

## **Head-to head comparisons– too many too early?**

### **A historical systematic review of antibiotic trials for treating mild to moderate COPD exacerbations**

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## **Abstract**

**Background:** Randomised trials comparing – head-to-head – different drugs are extremely valuable for clinical decision-making. It is scientifically and ethically sensible to demand strong evidence that a drug is effective by showing superiority over placebo before embarking on head-to-head comparisons of potentially ineffective drugs. Our aim was to study the evolution of evidence from placebo-controlled and pragmatic trials about the effects of antibiotics for the treatment of mild to moderate exacerbations of chronic obstructive pulmonary disease (COPD).

**Methods:** We conducted a historical systematic review. Through electronic databases and hand-searches, we identified placebo-controlled and pragmatic antibiotic trials for the treatment of mild to moderate COPD exacerbations. We compared the numbers of patients recruited in placebo-controlled and pragmatic trials between 1957 and 2005. Using cumulative meta-analysis of placebo-controlled trials we determined when, if ever, placebo-controlled trials had shown convincing evidence that antibiotics are effective in preventing treatment failure in patients with mild to moderate COPD exacerbations.

**Results:** The first pragmatic trial was published in 1963. It was followed by another 100 trials, enrolling a total of 34'029 patients. Over time, the cumulative odds ratio (OR) in placebo-controlled trials remained inconclusive throughout with ORs ranging from 0.61 (95% CI 0.16 to 2.24) to 1.38 (95% CI 0.72 to 2.64). The most recent estimate (1995) showed an odds ratio of 1.15 (95% CI 0.78-1.70,  $p=0.47$ ).

**Conclusion:** This historical analysis shows that the initiation of pragmatic antibiotic trials involving ten thousands of COPD patients with mild to

moderate exacerbations in the past 40 years was scientifically and, therefore, ethically questionable. This underscores the requirement to conduct or study systematic reviews of explanatory trials before conducting pragmatic trials.

## **Background**

The Helsinki declaration rightly emphasizes that one should be very careful before embarking on placebo-controlled trials[1]. Research participants have a right to the best available treatment. Worries about the "unethical use of placebo" continue[2]. However, how about the reverse scenario? Might there be cases where experimental treatment did not show superiority over placebo but where placebo controls were abandoned nevertheless, thus exposing patients to adverse effects and society to health care expenditures not offset by any beneficial effects?

There is a large number randomized trials comparing different antibiotics (without placebo control) for the treatment of exacerbations of chronic obstructive pulmonary disease (COPD). Although it may seem plausible that antibiotics are beneficial in COPD patients in whom bacteria are the cause of the exacerbation - in about 50% of patients[3] - there is evidence indicating that antibiotics have a short-term effect only in COPD patients with severe exacerbations but not in mild to moderate exacerbations[4]. Although head-to-head comparisons of different treatment options available in clinical practice can be very useful[5], an underlying assumption of such trials is that the treatments are effective compared to placebo[6-8]. While conducting a series of systematic reviews of treatments in COPD, we had the impression that in the evaluation of antibiotics for COPD exacerbations placebo-controlled trials had not preceded trials with head-to-head comparisons. We set out to test this hypothesis in a more systematic way. We counted the number of randomised trials of antibiotic treatment for mild to moderate exacerbations in COPD patients published in the last 50 years, determined whether they used a

placebo-control or conducted head-to-head comparisons, and contrasted the volume of trials with the results of a cumulative meta-analysis, using data from a recently published systematic review.

## **Methods**

### *Data sources and searches*

For identification of the antibiotics trials we used a comprehensive literature search described elsewhere[4]. In brief, information specialists (Bazian, London, UK, [www.bazian.com](http://www.bazian.com)) searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2005 issue 4), PREMEDLINE (1960 to 1965), MEDLINE (1966 to March 2006), EMBASE (1974 to March 2006), the Database of Abstracts of Reviews of Effectiveness (DARE, March 2006) for any randomised trials on antibiotics. Two reviewers independently assessed the titles and abstracts of all identified citations without imposing any language restrictions. We then ordered the full text of any article that seemed potentially eligible by one of the reviewers. The reviewers then evaluated the full text of retrieved articles and selected those meeting the inclusion criteria. Each reviewer's decisions were recorded in the Endnote file and any disagreements were resolved by consensus.

### *Study selection*

We included randomized trials comparing any antibiotic with another antibiotic (so-called "pragmatic trials") or with placebo ("explanatory trials") for the treatment of mild to moderate exacerbations in COPD patients. In this context, we define a pragmatic trial as a trial comparing two or more active treatments

irrespective of whether it applies strict or loose patient entry criteria[6, 9]. In explanatory trials, the treatment under evaluation is compared with an inactive control intervention, such as a placebo or a sham procedure. Explanatory trials allow for an estimation of the specific effects of the treatment and offer a proof of principle effectiveness[6].

As with any systematic review on this topic, a difficulty is that definitions of COPD varied over time. In particular, spirometry criteria have become widespread only after 1995 and we accepted a clinical diagnosis of COPD, chronic bronchitis or emphysema. However, in order to include only trials whose patients were very likely to have COPD we included studies only if patients with chronic bronchitis were at least 40 years of age and/or if at least 80% were smokers or ex-smokers. The presence of these characteristics (chronic bronchitis, age and smoking history) renders a diagnosis of COPD according to modern (spirometric) criteria extremely likely[10]. We defined patients to have 'mild to moderate exacerbations' if they needed any outpatient treatment (level I exacerbation) according to the Operational Classification of Severity of the European Respiratory and American Thoracic Societies[11].

#### *Data extraction and analysis*

For each trial, one reviewer recorded details about the type of trial (explanatory or pragmatic), year of publication and the number of included patients. A second reviewer checked data extraction for accurateness. We calculated the cumulative number of patients included in these trials over the years. We plotted the cumulative number of patients against the year of

publication. A systematic review of the placebo-controlled explanatory trials has been reported elsewhere[4]. We conducted a cumulative meta-analysis of the effects of antibiotics on treatment failure, commonly used as the main outcome, using the set of placebo-controlled explanatory trials. With the cumulative meta-analysis we determined when, if ever, placebo-controlled trials had shown convincing evidence that antibiotics are effective in preventing treatment failure in mild to moderate exacerbations. In a sensitivity analysis we included another trial[12] that we, as reported previously[4], excluded from the main analyses because we had major doubts about reported results. We were interested whether inclusion of this trial changed the cumulative odds ratio significantly. We conducted all analyses in STATA for windows version 9.2, Stata Corp; College Station, TX)

## **Results**

### *Explanatory and pragmatic trials*

Out of 15 placebo-controlled (explanatory) trials, seven enrolled outpatients with mild to moderate exacerbations. We identified a total of 212 pragmatic trials, of which 101 explicitly enrolled outpatients with mild to moderate exacerbations and 63 enrolled inpatients. In 48 trials, patients with any severity of exacerbations were enrolled or severity of the exacerbation could not be determined.

Figure 1 shows the cumulative number of explanatory and pragmatic trials as well as the number of enrolled patients between 1957 and 2005. Over this period of almost 50 years the 101 pragmatic trials enrolled a total of 34'029 patients with mild to moderate exacerbations.

The first pragmatic trial in 1963[13] included patients with mild to moderate exacerbations and compared sulphonamide to penicillin, with the aim of finding an antibiotic with fewer adverse events than oxytetracycline, the drug used in the three earlier placebo-controlled trials[14-16]. As in many of the following pragmatic trials[17], the role of antibiotics itself was not questioned. A common reason to justify a pragmatic trial was that antibiotics are effective against organisms most commonly associated with purulent sputum in chronic bronchitis such as *Haemophilus influenzae* and *Streptococcus pneumoniae*. Thus rather than citing evidence from placebo-controlled trials, they referred to the in-vitro activity of antibiotics (for example[18, 19]). Yet another group of pragmatic trials referred to placebo-controlled trials to justify their pragmatic trials but selectively cited only those trials with positive results[20, 21].

*Evidence about the effects of antibiotics in mild to moderate COPD exacerbations*

The 7 trials included a total of 990 outpatients with mild to moderate exacerbations. Figure 2 shows the cumulative meta-analyses for the five trials reporting on treatment failure. In one trial treatment failure was defined event-based by the need for further antibiotics[15] and in 4 trials a symptom-based definition of treatment failure was used[14, 22-24]. Cumulative odds ratios were around 1 (no effect of antibiotics) and never reached statistical significance. When we also included another trial[12] as explained above the cumulative odds ratio also remained non-significant (0.69, 95% CI 0.27-1.74,  $p=0.43$ ). In other words, cumulative evidence from placebo-controlled trials

did not show any effects of antibiotics on treatment failure in COPD patients with mild to moderate exacerbations.

The rationale for the first placebo-controlled trials was reported to be the uncertainty about the benefits of a “short course” or of “intermittent” antibiotic therapy for exacerbations[14-16]. The authors explicitly stated the short duration of antibiotic treatment because prophylactic long-term use of antibiotics to prevent exacerbations was quite common at that time[25]. Over the following 40 years, authors of explanatory trials argued that placebo-controlled trials are required because “the role of the [antibiotic] therapy is not clear”[22], or because “it is still not sufficiently clarified whether acute exacerbations of chronic bronchitis should be treated with antibiotics”[23]. These statements reflect the ongoing debate about the usefulness of antibiotics for COPD exacerbations.

## **Discussion**

Our historical analysis shows that many pragmatic trials of antibiotics for mild to moderate COPD exacerbations have been conducted although evidence never showed that antibiotics were effective at all. So, in this case the evaluation of antibiotics did not follow the general principle that explanatory trials must have shown that the treatment is better than placebo or a sham procedure, before pragmatic trials are to be conducted[8, 26].

Our study has some strengths and limitations. We used a comprehensive literature search to identify trials. The selection of a widely prescribed drug for a major disease makes our “case report” meaningful, because we could base

our historical analysis on a large number of trials. A limitation of systematic reviews in COPD is the evolution of definitions and classifications of COPD over the years. This raises uncertainty about the nature of the study populations included in trials published before 1995 or even before 2000. In many trials, patients with “chronic bronchitis” were included without presenting evidence about chronic airflow obstruction or poor reversibility of airflow obstruction.

We have focused in our analysis on one major treatment for COPD patients. It remains unclear if pragmatic trials are conducted frequently in other areas without an evidence base from explanatory trials. It is conceivable that this example of antibiotics is just the tip of the iceberg. A recent systematic review summarized explanatory and pragmatic trials of exercise for low back pain[27]. Pragmatic trials were conducted over the same period of time as the explanatory trials. The same applies to trials evaluating antidepressants for elderly people[28, 29] or antibiotics for acute otitis media in children[30, 31]. For these widely prescribed treatments for common conditions it remains as yet uncertain whether the conduct of pragmatic trials was scientifically and ethically justified.

Further studies are warranted to estimate the magnitude of the phenomenon that conduct of pragmatic trials is not solidly based on evidence from explanatory trials. We also need to find out what triggers investigators to conduct pragmatic trials too early. The reports on pragmatic trials on antibiotics shed some light on this tendency. High plausibility that an intervention works may be one of the most important reasons. For antibiotics, evidence is available about their in-vitro activity against bacteria that are

commonly found in COPD exacerbations. Intuitively, one may extrapolate this to the clinical situation. Physicians are also confirmed in their habit of antibiotic prescription because most outpatients with mild to moderate exacerbations recover within two weeks. Yet they do not seem to be aware of the 'natural' recovery rate (that is, without antibiotics) in these patients, which is 80% or more and equal to that in patients receiving placebo[4].

Last but not least, in a situation such as this, the pharmaceutical industry is also likely to be more interested in pragmatic trials. Once a treatment, such as antibiotics for COPD exacerbations, is established in clinical practice an attractive market is available. If a company wants to enter this market it needed to provide a trial showing clinical non-inferiority of a new antibiotic and some advantages in terms of adverse effects or costs. Hence, chance aside, even a new antibiotic lacking specific activity will not be inferior to any established antibiotic in COPD outpatients. This will make it relatively easy to get approval from regulatory agencies, as long as the drug is safe. Against this background, the value of the more than 100 pragmatic trials, with over 30'000 patients in total, remains doubtful.

## **Conclusion**

Our historical analysis shows that the evaluation of antibiotics for mild to moderate COPD exacerbations has been far from optimal. Pragmatic trials were conducted without any supporting evidence from explanatory trials. This phenomenon raises important scientific and ethical concerns and more studies are warranted to find out its prevalence, mechanisms, and its consequences in medicine. In the meantime, public funding bodies in

particular should encourage the careful conduct or study of pertinent systematic reviews before supporting the conduct of new trials.

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**Details of contributors**

All authors conceived the study idea; MP, PMB and GT designed the study; MP and DV collected the data; MP and GT analysed the data; all authors revised the manuscript and approved the final version of the submitted publication.

**Declaration of competing interests**

The author(s) declare that they have no competing interests.

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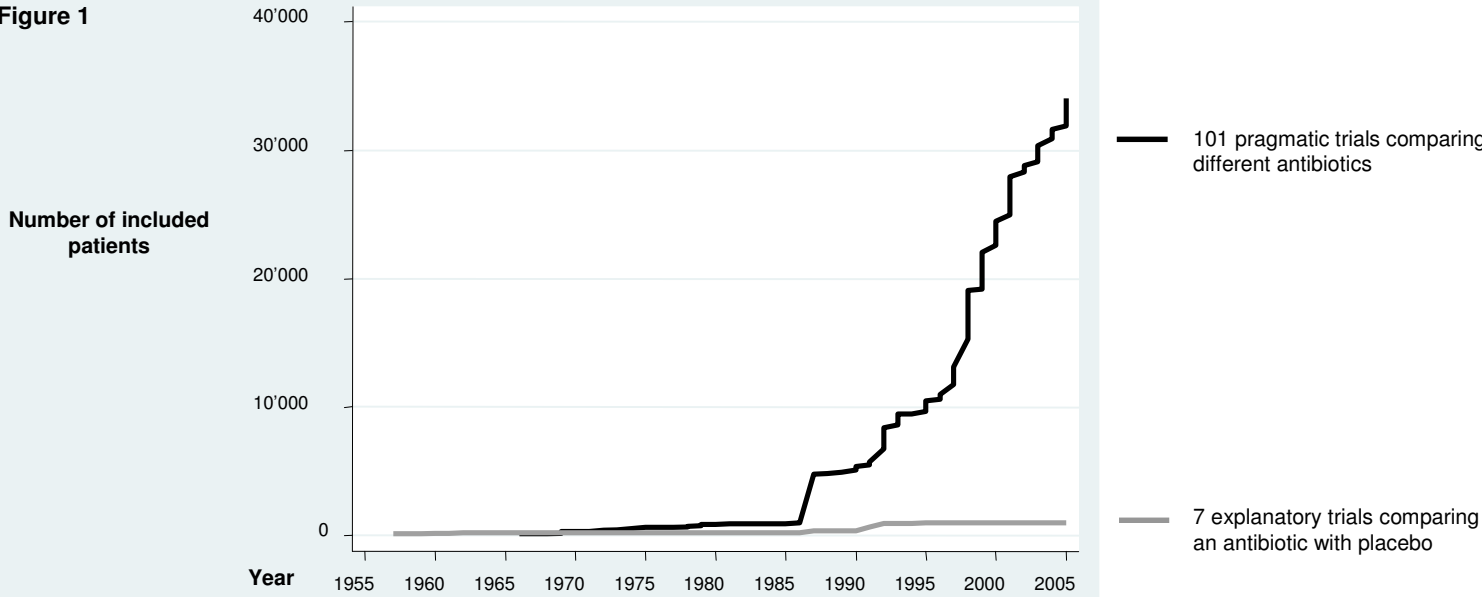
**Figure 1 Number of patients in antibiotic trials**

Cumulative number of patients COPD enrolled in explanatory and pragmatic trials evaluating antibiotics in patients with mild to moderate exacerbations from the first published trials until 2005.

**Figure 2 Evidence about the effects of antibiotics in COPD exacerbations**

Cumulative meta-analyses of placebo-controlled trials evaluating the effects of antibiotics on treatment failure in COPD patients with mild to moderate exacerbations.

**Figure 1**



**Number of trials**

Explanatory	0	2	3	3	3	3	3	4	7	7	7
Pragmatic	0	0	0	5	9	13	14	22	43	76	101

Figure 1

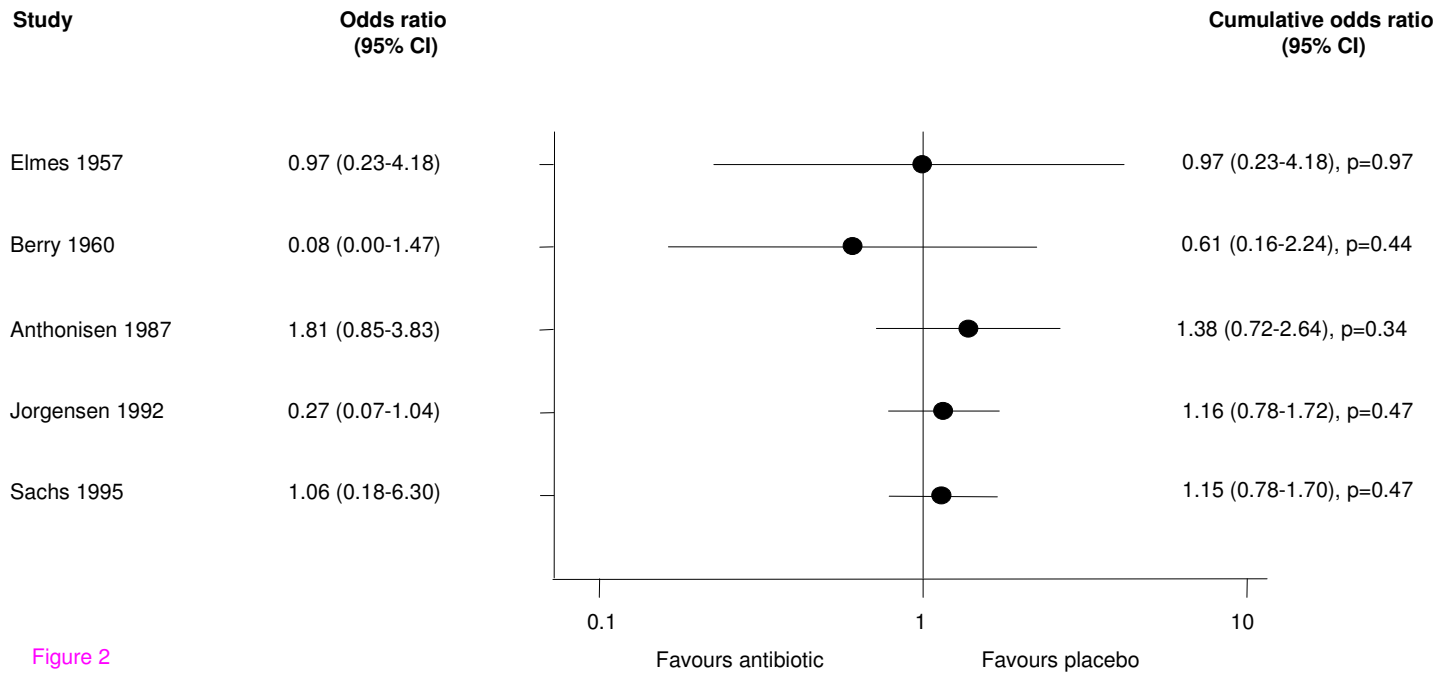
**Figure 2**

Figure 2

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