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Prescribing of Long-term Antibiotics to Adolescents in Primary Care: a Retrospective Cohort Study

Mark Lown, Sam McKeown, Beth Stuart, Nick Francis, Miriam Santer, George Lewith, Fanzhong Su, Michael Moore, Paul Little.

Mark Lown, GP and Clinical Lecturer, University of Southampton, Southampton.

Sam McKeown, Medical Student, University of Southampton, Southampton.

Beth Stuart, Medical Statistician, University of Southampton, Southampton.

Nick Francis, GP and Professor of Primary Care Research, University of Southampton, Southampton.

Miriam Santer, GP and Professor of Primary Care Research, University of Southampton, Southampton.

George Lewith, Professor of Health Research, deceased.

Fangzhong Su, Data manager, University of Southampton, Southampton.

Michael Moore, Professor of Primary Care Research, University of Southampton, Southampton.

Paul Little, Professor of Primary Care Research, University of Southampton, Southampton.

Address for correspondence:

Mark Lown. Primary Care Research Centre, Aldermoor Health Centre, Aldermoor Close, Southampton, SO16 5ST, UK. Tel: +44 2380 595000; E-mail: m.lown@soton.ac.uk

Abstract

Background: Antibiotic overuse is linked with increased risk of antimicrobial resistance. Long-term antibiotics are commonly used for treating acne and prophylaxis of urinary tract infection. Their contribution to the overall burden of antibiotic use is relatively unknown.

Aim: To describe the volume of commonly prescribed long-term (>= 28 days) antibiotic prescriptions in adolescents and young adults, trends over time and comparisons with acute prescriptions.

Design and Setting: Retrospective cohort study using UK electronic primary care records.

Methods: Patients born between 1979 and 1996 in the Care and Health Information Analytics database were included. Our main outcome measures were antibiotic prescription rates per 1000 person years, antibiotic prescription days per person year between ages 11-21.

Results: 320,722 participants received a total of 710,803 antibiotic prescriptions between the ages of 11-21 from 1998 to 2017. 191,443/710,803 (26.93%) prescriptions were for long-term antibiotics (≥28 days and ≤ 6 months in duration). Long-term antibiotics accounted for more than two-thirds (72.48%) of total antibiotic exposure (days per person year). Total long-term antibiotic prescribing peaked in 2013 at just under 6 days per person year and declined to around 4 in 2017.

Conclusions:

Amongst adolescents and young adults, exposure to long-term antibiotics (primarily lymecycline used for acne) was much greater than for acute antibiotics and is likely to make an important contribution to antimicrobial resistance. Urgent action is needed to reduce unnecessary exposure to long-term antibiotics in this group. Increasing the use of and adherence to effective, non-antibiotic treatments for acne is key to achieving this.

Keywords: Antibiotic prescriptions; General Practice; Antimicrobial resistance

How this fits in

Previous work investigating antibiotic prescribing in primary care has focused primarily on acute antibiotic prescribing, with an emphasis on antibiotic choice and the number of prescriptions issued. This study provides estimates of the overall burden of long-term antibiotic prescriptions in adolescents, which is higher than previously thought, and contributes much more than short term antibiotics to the number of days of antibiotics used, and is therefore likely to contribute significantly more to the promotion of antibiotic resistance. The use of long-term antibiotics (primarily tetracyclines for acne) contributes significantly to this burden. Non-antibiotic topical treatments are as effective as oral antibiotics for most people with acne, and steps to promote the effective use of these treatments may lead to reductions in antimicrobial resistance without impairing acne outcomes.

Introduction

Antimicrobial resistance (AMR) is a major threat to global health as new resistance mechanisms emerge and spread globally.[1] A growing number of common infections are becoming harder to treat due to AMR which can lead to longer hospital stays, higher medical costs and increased mortality.[1] Unnecessary and inappropriate use of antibiotics promotes the emergence and spread of resistant bacteria.[2] This effect not only increases the population-level carriage of organisms resistant to first line antibiotics, but can also increase the use of second line antibiotics in the community.[3] Up to half of all antibiotic usage is thought to be inappropriate.[4]

Increased consumption of antibiotics may not only produce greater resistance at the individual patient level but may also lead to greater resistance at the community, country, and regional levels.[5] Population-level antibiotic pressure may have more effect on an individual risk for resistant organisms than individual antimicrobial usage.[6] Exposure to an antibiotic induces resistance to that antibiotic, but can also induce resistance to other antibiotic classes.[7] Cross-resistance can occur via various mechanisms, such as co-selection, collateral resistance, collateral sensitivity, or by simply killing competing bacteria.[8]

Repeat use of antibiotics has a stronger association with antibiotic resistance than first use.[8] Both the dosage and duration of antibiotic therapy may have effects on resistance with lower doses and longer durations being linked with increased risk of AMR.[7] Reversal of resistance is complex and might persist for many years despite the introduction of antimicrobial containment and stewardship programs.[7] Prudent antibiotic prescribing has been identified as an important strategy to curb AMR including avoiding unnecessary prescriptions, delaying prescriptions when possible, favouring narrow-spectrum over broad-spectrum antibiotics and optimising treatment duration.[9,10]

Long-term antibiotics are commonly used for the treatment of acne[11,12] and prophylaxis of urinary tract infection[13] and population exposure to long courses of low-dose antibiotics are associated with increased risk of AMR. Treatment of acne with antibiotics is associated with an increased risk of common infections.[14,15] Acne affects over 90% of teenagers.[11] There are approximately 8 consultations per 100 person years for acne in 12-18 year olds in the UK and oral antibiotics are the most common acne-related medication prescribed.[16] Dermatologists prescribe more oral antibiotic courses per clinician than any other specialty, and many of these courses of antibiotics are prescribed for several months in duration.[17] Non-antibiotic treatments, particularly topical treatments, are more appropriate for the majority of acne.[12]

Previous work investigating antibiotic prescribing in primary care has focused on antibiotic choice[9] and the number of prescriptions issued rather than the number of units or prescription days. Describing antibiotic prescriptions linked to specific conditions or indications may underestimate total prescribing.[9] Other work has focused on the identification of inappropriate antibiotic use but did not consider long-term antibiotic prescriptions, whose contribution to the overall burden of antibiotic use is relatively unknown.[10]

We therefore determined the rates and trends and overall burden of long-term antibiotic prescriptions in an adolescent cohort in primary care in Hampshire UK.

Methods

Design and Setting

We performed a retrospective longitudinal population based cohort study using data from the Care and Health Information Analytics database (CHIA) for the period January 1998 to August 2017. The CHIA database is an anonymised analytical database with data from around 130 general practices across Hampshire containing information on over 1.24 million residents.[18] Data were accessed via the CHIA governance team and programming and extraction carried out by a member of the CHIA team. Extracted data included all antibiotic prescriptions. Data was not restricted based on consultations or Read codes (a coded thesaurus of clinical terms used in the NHS). Analysis were performed by year and denominators were calculated using all participants registered with a practice excluding those who were deceased or had moved out of area. We only included oral antibiotic prescriptions for tablets / capsules in the analysis.

We used the CHIA to extract prescription data for patients born between 1979 and 1996 who attended one of the included GP surgeries at least once during adolescence. Antibiotic classes and specific antibiotics were selected using British National Formulary (BNF which provides key information on the selection, prescribing, dispensing and administration of medicines in the UK) codes and both generic and brand names of antibiotics were included in the analysis for the antibiotics listed in Table 1. Long-term antibiotic prescriptions were defined as prescriptions for >= 28 days supply of antibiotics. This definition has been applied elsewhere for acne prescriptions.[15] The quantity of medication prescribed for each antibiotic was identified. Antibiotic prescriptions where the quantity prescribed was inferred (by dosing regimes) to be greater than 6 months were excluded as these were thought likely to be errors. (Issuing prescriptions for longer durations is not recommended. In England, for medicines commonly prescribed for long-term conditions, 93% of the total volume in 2019 was for three months or less. We selected long-term antibiotics based upon clinical indications listed in the BNF for acne and infection prophylaxis and some key short-term antibiotics for comparison. This accounted for 84.0 % of the extracted prescriptions. We excluded prescriptions for the remaining short-term antibiotics prescribed for > 28 days. This exclusion of these prescriptions together with those for > 6 months supply excluded 1.49% of the prescriptions.

Dosing regimes were inferred from the specific antibiotic and quantity supplied (Supplementary data Table S1). We included prescriptions for >= 56 oxytetracycline tablets in the long-term analysis as we decided there were no other likely indications. All analyses were undertaken in Stata statistical software version version 14.0 (StataCorp, College Station, TX, U.S.A.). The use of CHIA data within this study was approved by the Care and Health Information Governance Group.

Patient and Public Involvement

We are grateful to our PPI representative who provided input into this work and commented that the work was important particularly in terms of "informing future antibiotic prescribing guidelines in adolescents in order to weigh up the risk associated with prescribing prolonged courses."

Results

In total there were 320,722 participants who attended one of the included GP surgeries at least once during adolescence. We identified 1,703,786 antibiotic prescriptions issued between 01/01/1998 and 09/08/2017 at age 11 onwards. 122,571 prescriptions did not contain unit values for quantity of medication issued. We further excluded 102,523 liquid / solution prescriptions (as the duration could not accurately be inferred from quantity supplied). We limited our analysis to the 11 antibiotics listed in Table S1 (excluding 164,014 prescriptions). We further excluded 19,548 prescriptions with suspected invalid quantities > 28 days for short-term antibiotics and > 168 days for long-term antibiotics. We further restricted our analysis to prescriptions issued between ages 11 and 21 (584,327 exclusions). The following analysis includes a total of 710,803 prescriptions. The data selection / exclusion process is depicted in Figure 1. Table 1 lists a breakdown of the prescriptions included in the analysis by individual antibiotic. 157,056 participants (48.97%) had prescriptions issued between the ages of 11 and 21 and the median age at first prescription was 14 years. 11.01% of the CHIA cohort we described here were prescribed at least one course of long-term antibiotics during the entire study period. The median follow-up was 10 years. 50.29% of the participants were female and 49.71% male. Between 185 and 264 GP surgeries contributed data in each year. The denominator of participants was lower towards the end of the study due to the cohort selection (to enable long-term follow-up data to be analysed for future work). Supplementary data Table S2 details deprivation by decile of the cohort.

Figure 2 shows the rate of antibiotic prescriptions per 1000 person years in the cohort from 1998 to 2017. The rate of total antibiotic prescribing increased from 131 per 1000 person years in 1998 to just under 409 in 2012 and declined to around 306 in 2017.

Figure 3 depicts long-term antibiotic prescription rates per 1000 person years. Tetracyclines were often prescribed and minocycline and oxytetracycline were the most prescribed long-term antibiotics up until 2007, after which Lymecycline was the most commonly prescribed. Lymecycline prescribing increased to a peak of just over 69 prescriptions per 1000 person years in 2013, declining to 46 in 2017.

Figure 4 depicts long-term, short-term and total prescription days per person year. Total long-term antibiotic prescribing peaked in 2013 at just under 6 days per person year and declined to around 4 in 2017. Total short-term antibiotic prescription days peaked at just over 2 days per person year in 2014 and declined to 1.6 in 2017. Combining total prescription days and total prescriptions data yielded an average duration of 6.70 days for short-term prescriptions and 49 days for long-term prescriptions.

Figure 5 shows antibiotic prescription days per person year for the most commonly prescribed long-term antibiotics (lymecycline, oxytetracycline and minocycline) and also the most commonly prescribed short-term antibiotics (amoxicillin , flucloxacillin and penicillin v). In 1998, minocycline prescriptions totaled 0.89 days per person year compared with 0.19 for amoxicillin. Lymecycline prescriptions peaked at 3.87 days per person year in 2013 and declined to 2.84 in 2017 compared with 0.43 for penicillin V in the same year.

Discussion

Summary

This large community-based study demonstrates high rates of antibiotic exposure related to long-term antibiotic prescribing for adolescents and young adults primarily in the second decade of life. Long-term antibiotic prescribing accounted for more than two-thirds (72.48%) of total antibiotic expose days. A significant proportion of the cohort (11.01%) were prescribed at least one long-term antibiotic prescription, most commonly lymecycline which is commonly used in the treatment of acne.

Strengths and limitations

The frequency of antibiotic dosing was inferred from the quantity supplied which could affect the accuracy of our results although dosing regimes for the most commonly prescribed antibiotics including lymecycline and amoxicillin are likely to be correctly inferred. Medication adherence was unknown for both acute and long-term antibiotic prescriptions. We did not attempt to determine the indication for the antibiotic prescriptions although we did however include prescriptions that were not linked with Read codes. There was a significant number of prescriptions with missing quantity data (7.19%) and we did not include liquid preparations in the analysis. The proportion of scripts for each individual antibiotic was similar in the missing data group and those included in the analysis.

The CHIA encompasses extensive coverage of approximately 75% of the resident Hampshire population at the time of data extraction. Although not all local practices participate, those that are missing are dispersed across the catchment area, with varied rural/urban classification, socioeconomic deprivation and patient composition. We are not aware of any systematic differences to those practices whose data are present[19], and although Hampshire has lower antibiotic prescribing rates than the national average[20], the CHIA prescription rates are comparable to large national databases such as THIN (see below). Further research using other healthcare databases could help confirm our findings.

Comparison with existing literature

In this analysis of routinely collected UK general practice data in Hampshire, we found relatively similar prescribing rates of individual antibiotics to those obtained by Dolk et al using the THIN database including similar total antibiotic prescription rates (408 per 1000 person years in 2013 compared with 580 per 1000 per person years in patients aged under 19 in 2013).[9] A study using the CPRD database determined there were 489 prescriptions per 1000 person-years in 2017 (without age restrictions)[21] compared with 306 prescriptions in the currently presented cohort. The difference could be due to higher proportions of prescriptions for the elderly and very young patients included in the CPRD data. UK national data yielded an equivalent of 5 antibiotic days per person year in 2017 for the entire population compared with 5.66 in this cohort in 2017.[22] National data confirms an overall increase in antibiotic consumption in primary care peaking in 2014 and could have been driven by an increase in antimicrobial resistance[22]. National data has also confirmed a fall since the 2014 peak due to the introduction of national targets implemented for general practice with financial incentives, education tools for prescribers and patient leaflets.[22]

11.01% of participants aged 11-21 described here were prescribed at least one course of long-term antibiotics. Tetracyclines were the most commonly prescribed long-term antibiotics and this trend was observed in another study using the CPRD database.[16] Tetracyclines comprised 7.9% prescriptions in those aged under 19 years and 14.0% in those aged 19-65 in the Dolk[9] study compared with 19.4% (for all doxycycline, lymecycline, oxytetracycline and minocycline prescriptions) in 2014 in this study. In national data, lymecycline prescribing comprised 12.37% of all general practice antibiotic prescription days per person year in 2017.[22]

Lower rates of lymecycline prescribing were found using CPRD data[16] where prescriptions were extracted for patients who consulted with any acne Read codes (11.8 items per 1000 person years in 2013), but prescriptions may happen without a consultation code being recorded. Since we did not link prescriptions with Read codes or consultations, we have probably included a more complete assessment of relevant prescriptions in this study. There were relatively low rates of prescribing of antibiotics for UTIs in this cohort as indicated in table 2.

The number of antibiotic prescription days per person year for long term antibiotics was much greater than for commonly prescribed acute antibiotics and reflects considerable antibiotic exposure. In 2017, long-term antibiotics were prescribed at just under 4 days per person year compared with 1.7 days for acute prescriptions. This data suggests that long-term antibiotics (comprising around 70.38% of the total exposure in this cohort in 2017) and particularly lymecycline prescriptions compromise a major burden of antibiotic exposure in adolescents and young adults in the UK. It is feasible that this level of exposure could contribute significantly to AMR. A review and meta-analysis of fecal carriage of antibiotic resistant E. Coli in asymptomatic young people found that resistance to many primary care prescribed antibiotics is common and tetracycline resistance rates were high.[23] Furthermore, healthy children carry bacteria resistant to antibiotics to which they are not usually exposed and resistance to tetracyclines could be acquired from family members or other children.[24]

Lymeclyline is primarily prescribed for acne in adolescents and young adults and recently NICE guidance for acne has published recommendations which include non-antibiotic treatment choices for acne of any severity[12]. Recent research indicated that 1 in 4 acne patients are prescribed oral antibiotics during a new acne consultation[16]. Action is required to increase utilisation and adherence to alternative and effective topical therapies and for timely review of response to antibiotic therapy.

Treatment of acne with antibiotics is associated with an increased risk of common infections.[14,15] In a retrospective cohort study of 84 977 individuals with acne treated with a topical antibiotic, oral antibiotic, or both, the odds ratio of developing an upper respiratory tract infection diagnosed by a general practitioner was 2·15 times higher compared with patients not treated with antibiotics ($p<0·001$).[14] These findings were supported by a subsequent cross-sectional study, in which self reported pharyngitis was nearly twice as common in those exposed to oral antibiotics (66·7% compared to 36·2%).[15] A potential explanation for this finding may be the depletion of natural oral flora supported by the finding that re-colonisation therapy with a streptococcal spray has been shown to protect against recurrent infections.[25]

Antibiotics have been shown to have profound and sometimes persisting effects on the intestinal microbiota, characterised by diminished abundance of beneficial commensals and increased abundance of potentially detrimental microorganisms which can persist for years[26] and it is possible that long-term antibiotics may cause more profound and persistent changes. Long-term antibiotic use has been associated with an with a range of adverse outcomes including increased risk of colorectal adenoma,[27] an increased risk of future CVD events among elderly women at usual risk[28] and weight gain.[29] Tetracyclines are also used as growth promoters in livestock to promote host lipid metabolism, energy harvest and weight gain.[30] Tetracycline usage during the 4th decade of life was however associated with reduced odds of obesity at enrollment to the Sister study.[29] Other work using retrospective cohort data has suggested that long-term antibiotic use in healthy adolescents with acne was not associated with weight gain.[31]

Conclusions

Importantly, we have shown that in adolescence and young adulthood, population exposure to long-term antibiotics is larger than that for acute antibiotics in this cohort. Repeat use of long duration antibiotics is associated with greater risk of antimicrobial resistance and cross-resistance can occur where exposure to a specific antibiotic can induce resistance to other classes. Urgent action is needed by policy makers to curtail the use of long-term antibiotics, primarily lymecycline for acne and promote the use of and adherence to alternative management strategies.

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Transparency

MM is on the government advisory board for AMR (APRHAI). All other authors: none to declare.

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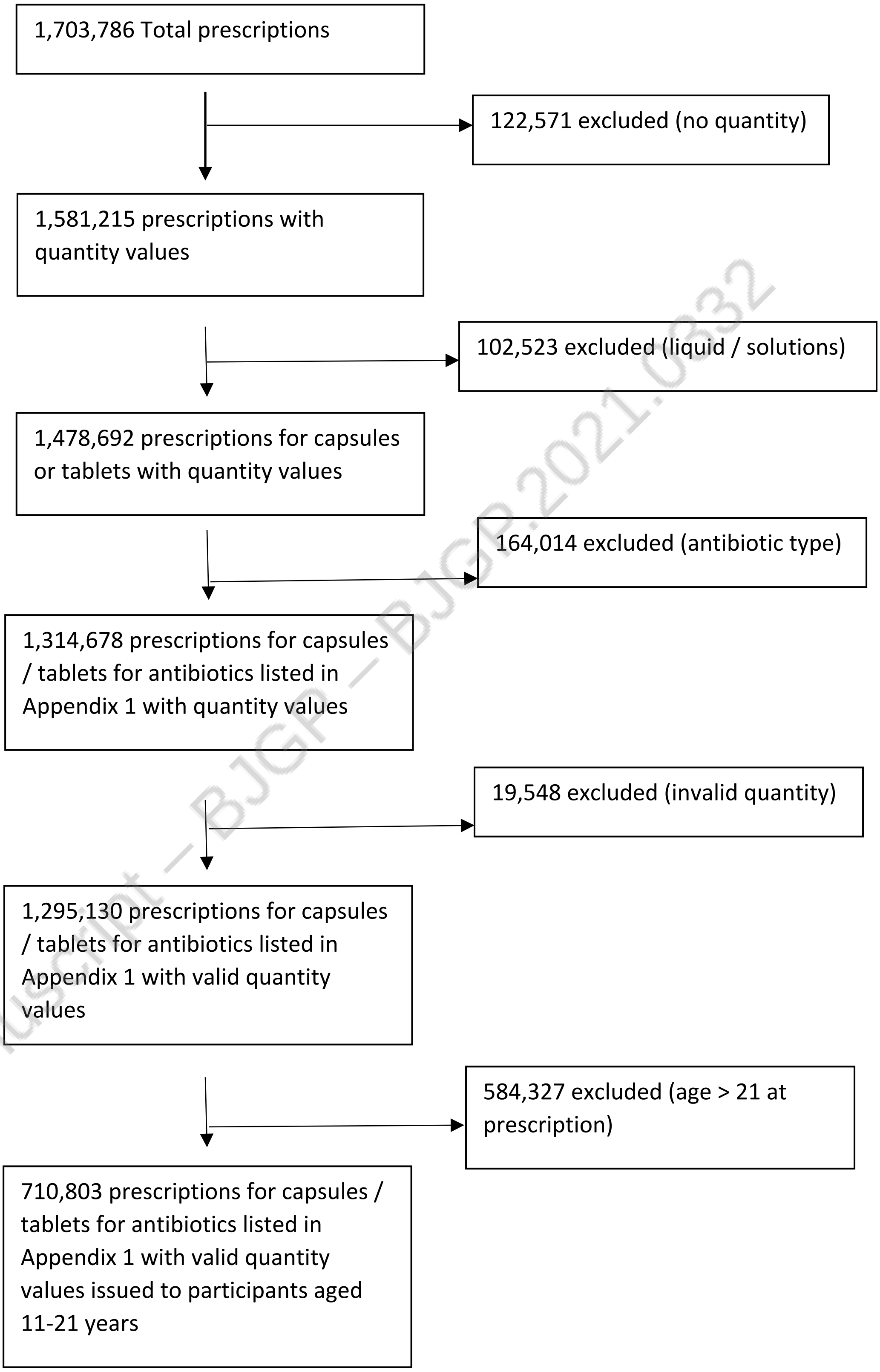

Figure 1 – Data selection / exclusion process.

Antibiotic	**Proportion of prescriptions**	**Proportion of prescription days**
Acute Amoxicillin	19.78%	7.18%
Acute Penicillin V	15.28%	4.48%
Acute Flucloxacillin	13.93%	5.70%
Acute Trimethoprim	8.57%	2.30%
Long-term Lymecycline	7.77%	24.16%
Long-term Oxytetracycline	7.63%	14.94%
Acute Erythromycin	7.56%	4.13%
Long-term Minocycline	6.07%	18.99%
Acute Co-amoxiclav	4.08%	1.77%
Long-term erthromycin	2.43%	5.31%
Acute Doxycycline	2.22%	1.38%
Long-term Doxycycline	1.92%	5.84%
Acute Nitrofurantoin	1.65%	0.57%
Long term Trimethoprim	0.67%	2.16%
Long-term Nitrofurantoin	0.44%	1.08%
Total Short-term	**73.07%**	**27.52%**
Total Long-term	**26.93%**	**72.48%**

Table 2 – Proportions of total prescriptions for individual antibiotics (710803 prescriptions) at age 11-21.

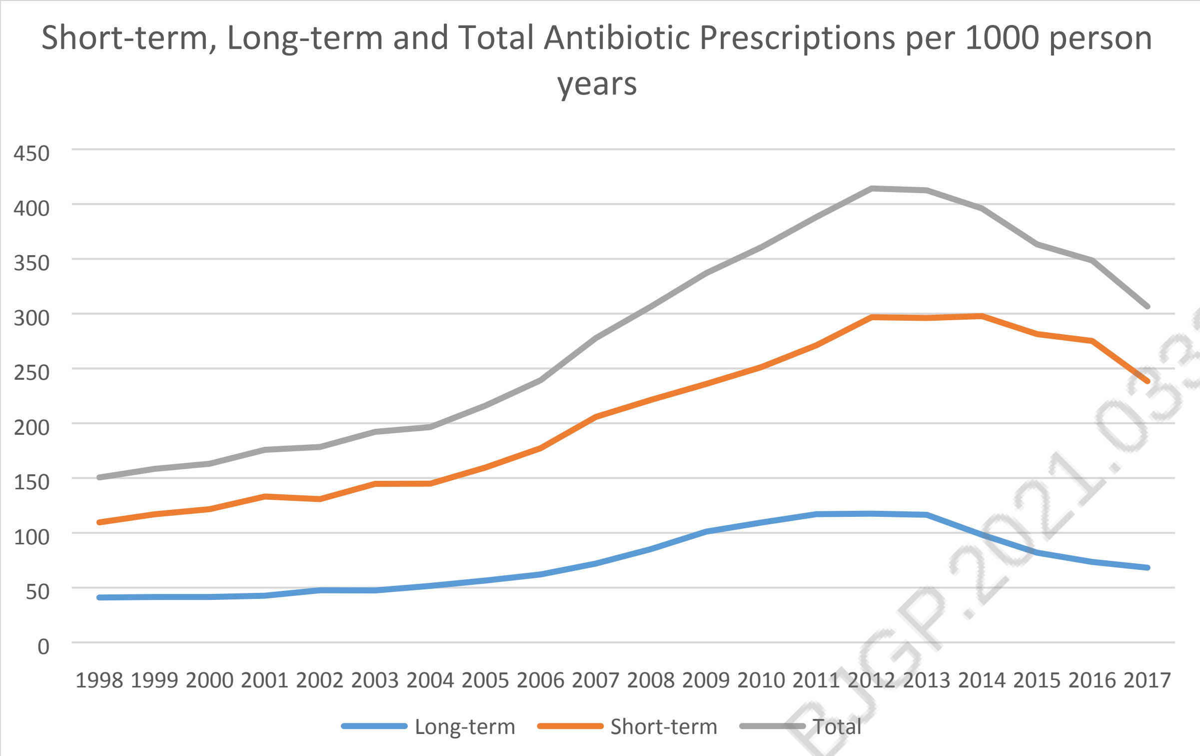

Figure 2 – Total antibiotic prescription items per 1000 person years (at age 11-21).

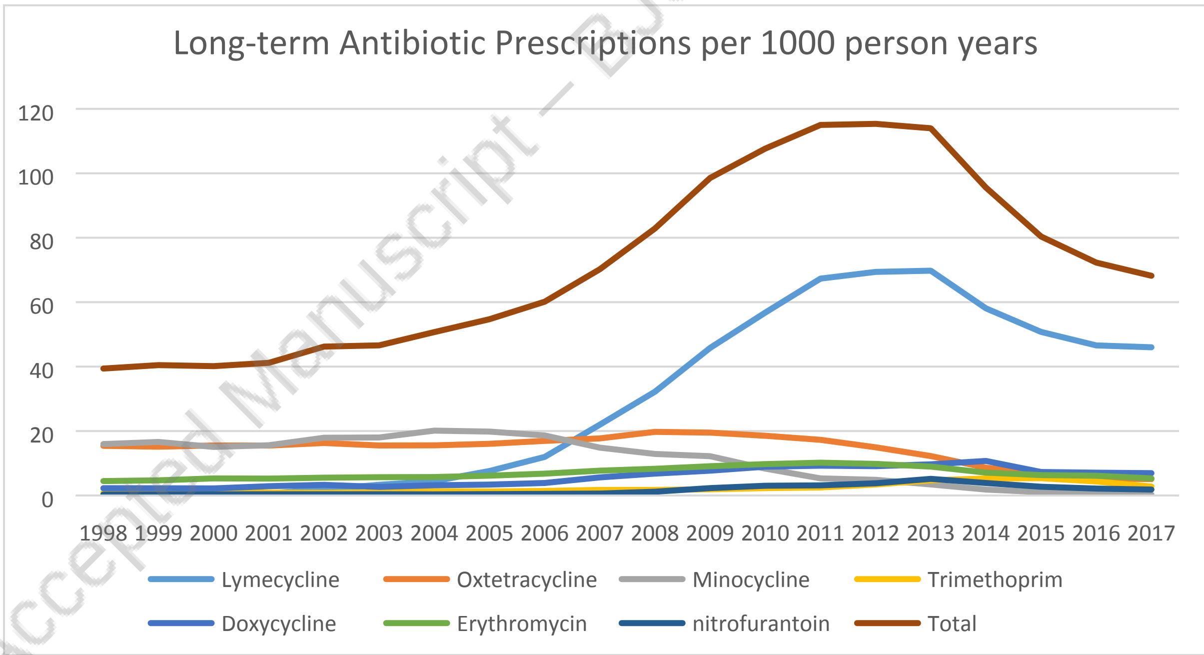

Figure 3 –Long-term antibiotic prescriptions per 1000 person years (at age 11-21)

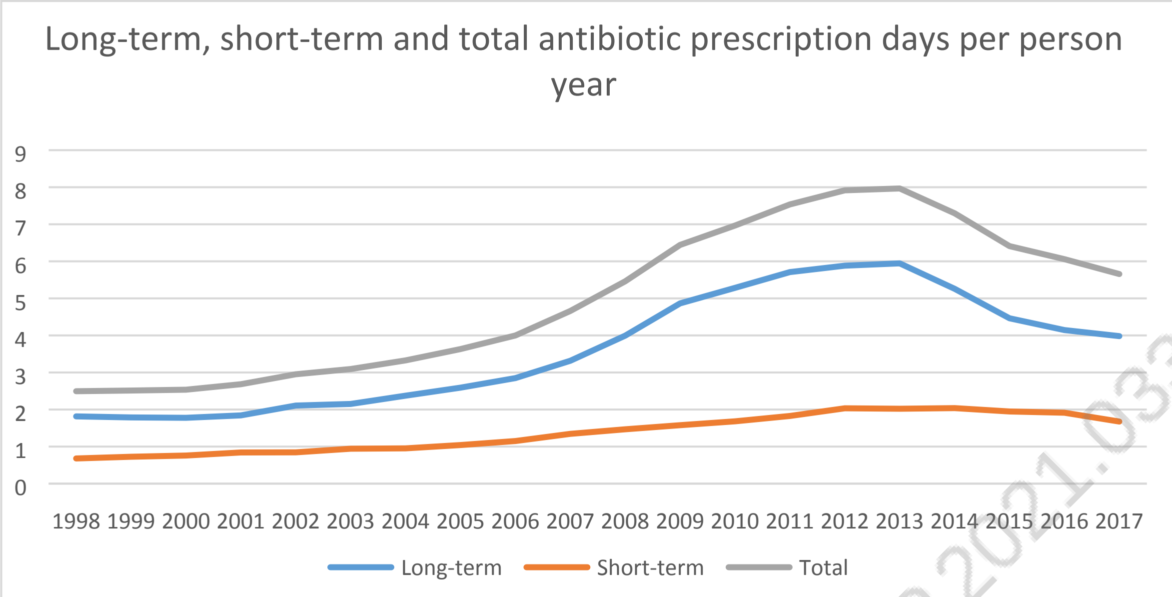

Figure 4 – Long-term, short-term and total antibiotic prescription days per person year (at age 11-21)

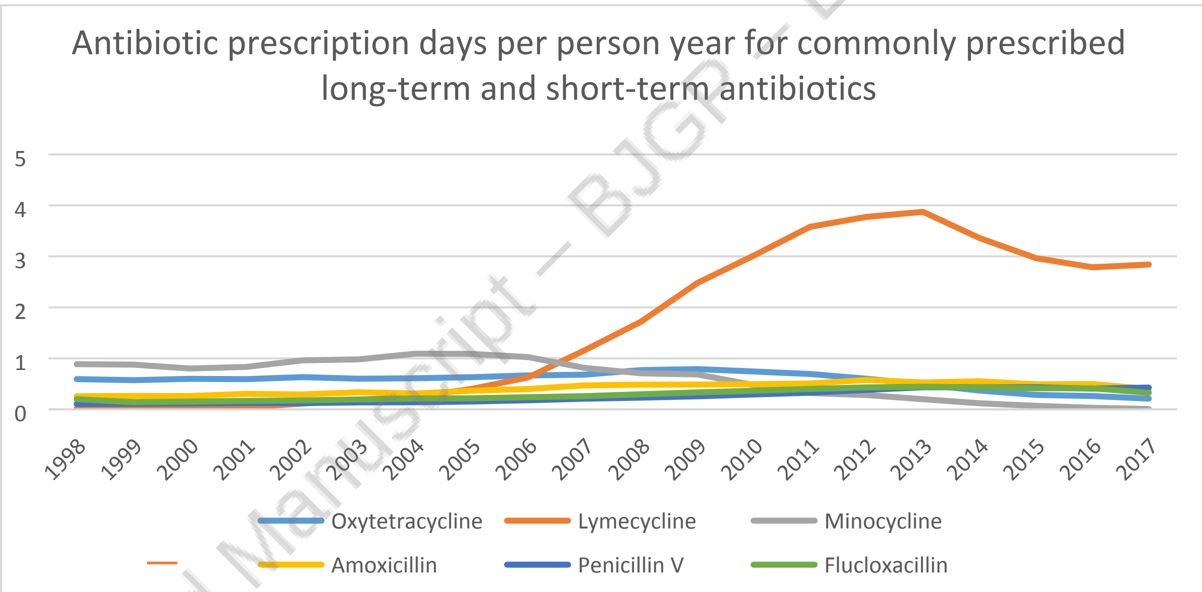

Figure 5 – Antibiotic prescription days per person year for commonly prescribed antibiotics (long-term lymecycline, oxytetracycline and minocycline vs short term amoxicillin, flucloxacillin and penicillin V) (at age 11-21)