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Gender differences in antibiotic prescribing in the community: a systematic review and meta-analysis

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Objectives: Determinants of inappropriate antibiotic prescription in the community are not clearly defined. The objective of this study was to perform a systematic review and meta-analysis evaluating gender differences in antibiotic prescribing in primary care.

Methods: All studies analysing antibiotic prescription in primary care were eligible. PubMed and MEDLINE entries with publication dates from 1976 until December 2013 were searched. The primary outcomes were the incidence rate ratio (IRR) (measured as DDD/1000 inhabitants/day) and the prevalence rate ratio (PRR) (measured as prevalence rate/1000 inhabitants) of antimicrobial prescription, stratified by gender, age and antibiotic class. Random-effects estimates of the IRR and PRR and standard deviations were calculated.

Results: Overall, 576 articles were reviewed. Eleven studies, comprising a total of 44 333 839 individuals, were included. The studies used data from prospective national (five studies) or regional (six studies) surveillance of community pharmacy, insurance or national healthcare systems. Women were 27% (PRR 1.27 ± 0.12) more likely than men to receive an antibiotic prescription in their lifetimes. The amount of antibiotics prescribed to women was 36% (IRR 1.36 ± 0.11) higher than that prescribed for men in the 16 to 34 years age group and 40% (IRR 1.40 ± 0.03) greater in the 35 to 54 years age group. In particular, the amounts of cephalosporins and macrolides prescribed to women were 44% (IRR 1.44 ± 0.30) and 32% (IRR 1.32 ± 0.15) higher, respectively, than those prescribed for men.

Conclusions: This meta-analysis shows that women in the 16 to 54 years age group receive a significantly higher number of prescriptions of cephalosporins and macrolides in primary care than men do. Prospective studies are needed to address reasons for gender inequality in prescription and to determine whether a difference in adverse events, including resistance development, also occurs.

Introduction

Antimicrobial resistance is an increasingly serious threat to global public health and to the achievements of modern medicine, according to a recent WHO report.[1] The selection of drug-resistant bacteria has significant consequences, not only at an individual level (i.e. increased risk of infection in a colonized patient) but also at an institutional level (i.e. increased risk of cross-transmission among hospitalized patients, environmental contamination and spread of resistance in the community).[2–4] The burden of resistance also includes increased healthcare costs from failure to respond to treatment, relapses and increased length of hospitalization, greater risk of complications and increased mortality. Numerous papers have demonstrated that antibiotic exposure is a major risk factor for the development of antibiotic resistance.[2,3,5] Most antibiotic use occurs in the community[6–8] and is intended to treat respiratory tract infections (RTIs), bronchitis or urinary tract infections (UTIs). Several reports found a rate of inappropriate prescriptions of 40% to 50% in outpatients with suspected RTIs.[9–11] Many different factors have been associated with inappropriate prescribing in this setting, including the knowledge, attitude and behaviour of the prescribing physician and the patient. Most large-scale antibiotic-awareness campaigns conducted at regional and national levels have focused on the patients and physicians to increase awareness of resistance and reduce requests for antibiotics.[12–15] However, these campaigns have not always been successful, and the determinants of antibiotic prescribing in the community need to be further defined.

Among other factors, patients' gender has been associated with differences in drug prescribing in the community.[16–22] According to Loikas *et al.*,[23] the largest gender difference in prevalence of medication use was for antibiotics (265.5 patients/1000 women and 191.3 patients/1000 men) followed by thyroid therapy (65.7 patients/1000 women and 13.1 patients/1000 men) and antidepressants (106.6 patients/1000 women and 55.4 patients/1000 men). Reasons for these discrepancies could not be completely explained on medical grounds.

The objective of this study was to systematically review the literature and, where appropriate, perform a meta-analysis of antibiotic prescriptions according to gender in primary care.

Methods

Type of outcome measures

Primary outcomes were the incidence rate ratio (IRR) and the prevalence rate ratio (PRR) of antibiotic prescribing. IRR was defined as the gender ratio (female to male) of prescribed DDD/1000 inhabitants (IN)/day, and PRR was defined as the gender ratio of patients with antibiotic prescription/1000 IN. IRR was stratified by age group (0–15, 16–34, 35–54, 55–74 and ≥75 years) and antibiotic class. The Anatomical Therapeutic Class antibiotic classification was used and included cephalosporins, macrolides, penicillins, quinolones and tetracyclines.

Search methods and selection of studies

All studies that analysed antibiotic prescription in patients who consulted their general practitioners, irrespective of patient age or study design (prospective or retrospective), were eligible. PubMed and MEDLINE entries with publication dates from 1976 until December 2013 were searched using the following search strategy: ('antibiotic AND usage AND community') and ('antibiotic AND prescription AND community AND gender'). Reference lists of retrieved articles were also searched. Experts in the field of antimicrobial stewardship were contacted for unpublished surveillance data. No language restriction was applied. Reviews, case reports and letters were not eligible.

Data extraction

Information collected included author, corresponding author, country, year of publication, year of study, duration, type of study, study population, antibiotic prescription (type and measurement) and reason for antibiotic prescription. Two authors independently assessed the eligibility of trials and extracted data. In cases of disagreement, a third reviewer was consulted. Data from each study were entered onto standardized forms, verified for consistency and accuracy, and entered into a computerized database. Authors were contacted if data were not available in the text. The reasons for excluding studies from the review were documented. The researchers were not blinded to study authors or location.

Data synthesis and assessment of risk of bias

The meta-analysis was performed in accordance with the Cochrane Collaboration recommendations[24] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Risk of bias was assessed independently of the two reviewers using the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS).[25] Random-effects estimates and 95% CIs were calculated for IRR and PRR using the R-package meta with the function metainc.[26] Heterogeneity statistics were performed by calculating I^2 and τ^2.[25,26] Heterogeneity was expressed as the 95% range of true distribution, estimated from effect size $\pm 2\times\tau$ (standard deviation of the distribution of the true effect size). Wald tests were used to test for significance of categorical variables. Pairwise comparisons of the effect sizes across various subgroups based on study characteristics were made using Bonferroni's correction method.

Spearman's rank correlation analysis was used for comparison of genderwise distribution of age-stratified antibiotic prescription (measured in DDD/1000 IN/day) with the commonly used antibiotics for a specific indication. Specifically, the IRRs for each treatment group (acne, skin infections, RTIs and UTIs) were correlated with the IRRs of overall antibiotics (DDD). Since the literature provides no specific guideline for interpretation of the Spearman's coefficient, the following cut-offs were applied: $0.0\leq r\leq 0.2$, no correlation; $0.2<r\leq 0.5$, small correlation; $0.5<r\leq 0.8$, significant correlation; and $0.8<r\leq 1.0$, full correlation.

Results

Characterization of included studies

We identified 576 abstracts through our literature search. The flow chart of study selection is presented in Figure 1. Eleven studies, including a total of 44 333 839 individuals from 10 countries (New Zealand, Spain, Sweden, Belgium, Italy, Israel, Denmark, Germany, England and Wales), met the inclusion criteria (Table 1). The studies used data from national (Sweden, Belgium, Denmark and Germany)[23,27,28] or regional (New Zealand, Spain, Italy, Israel, England, Wales and Denmark)[16,17,20,21,29] surveillance of pharmacy networks, insurance or national healthcare systems. Data from three databases, from Sweden, Germany and Italy, were unpublished (Table 1). All data were based on antibiotics dispensed, except for data from one study that was based on antibiotics prescribed.[21] Characteristics of studies are summarized in Table 1. Nine studies provided data on DDD and six studies provided data on the prevalence of prescriptions in the overall population (Table 1). All the studies had low risk of bias according to the RoBANS tool.[25]

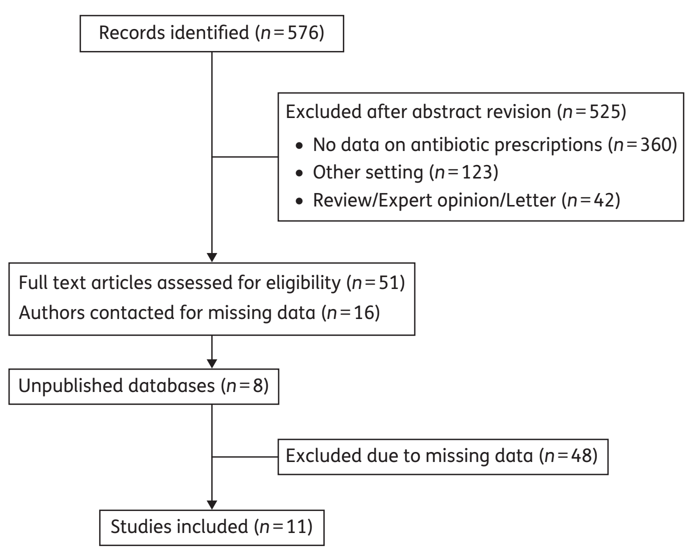

Figure 1. Flow chart of study selection.

Table 1. Characteristics of included studies

Authors	Country	Year of publication	Year of study	Duration (months)	Population	Variables analysed	Antibiotic consumption measure
Norris *et al.*[16]	New Zealand	2011	2005–06	12	4460	one-city antibiotic prescriptions by age and sex, ethnicity, residential location, socio-economic position, antibiotic classes	DDD/1000 IN/day, prevalence
Lallana-Alvarez *et al.*[20]	Spain	2012	2008	12	1 320 234	regional antibiotic prescriptions by age and sex, antibiotic classes	DDD/1000 IN/day, prevalence
National sales data on prescriptions, Public Health Agency of Sweden (Hellman J, unpublished)	Sweden	NA	2012	12	9 482 855	national antibiotic prescriptions drug sale data by age and sex, antibiotic classes	DDD/1000 IN/day
Regional Agency for Health and Social Care of Emilia-Romagna (Buttazzi R, Gagliotti C, Moro ML, unpublished)	Italy	NA	2012	12	607 733	regional antibiotic prescriptions in children (0–14 years) by age and sex	DDD/1000 IN/day
Coenen *et al.*[27]	Belgium	2014	2008–09	12	9 625 818	national antibiotic prescriptions	DDD/1000 IN/day
Health Data Authority, Data deliveries and medical product statistics, Danish National Institute for Health and Disease Control[28]	Denmark	NA	2012	12	22 352 024	national antibiotic prescription by age and sex, region, antibiotic classes	DDD/1000 IN/day, prevalence
Scientific Institute of National Health Insurance Schemes [Telschow C, Arzneimittelindex im Wissenschaftliches Institut der AOK (WIdO), unpublished]	Germany	NA	2012	12	69 716 216	national antibiotic prescriptions by age and sex, antibiotic classes	DDD/1000 IN/day
Low *et al.*[29]	Israel	2013	2000/2005/2010	36	11 178 726	Clalit Health Service antibiotic prescription by age, antibiotic classes	DDD/1000 IN/day
Majeed and Moser[21]	England/Wales	1999	1996	12	2 100 000	258 general practices antibiotic prescriptions by age and sex, antibiotic classes	prevalence
Loikas *et al.*[23]	Sweden	2013	2010	12	9 300 000	national antibiotic prescriptions by age and sex	prevalence
Vaccheri *et al.*[17]	Italy/Denmark	2002	1999	12	399 158	regional antibiotic prescriptions by age and sex, antibiotic classes	DDD/1000 IN/day, prevalence

NA, not applicable.

Antibiotic use, measured in DDD/1000 IN/day, varied among countries, age groups and antibiotic classes. After stratification by age, the prescribed DDD increased linearly with age, with the highest DDD prescribed to individuals ≥75 years old (Figure 2).

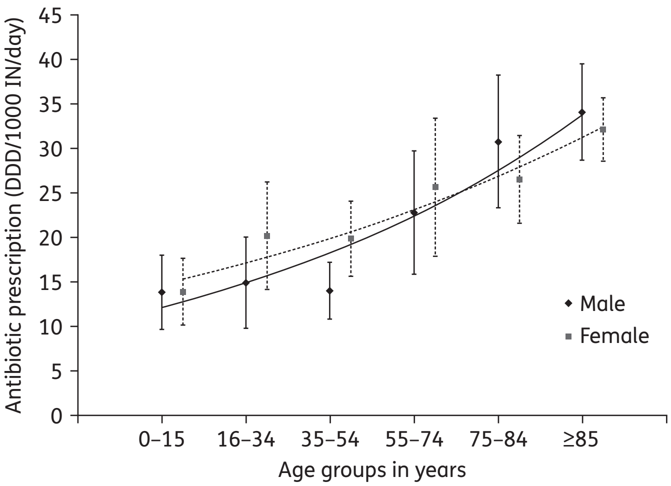

Figure 2. Pooled estimates of antibiotic prescriptions measured in DDD/1000 IN/day with 95% CI according to age groups and gender.

Countries with the highest antibiotic prescription rates (measured in DDD/1000 IN/day) were Belgium (27.17) and New Zealand (24.88). The lowest antibiotic prescription rates were observed in Sweden (12.34) and Denmark (15.85). Penicillins were the most commonly prescribed class of antibiotics (measured in DDD/1000 IN/day) (10.76) and cephalosporins the least prescribed (0.93). Only the Swedish database reported data on antibiotic substances categorized by most common indications. In the 16 to 74 years age group, women were provided with a higher number of DDD than men for antibiotics commonly used to treat RTIs and UTIs. Similar prescription patterns were observed for antibiotics commonly used for acne and skin and soft-tissue infections. The Spearman's rank correlation analysis of IRRs showed full correlation between antibiotics prescribed for RTI and age groups and gender (ρ: 1, $P=0.01$).

Meta-analysis

Overall, women were 27% more likely to receive a prescription for antibiotics than men. The gender difference in antibiotic prescription estimated both by the IRR [$1.25 \pm 2 \times \tau$ 0.193; (95% CI 1.15–1.35; I^2: 100%; $P<0.01$); Figure 3a] and by the PRR [1.27 ± 0.122; (95% CI 1.22–1.33; I^2: 99%; $P<0.01$); Figure 3b] was statistically significant. The amount of antibiotics prescribed to women in the 16 to 34 years age group was 36% (IRR 1.36 ± 0.11) higher than that for men and was 40% (1.40 ± 0.035) higher in the 35 to

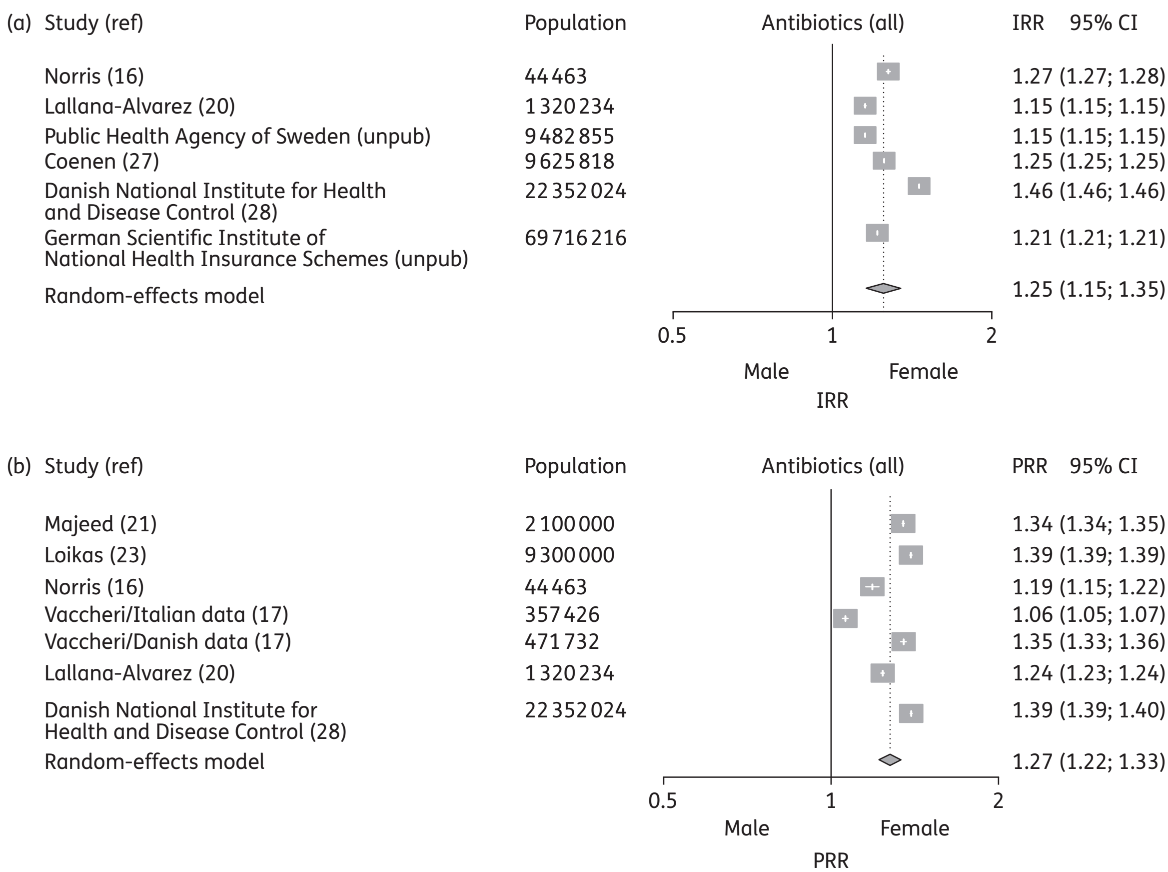

Figure 3. (a) Meta-analysis of antibiotic prescriptions in the community measured as IRR of prescribed DDD/1000 IN/day. (b) Meta-analysis of antibiotic prescriptions in the community measured as PRR of prescribed antibiotics/1000 IN.

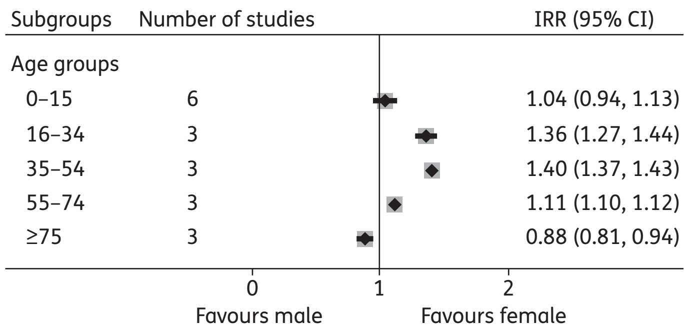

Figure 4. Summary forest plot of IRR and 95% CI by age groups.

54 years age group (Figure 4). The IRR was significantly higher in the 16 to 34 years and 35 to 54 years age groups than that in the older or younger groups ($P<0.001$). The IRRs also varied according to antibiotic class. The amount of macrolides prescribed to women was 32% higher (IRR 1.32 ± 0.151) than that for men, and the amount of cephalosporins prescribed was 44% higher (IRR 1.44 ± 0.298). For quinolones, no substantial difference of DDD between genders was observed. (IRR 1.09 ± 0.431).

Publication bias was not assessed, since fewer than 10 studies were included in each meta-analysis.

Discussion

Our data show that women are more likely than men to be prescribed cephalosporins and macrolides during their lifetimes. The summary estimates of incidence and prevalence suggest that the amount of antibiotics prescribed to women is about 25% higher than that for men and that women are about 27% more likely than men to receive antibiotic prescriptions. The age group of 16 to 54 years had the highest gender discrepancy in antibiotic prescription. The antibiotic classes with the highest gender differences were cephalosporins (44%) and macrolides (32%), commonly used for RTIs, while, unexpectedly, antibiotics commonly used to treat UTIs, such as quinolones, were almost equally distributed between the genders. To further test the hypothesis that the difference in prescription could be associated with the well-known difference in UTI prevalence between men and women, it would have been useful to analyse prescription data for nitrofurantoin and fosfomycin by gender, but unfortunately these data were not available in any of the databases. However, it is noteworthy to emphasize that the strong association between RTI and increased antibiotic prescription in women aged 16 to 54 years was also confirmed in the Swedish dataset and in a US study that analysed the rate of inappropriate antibiotic prescribing for acute RTI in ambulatory care.[9] The authors found that women had twice as many medical visits for RTI as men. In addition, female gender was associated with more inappropriate prescribing (male adjusted OR 0.74), defined as record of an ICD-9-CM code for viral RTI, viral bronchitis, viral pneumonia, influenza or pleurisy. However, epidemiological studies did not show an increased incidence of RTI in women. Falagas *et al.*[30] recently reported that males are more susceptible than females to otitis media, croup and lower RTI in all age groups.

Other reasons for gender differences in bacterial infections might be related to genetic background. The X chromosome's encoding for genes involved in regulation of immunity—such as Toll-like-receptors 7 and 8 (sensing viral pathogens), FOXP3 (transcription factor for regulatory T cells), CD40L (immunoglobulin class switching) and CD132 (X-linked severe combined immunodeficiency)—is differently represented in men and women. Further research is needed to assess the clinical impact of this difference.[31]

Difference in prescribing may also be driven by difference in social and behavioural factors. Women consult their general practitioners more frequently than men do.[32–35] Specifically, in a Dutch study, gender differences in yearly general-practitioner consultations were statistically significant for the young (18–22 years) and middle-age (45–49 years) groups, but this gender gap disappeared in the older age group (70–74 years).[32] These data were confirmed by an American study showing that women consult their general practitioners more frequently than men, although well known risk factors for bacterial infections (such as regular and heavy alcohol drinking, smoking, non-medical drug use and obesity) were more prevalent in men.[33]

Our data confirm that antibiotic prescriptions increase with age. This increase can easily be explained by physiological changes in specific immune-response patterns,[36] and higher use of antibiotics in the elderly population has already been documented.[18,37,38] The data also show a 'scissor phenomenon', with the trend of antibiotic prescribing in women and men inverted after 84 years of age, although not significantly. A possible explanation is the higher consultation rate of general practitioners[32] and increased UTI prevalence in men in this age group.

This meta-analysis has some limitations. First, prescription and dispensing do not equate to consumption. An overestimation may result from drugs that were not consumed, whereas an underestimation may occur for countries where antibiotics can easily be bought without medical prescription.[39] Second, the number of general-practitioner consultations is not available in any of the studies. This lack prevents us from defining with precision reasons for the overprescriptions for women. Third, when measuring consumption in DDD, the treatment duration and dosage affect the results. Fourth, an in-between country bias in DDD assignment was reported by Vander Stichele *et al.*[40] and Goossens *et al.*[41] Fifth, a significant heterogeneity measured using I^2 was detected for almost every subgroup. However, I^2 should be interpreted as the percentage of variability due to heterogeneity between studies rather than the sampling error and is in general of limited use in assessing clinically relevant heterogeneity. It is dependent on the precision and size of the studies included, and in the current analysis the sample size was very large, with a sampling error close to 0. Therefore, rather than I^2, the between-study variance τ^2 was used in our study. Finally, a lack of indications for the prescriptions limits the generalizability of the study.

In conclusion, women 16 to 54 years of age receive significantly more antibiotic prescriptions of cephalosporins and macrolides than men do. Current evidence on infectious-disease epidemiology by gender cannot fully explain this substantial difference.

Further research is necessary to determine whether a difference in adverse events, including resistance development, also occurs. In the struggle to balance rapid and successful treatment of an infection, minimizing possible adverse drug effects, and the urgent need to restrict antibiotic use in the community, physicians should keep in mind the risk of gender inequality of antibiotic prescription. Our results could play an influential role in designing antibiotic stewardship programmes that should also address reasons for gender inequality in prescription.

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Transparency declarations

None to declare.

Author contributions

W. S. and E. T. conceived and designed the study. W. S. and F. F. performed the literature review. H. S. and B. P. G. conducted the analysis of included studies. W. S. and E. T. wrote the first draft of the manuscript. W. S., H. S., B. P. G., F. F., J. H., B. E. and E. T. contributed to the writing of the article and agree with its content and conclusions.

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