and allocation list not provided to statistician until closure of data entry. Statistician independent of company that provided drugs.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analyses.
Selective reporting (reporting bias)	High risk	FEV_1 was measured but no data were provided. There was a Supervisory Board, but no rules are described for interim analyses or for stopping the trial. Author informed us that the role of the board was to monitor systematic reactions to the vaccine after 48 patients had been treated.
Other bias	High risk	Significant differences at baseline despite contrasting information in the trial report. One-sided significance level used in power calculation, although it is known that antibodies may be harmful.

Lang 2004b

Study characteristics	
Methods	Randomised, double-blind.
Participants	476 participants.
Interventions	Four doses of polyvalent pseudomonas vaccine (Aerugen Berna Vaccine) or placebo at 0, 2, 12 and 24 months, or placebo.
Outcomes	Primary: prevention of colonisation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Lang 2004b *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No data available.
Allocation concealment (selection bias)	Unclear risk	No data available.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no data available on the method.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data available.
Selective reporting (reporting bias)	High risk	No data are available, and we did not receive any data from the company when we requested them.
Other bias	Unclear risk	No data available.

Langford 1983

Study characteristics	
Methods	Randomised after matching for age and sex. No blinding.
Participants	37 randomised, 34 in analyses. Method of diagnosis of cystic fibrosis not stated. Age: 2 years to 18 years, free of *P. aeruginosa*. 17 children received vaccine and 17 were not immunised.
Interventions	Wellcome polyvalent pseudomonas vaccine (a freeze-dried blended extract of 16 international serotypes of *P. aeruginosa*). Three initial doses over a 3-month period, followed by yearly booster doses, all given subcutaneously. Dose of 0.25 ml given to those under 12 years and 0.5 ml to those over 12 years. The control group was not treated.
Outcomes	Time to *P. aeruginosa* infection (cultures approximately every 2 months), peak flow, Chrispin-Norman X-ray score and Shwachman score (measured annually). Specific Pseudomonas antibodies were measured (annually) but not reported in detail. Adverse events noted.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described.
Allocation concealment (selection bias)	Unclear risk	Method not described; paper states allocation was performed with no knowledge of clinical details.
Blinding (performance bias and detection bias) All outcomes	High risk	The control group was not treated.

Langford 1983 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Due to acquisition of pseudomonas infection between recruitment and vaccination in a number of participants in one group, several early values for peak flows were missing reducing the number of participants in whom this outcome could be assessed.
Other bias	High risk	Paper states that "several patients allocated to a group developed pseudomonas infection after the study commenced but before they could be entered and vaccinated", and the authors reported that "this led to some slight imbalance in sex distribution" despite the matching for sex. This suggests that some patients (no numbers are given in any of the publications) with a poor prognosis who were allocated to the vaccine group were either excluded from the trial or later changed status and were referred to the control group.

P. aeruginosa: *Pseudomonas aeruginosa*

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

Study	Reason for exclusion
Day 1984	Not possible to assess whether this was a randomised trial as it has only been published as an abstract, in 1984; 10 CF children received a vaccine with 16 components (Wellcome BA 4162), 11 received placebo. No clinical outcomes were reported.
Gibbs 1970	Non-randomised study with "blindly-selected controls" where 30 CF children received a heptavalent vaccine of pseudomonas and 30 control CF children received placebo injections. No clinical outcomes were reported.
Lang 2004a	Non-randomised study where 26 CF participants received an octavalent-polysaccharide-toxin A conjugate vaccine and a control group of 26 age and sex-matched CF participants was chosen retrospectively.

APPENDICES

Appendix 1. PubMed search strategy

vaccin* AND cystic fibrosis

WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	Due to a lack of research in this area the Editorial Board of the Cystic Fibrosis and Genetic Disorders Review Group have decided to no longer update this review.

HISTORY

Protocol first published: Issue 2, 1998
Review first published: Issue 1, 1999

Date	Event	Description
17 August 2015	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any potentially eligible trials for inclusion in this review. The plain language summary has been updated to a new format.
17 August 2015	New citation required but conclusions have not changed	As no new references have been included in this update of the review, our conclusions remain the same.
30 May 2013	New citation required but conclusions have not changed	There are no new studies included at this update of the review and our conclusions have not changed.
30 May 2013	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any potentially eligible new studies for this review. A search in PubMed did not identify any potentially eligible new studies for this review.
25 May 2011	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register and PubMed did not identify any new references potentially eligible for inclusion in the review.
12 June 2009	New search has been performed	A search of the Group's Trials Register did not identify any new references eligible for inclusion in this review.
13 August 2008	Amended	Converted to new review format. Plain language summary has been updated in line with current guidance from The Cochrane Collaboration.
13 August 2008	New citation required and conclusions have changed	Conclusions changed in light of newly included evidence.
13 August 2008	New search has been performed	In this update, two more trials were included, with 483 and 476 patients, respectively (Döring 2007; Lang 2004b). In the previous version of the review, only one small trial of 37 patients was included (Langford 1983).
7 February 2007	New search has been performed	Minor update
27 February 2006	Amended	Mary Keogan has ceased to be involved with this review; Helle Krogh Johansen has taken on the role of lead author and Peter C Gøtzsche has joined the review as co-author.
27 February 2006	New search has been performed	Additional information has been added to the only included study (Langford 1983); another study (Day 1984) has been moved from the 'Studies awaiting assessment' section to excluded studies. The search of the Cochrane Cystic Fibrosis (CF) and Genetic Disorders Group's CF trials register found one new reference to a study that was already included in the 'Ongoing studies' section of the review (Döring 2007). This study has now been moved to the 'Studies awaiting assessment' section. An additional reference to an excluded study (Lang 2004a), which was previously listed as Cryz 1997, has been added.

Date	Event	Description
		Information on an ongoing study has been included in the 'Characteristics of ongoing studies' table (Lang 2004b).
16 December 2002	New search has been performed	The search of the Cochrane Cystic Fibrosis (CF) and Genetic Disorders Group's CF trials register found no new trials eligible for inclusion in the review.
16 December 2002	Amended	The section "Types of outcome measures" was re-formatted in line with updated guidelines from the Group's editorial team.
19 November 2001	New search has been performed	Minor update

CONTRIBUTIONS OF AUTHORS

The review was designed by Mary Keogan and Helle Krogh Johansen. Both contributed to critical appraisal of papers and data extraction; MK was lead author and drafted the review and subsequent updates, HKJ commented on the drafts.

As from Issue 1, 2006, MK was no longer involved with the review, and Peter C Gøtzsche became co-author. From this issue, HKJ and PG contributed to appraisal of papers, data extraction and interpretation, and to the writing of the manuscript.

HKJ and PCG are guarantors of the review.

DECLARATIONS OF INTEREST

Helle Krogh Johansen declares no known conflict of interest.

Peter C Gøtzsche declares no known conflict of interest.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Cystic Fibrosis [*complications] [microbiology]; Pseudomonas aeruginosa [immunology]; Pseudomonas Infections [complications] [*prevention & control]; Pseudomonas Vaccines [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans