CHIEF SCIENTIST OFFICE

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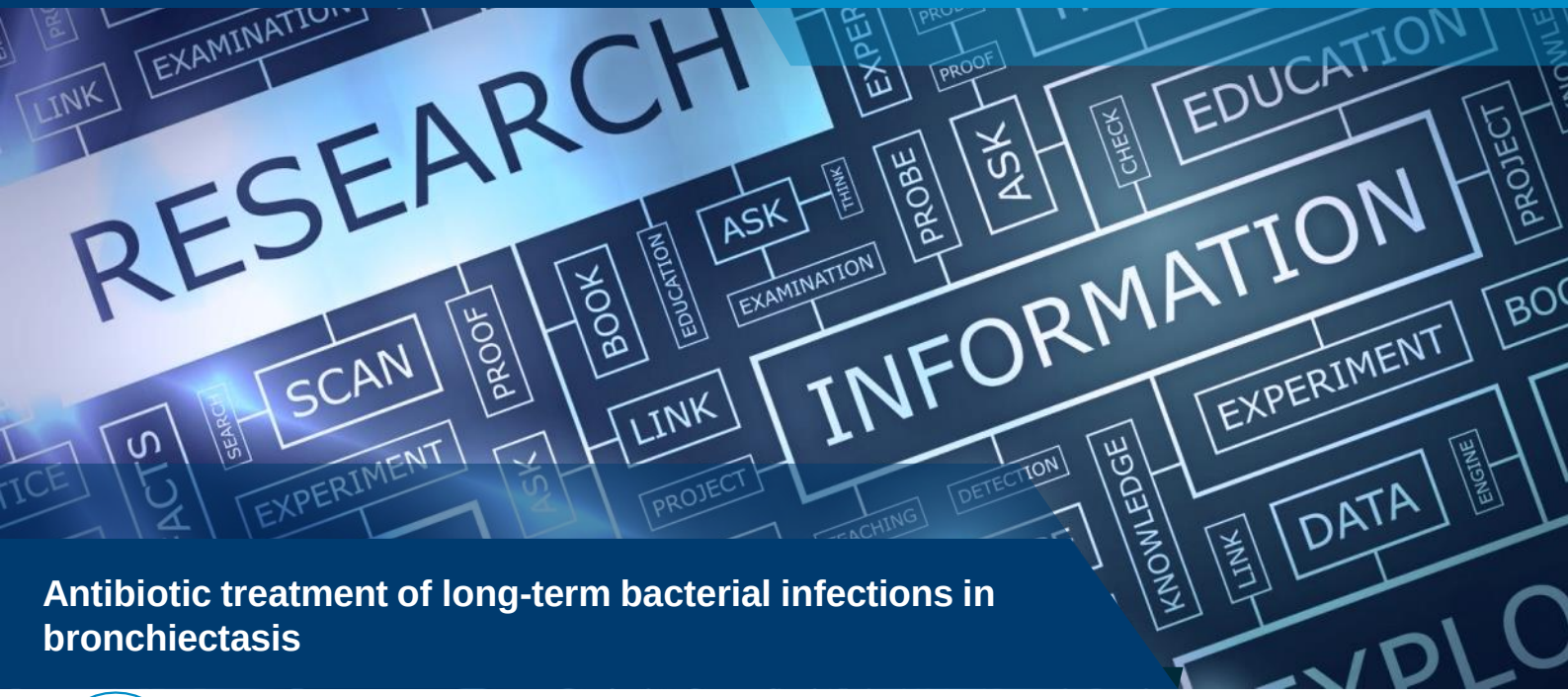
RESEARCH PROJECT BRIEFING



Antibiotic treatment of long-term bacterial infections in bronchiectasis

INTRODUCTION and AIMS

Treatment of long-term bacterial infections in patients with bronchiectasis are often unsuccessful. There have been multiple clinical trials to try to find out which antibiotic can treat these infections best, however, because of undefined differences between the patients they have been unsuccessful.

1) To characterise the difference between people with bronchiectasis with *Pseudomonas* (long term bacterial) infections, including: how ill patients are; what other bacteria are in their lungs (microbiome); if their immune system responds to bacteria differently; and if what country patients live in changes how patients benefit from antibiotics.
2) To find out if differences between the types of bacteria in patients' lung influence how ill they are.
3) See if the differences in patient's microbiome can explain variation seen in antibiotic trials in bronchiectasis.

KEY FINDINGS

1) Patients with *Pseudomonas* infections are very different from each other. If patients had more types of bacteria in their lungs they had lower levels of inflammation (inappropriate immune response).
2) Patients' microbiomes (different types of bacteria living in the lungs) are different, depending on where patients live in the world.
3) Variation between patient's microbiome may determine how many chest infections patients have each year.
4) Differences in patients' microbiomes can explain variation between antibiotics trials which was not explained by clinical trial results.
5) Future trials factoring in microbiome differences may lead to successful antibiotics trials in bronchiectasis to tell us which antibiotics benefit patients.

WHAT DID THE STUDY INVOLVE?

1) We carried out microbiome sequencing on sputum (phlegm) from 377 patients in two antibiotic trials. This shows us all the types of bacteria in the lungs.
2) We studied the immune responses in patients' lungs by performing sputum (phlegm) proteomics on 164 samples from an antibiotic trial in bronchiectasis.
3) We combined extensive clinical information about patients, with the data on bacteria present in their lungs, and their immune responses, to identify differences between patients. We used these differences between patients to adjust antibiotic trial results to see if they were then more similar to each other.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Patients with *Pseudomonas* infections are different from each other

We studied 377 patients with bronchiectasis and long-term *Pseudomonas* infections from across the world. These patients had taken part in one of two clinical trials of antibiotics, where one trial had shown a benefit, and the other had failed to show a benefit, of antibiotic treatment in bronchiectasis. All patients which had phlegm left over from analysis in the the two clinical trials were included in this study. These results are important to the 12,000 -18,000 patients with bronchiectasis in Scotland, as *Pseudomonas* is one of the most common infection associated with worse quality of life, and patients pass away earlier than expected. Patients from Scotland were in these trials, so these results fully apply to them.

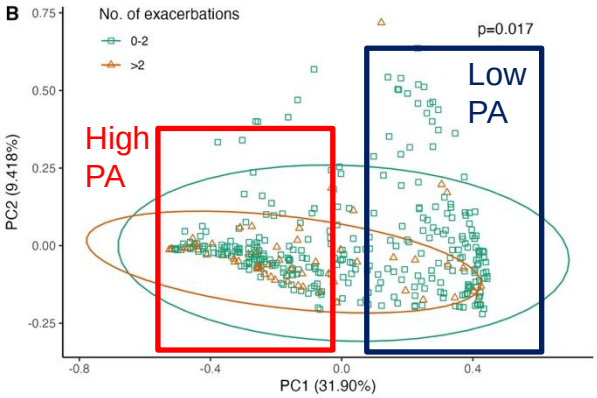


Image 1: microbiome study showing differences in patients with bronchiectasis related to *Pseudomonas* (PA) levels and exacerbation number.

We first used a highly detailed technique for studying all of the bacteria present sputum (phlegm) samples from people with bronchiectasis. We found that, even though all patients had a *Pseudomonas* infection, the other bacteria in their lungs were highly different between patients. We found that if patients had more variety in the bacterial species in their lungs they had fewer chest infections (Image 1).

We also used another powerful technique to look at all proteins in sputum (phlegm) samples from people with bronchiectasis and *Pseudomonas* infections. Here we found patients also have very different levels of proteins present in their lungs linked to different immune responses in patients (Image 2). The proteins associated with high levels of inflammation were from neutrophils (the most common type of white blood cells). Patients with low levels of inflammation in their lungs were more likely to clear the *Pseudomonas* infections especially if they were on antibiotic treatment.

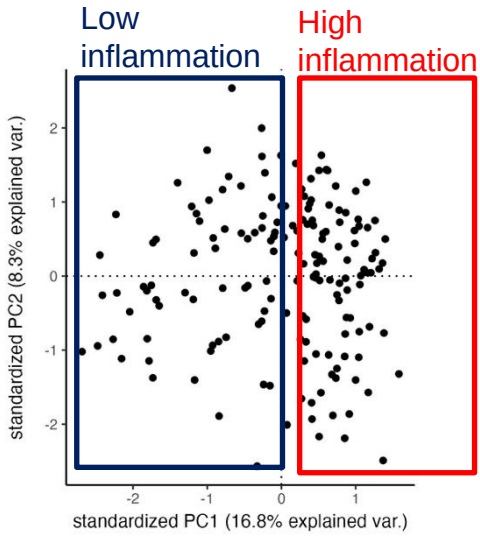


Image 2: proteomics in patients with *Pseudomonas* infections and bronchiectasis.

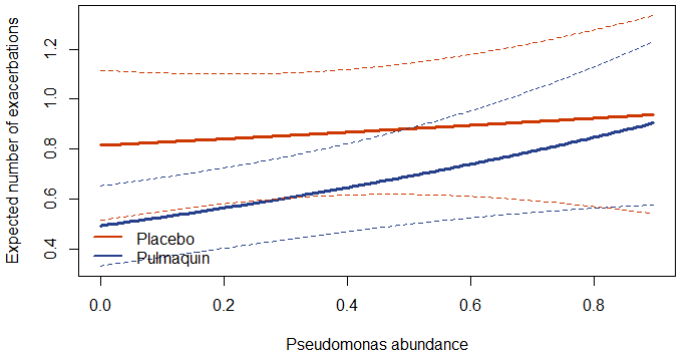


Image 3: *Pseudomonas* levels influence on patient's exacerbations in antibiotic treatment (blue) and non-treatment (red) groups.

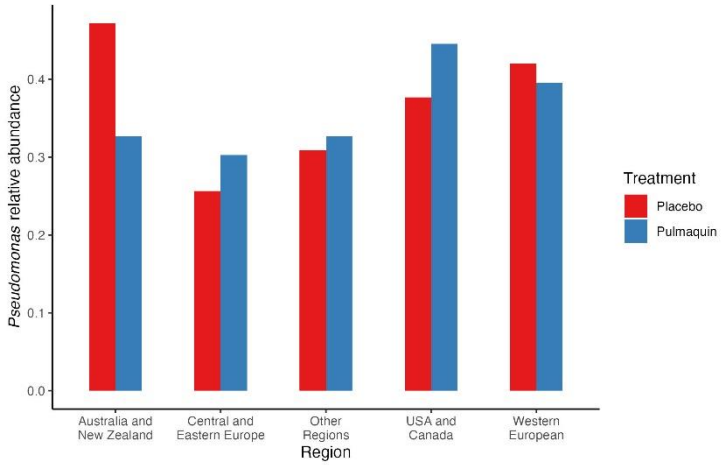


Image 4: *Pseudomonas* levels in different regions and in antibiotic treatment (blue) and non-treatment (red) groups.

Differences in patient's microbiome relate to differences in clinical information and between countries

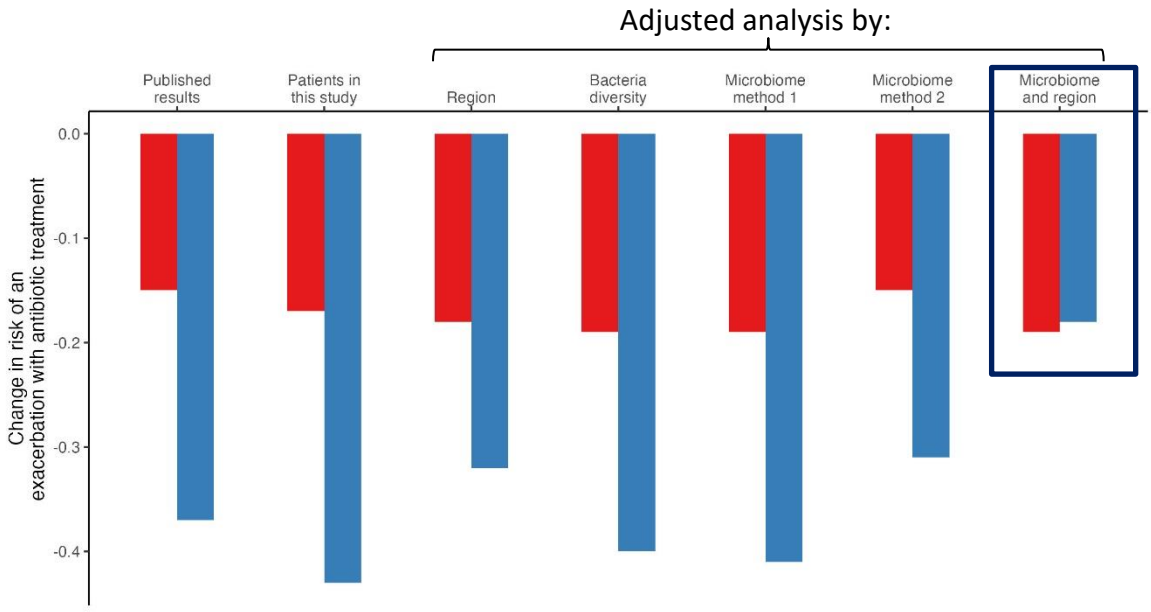
We looked to see how different levels of bacteria in patient's lungs related to their frequency of chest infections. Here were found that the levels of different bacteria were related to the number of chest infections they had. Patients with low levels of *Pseudomonas* compared to other bacteria were more likely to respond well to antibiotics and have fewer chest infections (Image 3).

We also found that patients microbiomes change by where patients live across the world. There were also differences in patient's microbiome in the antibiotic treatment group compared to the non-treatment group (Image 4).

These differences in patient's microbiomes could be impacting why antibiotic trials show inconsistent results in patient with *Pseudomonas* infections and bronchiectasis.

Adjusting antibiotic trial results for differences in the microbiome and geographical regions

We looked at the results from the two antibiotic trials to see if we could use statistical methods to adjust the results, considering differences in patient's microbiome and regional differences. We found, if we adjusted the results based on patients characteristics (age, sex, lung function and region) alone, this did not explain the inconsistency between the antibiotic trials. However, when we adjusted by patient's regions and microbiome this made the results from both antibiotic trials very similar (Image 5).



Results from both trials are very similar when adjusting for region and microbiome.

Image 5: Adjustment of antibiotic trial (ORBIT) results by regional and microbiome factors.

WHAT IMPACT COULD THE FINDINGS HAVE?

- These results show patients with *Pseudomonas* infections are very different from each other. Therefore, we need to choose antibiotics in the future based on these differences.
- At the moment, there isn't a licenced antibiotic treatment for *Pseudomonas* infections in bronchiectasis, so we don't know which antibiotics work best for patients. To be licenced, we need successful clinical trials of antibiotics. These findings could lead to successful trials of antibiotics to treat *Pseudomonas* infections in bronchiectasis by increasing the number of people taking part in antibiotic trials and taking into account their geographical location and other bacteria in their lungs.
- We have identified bacteria species and substances which could be measured in phlegm which could be used to predict if patients will respond to antibiotic treatments.

HOW WILL THE OUTCOMES BE DISSEMINATED?

This project will lead to several publications which are currently in progress and will be published in peer reviewed scientific journals. "Endotypes of *Pseudomonas aeruginosa* infection in bronchiectasis are associated with inhaled antibiotic response" has been submitted to a high impact journal and published as a preprint. Results have been disseminated to the professional community through presentations at the World Bronchiectasis Conference, European Respiratory Society conferences, European Society of Clinical Microbiology and Infectious Diseases conference, British association for lung research conference, 6th Forum on Respiratory Tract Infections conference and Scottish Immunology Groups Network conference. Results in progress have been shared with the European Lung Foundation patient advisory group. Final results will be shared with the local patient advisory group in the new year which will inform our next steps.

CONCLUSION

- Patients with *Pseudomonas* infections with bronchiectasis are very different from each other. These results can explain inconsistencies between trials of antibiotics and inform us how a successful clinical trial needs to be designed so there can be a licenced antibiotic for patients. With a successful treatment of *Pseudomonas* infections, we would expect patients' quality of life and life expectancy to increase.
- The next steps for this work is to develop a test to find out which patients will respond to antibiotics.

RESEARCH TEAM & CONTACT

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