Comparative estimated effectiveness of antibiotic classes as initial and secondary treatments of respiratory tract infections: longitudinal analysis of routine data from UK primary care 1991–2012

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ABSTRACT

Purpose To compare the estimated effectiveness of seven frequently prescribed antibiotic classes as initial and secondary treatments of upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs) 1991–2012. The main outcome measure was a surrogate for estimated antibiotic effectiveness.

Methods Routine, primary care data from the UK Clinical Practice Research Datalink (CPRD) were used. Having established standardized criteria representing antibiotic treatment failure, estimated treatment effectiveness rates were calculated as one minus the treatment failure rate. For each year from 1991 to 2012, estimated effectiveness rates by treatment line, indication, and sub-indication were calculated. These were presented by antibiotic class, with a sub-analysis for the macrolide clarithromycin.

Findings From approximately 58 million antibiotic prescriptions in CPRD, we analyzed 8,654,734 courses of antibiotic monotherapy: 4,825,422 courses (56%) were associated with URTI; 3,829,312 (44%) were associated with LRTI. Amino-penicillins (4,148,729 [56%]), penicillins (1,304,561 [18%]), and macrolides (944,622 [13%]) predominated as initial treatments; macrolides (375,903 [32%]), aminopenicillins (275,866 [23%]), and cephalosporins (159,954 [14%]) as secondary treatments. Macrolides had estimated effectiveness rates ≥80% across the study period as initial treatments of URTI and LRTI. In secondary use, only macrolides maintained these rates: 80.7% vs. 79.8% in LRTI, 85.1% vs. 84.5% in throat infections, 80.7% vs. 82.3% in nasal infections, 83.5% vs. 83.8% in unspecified URTI in 1991 and 2012, respectively.

Implications After more than two decades, macrolides remained amongst the most effective antibiotic classes for both URTI and LRTI in initial and secondary antibiotic treatment when a further antibiotic course was prescribed.

Limitations Antibiotic treatments were classified as intention to treat. It is unknown whether the prescription was redeemed or taken correctly. We do not know the etiology of these infections, therefore evidence of antibiotic non-response may relate to sub-optimal diagnosis and inappropriate treatment rather than antibiotic effectiveness for true bacterial infections.

Introduction

Bacterial resistance is associated with inappropriate prescription and overuse of antibiotics. Despite widespread publicity and public concern about antibiotic resistance, the use of antibiotics in the community continues to increase. In a recent study we evaluated the estimated effectiveness of the 10 antibiotics most frequently prescribed as initial treatments for four common infection classes. More than one in 10 prescriptions for antibiotics in the community were associated with evidence of non-response (‘treatment failure’) as defined by standardized criteria. From 1991 to 2012, evidence for non-response to antibiotic treatment increased by 12% overall, with the greatest increase occurring from the year 2000 and in lower respiratory tract infections, where it increased by 35%. Most of the instances of non-response (94%) occurred where patients were treated with antibiotics not recommended as first-line treatment in primary-care guidelines.

In order to better understand treatment progression where the initial antibiotic treatment is unsuccessful, here we characterize and compare the estimated effectiveness of seven frequently prescribed antibiotic classes as initial and secondary treatments of upper and lower respiratory tract infections. To our knowledge, only two previous studies have attempted to address outcomes of treatment with a second course of antibiotics in primary care. In 2000, a retrospective analysis by

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Supplemental data for this article can be accessed here.

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Piccirillo and colleagues compared the estimated effectiveness and cost of first-line antibiotics prescribed as initial treatments for acute uncomplicated sinusitis with those of second-line antibiotics prescribed subsequently. More recently, Dimopoulos and colleagues published a meta-analysis of trials comparing the efficacy and safety of first-line and second-line antibiotics as treatments of acute exacerbation of chronic bronchitis. However, in both studies antibiotics were analyzed by their first-choice and second-choice status according to treatment guidelines.

In general, guidelines recommend broad-spectrum penicillins and tetracyclines as first-choice antibiotic classes for lower respiratory tract infections. Macrolides are recommended as an alternative treatment in cases of allergy to penicillin derivatives. Acute bronchitis is usually self-limiting, and trial data suggest little or no benefit from antibiotics in otherwise healthy people, with no evidence to support the use of one antibiotic over another. Aminopenicillins, such as amoxicillin, are effective in treating most bacteria that cause acute bronchitis, and these are recommended as first-choice agents. Tetracyclines are frequently recommended as second-line therapy. For the treatment of pneumonia in ambulatory care, the choices of treatment include the broad-spectrum penicillins, macrolides, or tetracyclines. If the infection is unresponsive within 48 hours, referral or combined therapy should be used.

As with most lower respiratory tract infections, most upper respiratory tract infections are of viral origin. Antibiotics are usually prescribed empirically, with many viral infections being inappropriately treated with antibiotics: when recovery does not ensue, patients may assume the antibiotic has not worked and request a subsequent antibiotic. Evidence of non-response may indicate problems with diagnosis rather than the effectiveness of the antibiotic. However, where antibiotics are indicated, penicillins are the treatment of choice for acute sore throat infections (pharyngitis, tonsillitis, or laryngitis), and macrolides are recommended as an alternative treatment in cases of penicillin allergy. For severe sinusitis, aminopenicillins are recommended for first-line use; in cases of hypersensitivity, tetracyclines or macrolides are recommended. Cephalosporins, quinolones, or trimethoprim/sulfonamide are considered reserve antibiotics, not normally recommended for the treatment of respiratory tract infection in ambulatory care.

Here, using a large primary care data source from the UK, we have evaluated the prescription patterns and surrogate evidence of estimated effectiveness rates of seven commonly prescribed antibiotic classes as they are used in routine primary care as initial and secondary treatments of respiratory tract infections.

Methods

Data source

We used data from the UK Clinical Practice Research Datalink (CPRD). This longitudinal anonymized research database derived from nearly 700 primary-care practices contains records from more than 14 million individuals. The computerized data, generated in the course of routine healthcare by general practitioners (GPs) and associated staff, include demographic and lifestyle information, drug prescriptions, medical history, clinical investigation results, and hospital referrals. Diagnoses in CPRD are recorded using the Read code classification, a UK general practice standard, and have been validated in a number of studies, showing a high positive predictive value. Prescription data are well documented in CPRD, as they are both generated within and automatically recorded by the GP’s clinical software. Drugs issued in secondary care or over the counter are not recorded and are outside the scope of this study.

The current study received ethical approval by the CPRD Independent Scientific Advisory Committee on 31 October 2013, protocol number 13_168R.

Identification and characterization of antibiotic monotherapies

We selected all antibiotic prescriptions in the CPRD data that were issued to patients flagged by CPRD as being of acceptable research quality. From these, courses of antibiotic monotherapy were identified as one or more consecutive prescriptions for a single antibiotic drug separated by no more than 30 days and uninterrupted by prescriptions for any other antibiotic. Multiple courses could be identified for each patient. A course of antibiotic monotherapy was defined as the initial treatment for an episode of infection if there was no prescription for any other antibiotic in the 30 days preceding the first (index) antibiotic prescription. An antibiotic monotherapy was defined as a secondary treatment if it was preceded by an initial treatment within 30 days of its index prescription.

The indication for a prescription is not recorded with CPRD’s prescription data; therefore, the indication for an antibiotic monotherapy had to be inferred from the temporal relationship between the prescriptions comprising the monotherapy (and, if a secondary monotherapy, its preceding, initial monotherapy) and the recording of a diagnostic code for upper or lower respiratory tract infection (as described in Supplementary Figure 1). Relevant diagnostic codes were selected and classified by two clinical raters (a pharmacist and a GP), who each had to agree upon the selection. Codes representing upper respiratory tract infection were further classified by sub-indication: throat infections (tracheitis, laryngitis, pharyngitis, and tonsillitis), nasal infections (rhinitis and sinusitis), and unspecified. Lower respiratory tract infections were classified by sub-indication as bronchitis, pneumonia, and not otherwise specified. Courses of antibiotic monotherapy that did not have a single associated sub-indication were excluded.

Antibiotic monotherapies were further excluded if they were initiated before 1991 or after 2012, or if the interval from the patient’s registration to initiation of treatment was less than 365 days. The latter criterion was used to ensure that patients’ prior morbidity could be assessed.

From the remaining antibiotic monotherapies, those belonging to the seven antibiotic classes most frequently prescribed in the data set for respiratory tract infections were
selected: aminopenicillins, cephalosporins, penicillins, quinolones, tetracyclines, trimethoprim/sulfonamides, and macrolides. Numbers of initial and secondary monotherapies for each class and for each sub-indication were calculated, with a separate analysis focusing on the macrolide clarithromycin. Supplementary Figure 2 illustrates the overall process of selecting study data.

**Estimated effectiveness**

The proportion of antibiotic treatment courses for which there is evidence of non-response was evaluated as a proxy measure of the estimated effectiveness of the therapy. As in our previous study, we defined antibiotic treatment failure as the earliest occurrence of any of five events:

1. A different antibiotic dispensed between 1 and 30 days from the last prescription of the antibiotic monotherapy
2. A GP record of hospitalization with an infection-related diagnostic code within 30 days of antibiotic initiation
3. A GP referral to a specialist service within 30 days of antibiotic initiation, where the specialty type was infection-related (e.g. medical microbiology) or the referral had an infection-related diagnostic code
4. A GP record of an emergency department visit within 3 days of antibiotic initiation
5. A GP record of death with an infection-related diagnostic code, within 30 days of antibiotic initiation.

If an initial monotherapy with an antibiotic drug was followed, within 30 days, by a secondary monotherapy with a different antibiotic of the same class, the initial treatment was judged to have failed, and a failure at initial therapy level was recorded for that antibiotic class.

Treatment estimated effectiveness rates were then calculated as one minus the treatment failure rate.

**Statistical analyses**

For each year from 1991 to 2012 we calculated estimated effectiveness rates by treatment line (initial or secondary), indication (upper and lower respiratory tract infection), and by sub-indication (e.g. throat infection, bronchitis). These were presented by antibiotic class, with a sub-analysis for the macrolide clarithromycin. In addition, the changes over time in antibiotic classes used to treat each indication and sub-indication were assessed.

Initial data processing was undertaken with Microsoft SQL Server 2012.

**Results**

**Baseline characteristics**

Patients' baseline characteristics at antibiotic initiation are summarized for each indication and sub-indication and by each antibiotic class in Table 1.

In upper respiratory tract infections, penicillins were initially prescribed to patients with an average age of 24 years, the youngest group for all classes; patients prescribed initial quinolones or tetracyclines were on average about twice as old as those prescribed penicillins (Table 1). In lower respiratory tract infections, initial therapies with quinolones were prescribed to the oldest and the least healthy group of patients. The mean age and use of co-medication was higher in patients who were prescribed a second antibiotic for all antibiotic classes.

**Initial and secondary antibiotic monotherapies**

The dataset contained records of 58,450,68 relevant prescriptions. We identified 7,471,893 initial antibiotic monotherapies prescribed to 4,788,675 patients (more than one therapy could be included for each patient; 4,285,861 monotherapies (57.4% in 2,827,184 patients) were associated with a diagnostic of upper respiratory tract infection and 3,186,032 monotherapies (42.6%, in 1,961,491 patients) with a diagnosis of lower respiratory tract infection (Table 2).

Of the initial antibiotic monotherapies associated with upper respiratory tract infection, 1,827,512 (42.6%) had diagnostic codes for the sub-indication of throat infection and 951,617 (22.2%) had codes for nasal infection, whilst 1,506,732 (35.2%) had no further detail ('unspecified').

Of the initial antibiotic monotherapies associated with lower respiratory tract infection, 593,456 (18.5%) had diagnostic codes for the sub-indication of bronchitis, and 17,105 (0.5%) had diagnostic codes for pneumonia. However, detailed diagnostic codes were not entered by GPs for the majority (2,575,471 [80.8%]) of the initial antibiotics for lower respiratory tract infection; results for lower respiratory tract infections are therefore not presented by sub-indication (Table 2).

For initial treatment overall, the most prescribed antibiotic classes were aminopenicillins (4,148,729 [55.5%]), followed by penicillins (1,304,561 [17.5%]) and macrolides (944,622 [12.6%]) (Table 2).

A total of 1,182,841 antibiotic monotherapies for 1,050,265 patients were second courses, preceded, within 30 days, by an initial course with a different antibiotic (Table 2). Of these, 539,561 monotherapies (46.0%) were associated with upper respiratory tract infection and 643,280 (54.0%) with lower respiratory tract infection.

Of the secondary monotherapies associated with upper respiratory tract infection, 211,444 (39.2%) had diagnostic codes for the sub-indication of throat infection and 143,938 (26.7%) had codes for nasal infection, whilst 184,179 (34.1%) were unspecified (Table 2).

As with the initial antibiotic therapies, most second courses of therapy for lower respiratory tract infections (524,808 [81.6%]) did not have more detailed diagnostic codes enabling sub-indication to be determined. However, 111,772 monotherapies (17.4%) had diagnostic codes for the sub-indication of bronchitis and 6700 (1%) for pneumonia (Table 2). Results for secondary therapies associated with
lower respiratory tract infections are therefore not presented by sub-indication.

Macrolides were the antibiotic class most commonly prescribed as a second therapy (375,903 [31.8%]), followed by the aminopenicillins (275,866 [23.3%]) and cephalosporins (159,954 [13.5%]). Compared with initial antibiotic therapy, the proportion of penicillin monotherapies was low (95,625 [8.1%] (Table 2).

For both initial and secondary courses of antibiotic treatment, there were clear trends in prescribing a particular
## Table 2. Therapies in each antibiotic class by diagnosis.

| Indication   | All prescriptions | Aminopenicillins | Cephalosporins | Penicillins | Quinolones | Tetracyclines | Trimethoprim/ Sulfonamide | Macrolides* | Clarithromycin |
|--------------|------------------|------------------|----------------|-------------|------------|--------------|--------------------------|-------------|---------------|
| **First-line treatment** | | | | | | | | |
| LRTI         | 7,471,893        | 4,148,729 (55.5%)| 387,387 (5.2%)  | 1,304,561 (17.5%) | 77,752 (1.0%)  | 483,037 (6.5%)  | 125,805 (1.7%)  | 944,622 (12.6%)  | 241,559 (3.2%)  |
| Bronchitis   | 593,456 (18.6%)  | 410,699          | 37,157          | 10,546      | 38,751      | 13,052      | 77,338      | 25,395      |
| Pneumonia    | 17,105 (0.5%)    | 9162             | 1337            | 602         | 823         | 643         | 659         | 3879         | 1857         |
| Unspecified  | 2,575,471 (80.8%)| 1,817,236        | 164,948         | 33,052      | 46,566      | 104,341     | 42,877      | 366,451      | 123,759      |
| URTI         | 4,285,861 (57.4%)| 1,911,632        | 183,495         | 1,264,994   | 19,817      | 339,302     | 69,217      | 496,954      | 90,548       |
| Throat       | 1,827,512 (42.6%)| 91,648           | 47,305          | 548         | 6517        | 2046        | 13,558      | 2703         | 17,424       | 3133         |
| Nasal        | 951,617 (22.2%)  | 2,1668           | 2958            | 6727        | 743         | 3289        | 1487        | 1748         |
| Sinusitis    | 901,010          | 498,188          | 42,225          | 12,147      | 7862        | 243,165     | 17,869      | 79,554       | 21,941       |
| Unspecified  | 1,506,732 (35.2%)| 1,003,872        | 78,247          | 133,201     | 7784        | 61,245      | 30,592      | 191,791      | 35,667       |
| **Second-line treatment** | | | | | | | | |
| LRTI         | 1,182,841        | 275,866 (23.3%)  | 159,954 (13.5%) | 95,625 (8.1%)  | 71,492 (6.0%)  | 138,174 (11.7%) | 65,827 (5.6%)  | 375,903 (31.8%) | 147,662 (12.5%) |
| Bronchitis   | 111,772 (17.4%)  | 25,322           | 15,965          | 3155        | 9798        | 14,074      | 6614        | 36,844       | 16,627       | 1316         |
| Pneumonia    | 6700 (1.0%)      | 821              | 226             | 801         | 476         | 264         | 2630        | 1316         |
| Sinusitis    | 524,808 (81.6%)  | 120,111          | 76,068          | 15,835      | 44,119      | 53,425      | 26,828      | 186,422      | 87,284       |
| URTI         | 539,561 (45.6%)  | 128,951          | 67,100          | 76,409      | 16,774      | 70,199      | 32,121      | 148,007      | 51,352       |
| Throat       | 211,444 (39.2%)  | 2876             | 1827            | 1264        | 477         | 1487        | 875         | 3772         | 1204         |
| Nasal        | 143,938 (26.7%)  | 2876             | 1827            | 1264        | 477         | 1487        | 875         | 3772         | 1204         |
| Sinusitis    | 135,863          | 13,697           | 5213            | 5840        | 44,053      | 7600        | 243,800     | 9857         |
| Unspecified  | 184,179 (34.1%)  | 48,784           | 28,180          | 14,527      | 6936        | 15,974      | 12,722      | 57,056       | 17,639       |

*All macrolides prescriptions, including clarithromycin.

LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.
antibiotic class for sub-indications within upper respiratory tract infections: penicillins were the antibiotic class most frequently prescribed for throat infection (e.g. 65% of tonsillitis) and tetracyclines were most often prescribed for sinusitis. The macrolide clarithromycin was most commonly prescribed for lower respiratory tract infection, and its prescription rate increased from 3.2% in initial treatment to 12.5% in secondary treatment (Table 2). By the end of the 22 year study period, clarithromycin was the most commonly prescribed macrolide for lower respiratory tract infection, accounting for 65.7% of initial monotherapies and 75.9% of secondary monotherapies. For upper respiratory tract infections, this was 44.7% in initial and 55.4% in secondary treatments.

Estimated antibiotic treatment effectiveness

The estimated effectiveness rates of antibiotic treatment by antibiotic class for the years 1991 and 2012 are detailed in Table 3; the change in rates over the study period is illustrated in Figure 1 for initial antibiotic treatment and in Figure 2 for secondary treatment.

For initial treatment, antibiotic classes differed considerably in their estimated effectiveness rates across selected infections. For example, when used as the initial treatment of throat infection, penicillins had a consistently high estimated effectiveness rate over time (90.0% in 1991 vs. 90.6% in 2012); however, when prescribed to treat sinusitis, their estimated effectiveness rate decreased from 77.9% in 1991 to 65.5% in 2012, whilst in lower respiratory tract infections, there was a steep decrease in estimated effectiveness rate, from 71.1% in 1991 vs. 18.7% in 2012.

Trimethoprim/sulfonamides as initial treatments showed a substantial decrease in the estimated effectiveness rate between 1991 and 2012, dropping from 78% to 19.3% in throat infection, 84.3% to 44.1% in nasal infections, 85% to 51% in unspecified upper respiratory tract infections, and 77% to 24.2% in lower respiratory tract infection. However, when used as a secondary treatment, their estimated effectiveness rates from 1991 to 2012 decreased at a much lower rate, from 81.6% to 74.2% in throat infection, 80.7% to 75.9% in nasal infections, 81.4% to 78.5% in unspecified upper respiratory tract infection, and 79.8% to 64.5% in lower respiratory tract infection.

The estimated effectiveness rates for initial treatment with quinolones were stable for nasal infection (77.9% in 1991 and 71.8% in 2012) by comparison with other indications (dropping from 74.1% to 54.1% in throat infection, which is the lowest rate observed for any antibiotic class in any indication.)

Table 3. Estimated first- and second-line antibiotic treatment effectiveness rates in the first (1991) and last (2012) years of the study period by antibiotic class and by indication with rank order indicated in parentheses.

|                         | Antibiotic treatment effectiveness rates | 2012 | 2011 | 2012 | 2011 |
|-------------------------|-----------------------------------------|------|------|------|------|
|                         | First line                               | % (rank order) | % (rank order) | % (rank order) | % (rank order) |
| LRTI                    | Clarithromycin                           | 80.6 | 81.6 | 80.1 | 76.3 |
|                         | Aminopenicillins                         | 80.8 | 84.9 | 71.6 | 79.8 |
|                         | Macrolides                              | 79.9 | 83.2 | 79.8 | 80.7 |
|                         | Tetracyclines                            | 74.9 | 83.4 | 76.9 | 80.5 |
|                         | Cephalosporins                           | 67.4 | 78.7 | 68.5 | 78.6 |
|                         | Quinolones                              | 66.0 | 77.8 | 71.3 | 80.3 |
|                         | Trimethoprim/Sulfonamide                 | 24.2 | 77.0 | 64.5 | 79.8 |
|                         | Penicillins                              | 18.7 | 71.1 | 72.1 | 78.4 |
| Throat infections       | Clarithromycin                           | 87.6 | 88.9 | 85.3 | 80.8 |
|                         | Penicillins                              | 90.6 | 90.0 | 82.9 | 82.6 |
|                         | Macrolides                              | 87.7 | 87.2 | 84.5 | 85.1 |
|                         | Aminopenicillins                         | 84.2 | 86.6 | 84.4 | 84.3 |
|                         | Cephalosporins                           | 81.2 | 82.9 | 81.6 | 82.0 |
|                         | Tetracyclines                            | 69.3 | 82.5 | 84.3 | 84.5 |
|                         | Quinolones                              | 54.1 | 74.1 | 78.7 | 86.5 |
|                         | Trimethoprim/Sulfonamides                | 19.3 | 78.0 | 74.2 | 81.6 |
| Nasal infections        | Clarithromycin                           | 84.9 | 88.9 | 82.6 | 68.0 |
|                         | Tetracyclines                            | 86.7 | 88.3 | 83.9 | 82.9 |
|                         | Aminopenicillins                         | 86.6 | 88.0 | 80.9 | 82.7 |
|                         | Macrolides                              | 84.4 | 84.7 | 82.3 | 80.7 |
|                         | Cephalosporins                           | 76.1 | 80.4 | 77.7 | 82.2 |
|                         | Penicillins                              | 71.8 | 77.9 | 77.8 | 80.7 |
|                         | Quinolones                              | 65.5 | 77.3 | 82.9 | 85.7 |
|                         | Trimethoprim/Sulfonamides                | 44.1 | 84.3 | 70.4 | 79.1 |
| Unspecified URTI        | Clarithromycin                           | 86.7 | 77.3 | 82.8 | 83.6 |
|                         | Aminopenicillins                         | 88.7 | 88.8 | 80.2 | 84.4 |
|                         | Macrolides                              | 87.2 | 89.4 | 83.8 | 83.5 |
|                         | Tetracyclines                            | 82.4 | 87.7 | 84.5 | 86.3 |
|                         | Penicillins                              | 82.3 | 85.9 | 79.5 | 80.6 |
|                         | Cephalosporins                           | 75.7 | 83.5 | 75.5 | 82.6 |
|                         | Quinolones                              | 66.9 | 80.9 | 77.8 | 86.6 |
|                         | Trimethoprim/Sulfonamides                | 51.9 | 85.0 | 75.0 | 81.4 |

LRTI, lower respiratory tract infection; UTRI, upper respiratory tract infection.

Clarithromycin response rates are included in the class "Macrolides".
80.9% to 66.9% in unspecified upper respiratory tract infections, and 77.8% to 66.0% in lower respiratory tract infections. The estimated effectiveness rates for quinolones as a secondary monotherapy were higher than those observed when this class was used as an initial treatment. For secondary and initial treatment of throat infections, quinolones had a respective estimated effectiveness rate of 86.5% vs. 74.1% in 1991 and 78.7% vs. 54.1% in 2012; for nasal infections, 80.7% vs. 77.9% in 1991 and 77.8% vs. 71.3% in 2012; for unspecified upper respiratory tract infections, 86.6% vs. 80.9% in 1991 and 77.8% vs. 66.9% in 2012; and for lower respiratory tract infections, 80.3% vs. 71.3% in 1991 and 71.3% vs. 66% in 2012. For macrolides and aminopenicillins, estimated initial treatment effectiveness rates were stable and at or above 80% throughout. Aminopenicillins had an average estimated effectiveness rate of 85.5% in throat infection, 87% in nasal infection, 88.7% in unspecified upper respiratory tract infections, and 83.3% in lower respiratory tract infections. Macrolides had an average estimated effectiveness rate of 87.6% in throat infection, 84.5% in nasal infection, 87.3% in unspecified upper respiratory tract infection, and 72.3% in lower respiratory tract infection. For secondary treatment, there was a less prominent decrease in estimated effectiveness rates for all antibiotic classes. In 2012, macrolides were the only class with treatment estimated effectiveness rate above or equal to 80% for all selected infections.

Clarithromycin's estimated effectiveness rates as a secondary treatment for both lower and upper respiratory tract infections were relatively high and stable from 1998 onwards. In 2012, patients responded to clarithromycin in at least 80% of instances in all respiratory tract infections and as both initial and secondary treatment.

The initial and secondary estimated effectiveness rates of cephalosporins showed similar patterns across all infection classes. When used for throat infections, their estimated effectiveness rates were 82.9% and 82% in 1991 and 81.2% and 81.6% in 2012 for initial and secondary treatment, respectively. For nasal infections, initial and secondary treatment estimated effectiveness rates were 80.4% and 82.2% in 1991 and 76.1% and 77.7% in 2012, respectively. For unspecified upper respiratory tract infections, these were 83.5% and 82.6% in 1991 and 75.7% and 75.5% in 2012, respectively. However, when cephalosporins were used to treat lower respiratory tract infections there were lower estimated effectiveness rates of 78.7% and 78.6% in 1991 and 67.4% and 68.5% in 2012 for initial and secondary treatment, respectively.

Figure 1. Estimated first-line antibiotic treatment effectiveness rates over the study period 1991–2012 for different antibiotic classes in selected infections.
Initial treatment with tetracyclines had a decreasing estimated effectiveness rate over time, from 82.5% in 1991 to 69.3% in 2012 for throat infection, and 83.4% in 1991 to 74.9% in 2012 for lower respiratory tract infection. Secondary treatment with tetracyclines showed a constant estimated effectiveness rate over time: in 2012 their estimated effectiveness rates were 84.3% for throat infection, 83.9% for nasal infection, 84.5% for unspecified upper respiratory tract infection, and 76.9% for lower respiratory tract infection.

**Discussion**

To our knowledge, this is the first study using real-world data from UK primary care to describe how different antibiotic classes have been prescribed by GPs as initial and secondary treatments of respiratory tract infections. These data demonstrate that the antibiotic classes selected by GPs as initial (first-line antibiotic) treatments were generally consistent with prescribing guidelines. Most of the lower respiratory tract infections were not given more detailed diagnoses by the GPs, because there was no difference in choice of antibiotic in the subclasses.

Treatment failure rates, as we defined them, were comparable between indications: nearly 20% of the antibiotic therapies for lower respiratory tract infection and about 12% of those for lower respiratory tract infection required the prescription of a second, different antibiotic. Where a second course was needed, more than one in 10 of these were not effective and were followed by a further (i.e. third-line) course of antibiotic therapy.

As we reported in our earlier study of initial treatment failure in commonly prescribed antibiotics, drugs in the amoxicillin and macrolide classes showed a relatively stable estimated effectiveness rate from 1991 to 2012, and by 2012 these were the only classes that succeeded in more than three out of four therapies. Penicillins, trimethoprim/sulfonamides, and cephalosporins had the highest failure rate and showed the highest increase in failure rate over the study period. The failure rate of penicillins increased by more than 150% from 1991, and by 2012 less than two in 10 therapies were effective as initial treatments for lower respiratory tract infections.

For subsequent treatments, after an initial unsuccessful antibiotic course, estimated antibiotic effectiveness rates were
relatively stable for the most commonly prescribed classes and in those recommended as initial or secondary treatment, such as aminopenicillins and macrolides. However, effectiveness rates were lower for aminopenicillins than for macrolides and tetracyclines.

For throat infections, penicillins and macrolides were the only classes succeeding in more than 85% of initial prescriptions by the end of evaluation period. For subsequent prescriptions, tetracyclines, macrolides and aminopenicillins resulted in a need for fewer subsequent antibiotic courses. For nasal infections such as sinusitis and rhinitis, tetracyclines and aminopenicillins were the only two classes succeeding in more than 85% of initial treatments at the end of evaluation period. Regarding secondary antibiotics, tetracyclines, macrolides, aminopenicillins, and penicillins seem good alternatives, with an estimated effectiveness rate between 80% and 85%.

For unspecified upper respiratory tract infections, only aminopenicillins and macrolides responded in more than 85% of initial treatments at the end of the evaluation period. When used as secondary treatments, macrolides and tetracyclines appear to be the best classes, having comparable estimated effectiveness rates.

**Strengths and limitations of the study**

Many of the strengths and limitations of our analyses have largely been detailed previously. For the current analyses, we used a subset of the larger dataset created for our original study in order to concentrate on two common infection categories, comprising 7.4 million antibiotic prescriptions for 4.7 million patients.

Exposure to the selected antibiotic treatments was inferred from the prescribing records without evidence of actual intake (adherence). However, it seems reasonable to assume that patients took the initial treatment course before receiving a prescription for a subsequent antibiotic. Patients receiving a combination of antibiotics after an initial antibiotic were excluded. This is only recommended for cases of community acquired pneumonia; since a diagnosis of pneumonia was only associated with 1% of secondary treatments, this is unlikely to have influenced the overall results. We were not able to determine how many of the prescriptions were ‘delayed prescriptions’ since advice to delay taking antibiotics is not specifically coded.

We have no evidence of the etiology of the infections included in these analyses. Many of the antibiotics would have been prescribed for viral conditions and therefore would be unlikely to improve the natural course of the infection. Patients and clinicians may have assumed that this non-response was the result of antibiotic ineffectiveness, and patients might then, once again inappropriately, be prescribed a subsequent antibiotic. Also, many viral infections treated with antibiotics would have been short-lived, with rapid recovery mistakenly linked to the effectiveness of the prescribed antibiotic. Thus, our measure of presumed effectiveness (no further antibiotic prescriptions or hospital consultations or admissions for that illness episode) and, indeed, evidence of treatment non-response (identified, largely, through subsequent antibiotic prescriptions) may simply be a function of sub-optimal diagnosis. This may be particularly true of lower respiratory tract infections such as bronchitis.

**Implications of the study**

The recommendation to prescribe aminopenicillins, tetracyclines, and macrolides as initial treatments for lower respiratory tract infection was generally followed by the GPs, and the resulting treatment effectiveness rates according to our definitions suggest that this is good practice. The recommendations for second courses of an antibiotic, when the initial treatment did not, in all likelihood, resolve the symptoms (treatment non-response), are less clear. It is conceivable that these infections were harder to treat or that the patient had reduced defense mechanisms. However, based on our data, we found that the treatment effectiveness rates of secondary antibiotic courses with aminopenicillins, tetracyclines and macrolides were no lower than those of initial treatment courses, suggesting that the secondary antibiotic was an effective treatment.

For lower respiratory tract infections, the penicillins, trimethoprim/sulfonamides, quinolones, and cephalosporins had the lowest and most steeply decreasing estimated effectiveness rates as initial treatments over the study period. As secondary treatments their estimated effectiveness rates were also lower. These classes should probably be avoided as initial or secondary treatments unless there is good reason to prescribe them, such as established microbiological susceptibility, improvement of compliance, or issues of co-medication or comorbidity. These antibiotics might have been prescribed instead of the recommended initial agents because the clinicians thought the patient was more ill or had been exposed to the first-choice agent relatively recently. However, in the light of the poor effectiveness rates for these agents, this is not generally recommendable. In upper respiratory tract infections, aminopenicillins were the initial antibiotic of choice; in contrast to lower respiratory tract infections, more detailed diagnoses for sub-indications were more frequently recorded by GPs and these were reflected in the choice of antibiotic.

Penicillins were the treatment of choice for pharyngitis and tonsillitis, whilst tetracyclines were most frequently prescribed for sinusitis and rhinitis. Fewer of these infections required a second antibiotic course; many upper respiratory tract infections will have been viral and would have resolved spontaneously, but GPs also followed recommendations about which antibiotic class to prescribe. Our resulting treatment effectiveness rates suggest that the macrolide class is a good alternative, especially as secondary therapy. However, prospective observational cohort studies that include etiological diagnosis and measures of illness severity, adherence, and patient reported outcomes will be required to address this question less speculatively.

**Conclusions**

After more than two decades on the market, newer macrolides such as clarithromycin are still amongst the most
effective antibiotic classes for the treatment of lower and upper respiratory tract infection, both as an initial therapy and as a secondary therapy where the initial course was unsuccessful. At the end of the study period, clarithromycin had become the most prescribed compound within the macrolide class. Our analysis of antibiotic prescription habits suggests that, in the UK, primary care physicians generally prescribe antibiotics in accordance with guidelines and, where this is the case, that these treatments can be considered generally effective.

**Transparency**

**Declaration of funding**

The study was funded by Mylan Pharmaceuticals.

*Author contributions:* C.J.C., H.d.V. and M.O. developed the study protocol. Data extraction and analysis were carried out by E.B. and S.J.-J., supervised by C.J.C. C.C.B. advised on the study question, analysis plan, and interpretation of the study findings and contributed to drafting the final report. C.L.M. provided statistical expertise. Because of the conditions of the data license, co-authors from the funding body did not have access to the source data from the Clinical Practice Research Datalink, although they did have access to processed data. All other authors had full access to all of the study data (including statistical reports and tables). All authors contributed to, read, and approved the final manuscript, and all authors take responsibility for the integrity of the data and the accuracy of the data analysis. C.J.C. is guarantor.

**Declaration of financial/other relationships**

C.L.M. has disclosed that he is a contractor of Pharmatelligence, a research consultancy receiving funding from pharmaceutical companies (including Mylan and AstraZeneca). C.J.C. has disclosed that he is a director of Pharmatelligence, reports research grants from various health-related organizations, including Abbott, ALK, Astellas, AstraZeneca, Bristol-Myers Squibb, Diabetes UK, the Engineering and Physical Sciences Research Council, the EASD, Ferring, GSK, Jenson (Internis), Lilly, the Medical Research Council, Medtronic, MSD, the National Health Service, Norgine, Pfizer, Sanofi-Aventis, Shire and Wyeth, and consults for Amylin, Aryx, Astellas, Boehringer Ingelheim, Bristol-Myers Squibb, Diabetes UK, Eisai, Ferring, GSK, Ipsen, Lilly, Medtronic, MSD, Pfizer, Sanofi-Aventis, Takeda, and Wyeth. E.B. and S.J.-J. have disclosed that they are employees of Pharmatelligence. C.C.B. has disclosed that he has received a research grant in kind from Alere in support of a publically funded study of COPD and has received honoraria from Alere and the Alliance for the Prudent Use of Antibiotics for presentations on point-of-care testing and diagnostics in primary care. H.d.V. has disclosed that she is an employee of Mylan. M.O. has disclosed that he is a former employee of Mylan, currently an employee of AstraZeneca.

CMRO peer reviewer 1 has disclosed that he is a consultant to Teva and Pliva Zagreb; and is on the speakers’ bureau of Astellas. CMRO peer reviewer 2 has no relevant financial or other relationships to disclose.

**Acknowledgments**

We thank Monica S. Rocha of Mylan EPD for her help with the figures and in critically reviewing the manuscript and Dr. Chris Poole for developing the Read code lists.

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