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Long-term oral antibiotic use in people with acne vulgaris in UK primary care: a drug utilization study

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Abstract

Background The inappropriate use of antibiotics is understood to contribute to antimicrobial resistance. Oral antibiotics are regularly used to treat moderate-to-severe acne vulgaris. In practice, we do not know the typical length of oral antibiotic treatment courses for acne in routine primary care and what proportion of people receive more than one course of treatment following a new acne diagnosis.

Objectives To describe how oral antibiotics are prescribed for acne over time in UK primary care.

Methods We conducted a descriptive longitudinal drug utilization study using routinely collected primary care data from the Clinical Practice Research Datalink GOLD (2004–2019). We included individuals (8–50 years) with a new acne diagnosis recorded between 1 January 2004 and 31 July 2019.

Results We identified 217 410 people with a new acne diagnosis. The median age was 17 years [interquartile range (IQR) 15–25] and median follow-up was 4.3 years (IQR 1.9–7.6). Among people with a new acne diagnosis, 96 703 (44.5%) received 248 560 prescriptions for long-term oral antibiotics during a median follow-up of 5.3 years (IQR 2.8–8.5). The median number of continuous courses of antibiotic therapy ($\geq$ 28 days) per person was four (IQR 2–6). The majority (n = 59 010, 61.0%) of first oral antibiotic prescriptions in those with a recorded acne diagnosis were between the ages of 12 and 18. Most (n = 71 544, 74.0%) first courses for oral antibiotics were for between 28 and 90 days. The median duration of the first course of treatment was 56 days (IQR 50–93 days) and 18 127 (18.7%) of prescriptions of $\geq$ 28 days were for < 6 weeks. Among people who received a first course of oral antibiotic for $\geq$ 28 days, 56 261 (58.2%) received a second course after a treatment gap of $\geq$ 28 days. The median time between first and second courses was 135 days (IQR 67–302). The cumulative duration of exposure to oral antibiotics during follow-up was 255 days (8.5 months).

Conclusions Further work is needed to understand the consequences of using antibiotics for shorter periods than recommended. Suboptimal treatment duration may result in reduced clinical effectiveness or repeated exposures, potentially contributing to antimicrobial resistance.

What is already known about this topic?

- Long-term oral antibiotics are frequently used to treat acne.
- Antimicrobial resistance is one of the leading causes of death worldwide and the prolonged use of antibiotics in the treatment of skin conditions may contribute to this burden.

What does this study add?

- In total, 66% of people who receive an oral antibiotic course for acne subsequently receive a further course.
- Although acne guidelines recommend antibiotic therapy for $\geq$ 3 months, most receive a median of 56 days per course with a median gap between first and second courses of 135 days.
- People with acne receive a median of four oral antibiotic courses over a follow-up of 5.3 years (with a median cumulative duration of 255 days).

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Topical and oral antibiotics are commonly prescribed for the treatment of acne vulgaris, a chronic skin disorder with onset predominantly in adolescence. Prevalence studies show that the majority (80–100%) of adolescents experience acne and that 20% are moderately to severely affected.[1] The high prevalence of acne means that antibiotics are often prescribed in the adolescent population, for variable durations ranging from 6 weeks to many months and, in some cases, years.[2,3] Although acne guidelines vary, most recommend antibiotics are continued for ≥3–4 months with some mentioning treatment effectiveness begins, or can be assessed at, 6 weeks.[4–9] Guidelines also state that each 3- to 4-month course can be repeated if acne recurs. Tetracyclines and macrolides are the two most commonly prescribed oral antibiotic classes for acne with varying average use durations depending on treatment setting. Trimethoprim is often prescribed as a second-line antibiotic for acne.[3,10]

Overuse of oral antibiotics is known to cause antimicrobial resistance (AMR) as repeated and sustained antibiotic exposure allows microbes to develop mechanisms to avoid them.[11] The use of oral antibiotics for acne may also lead to antibiotic resistance of flora at other body sites.[11] AMR is one of the leading causes of death worldwide with almost five million deaths associated with bacterial AMR.[12] Without interventions, future infection-related deaths because of AMR are estimated at 10 million per year, and by 2050, the cost of AMR could reach 100 trillion US dollars.[13] We do not know how long-term oral antibiotics for acne have an impact on bacterial flora elsewhere in the body, and affect AMR.

The effectiveness of antimicrobial stewardship – a framework to ensure judicious use of antibiotics – has been demonstrated for infections such as urinary tract or respiratory tract infections in care homes, but not for acne and the younger population predominantly affected.[14] To ensure the successful implementation of an antimicrobial stewardship framework in acne treatment, we first need to understand how antibiotics are used for acne. We currently do not know how antibiotics for acne are prescribed in the UK beyond 1 year, the duration of treatment courses, and if individuals are prescribed multiple courses of antibiotic therapy over time. In the context of AMR, it is important to understand how those with moderate-to-severe acne are prescribed antibiotics over time as acne guidelines recommend further oral antibiotics if acne relapses. Without evidence regarding current antibiotic prescribing in acne, there will be little impetus to change practice.[15,16] The overall aim of this study is therefore to describe how people with acne are managed with oral antibiotics in UK primary care over the course of their disease, specifically duration of oral antibiotic courses and how often multiple courses of oral antibiotics are required.

Patients and methods

Study design and setting

We undertook a descriptive study using routinely collected UK primary care health record data from between 1 January 2004 and 31 July 2019. We described the use of tetracyclines, macrolides and trimethoprim for acne, including the total number of courses (of ≥28 days) prescribed during follow-up, the duration of the first two courses of antibiotic therapy and the specific classes of antibiotics prescribed (see Appendix S1 in the Supporting Information for a definition of terms).

Data source

The UK Clinical Practice Research Datalink (CPRD) GOLD is a database of primary care electronic health record data from over 600 GP practices and is broadly representative of the UK population in terms of age, sex and ethnicity.[17] The CPRD holds information on diagnoses, prescriptions and demographics for approximately 7% of the UK population.[18]

Study population

We included people aged 8–50 years, who were registered with primary care practices contributing to the CPRD that met CPRD quality control standards. Individuals were eligible for inclusion if they had ≥1 year of GP registration prior to their first record of an acne morbidity code (to ensure that we included people with newly diagnosed acne and robustly captured their baseline health status). We identified people with ≥1 record of an acne diagnostic code between 1 January 2004 and 31 July 2019 and no acne morbidity code or prescription for acne medication (contained in the acne British National Formulary chapter and excluding oral antibiotics) for acne in the 365 days before their first acne record to capture newly diagnosed acne more reliably. Follow-up started at the first recorded acne diagnosis on or after 1 January 2004 and ended at the earliest of the following: death; end of registration with the practice; the last date that data were collected from the practice; or the study end date (31 July 2019).

Study measures

Acne was defined based on a record of one acne diagnostic morbidity code in primary care. We excluded morbidity codes for rare forms of acne such as chloracne or tropical acne from our list of morbidity codes used to identify acne to exclude acne caused by a clear trigger and therefore unlikely to recur.

Acne-related antibiotic exposure was identified using primary care prescribing records recorded on, or after, the date of the first acne diagnostic record. Antibiotic exposure was defined using prescriptions for oral antibiotic classes commonly prescribed in primary care for acne: tetracyclines, macrolides and trimethoprim. All code lists are available on datacompass.lshtm.ac.uk. Antibiotic courses with a duration of ≥28 days were considered as long term and antibiotics prescribed for acne (Appendix S1). We defined long-term courses of antibiotic therapy as (i) a single prescription of ≥28 days; or (ii) ≥2 consecutive antibiotic prescriptions of any duration with a gap of ≤28 days between the end of one prescription and the start of the next totalling 28 days or longer. Antibiotics for a duration of <28 days we considered short term. We considered individuals to be on a continuous course of antibiotic therapy during any gaps in prescribing of ≤28 days (Figure 1a–c). Upon creating continuous courses from individual prescriptions, we assumed antibiotics with durations of <28 days were unlikely to be for acne.[19]

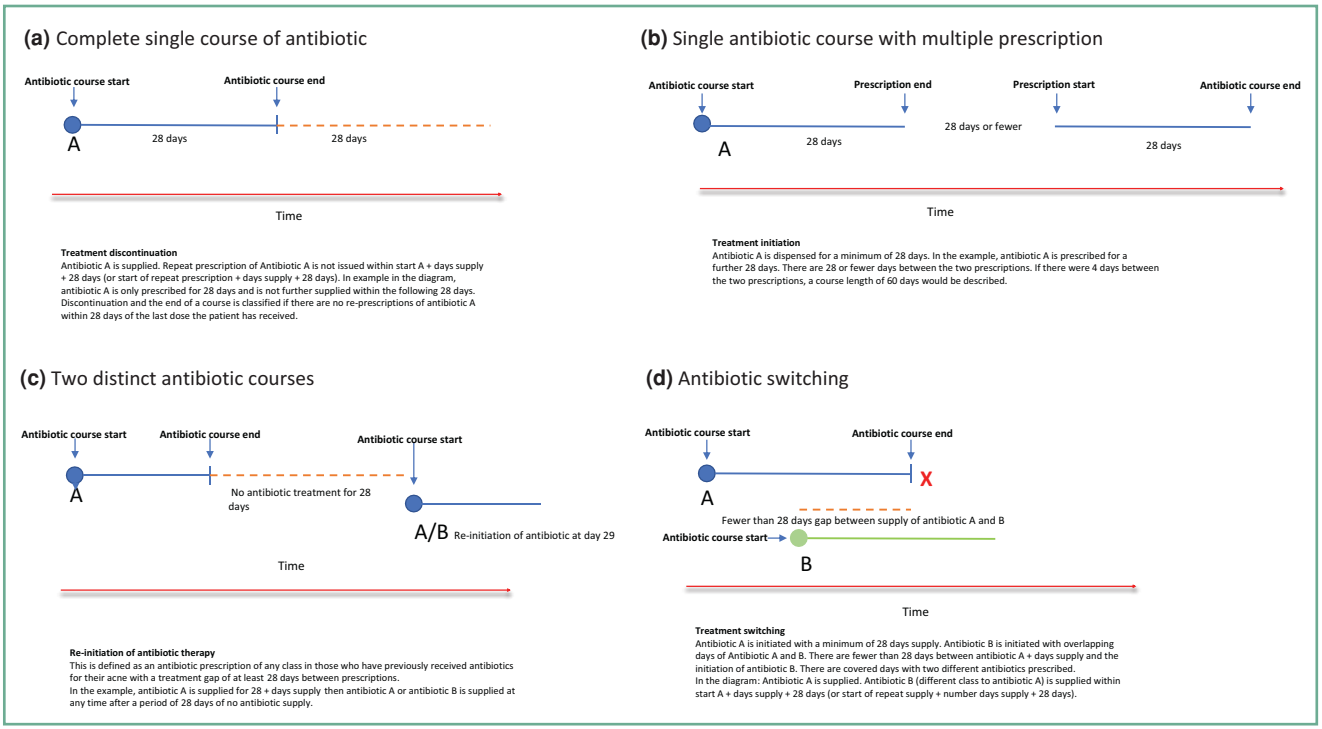

Figure 1 (a) Complete single course of antibiotic. Treatment discontinuation: Antibiotic A is supplied. Repeat prescription of Antibiotic A is not issued within start A + days supply + 28 days (or start of repeat prescription + days supply + 28 days). In (a), antibiotic A is only prescribed for 28 days and is not further supplied within the following 28 days. Discontinuation and the end of a course is classified if there are no re-prescriptions of antibiotic A within 28 days of the last dose the patient has received. (b) Single antibiotic course with multiple prescription. Treatment initiation: Antibiotic A is dispensed for a minimum of 28 days. In (b), antibiotic A is prescribed for a further 28 days. There are ≤ 28 days between the two prescriptions. If there were 4 days between the two prescriptions, a course length of 60 days would be described. (c) Two distinct antibiotic courses. Re-initiation of antibiotic therapy: this is defined as an antibiotic prescription of any class in those who have previously received antibiotics for their acne with a treatment gap of ≥ 28 days between prescriptions. In (c), Antibiotic A is supplied for 28 + days supply then antibiotic A or antibiotic B is supplied at any time after a period of 28 days of no antibiotic supply. (d) Antibiotic switching. Treatment switching: Antibiotic A is initiated with a minimum of 28 days supply. Antibiotic B is initiated with overlapping days of Antibiotic A and B. There are < 28 days between antibiotic A + days supply and the initiation of antibiotic B. There are covered days with two different antibiotics prescribed. In (d), Antibiotic A is supplied. Antibiotic B (different class to antibiotic A) is supplied within start A + days supply + 28 days (or start of repeat supply + number of days supply + 28 days).

We assumed a course of antibiotic therapy started on the day it was prescribed. We chose 28 days between prescriptions to allow sufficient time for people to request a repeat prescription and collect their antibiotics from pharmacies.[20] If there was a new class of antibiotic prescribed < 28 days from the end date of a previously prescribed antibiotic, we ended the prescription of the first antibiotic class as intended on the prescription. Antibiotic class switches were classified if prescriptions for two different classes of antibiotic had overlapping covered days (days where there were two antibiotics prescribed), or a new antibiotic class was prescribed within 28 days of the last covered day of the first antibiotic prescription (Figure 1d). We described time in person-years on any of the three classes of antibiotic overall.

To reflect early adolescent, adolescent, early adult and adult acne, we categorized age as: 8–11, 12–18, 19–25, 26–35 and 36–50 years. To reflect changes in recording practices and acne prescribing guidelines, we divided calendar time into the following periods: 2004–2008, 2009–2013 and 2014–2019.[4,5,8] We divided prescription duration into the following categories: 28–41 days (category chosen to reflect that effectiveness of antibiotics may be assessed at week six[4,7,9,21]), 42–90 days, 91–180 days, 181–365 days and > 365 days. Based on a UK census, we categorized ethnicity in five categories: White, South Asian, Black, mixed/other, and missing or unknown.[17] We defined deprivation using individual-level quintiles of the Index of Multiple Deprivation and, where individual-level data were not available, at practice level.[22]

Statistical analysis

Study population characteristics

We described characteristics (median follow-up, age, sex, calendar period at first acne diagnosis, deprivation and ethnicity) of the overall study population including everyone with their first acne diagnosis recorded between 1 January 2004 to 31 July 2019. We then described the same characteristics for subgroups of people with acne based on whether or not they received antibiotics: (i) those who received no oral antibiotics; (ii) those who received a short course of oral antibiotics (of durations < 28 days); and (iii) those who received ≥ 28 days of an oral antibiotic in a single course.

Overall prescription patterns

We described median follow-up and median duration of all antibiotic courses (short and long term) during follow-up. We described the median number of courses (Appendix S1)

of oral antibiotic with durations of ≥28 days per individual during follow-up.

First prescription of long-term antibiotic after acne diagnosis and time spent on antibiotic

Of those with acne who had ≥1 long-term antibiotic prescription (i.e. who received ≥28 days of an oral antibiotic), we described the characteristics (sex, age, calendar period of prescription, deprivation and ethnicity) of individuals when they had their first antibiotic prescription of ≥28 days (Appendix S1). We described characteristics overall for those with first prescriptions for any of the three antibiotic classes, and subsequently stratified by specific antibiotic class (tetracycline, macrolide, trimethoprim). We also described first prescriptions for each of the three classes by sex and age category. In addition, we described the median time between acne diagnosis and first acne prescription. We calculated person-time spent on antibiotics as percentages of total person-time in specific strata of sex, age category during the time recipients were prescribed the antibiotic, calendar period when they were prescribed the antibiotic, deprivation and ethnicity.

Prescription duration

Long-term prescriptions (of ≥28 days) and missing data

We described the median duration of all long-term antibiotic courses and the missing data associated with prescription duration. The median duration of all oral antibiotic prescriptions in people who received ≥28 days of oral antibiotic was entered for any prescriptions with a missing duration. We described antibiotic class switches (Figure 1d) and the median gap between all courses by looking at the time between the last covered day of a course and the start date of a new course. We also calculated median cumulative duration spent on any of the three antibiotic classes of interest per person during follow-up.

First prescription (of ≥ 28 days)

We described the first antibiotic course length after an acne morbidity code, divided into categories of duration by antibiotic class as well as the median duration of the first course of antibiotic of ≥28 days.

Second antibiotic prescription for ≥ 28 days

We calculated the proportions of those receiving a first antibiotic of ≥28 days who subsequently received a second antibiotic with a treatment gap of ≥28 days between prescriptions. We also described the class of the second antibiotic received relative to the first by cross-tabulating class of the first antibiotic against class of the second antibiotic. In addition, we also looked at the duration of the second course and the median gap between the first and second course.

Sensitivity analysis

In our main analysis, we defined continuous courses of antibiotic therapy allowing a gap of ≤28 days between consecutive prescriptions and in our sensitivity analysis we reduced this to 14 days to allow for the possibility that less time would be needed for individuals to request a repeat prescription and have their medication dispensed.

Patient involvement

A focus group of eight patient or carer representatives helped guide the interpretation of our findings. The focus group were recruited through an open advertisement on www.peopleinresearch.org.

Ethics

The study protocol was approved by CPRD's Independent Scientific Advisory Committee (Protocol number: 19_168) and the London School of Hygiene and Tropical Medicine's Ethics Committee (Reference number: 17 864).

Results

Study population characteristics

We identified 217 410 people with a first diagnosis of acne between 1 January 2004 and 31 July 2019 who were eligible for inclusion (Figure 2). Median follow-up for all participants was 4.3 years [interquartile range (IQR) 1.9–7.6 years] and the median age was 17 years (IQR 15–25).

The overall study population included more females ($n=142\ 789$, 65.7%) than males ($n=74\ 621$, 34.3%) (Table 1). Of the total study population, 96 703 (44.5%) had a prescription for one of the oral antibiotics included in the study (tetracycline, macrolide or trimethoprim) for a minimum duration of 28 days on or after the date of their first acne diagnostic code. For those receiving an oral tetracycline, macrolide or trimethoprim antibiotic for ≥28 days, median duration of follow-up was 5.3 years (IQR 2.8–8.5) compared with 5.8 years (IQR 3.3–9.0) for those treated with an antibiotic for <28 days and 2.6 years (IQR 1.1–5.3) for those individuals who received no antibiotic prescriptions during follow-up. More females ($n=57\ 229$, 59.2%) with an acne code were prescribed an antibiotic associated with acne for ≥28 days than males (39 474 40.8%). Ethnicity data were missing or unknown for 60.7% ($n=58\ 712$) of those in the long-term use group.

Overall prescription patterns

During the median follow of up 5.3 years (IQR 2.8–8.5), participants had a median of four individual courses of long-term antibiotic (IQR 2–6); 13 452 of 96 703 people (13.9%) were prescribed ≥5 courses, and 1715 (1.8%) people were prescribed ≥10 or more courses (Figure 3). The median duration of long-term antibiotic courses was 56 days (IQR 47–88) (Table 2). The median follow-up of people with ≥10 long-term courses was 10 years (IQR 7.6–12.3) and the median follow-up for people with ≤9 long-term courses was 5.2 years (IQR 2.7–8.4).

First prescription of long-term oral antibiotic after acne diagnosis and time spent on antibiotics

Of 96 703 individuals prescribed a long-term oral antibiotic (regardless of antibiotic class), $n=59\ 010$ (61.0%) were initiated between the ages of 12 and 18 years (Table 3). More females than males were prescribed oral antibiotics than

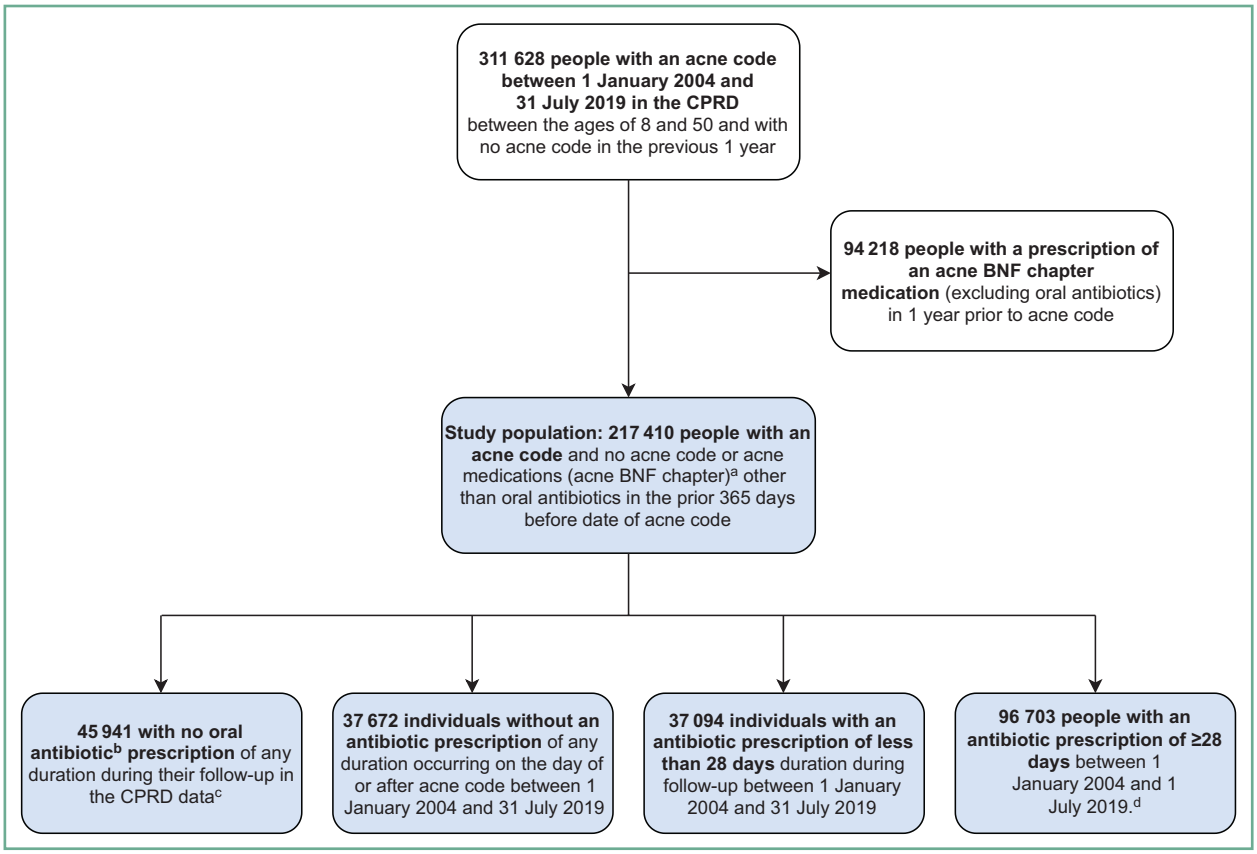

Figure 2 Identification of study participants. Only data from practices that met quality control standards were included and only individuals who had been registered at the practice for 1 year prior to study entry were included. BNF, British National Formulary; CPRD, Clinical Practice Research Datalink. [a]Acne medication found in the acne BNF chapter. [b]Antibiotic typically prescribed for acne (tetracycline, macrolide or trimethoprim). [c]Not restricted to follow-up period of study 1 January 2004 to 31 July 2019. [d]Continuous courses have been constructed if duration between subsequent prescriptions of the same antibiotic class is < 28 days.

males throughout all age categories; however, proportions were similar between the ages of 12 and 18 [for example $n = 2021$ (83.6%) of females between 8 and 11 years and $n = 23\,192$ (46.2%) of females between 12 and 18 years were prescribed a tetracycline, Table S1; see Supporting Information].

A smaller proportion ($n = 21\,075/96\,703$, 21.8%) of first prescriptions of long-term antibiotic were issued between 2014 and 2019 compared with 2004 and 2008 ($n = 37\,719$, 39.0%) and 2009–2013 ($n = 37\,909$, 39.2%).

The median gap between acne diagnosis and first antibiotic prescription was 170 days (IQR 28–566). Most people ($n = 83\,393$, 84.6%) who were treated with a long-term antibiotic received a tetracycline as their first-line antibiotic.

Of the total population with an acne code (217 410 individuals with 1 102 202 person-years of follow-up), 19.4% (213 721 person-years) of time was spent on long-term oral antibiotic treatment during follow-up (prescriptions lasting ≥ 28 days) (Table 4). The greatest proportion of total follow-up spent on long-term oral antibiotics was in those aged 8–11 years (2509/5708 person-years, 44.0%) followed by 12–18 years (101 332/356 339 person-years, 28.4%).

The proportion of time spent on an oral antibiotic for acne varied with calendar period: (i) 2004–2008, 31.1% of study population follow-up (54 525 person-years on antibiotic/175 526 person-years); (ii) 2009–2013, 22.5% of study population follow-up (102 544 person-years on antibiotic/456 566 person-years); and (iii) 2014–2019 12.1% of study population follow-up (56 651 person-years on antibiotic/470 110 person-years).

Prescription duration

Long-term prescriptions (of ≥ 28 days) and missing data

The median duration of all oral antibiotic prescriptions in people who received a long-term antibiotic ($n = 248\,560$ total number of prescriptions for 96 703 people) was 56 days (IQR 47–88); for 1.9% of prescriptions (4816 prescriptions for 4428 people) the antibiotic duration was missing, and median duration of 56 days was entered. Overall, 4494 (4.6%) people switched antibiotic class during a course of treatment, that is, they had received two prescriptions for different classes of antibiotic (with antibiotic covered days overlapping or, < 28 days between them) (Figure 1d). The median gap between all courses was 119 days (IQR 64–260 days). The median cumulative duration spent on antibiotics per person during follow-up was 255 days (IQR 130–455).

Table 1 Characteristics of the study population

Characteristic	Overall study population: people with an acne diagnosis ($n=217\,410$)[a]	No antibiotics prescribed during follow-up[b] ($n=83\,613$)	Any acne antibiotic with a duration of <28 days during follow-up (short duration) ($n=37\,094$)[b,c]	Antibiotic given for a minimum duration of 28 days at any time on the day of or after first acne (long duration) ($n=96\,703$)[b,d]
Follow-up in years, median (IQR)	4.3 (1.9–7.6)	2.6 (1.1–5.3)	5.8 (3.3–9.0)	5.3 (2.8–8 .5)
Sex				
Female	142 789 (65.7)	55 167 (66.0)	30 393 (81.9)	57 229 (59.2)
Male	74 621 (34.3)	28 446 (34.0)	6701 (18.1)	39 474 (40.8)
Age at acne diagnosis, years				
8–11	7082 (3.3)	2861 (3.4)	843 (2.3)	3378 (3.5)
12–18	120 094 (55.2)	44 464 (53.2)	16 620 (44.8)	59 010 (61.0)
19–25	39 269 (18.1)	15 966 (19.1)	7797 (21.0)	15 506 (16.0)
26–35	34 383 (15.8)	14 121 (16.9)	7744 (20.9)	12 518 (12.9)
36–50	16 582 (7.6)	6201 (7.4)	4090 (11.0)	6291 (6.5)
Calendar period at acne diagnosis				
2004–2008	78 469 (36.1)	24 345 (29.1)	16 405 (44.2)	37 719 (39.0)
2009–2013	83 888 (38.6)	31 396(37.6)	14 583 (39.3)	37 909 (39.2)
2014–2019[e]	55 053 (25.3)	27 782 (33.2)	6106 (16.5)	21 075 (21.8)
Quintiles of IMD				
1 (least deprived)	48 282 (22.2)	18 046 (21.6)	7387 (19.9)	22 861 (23.6)
2	36 837 (16.9)	14 013 (16.8)	5904 (15.9)	16 922 (17.5)
3	41 815 (19.2)	16 227 (19.4)	7168 (19.3)	18 419 (19.0)
4	41 004 (18.9)	15 888 (19.0)	7317 (19.7)	17 794 (18.4)
5 (most deprived)	49 472 (22.8)	19 445 (23.3)	9318 (25.1)	20 707 (21.4)
Ethnicity				
White	77 085 (35.5)	29 565 (35.4)	14 105 (38.0)	33 415 (34.6)
South Asian	6509 (3.0)	3173 (3.8)	954 (2.6)	2382 (2.5)
Black	3150 (1.4)	1674 (2.0)	402 (1.1)	1074 (1.1)
Other/mixed	3105 (1.4)	1586 (1.9)	399 (1.1)	1120 (1.2)
Missing	127 561 (58.7)	47 615 (57.0)	21 234 (57.2)	58 712 (60.7)

Data are *n* (%) unless otherwise specified. IMD, Index of Multiple Deprivation; IQR, interquartile range; long duration, ≥28 days; short duration, <28 days. [a]Between 1 January 2004 and 31 July 2019, between the ages of 8 and 50 years, having not had an acne-related medication other than oral antibiotics in the previous 365 days prior to acne code. [b]Between 1 January 2004 and 31 July 2019. [c]Antibiotic prescription with durations of <28 days with prescription dates on the day of the acne code or after. Total course of therapy <28 days despite formation of continuous courses. [d]Antibiotic prescription for a minimum duration of 28 days prescribed with acne diagnostic code preceding or on the same day as the prescription. [e]To 31 July 2019.

First prescription of long-term antibiotic

Most people, ($n=71\,544$, 74.0%) treated with a long-term antibiotic after acne diagnosis received their first course of antibiotic with a duration lasting between 28 and 90 days with a treatment gap of ≥28 days from course completion before receiving a further antibiotic prescription and 18 127 (18.7%) received their first antibiotic prescription for <6 weeks (Table 2).[4,5] The median duration of first antibiotic prescriptions after an acne diagnosis was 56 days (IQR 50–93).

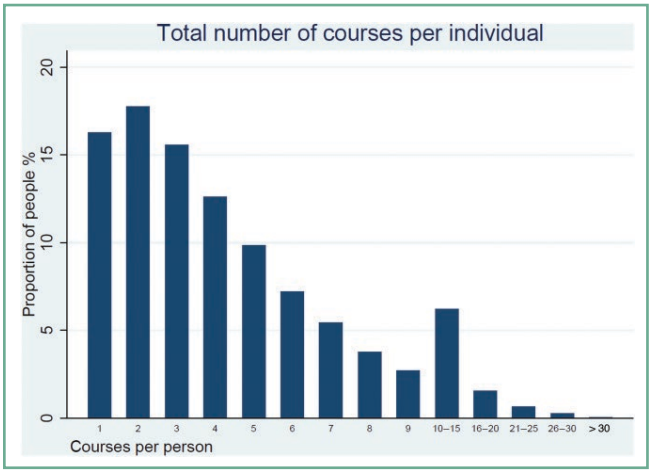

Figure 3 Total number of courses per individual (proportion of people, $n=96\,703$). Median number of courses per person is five (interquartile range 2–6).

Second long-term antibiotic prescription

Overall, 58.2% ($n=56\,261/96\,703$) of people who received a first course of antibiotic received a second course of antibiotic, with a gap of ≥28 days between consecutive courses of therapy (Table 5). Of those who received a first course of long-term antibiotic, 31–59% received a second course of antibiotic depending on first-line antibiotic class: tetracycline 58.6% ($n=47\,920$), macrolide 59.2% ($n=7796$); and trimethoprim 31.1% ($n=545$).

Most individuals who initiated tetracycline antibiotics who received a second course were subsequently treated with tetracyclines ($n=41\,211$, 86.0%); of those who were first treated with a macrolide, $n=3984$ (51.1%) subsequently received a tetracycline and $n=3672$ (47.1%) received a macrolide as their second course (Table 5). Of those who were first treated with trimethoprim, most were subsequently treated with either a tetracycline ($n=243$, 44.6%) or further trimethoprim ($n=242$, 44.4%).

Of the 56 261 people who received a second antibiotic, $n=11\,953$ (21.2%) were prescribed for <6 weeks and $n=31\,463$ (55.9%) were prescribed for between 6 weeks

Table 2 Number of people ($n=96\,703$) and duration (treatment course length) category of first oral antibiotic exposure on the day of or after acne code, second antibiotic exposure ($n=56\,261$) and all antibiotic exposures ($n=248\,560$)[a]

Antibiotic	People with prescription exposure length 28–41 days, *n* (%)	People with prescription exposure length 42–90 days, *n* (%)	People with prescription exposure length 91–180 days, *n* (%)	People with prescription exposure length 181–365 days, *n* (%)	People prescription exposure with length > 365 days, *n* (%)
First course					
All antibiotics ($n=96\,703$)	18 127 (18.7)	53 417 (55.2)	18 170 (18.8)	5658 (5.9)	1331 (1.4)
Tetracycline ($n=83\,393$)	14 162 (17.0)	46 538 (55.8)	16 362 (19.6)	5155 (6.2)	1176 (1.4)
Macrolide ($n=12\,075$)	3654 (30.3)	6164 (51.1)	1677 (13.9)	461 (3.8)	119 (1.0)
Trimethoprim ($n=1235$)	311 (25.2)	715 (57.9)	131 (10.6)	42 (3.4)	36 (2.9)
Second course					
All antibiotics ($n=56\,261$)	11 953 (21.2)	31 463 (55.9)	9653 (17.2)	2531 (4.5)	659 (1.2)
Tetracycline ($n=47\,920$)	10 024 (20.9)	27 195 (56.8)	8207 (17.1)	2021 (4.2)	471 (1.0)
Macrolide ($n=7796$)	1811 (23.2)	3970 (50.9)	1371 (17.6)	476 (6.1)	168 (2.2)
Trimethoprim ($n=545$)	118 (21.7)	298 (54.7)	75 (13.8)	34 (6.2)	20 (3.7)
All courses					
All antibiotics[b] ($n=248\,560$)	53 804 (21.6)	137 076 (55.1)	42 826 (17.2)	11 943 (4.8)	2911 (1.2)
Tetracyclines ($n=204\,893$)	39 850 (19.4)	115 044 (56.1)	37 000 (18.1)	10 507 (5.1)	2492 (1.2)
Macrolides ($n=38\,459$)	12 489 (32.5)	19 248 (50.0)	5151 (13.4)	1242 (3.2)	329 (0.9)
Trimethoprim ($n=5208$)	1465 (28.1)	2784 (53.5)	675 (13.0)	194 (3.7)	90 (1.7)

Data are *n* (row%). [a]Treatment gap of ≥28 days between courses. Median duration of first course 56 days [interquartile range (IQR 50–93)], median duration of second course 56 days (IQR 50–93 days) and median duration all courses 56 days (IQR 47–88). Continuous courses from individual prescriptions were formed if an antibiotic within the same class was prescribed within 28 days of the start date of the current prescription unless the antibiotic class was changed – in this case two individual courses are described. [b]All antibiotic courses during follow-up.

and 3 months (Table 2). The median duration of second courses was 56 days (IQR 50–93 days). The median gap between the first and second course was 135 days (IQR 67–302 days).

Sensitivity analysis

A sensitivity analysis (Tables S2–S4; see Supporting Information) altering the gap allowed between prescriptions to define continuous courses of therapy from 28 days to

Table 3 Characteristics of individuals ($n=96\,703$) prescribed an oral antibiotic (overall and by antibiotic class) for ≥28 days between 1 January 2004 and 31 July 2019 (first prescription)

Characteristic	All antibiotics ($n=96\,703$, 100%)	Antibiotic class		
		Tetracycline ($N=83\,393$, 86.2%)	Macrolide ($N=12\,075$, 12.5%)	Trimethoprim ($N=1235$, 1.3%)
Sex				
Female	57 229 (59.2)	48 338 (58.0)	7861 (65.1)	1030 (83.4)
Male	39 474 (40.8)	35 055 (42.0)	4214 (34.9)	205 (16.6)
Age at diagnosis, years				
8–11	3378 (3.5)	2325 (2.8)	995 (8.2)	58 (4.7)
12–18	59 010 (61.0)	51 565 (61.8)	6930 (57.4)	515 (41.7)
19–25	15 506 (16.0)	13 550 (16.2)	1695 (14.0)	261 (21.1)
26–35	12 518 (12.9)	10 585 (12.7)	1697 (14.1)	236 (19.1)
36–50	6291 (6.5)	5368 (6.4)	758 (6.3)	165 (13.4)
Calendar period[a]				
2004–2008	37 719 (39.0)	31 336 (37.6)	5807 (48.1)	576 (46.6)
2009–2013	37 909 (39.2)	32 955 (39.5)	4459 (36.9)	495 (40.1)
2014–2019	21 075 (21.8)	19 102 (22.9)	2809 (23.3)	164 (13.3)
Quintiles of IMD				
1 (least deprived)	22 861 (23.6)	19 980 (24.0)	2593 (21.5)	288 (23.3)
2	16 922 (17.5)	14 754 (17.7)	1960 (16.2)	207 (16.8)
3	18 419 (19.0)	15 735 (18.9)	2394 (19.8)	290 (23.5)
4	17 794 (18.4)	15 127(18.1)	2465 (20.4)	201 (16.3)
5 (most deprived)	20 707 (21.4)	17 794 (21.3)	2663 (22.1)	249 (20.2)
Ethnicity				
White	33 415 (34.6)	28 800 (34.5)	4081 (33.8)	534 (43.2)
South Asian	2382 (2.5)	2111 (2.5)	256 (2.1)	15 (1.2)
Black	1074 (1.1)	940 (1.1)	124 (1.0)	10 (0.8)
Mixed/Other	1120 (1.2)	1006 (1.2)	101 (0.8)	13 (1.1)
Missing	58 712 (60.7)	50 536 (60.6)	7513 (62.2)	663 (53.7)

Data are *n* (%). IMD, Index of Multiple Deprivation. [a]Calendar period during which antibiotic prescribed.

Table 4 Population characteristics and time spent on oral antibiotics throughout follow-up[a]

Characteristic	Denominator ($n=217\,410$ people with acne code)	People with ≥28 days of oral antibiotic ($n=96\,703$)
All, total person-years	1 102 202	213 721 (19.4)
Sex		
Female	708 283	141 050 (19.9)
Male	393 919	72 671 (18.4)
Age band,[b] years		
8–1 1	5708	2509 (44.0)
12–18	356 339	101 332 (28.4)
19–25	354 488	52 038 (14.7)
26–35	230 272	33 881 (14.7)
36–50	155 396	23 961 (15.4)
Calendar period[c]		
2004–2008	175 526	54 525 (31.1)
2009–2013	456 566	102 544 (22.5)
2014–2019	470 110	56 651 (12.1)
Quintiles of IMD		
1 (most deprived)	241 285	49 632 (20.6)
2	179 364	36 049 (20.1)
3	208 237	40 109 (19.3)
4	212 805	40 228 (18.9)
5 (least deprived)	260 511	47 704 (18.3)
Ethnicity		
White	378 553	74 596 (19.7)
South Asian	26 937	4709 (17.5)
Black	12 514	1848(14.8)
Other or mixed	12 041	1993 (16.6)
Missing	672 156	130 574 (19.4)

IMD, Index of Multiple Deprivation. [a]Data are person-years (% of total person-time in specific strata). Denominators calculated from study population ($n=217\,410$). [b]Age band of recipient when antibiotic prescribed. [c]Calendar period during which antibiotic prescribed.

14 days when constructing consecutive courses is reported in Appendix S2 (see Supporting Information).

Discussion

This descriptive study has highlighted that over 40% of people diagnosed with acne are prescribed an oral antibiotic for ≥28 days over a median follow-up of 4.3 years for the overall study population following acne diagnosis, and that almost 60% of people subsequently have a repeat course of long-term antibiotic with a median gap between the first and second course of 4.5 months. Our findings showed most people with acne who are treated with antibiotics receive a first antibiotic prescription of between 28 and 90 days of duration with a median duration of 56 days and almost 20% receive <6 weeks of oral antibiotics without a further prescription within 28 days of course completion. The median number of courses of long-term antibiotic was four (IQR 2–6) and 13.9% of people receiving long-term antibiotics had ≥5 courses during follow-up. The median cumulative duration spent on antibiotics per person during a median 5.3 years of follow-up was 255 days, or 8.5 months for those prescribed an oral antibiotic for ≥28 days. Our data showed a smaller percentage of males consult their GP and are coded for acne (34.3% males vs. 65.7% females), and of those coded for acne, fewer males were prescribed a long-term oral antibiotic than females (40.8% males vs. 59.2% females). We

Table 5 Second course: the proportion of people with acne prescribed an antibiotic receiving a second course of antibiotic[a]

First antibiotic course ($n=96\,703$)	Second antibiotic course ($n=56\,261$, 58.2%), people receiving second course of antibiotic for a minimum continuous exposure of 28 days, *n* (%)	
	Second antibiotic	*n* (%)
Tetracycline ($n=81\,777$)		47 920/81 777 (58.6)
	Tetracycline	41 211/47 920 (86.0)
	Macrolide	602/47 9205 (12.6)
	Trimethoprim	684/47 920 (1.4)
Macrolide ($n=13\,175$)		7796/13 175 (59.2)
	Tetracycline	3984/7796 (51.1)
	Macrolide	3672/7796 (47.1)
	Trimethoprim	140/7796 (1.8)
Trimethoprim ($n=1751$)		545/1751 (31.1)
	Tetracycline	243/545 (44.6)
	Macrolide	60/545 (11.0)
	Trimethoprim	242/545 (44.4)

[a]That is >28 days after the first course. Second antibiotic exposure relative to first with treatment gap of ≥28 days between courses.

found the majority of first prescriptions of long-term antibiotics in people with acne were for tetracyclines.

This is the first study to our knowledge to determine oral antibiotic prescribing practices over a 15-year period with a median follow-up of 5.3 years in UK primary care. Our study used a large, representative data source from general practices across the UK. Although the use of routinely collected health data provides real-world data, there are certain limitations. Given acne affects predominantly younger people, there may be a higher proportion of people transferring out of the practice, and hence who are lost to follow-up as they move to live elsewhere and this may be supported by the finding that the median follow-up of people who receive antibiotics (both $<$ or $\geq$ 28 days in duration) is longer (5.8 and 5.3 years, respectively) than for people who receive no antibiotic prescriptions (2.6 years). Young people may opt to stay registered with their original GPs if they are receiving longer-term treatment for their acne. Bias could be introduced if people were not registered with their GP for a sufficient duration to be prescribed long-term therapy and are prescribed antibiotics elsewhere – this would underestimate antibiotic exposure in this highly mobile population. People who were prescribed $\geq$ 10 courses had longer follow-up in the cohort, suggesting it is possible people with less follow-up may have further oral antibiotics for acne at another general practice where data are not recorded by the CPRD.

We defined our study population using acne diagnostic codes. It is possible that people in our population have acne coexisting with another condition requiring long-term oral antibiotic use of a similar class used to treat acne, for example recurrent urinary tract infections or hidradenitis suppurativa. In this situation, it would be difficult to ascertain what condition the long-term antibiotic was specifically prescribed for. We believe the number of people with two diagnoses requiring long-term antibiotics would be small and therefore unlikely to affect our results. Removing people with acne and a further diagnosis requiring long-term antibiotics of a similar class to acne may have introduced selection bias.

To define the antibiotic for acne, we ensured that the oral antibiotic classes used for acne needed to be prescribed for a minimum duration of 28 days thereby excluding some infective conditions for which the antibiotics could be prescribed for; however, this may mean we underestimate the use of shorter courses for acne. Given acne guidelines recommending longer courses (present and historic), shorter courses of antibiotic intended for acne would be rare. Additionally, trimethoprim may be prescribed long term for urinary tract infection prophylaxis, however, trimethoprim only accounts for 2.1% of all prescriptions.[23] The CPRD is broadly representative of the UK population in terms of ethnicity; however, data on ethnicity were incomplete with 60.7% missing or unknown in the long-term antibiotic use group, and hence conclusions about prescribing by ethnicity are limited.

Shorter treatment durations may be because repeat prescriptions are not obtained or people are unaware that the course is to be continued, or they do not request or are not issued their second prescription. People may not request a further prescription if they have already seen an improvement in their acne to a satisfactory level. Local prescribing policies, the patient's personal circumstances and the GP's personal prescribing preferences may influence the duration of each prescription. Shorter treatment durations per course may also reflect poor adherence, for example if people do not begin courses on the day of the prescription or miss doses therefore requesting their subsequent prescriptions later than expected. Shorter than recommended treatment durations may mean courses are less effective at treating acne, and therefore may mean courses need to be repeated and antibiotic exposures are higher than necessary. Such intermittent and prolonged use of antibiotics may contribute to selection pressure and give bacteria the opportunity to develop mechanisms to withstand the effects of antibiotics and therefore contribute to the overall burden of AMR.[11]

Our study assessed the number of courses and duration of oral antibiotics people with acne receive at the population level over time. Acne guidelines recommend a 3- to 4-month course of oral antibiotic to be repeated twice, and if there is no treatment response to refer the patient to specialist dermatology care.[9] In contrast to guideline recommendations, we found the median number of antibiotic courses prescribed was four, with a large proportion of individuals receiving five or more courses. We also noted a median duration between courses of 119 days. It is therefore unclear if the median number of courses prescribed reflects non-treatment response or relapse after remission.

The majority of first prescriptions for acne were with a tetracycline and this is consistent with clinical guidelines.[4–6] A possible explanation for fewer males being prescribed an oral antibiotic for acne than females may be that female patients are seeing their GP and seeking medical treatment for their acne more than male patients. A study using CPRD data in 2017 looked at prescriptions of all acne medication; however, patients were followed up for 1 year, so it may not have been possible to ascertain if people received a second course of oral antibiotic, and the duration of the second course.[19] A study using primary care date from The Health Improvement Network (THIN) found median duration of tetracycline therapy in people with acne between 12 and 22 years of age was 112 days, but we do not know if antibiotic courses were repeat prescribed for individuals during follow-up.[3] Given THIN and CPRD include similar populations, differences in findings may be because of how courses of therapy were defined. The THIN study, allowed further antibiotic prescriptions within 180 days of the start of the first prescription to be combined into one course. A US study of health insurance claims data found the number of courses of oral antibiotics per 100 individuals with acne was approximately 20 and the median duration of therapy was 129 days when antibiotics were prescribed by a nondermatologist.[10] Studies have previously looked at the concomitant prescription of topical acne therapy recommended in acne guidelines using UK primary care data therefore this work was not replicated here.[3,19]

In conclusion, this study found that people with acne have a median of 56 days of oral antibiotic per course and that a median of four courses are prescribed per person with a cumulative duration of oral antibiotic exposure of 8.5 months during follow-up. Given bacterial AMR is one of the leading causes of death worldwide, and the aetiology of acne is multifactorial and not a classic infectious disease, the widespread use of long-term antibiotics for acne in a relatively healthy, young population requires further investigation.[12,13] Alternative therapy for acne may reduce exposure to oral

antibiotics. Future work may include further describing the oral antibiotics prescribed for acne by subclass given varying subclasses of an antibiotic class may cause varying degrees of resistance.[24] High-quality prospective studies investigating the impact of long-term oral antibiotic use for acne and AMR are imperative, so that antibiotic prescribing practices for acne can be modified if needed. More rigorous prescribing practices and the implantation of algorithms or prescribing tools could be beneficial to ensure antibiotics are prescribed according to guidelines.

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Conflicts of interest

D.J.M. has consulting relationships with Janssen and Pfizer (the relationships are not related to acne or antibiotics; hidradenitis and venous dermatitis, respectively) and has funding from Pfizer (KIR genetics and atopic dermatitis). The other authors declare they have no conflicts of interest.

Data availability

All codelists are available on datacompass.lshtm.ac.uk. Some investigators had access to the deidentified data in CPRD Gold to create the study population.

Ethics statement

This study protocol has been approved by ISAC.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.