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ORIGINAL ARTICLE
COPD

Cost-effectiveness of antibiotics for COPD management: observational analysis using CPRD data

Sarah J. Ronaldson[1], Anan Raghunath[2], David J. Torgerson[1] and Tjeerd Van Staa[3]

Affiliations: [1]York Trials Unit, Dept of Health Sciences, University of York, York, UK. [2]James Alexander Family Practice, Hull, UK. [3]Health eResearch Centre, Farr Institute for Health Informatics Research, University of Manchester, Manchester, UK.

Correspondence: Sarah J. Ronaldson, York Trials Unit, Dept of Health Sciences, University of York, Heslington, York, YO10 5DD, UK. E-mail: sarah.ronaldson@york.ac.uk

ABSTRACT It is often difficult to determine the cause of chronic obstructive pulmonary disease (COPD) exacerbations, and antibiotics are frequently prescribed. This study conducted an observational cost-effectiveness analysis of prescribing antibiotics for exacerbations of COPD based on routinely collected data from patient electronic health records.

A cohort of 45 375 patients aged 40 years or more who attended their general practice for a COPD exacerbation during 2000–2013 was identified from the Clinical Practice Research Datalink. Two groups were formed ("immediate antibiotics" or "no antibiotics") based on whether antibiotics were prescribed during the index general practice (GP) consultation, with data analysed according to subsequent healthcare resource use. A cost-effectiveness analysis was undertaken from the perspective of the UK National Health Service, using a time horizon of 4 weeks in the base case.

The use of antibiotics for COPD exacerbations resulted in cost savings and an improvement in all outcomes analysed; *i.e.* GP visits, hospitalisations, community respiratory team referrals, all referrals, infections and subsequent antibiotics prescriptions were lower for the antibiotics group. Hence, the use of antibiotics was dominant over no antibiotics.

The economic analysis suggests that use of antibiotics for COPD exacerbations is a cost-effective alternative to not prescribing antibiotics for patients who present to their GP, and remains cost-effective when longer time horizons of 3 months and 12 months are considered. It would be useful for a definitive trial to be undertaken in this area to determine the cost-effectiveness of antibiotics for COPD exacerbations.

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Prescribing antibiotics for patients presenting to their GP with COPD exacerbations was found to be cost-effective http://ow.ly/F7Pe30bYBEs

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Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory disease that is characterised by airflow obstruction that is not fully reversible, with an estimated 3 million people having COPD in the UK [1]. People living with COPD often experience exacerbations, which are acute in onset and involve a rapid and sustained worsening of symptoms beyond normal day-to-day variations [1]. Symptoms that are commonly reported for COPD exacerbations comprise worsening breathlessness, cough, increased sputum production and change in sputum colour [1]. Exacerbations are associated with worse quality of life, faster disease progression and increased mortality, with acute exacerbations accounting for approximately 100 000 hospital admissions per year, at a cost of £236.6 million [2]. COPD patients are estimated to experience approximately 0.5–3.5 exacerbations per year [3].

It is often difficult to determine the cause of COPD exacerbations (*i.e.* whether viral, bacterial or environmental), and antibiotics are frequently prescribed [4]. A recent Cochrane review assessed the effects of antibiotics for the management of acute COPD exacerbations in terms of the impact on treatment failure and other patient-important outcomes [4]. Inconsistent findings were identified for outpatients and inpatients, whereas for patients admitted to an intensive care unit (ICU), antibiotics for COPD exacerbations demonstrated large and consistent beneficial effects for all outcomes [4]. The majority of randomised trials included in the review related to a secondary-care rather than a GP setting [4]. However, considerable health care provision for COPD patients takes place in general practices, so it is valuable to be aware of the impact of prescribing antibiotics for exacerbations in patients who visit their general practitioners (GPs). In addition, there is a paucity of evidence regarding the cost-effectiveness of prescribing antibiotics to patients who attend their general practice with a COPD exacerbation.

Observational data may be used when randomised controlled trial (RCT) data are not available [5]. Our study utilised anonymised electronic health records (EHRs) from a large number of general practices across the UK. The aim of this study was to conduct an observational cost-effectiveness analysis of prescribing antibiotics for COPD exacerbations. The following outcomes were analysed: further GP visits, hospital admissions, community respiratory team referrals, antibiotics prescriptions, infections and all referrals, for up to a 12 month period after the initial exacerbation. The analysis also aimed to illustrate the type of economic evaluation that can be undertaken using EHRs, as part of a study that investigated the opportunities and challenges of pragmatic point-of-care RCTs using routinely collected EHRs, with full details reported elsewhere [5].

Methods

The Clinical Practice Research Datalink (CPRD) is an observational data research service that aims to maximise the way that anonymised National Health Service (NHS) clinical data can be linked in order to facilitate observational research and research outputs that are of benefit for improving and safeguarding public health (www.cprd.com). Over 890 clinical reviews and papers have used the CPRD [6] (formerly known as the General Practice Research Database), covering a broad range of analyses. We summarise the methods here for an observational retrospective cohort analysis. Separate ethical approval was not required for this study; the CPRD group has obtained approval from a multicentre research ethics committee for all purely observational research using anonymised CPRD data.

Patient selection and inclusion

A cohort of patients was identified from the CPRD by searching for patients who attended at their general practice for a COPD exacerbation between 2000 and April 2013. Individuals were selected on the basis of being a COPD patient aged 40 years or more and having a COPD exacerbation at least 1 year after the start of data collection. Where a patient had multiple COPD exacerbations, one was randomly selected, and where multiple COPD exacerbations were recorded within a 6 week period, the first one was used to identify patients. The date of attendance for COPD exacerbation was defined as the index date. Files were extracted from the CPRD using codes and terms for GP consultations, referrals, antibiotics, infections, community respiratory team referrals and hospitalisations. The codes used for the extraction of information from the CPRD are available in a supplementary file (specifically for the identification of COPD exacerbations, COPD status and infections). Using these data, two groups were formed based on whether antibiotics were prescribed during the index GP consultation. Patients who died before the cut-off point (*i.e.* at 4 weeks after the index visit, for the base-case analysis) were excluded from the analysis.

Economic evaluation

We conducted a cost-effectiveness analysis to evaluate the use of immediate antibiotics *versus* no antibiotics for COPD exacerbation management in terms of the impact on subsequent resource utilisation. The analysis was undertaken from the perspective of the UK NHS, so only direct healthcare costs were included. In the base case, the time horizon of the evaluation was 4 weeks after the index visit for the

COPD exacerbation. We also evaluated at 3 months and at 12 months after the index visit. Due to the short time horizon of the base-case analysis, discounting of costs or outcomes was not necessary; adjustment for time preference would only be required where follow-up is longer than 1 year.

Resource use and unit costs

Resource use was assessed for both groups and compared to investigate whether any differences arose due to the use of antibiotics for COPD exacerbations. The following resource use areas were included in the analysis: GP visits, hospital admissions, community respiratory team referrals and all referrals. Antibiotics prescriptions and infections data were also assessed. Unit costs were applied to each item, with total costs generated by multiplying the quantities of resources utilised by the unit cost. Unit costs were derived from national costing sources comprising NHS Reference Costs 2011-12 [6], PSSRU Unit Costs of Health and Social Care [7] and the *British National Formulary*. Table 1 shows the unit costs used for the different resource items. Healthcare resource use results were presented in terms of their mean value and standard deviation, with 95% confidence intervals. All costs were reported as 2012 costs in pounds sterling (£).

Outcomes and presentation of results

The following outcomes were evaluated: GP visits, community respiratory team referrals, referrals, hospital admissions, antibiotics prescriptions and infections. The outcomes were summarised for both groups in terms of mean value, standard deviation and mean difference (with 95% CI) between the groups. The results from the cost-effectiveness analyses were presented in terms of incremental cost-effectiveness ratios (ICERs), *i.e.* the additional cost per extra unit of benefit. However, there are circumstances where it is not appropriate to calculate the ICER, *i.e.* where dominance occurs (better outcomes at lower cost). The ICERs were calculated as follows:

$$\text{ICER} = \frac{\text{Cost(Antibiotics group)} - \text{Cost(No antibiotics group)}}{\text{Effect(Antibiotics group)} - \text{Effect(No antibiotics group)}}$$

The following ICERs were estimated where appropriate: cost per GP visit averted; cost per community respiratory team referral averted; cost per referral averted; cost per hospital admission averted; cost per antibiotics prescription averted; and cost per infection averted.

Statistical analysis

Analyses were undertaken using Stata version 13.0 software (StataCorp, College Station, TX, USA). Demographic and clinical variables were compared according to group. The difference in costs and outcomes, with 95% confidence intervals, were presented. Poisson regression was used in the first instance to analyse the factors that determined the number of resource use counts over the analysis period. However, the data were found to significantly deviate from a Poisson distribution, so negative binomial regression was used. Differences in resource use were expressed as incidence rate ratios (IRRs). For the mean difference in costs, a linear regression was used. We adjusted for covariates that could influence the results, specifically age, sex, smoking history, body mass index (BMI) and ethnicity. Differences between the groups were found to be statistically significant if $p<0.05$.

TABLE 1 Unit costs of healthcare resource use items and other costs

Item	Unit cost £	Details
GP visit	43	Cost of a GP consultation assumed to last for 11.7 minutes [7]
Referral to community respiratory team	76	Community and Outreach Nursing Services: Specialist Nursing (CN203DAF) [6]
Referral	136	Average of a general medical referral (£150) and a general surgical referral (£121), sourced from outpatient attendance data [6]
Hospital inpatient stay	1350	Average of 10 COPD-related HRG codes, across all inpatient settings [6]
Antibiotic prescription	8	Average of 10 most commonly occurring antibiotics reported by the analysis
Treatment of infection	791	Average of three commonly occurring CPRD infections codes, sourced from total HRG data [6]

GP: general practice; COPD: chronic obstructive pulmonary disease; HRG: health resource group.

Results

Base-case results

A total of 45 375 patients aged 40–104 years were selected from the UK CPRD data; of these, 27 904 (61.5%) were in the "antibiotics" group and 17 471 (38.5%) in the "no antibiotics" group. The population under consideration had a mean±SD age of 71.0±10.5 years, with 50% being male, so the sex mix was found to be almost exactly equal, in contrast to other series, which can show a male predominance. The two groups were comparable in terms of age, sex, BMI, ethnicity, smoking history and number of cigarettes smoked per day (table 2). COPD status varied slightly between the groups. Data were missing for a larger proportion of the "no antibiotics" group, with n indicating the total number of valid (*i.e.* non-missing) values in table 2. The "antibiotics" group tended to have a slightly larger proportion with normal and mild COPD and fewer with moderate and severe COPD when compared to the "no antibiotics" group. The patients included in our study were predominantly located in England (76%), with 11% in Wales, 10% in Scotland and the remaining 3% in Northern Ireland.

Analysis

A total of 891 patients who died before the 4 week cut-off point were dropped from the analysis. A further 1759 patients were excluded on the basis of missing data relating to the model covariates. Hence, 42 725 patients were included in the analysis. Figure 1 summarises the data flow through the study. We adjusted for the following covariates in our analyses: age, sex, smoking history, BMI and ethnicity. However, for infections, referrals and community respiratory team referrals data, the models did not converge when all covariates were included; accordingly, the ethnicity variable was dropped in order for the models to be valid.

TABLE 2 Characteristics of patients with a chronic obstructive pulmonary disease (COPD) exacerbation

	Total patients	Antibiotics	No antibiotics
Patients	45 375	27 904	17 471
Sex			
Male	22 665 (50.0%)	13 944 (50.0%)	8721 (49.9%)
Female	22 710 (50.0%)	13 960 (50.0%)	8750 (50.1%)
Age years	71.0±10.5 (39.5–104.7)	70.0±10.4 (39.5–103.5)	72.6±10.4 (39.6–104.7)
BMI kg·m^{-2}	26.4±6.3 (10.0–68.3)	26.7±6.2 (10.0–65.3)	25.9±6.4 (11.3–68.3)
Cigarettes per day[#]	14.2±11.3 (1–100)	14.4±11.2 (1–100)	14.0±11.5 (1–100)
Smoking history	n=45 202	n=27 847	n=17 355
Non-smoker	4986 (11.0%)	3011 (10.8%)	1975 (11.3%)
Past smoker	22 297 (49.3%)	13 550 (48.7%)	8747 (50.4%)
Current smoker	17 919 (39.6%)	11 286 (40.5%)	6633 (38.2%)
COPD status[¶]	n=9834	n=6342	n=3492
Mild	3336 (33.9%)	2258 (35.6%)	1078 (30.9%)
Moderate	3897 (39.6%)	2603 (41.0%)	1294 (37.1%)
Severe	2432 (24.7%)	1384 (21.8%)	1048 (30.0%)
Very severe	169 (1.7%)	97 (1.5%)	72 (2.1%)
Ethnicity			
Bangladeshi	14 (0.03%)	9 (0.03%)	5 (0.03%)
Black	55 (0.12%)	33 (0.12%)	22 (0.13%)
Chinese	7 (0.02%)	5 (0.02%)	2 (0.01%)
Indian	60 (0.13%)	41 (0.15%)	19 (0.11%)
Mixed	15 (0.03%)	12 (0.04%)	3 (0.02%)
Other ethnic group	10 (0.02%)	5 (0.02%)	5 (0.03%)
Any other Asian	23 (0.05%)	19 (0.07%)	4 (0.02%)
Pakistani	23 (0.05%)	165 (0.06%)	7 (0.04%)
Unknown race	32 746 (72.17%)	19 622 (70.32%)	13 124 (75.12%)
White	12 422 (27.38%)	8142 (29.18%)	4280 (24.50%)
Practice location			
England	34 673 (76.4%)	21 447 (76.9%)	13 226 (75.7%)
Northern Ireland	1300 (2.9%)	662 (2.4%)	638 (3.7%)
Scotland	4565 (10.1%)	2697 (9.7%)	1868 (10.7%)
Wales	4837 (10.7%)	3098 (11.1%)	1739 (10.0%)

Data are presented as mean±SD (range) unless otherwise stated. BMI: body mass index. [#]: for current smokers; [¶]: severity of COPD as based on medical codes.

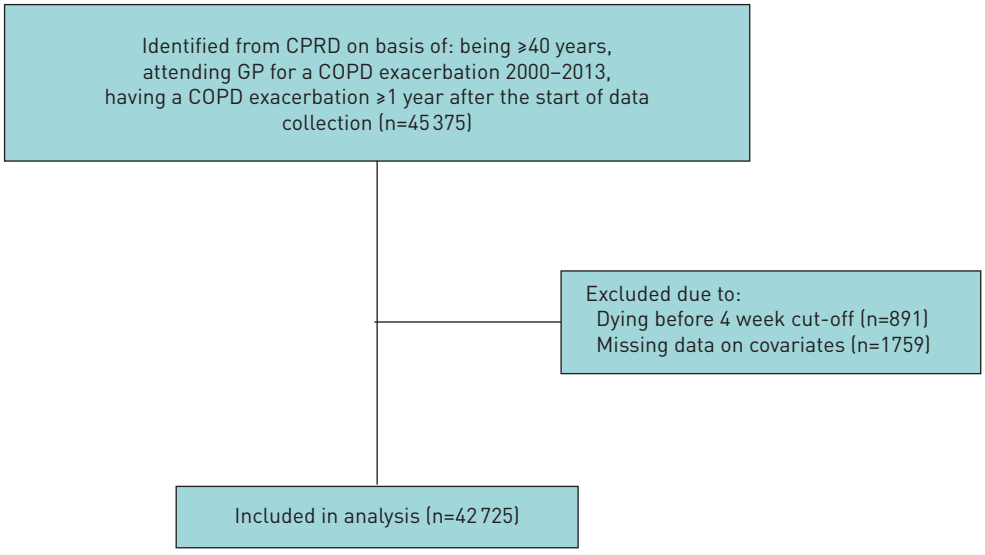

FIGURE 1 Data flow through the study. CPRD: Clinical Practice Research Datalink; GP: general practice; COPD: chronic obstructive pulmonary disease.

Resource use

The raw unadjusted mean resource utilisation data for the two groups are presented in table 3, and IRRs are presented in table 4. For all outcomes, the antibiotics group used the least number of resources.

Among the 42 725 patients included in the analysis, the incidence rate ratio for GP consultations was 0.65 (95% CI 0.64–0.66) for the "no antibiotics" group compared to the "antibiotics" group. This indicates a significantly lower number of GP consultations in the "antibiotics" group than in the "no antibiotics" group. The "no antibiotics" group had over three times more hospitalisations for the 4 week period (IRR 0.30, 95% CI 0.27–0.33), so hospitalisation outcomes were better for the "antibiotics" group. The infections analysis showed a slight decrease in the number of infections for the "antibiotics" group compared to the "no antibiotics" group (IRR 0.91, 95% CI 0.84–0.99).

Non-significant findings were found for the following analyses: antibiotics prescriptions (IRR 0.99, 95% CI 0.96–1.03), referrals (IRR 0.96, 95% CI 0.89–1.03) and community respiratory team referrals (IRR 0.75, 95% CI 0.42–1.31) analyses. Therefore, the use of antibiotics was associated with fewer, but not significantly fewer, subsequent antibiotics prescriptions, referrals and community respiratory referrals than no antibiotics.

Costs

The mean adjusted (unadjusted) cost per patient for the "antibiotics" group was estimated to be £748 (£726), in comparison to £1911 (£1948) for the "no antibiotics" group (table 5).

TABLE 3 Resource use according to use of antibiotics or no antibiotics at index visit for chronic obstructive pulmonary disease exacerbation

	Antibiotics	No antibiotics
Patients	26 822	15 903
GP visits	4.971±4.622 (4.921–5.021)	7.733±6.233 (7.637–7.830)
Referrals to community respiratory team	0.001±0.037 (0.001–0.002)	0.002±0.043 (0.001–0.002)
Referrals	0.091±0.343 (0.087–0.095)	0.095±0.343 (0.090–0.101)
Hospitalisations	0.326±2.091 (0.302–0.350)	1.138±4.038 (1.032–1.243)
Antibiotic prescriptions	0.352±0.627 (0.344–0.359)	0.353±0.662 (0.343–0.363)
Infections	0.073±0.230 (0.696–0.767)	0.081±0.319 (0.076–0.086)

Data are presented as mean±SD (95% CI). Interpretation of resource use: for example, for general practice (GP) visits, patients in the "antibiotics" group had 4.97 visits to the GP, on average, compared to 7.73 in the "no antibiotics" group over the base-case period of 4 weeks; hence, the average number of GP visits was higher for the "no antibiotics" group.

TABLE 4 Incidence rate ratios for "antibiotics" group compared with "no antibiotics" group

Resource use item	Incidence rate ratio (95% CI)
GP consultations	0.65 (0.64–0.66)
Referrals to community respiratory team	0.75 (0.42–1.31)
Referrals	0.96 (0.89–1.03)
Hospitalisations	0.30 (0.27–0.33)
Antibiotic prescriptions	0.99 (0.96–1.03)
Infections	0.91 (0.84–0.99)

GP: general practice.

Cost-effectiveness analysis

The results indicate that the use of antibiotics for COPD exacerbations resulted in cost savings and an improvement in all outcomes analysed; *i.e.* GP visits, hospitalisations, community respiratory team referrals, all referrals, antibiotics prescriptions and infections were lower for the "antibiotics" group (table 6). Hence, the use of antibiotics was dominant over no antibiotics.

Results at 3 months and 12 months

When 3 month and 12 month time horizons were considered, all outcomes remained more favourable for patients in the antibiotics group, on average; *i.e.* antibiotics use was associated with fewer GP visits, community respiratory team referrals, hospitalisations, infections, "antibiotics" prescriptions and total referrals. Statistically significant results were found for GP visits, community respiratory team referrals and hospitalisations for both the 3 month and 12 month analyses; *i.e.* the antibiotics group had significantly fewer visits. For the "antibiotics" group, total referrals were significantly lower in the 3 month analysis, and antibiotics prescriptions were significantly lower in the 12 months analysis.

Discussion

The retrospective, observational cost-effectiveness analysis using almost 43 000 EHRs from the CPRD found that patients who were prescribed antibiotics during a GP consultation for a COPD exacerbation had lower subsequent GP consultations, hospitalisations and infections over a 4 week period following the exacerbation when compared to patients who were not prescribed antibiotics. No significant difference in subsequent antibiotics, all referrals and community respiratory team referrals was identified. Our findings showed that patients who received antibiotics had lower costs due to fewer GP visits, hospital inpatient stays, infections, referrals, community respiratory team referrals and subsequent antibiotics prescriptions, although it should be noted that not all demonstrated significant differences.

It was useful to compare the 4 week findings of the base-case analysis with those in the longer term, *i.e.* at 3 months and 12 months. The findings remained the same for our 3 month and 12 month analyses, in terms of consistently lower mean costs resulting from lower resource use for the antibiotics group. The only exception was for infections, which were marginally higher (raw unadjusted mean only) for those prescribed antibiotics in the 12 month analysis, although not statistically significant.

There may be several reasons for clinicians in primary care not prescribing antibiotics: clinical presentation, previous experience, patient choice, but also some or many patients may not have had a diagnostic code of COPD on their records, or a past apparently "normal spirometry". On the one hand there is evidence and pressure on GPs to reduce and/or avoid using antibiotics, yet in COPD exacerbations, the threshold for initiating antibiotics is necessarily lower to avoid potential complications.

TABLE 5 Cost per patient

	Antibiotics	No antibiotics	Incremental
Patients	26 822	15 903	
Adjusted cost per patient £	748±25 [700–797]	1911±32 [1847–1974]	−1162±41 [−1243–−1083]
Unadjusted cost per patient £	726±25 [677–775]	1948±32 [1885–2011]	−1222±41 [−1302–−1142]

Data are presented as mean±SE (95% CI) unless otherwise stated.

TABLE 6 Cost-effectiveness

	Antibiotics	No antibiotics	Incremental	ICER
Cost per patient[#] £	748±25 (700–797)	1911±32 (1847–1974)	−1162±41 (−1243– −1083)	
GP visits per patient[¶]	5.00±0.03 (4.95–5.05)	7.67±0.05 (7.57–7.76)	−2.67±0.03 (−2.77– −2.57)	Dominant[+]
CRT referrals per patient[¶]	0.0012±0.0002 (0.0007–0.0016)	0.0016±0.0003 (0.0009–0.0023)	−0.0004±0.0004 (−0.0012–0.0004)	Dominant[+]
Referrals per patient[¶]	0.091±0.002 (0.087–0.095)	0.095±0.003 (0.090–0.100)	−0.004±0.003 (−0.011–0.003)	Dominant[+]
Hospitalisations per patient[¶]	0.330±0.013 (0.305–0.355)	1.111±0.053 (1.001–1.216)	−0.781±0.044 (−0867– −0.695)	Dominant[+]
Antibiotic prescriptions per patient[¶]	0.351±0.004 (0.343–0.359)	0.354±0.005 (0.344–0.364)	−0.003±0.006 (−0.016–0.010)	Dominant[+]
Infections per patient[¶]	0.073±0.002 (0.070–0.077)	0.081±0.003 (0.076–0.085)	−0.008±0.003 (−0.014– −0.002)	Dominant[+]

Data are presented as mean±SE (95% CI). ICER: incremental cost-effectiveness ratio; GP: general practice. [#]: adjusted costs per patient; [¶]: adjusted outcomes; [+]: lower costs and better outcomes (*i.e.* lower resource use, *e.g.* fewer GP visits).

The recent Cochrane review on the use of antibiotics for COPD exacerbations found there to be no statistically significant effect on hospital length of stay in inpatients [4] and no specific healthcare resource use was reported by the included trials in terms of the type analysed in this study. As previously stated, the review included studies that mainly focused on patients with more severe COPD exacerbations who were referred to hospitals, rather than a more diverse group of patients in general practice. Our observational analysis findings add to the evidence base regarding the impact of antibiotics prescription for COPD patients experiencing exacerbations in primary care. The analysis was based on a large patient sample, where resource use was explored for those who attended their general practice regarding a COPD exacerbation. Hence, we were able to evaluate actual patient data rather than making assumptions regarding resource utilisation. It should also be noted that the inclusion of those patients with COPD who have never smoked could be classed as a limitation, and the diagnosis for the 11% of patients that this applied to could be considered to be questionable.

Data were available regarding the reason for inpatient stay for the hospitalisations data, so, in theory, it would have been possible to cost more precisely according to the particular health resource group (HRG) code. However, due to the volume of codes for which costs would need to have been attached, a representative cost was applied instead. This is, of course, a simplification, and it should be kept in mind when interpreting the results. When attaching a cost to the relevant CPRD code, the closest match available was taken from NHS Reference Costs, as in some cases the CPRD and HRG codes did not correspond exactly. Assumptions were made around the estimation of costs for infections and antibiotics prescriptions, based on the available data. The use of the several assumptions that were made around the costs in the study is a limitation to note. The review on antimicrobial resistance by O'Neill [8] highlights the substantial potential impact of rising drug resistance. However, the cost of antimicrobial resistance developing from antibiotic use was not included in the present analysis, and this is acknowledged as a limitation.

The analysis also assumed that the patients in the "antibiotics" group who were prescribed antibiotics at the index GP consultation actually received the antibiotics that they were prescribed; however, there is the possibility that they did not. Although data regarding whether patients were prescribed a "rescue pack" were available, the information was related to the date of prescribing and not the date it was used by a patient. Data were not provided regarding the number of exacerbations experienced prior to the index visit, which would have been useful to analyse because those more frequent exacerbators are likely to have greater morbidity and healthcare utilisation, with GPs perhaps avoiding repeated antibiotic courses where possible. It is also worthy to note that the data set that we used may be biased, in that patients who are prescribed antibiotics may be more severe than patients who are not prescribed antibiotics, so the groups may be unbalanced in terms of patient characteristics. This highlights the importance of conducting an RCT in general practices that would remove such bias from an analysis.

Ideally, a cost-utility analysis would be conducted to generate the cost per quality-adjusted life-year (QALY) associated with antibiotics use. However, QALYs were not available for the population under analysis, so a cost-utility analysis was not undertaken. Future collection of quality-of-life values for such COPD exacerbation patients would be worthwhile.

There is a lack of spirometric data in making the diagnosis of COPD, with it being known that over a quarter of patients on GP COPD registers do not fulfil the spirometric criteria when retested [9]. The COPD diagnosis may thus not be robust. While COPD remains a diagnosis confirmed on spirometry, it is well known that patients aged over 45 years and long-standing smokers, with previous repeated chest

infections, remain good surrogate markers for COPD diagnosis. It is also worthwhile to note that there was a high level of missing data for the COPD status variable reported.

Due to the limited information regarding COPD exacerbation events included in the study, the analysis relied on the coding of the encounter, which may not be fully accurate. This in turn means that it is not possible to gauge how unwell the patients in the two groups were compared to one another, which may affect their subsequent clinical course.

There was an issue with missing data in the study, particularly around patients' ethnicity. Missing data can be inherent in large database studies of COPD and, while they are not necessarily avoidable or detrimental, can affect interpretation of the results. The high level of missing data for some of the variables featured in the analysis should therefore be considered when interpreting the findings. In addition, although the analysis controlled for covariates believed to influence the results, there is the possibility of confounding due to further potential confounders not being controlled for. Other variables such as associated morbidity and medications, including the use of oral steroids, could have influenced the results.

There may be several reasons for clinicians in primary care not prescribing antibiotics: clinical presentation, previous experience, patient choice, but also some or many patients may not have had a diagnostic code of COPD on their records, or a past apparently "normal spirometry". Other reasons may include indirect consultation over the telephone with a patient or carer, palliative care patients, recording issues following home visits, or the patient has their own supply of antibiotics previously provided. On the one hand there is evidence and pressure on GPs to reduce and/or avoid using antibiotics, but in COPD exacerbations, the threshold for initiating antibiotics is necessarily lower to avoid potential complications.

Nevertheless, the findings from this study, apart from highlighting the potential importance of GPs initiating antibiotics early in COPD exacerbations, also raise the issue of being vigilant and aware of the risks of not prescribing antibiotics leading to potential complications of hospitalisation and increased use of NHS resources. Although not a direct conclusion of this study, the findings nevertheless raise the need for careful clinical assessment and review of those patients with COPD exacerbations who are at the severe end of the spectrum.

In conclusion, a large observational patient data set derived from EHRs was used to illustrate the type of analysis that can be undertaken using trials that are carried out *via* the CPRD or similar databases. The use of antibiotics for patients who present to their GP with a COPD exacerbation was found to be dominant over (*i.e.* compared favourably with) the use of no antibiotics, as it resulted in cost savings and improved outcomes (*i.e.* reduced resource use, infections and subsequent antibiotics prescriptions). However, it should be noted that no significant differences were identified for subsequent antibiotics, all referrals and community respiratory team referrals. Our 4 week analysis suggests that the use of antibiotics for COPD exacerbations is a cost-effective alternative to not prescribing antibiotics for patients who present to their GP and remains cost-effective when longer time horizons of 3 months and 12 months are considered. It would be useful for a definitive trial to be undertaken in this area to determine the cost-effectiveness of antibiotics for COPD exacerbations.

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