

## Outpatient Macrolide Antibiotic Prescribing in the United States, 2008–2011

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National Ambulatory Medical Care Survey data were used to assess outpatient macrolide prescribing and selection. Conditions for which macrolides are firstline therapy represented 5% of macrolide prescribing. Family practitioners selected macrolides for children more frequently than pediatricians. Macrolides are an important antibiotic stewardship target.

**Keywords.** antibacterial agents; antibiotic; inappropriate prescribing; macrolide antibiotics.

Antibiotic use is the most important modifiable driver of antibiotic resistance, making judicious use of antibiotics critical to combatting antibiotic resistance. An estimated 30% of outpatient antibiotic prescribing in the United States is unnecessary [1]. Antibiotic prescribing for sinusitis, otitis media, and pharyngitis frequently results in nonrecommended antibiotic prescribing, with macrolides being the most common alternative antibiotic class prescribed [2]. Macrolides are infrequently recommended firstline therapies, suggesting that they are overprescribed. Previous research suggests variability in overall antibiotic prescribing rates among medical specialties [3], but whether this variability extends to macrolide antibiotic prescribing is unclear. Our objectives were to identify the most frequent diagnoses associated with macrolide prescribing among children and adults and to examine patient- and clinician-level factors associated with inappropriate macrolide selection.

### METHODS

The National Ambulatory Medical Care Survey (NAMCS) [4] from 2008–2011 was used to identify outpatient visits with macrolide prescriptions. In NAMCS, visits are sampled among

nonfederal, office-based physicians using 3-stage probability sampling for geographic regions, physicians, and then clinical visits within a 1-week reporting period. Reporting periods are distributed randomly throughout the year, and weights are assigned to visits to produce national estimates of antibiotic prescribing. Estimates are adjusted for physician and item non-response. Our analyses use publicly available, de-identified data from subjects deemed nonhuman by the National Center for Emerging and Zoonotic Diseases human subjects advisor and as such did not require institutional review board review. Captured at each visit are patient demographic characteristics and visit characteristics, including up to 3 diagnoses and 8 medications prescribed, continued, or provided at the visit. Text diagnoses abstracted from medical records are translated to *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes by medical coders.

We classified diagnoses into 3 mutually exclusive categories based on clinical guideline recommendations. “Macrolides firstline” includes conditions for which macrolides are a firstline therapy (eg, community-acquired pneumonia); “macrolides not firstline” includes conditions for which antibiotics may be recommended but macrolides are not firstline therapy (eg, acute sinusitis); and “antibiotics unnecessary” includes conditions for which antibiotics are unnecessary or antibiotic indications are unclear (eg, acute bronchitis) (Appendix Table 1). For conditions for which clinical guidelines are lacking, The Johns Hopkins Antibiotic Guide [5] was used to determine macrolide appropriateness. For visits with multiple diagnoses, we assigned a single diagnosis by giving priority to diagnoses in the following order: “macrolide firstline,” “macrolide not-firstline,” and, last, “antibiotics unnecessary.” For example, a visit with both community-acquired pneumonia (macrolide firstline) and acute bronchitis (antibiotics unnecessary) listed as diagnoses would be classified as “macrolide firstline.” We excluded visits requiring parenteral antibiotics with no mention of oral antibiotics.

To identify patients and clinician characteristics associated with macrolide selection, multivariable logistic regression was used with the outcome variable of macrolide prescribing among visits with antibiotics prescribed (i.e., macrolide selection). Variables included in the model were diagnostic category, patient age group (pediatric or adult), sex (male or female), race (white or nonwhite), medical specialty of clinician (pediatrics, internal medicine, family/general practice, or other specialty), insurance status (private or nonprivate), US Census region (West, South, Northeast, and Midwest), and metropolitan statistical area (metropolitan or nonmetropolitan). STATA 12 (StataCorp, College Station, TX) was used to perform statistical analyses. Estimates with fewer than 30 observations, or those

Received 21 June 2017; editorial decision 29 September 2017; accepted 4 October 2017.

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Open Forum Infectious Diseases®

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with a standard error of 30% or less, were not considered reliable and thus were not included. Visits were weighted to account for the multistage probability survey design. Alpha <0.05 was considered statistically significant.

## RESULTS

In 2008–2011, 2399 visits led to macrolide prescriptions in NAMCS, and the mean national estimate of doctors' office visits resulting in macrolide prescriptions was 24.4 million annually (9.0 million pediatric visits and 15.4 million adult visits) (Appendix Table 2). Conditions for which macrolides are a firstline recommended therapy represented only 5% (7% of pediatric and 5% of adult macrolide prescriptions) of all visits in which macrolides were prescribed (Appendix Table 3). Conditions for which antibiotics are unnecessary represented 52% (40% of pediatric and 60% of adult prescriptions) of macrolide prescriptions. The most common diagnoses associated with macrolide prescriptions were sinusitis (18% of visits), bronchitis/bronchiolitis (14%), viral upper respiratory infection (URI; 11%), and pharyngitis (11%). Among pediatric visits, acute otitis media accounted for 16% of macrolide prescribing. After controlling for age, diagnostic tier, and other patient characteristics, family practitioners had higher odds of selecting macrolides for children compared with pediatricians (adjusted odds ratio [AOR], 1.42; 95% confidence interval [CI], 1.05–1.94) (Table 1). No clinician specialty-level differences were identified for macrolide selection among adults. Other factors significantly associated with differences in macrolide selection included age group (pediatric visits), geographic region (both pediatric and adult visits), and insurance status (adult visits).

## DISCUSSION

Only a small proportion (5%) of macrolide prescribing is for conditions for which macrolides are a firstline therapy. When examining risk factors associated with higher macrolide prescribing, visits by children to family practitioners were more likely to result in macrolide selection compared with pediatrician visits. Significant differences in macrolide prescribing were associated with insurance type, geographic region, and age group. Nonrecommended macrolide prescribing is concerning given the importance of minimizing both antibiotic resistance and direct patient harms incurred due to inappropriate antibiotic use.

Macrolides as a specific antibiotic class are a viable target for outpatient antibiotic stewardship efforts due to their widespread overuse. Azithromycin is the single most commonly prescribed outpatient antibiotic in the United States, accounting for 54.1 million prescriptions in 2011, or 174 prescriptions per 1000 persons [3]. Macrolides are the second most common antibiotic class prescribed in the United States [3]. However, the small proportion of macrolide prescriptions representing firstline

recommended therapy in our study suggests that inappropriate macrolide prescribing is highly prevalent.

Inappropriate macrolide prescribing can be broadly categorized as either unnecessary antibiotic use or inappropriate macrolide selection. Unnecessary antibiotic use for bronchitis and viral URI represent easy targets for stewardship interventions as visits for these conditions should not result in an antibiotic. The high proportion of macrolide prescribing represented for conditions for which antibiotics may be indicated, but for which macrolides are not firstline, suggests that much opportunity for improvement remains regarding macrolide selection. Macrolides are frequently prescribed for sinusitis, acute otitis media, and pharyngitis. However, macrolides are a suboptimal choice for treating these infections due to increasing levels of *Streptococcus pneumoniae* and group A *Streptococcus* macrolide resistance [6–8]. Concern for decreasing effectiveness has led to national guidelines recommending against using macrolides for acute otitis media and sinusitis, regardless of penicillin allergy [6, 7]. However, macrolides are recommended for penicillin allergy in pharyngitis, and penicillin allergy evaluation may help address inappropriate macrolide selection [8]. Both unnecessary antibiotic use and inappropriate macrolide selection are inconsistent with known best practices for outpatient infections and put patients at risk for suboptimal outcomes and preventable adverse drug events. As increases in macrolide prescribing have been associated with increases in antibiotic resistance [9, 10], it is imperative that antibiotic stewardship efforts reserve macrolides for infections that clearly benefit from macrolide treatment, such as community-acquired pneumonia, sexually transmitted infections, shigellosis, or pertussis.

For pediatric visits resulting in antibiotic prescriptions, family practitioners were more likely to select macrolides compared with pediatricians, when controlling for patient age, diagnosis, and other factors. Differences between family practitioners and pediatricians regarding management of pediatric patients have been observed [11], but less is known regarding factors that may contribute to differences in antibiotic selection. This finding highlights meaningful differences in antibiotic selection for pediatric visits depending on clinician specialty. All clinicians providing care to children need to be engaged in outpatient stewardship, and outpatient pediatric stewardship initiatives need to extend beyond pediatricians. Stewardship efforts targeting family practitioners may be particularly important given their higher odds of macrolide selection for pediatric visits. Finally, for children, older patient age and private insurance were associated with higher levels of macrolide prescribing, and these may be considerations for targeted outpatient stewardship outreach.

Our study has limitations. We are unable to verify the accuracy of clinician-assigned diagnoses, and we are unable to stratify

**Table 1. Characteristics Associated With Macrolide Prescribing Among Pediatric and Adult Physician Office Visits Resulting in an Antibiotic, 2008–2011**

Characteristic	Pediatric Visits		Adults Visits	
	Visits in Which Macrolides Were Selected (95% CI), %	AOR (95% CI)	Visits in Which Macrolides Were Selected (95% CI), %	AOR (95% CI)
<b>Age, y</b>				
0–2	16 (13–19)	1.00	N/A	N/A
3–9	23 (20–27)	1.63 (1.24–2.13)	N/A	N/A
10–19	27 (24–30)	1.97 (1.51–2.58)	N/A	N/A
20–64	N/A	N/A	22 (20–23)	1.00
≥65	N/A	N/A	17 (14–21)	0.88 (0.68–1.13)
<b>Diagnosis</b>				
Macrolides firstline	54 (41–66)	1.00	43 (34–51)	1.00
Macrolides not firstline	17 (15–20)	0.16 (0.09–0.27)	17 (15–19)	0.23 (0.15–0.36)
Antibiotics unnecessary	31 (27–36)	0.35 (0.21–0.60)	22 (20–25)	0.40 (0.25–0.65)
<b>Region</b>				
Northeast	25 (20–31)	1.00	27 (21–33)	1.00
Midwest	19 (16–23)	0.67 (0.46–0.97)	20 (17–22)	0.57 (0.40–0.81)
South	23 (20–28)	1.00 (0.69–1.45)	18 (16–20)	0.58 (0.40–0.84)
West	22 (17–28)	0.88 (0.55–1.42)	20 (17–24)	0.69 (0.45–1.06)
<b>Specialty</b>				
Pediatrics	21 (18–24)	1.00	N/A	N/A
Internal medicine	N/A	N/A	23 (20–27)	1.00
Family/general practice	30 (26–35)	1.42 (1.05–1.94)	25 (23–27)	1.17 (0.89–1.53)
Other specialty <sup>a</sup>	19 (16–24)	0.64 (0.46–0.88)	13 (10–17)	0.46 (0.32–0.66)
<b>Sex</b>				
Male	23 (20–26)	1.00	21 (18–23)	1.00
Female	22 (20–25)	0.93 (0.78–1.12)	20 (19–22)	0.99 (0.84–1.17)
<b>Insurance</b>				
Private	24 (21–27)	1.00	22 (20–24)	1.00
Nonprivate <sup>b</sup>	22 (19–25)	0.85 (0.69–1.05)	18 (16–20)	0.79 (0.65–0.95)
<b>Race</b>				
White	23 (20–25)	1.00	20 (18–22)	1.00
Nonwhite	23 (19–27)	0.91 (0.71–1.17)	23 (19–27)	1.28 (1.01–1.62)
<b>Gender</b>				
Male	23 (20–26)	1.00	21 (18–23)	1.00
Female	22 (20–25)	0.93 (0.78–1.12)	20 (19–22)	0.99 (0.84–1.17)
<b>Metropolitan statistical area</b>				
Nonmetropolitan	21 (17–27)	1.00	20 (17–23)	1.00
Metropolitan	23 (20–25)	1.25 (0.92–1.70)	21 (19–22)	1.11 (0.88–1.40)
<b>Year</b>				
2008	22 (18–27)		18 (16–21)	
2009	22 (18–27)		19 (17–22)	
2010	23 (19–27)		22 (18–27)	
2011	23 (20–28)		22 (18–26)	

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

<sup>a</sup>Internal medicine visits for children and pediatric visits for adults were classified as Other specialty.

<sup>b</sup>Includes Medicare, Medicaid, Children's Health Insurance Plan, self-pay, and other nonprivate insurance.

prescribing by provider type (eg, physician assistants and nurse practitioners). NAMCS collects a sample of office-based visits rather than patients; therefore, it is possible that multiple visits for the same illness episode may be captured. Finally, telephone or e-mail encounters are not captured. However, NAMCS is nationally representative and combines prescribing information with clinical data. Four years of data were needed to combine to increase sample size, and sampling changes in 2012 limited

the comparability of more recent data to previous years. No information about drug allergy is included in NAMCS, so there was no information about drug allergy accounted for in our analyses.

Outpatient antibiotic stewardship in the United States has largely focused on improving antibiotic prescribing by targeting specific conditions for improvement. However, our study suggests that macrolides may warrant a novel

stewardship approach by targeting this particular class of antibiotics. The *Core Elements of Outpatient Antibiotic Stewardship* provides a framework for improving antibiotic prescribing, including macrolides, among both individual clinicians and organizations involved in outpatient health care [12]. Meaningful improvements in antibiotic resistance and patient safety can be made through intentional and concerted efforts aimed at optimizing antibiotic use, including macrolide antibiotics.

### Acknowledgements

**Author contributions.** Mr. Sanchez and Dr. Fleming-Dutra had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: all authors. Acquisition and interpretation of data: all authors. Drafting of the manuscript: Sanchez, Fleming-Dutra, Hicks. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Shapiro, Hersh. Administrative, technical, or material support: Sanchez, Fleming-Dutra. Study supervision: Fleming-Dutra, Hicks.

**Disclaimer.** The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of Centers for Disease Control and Prevention.

**Financial support.** Funding for this study was provided by the Centers for Disease Control and Prevention (Atlanta, GA).

**Potential conflicts of interest.** All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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## APPENDIX

**Appendix Table 1. Tiered Classification of Diagnoses by Macrolide Treatment Recommendations**

Category	Assigned Diagnoses
Macrolides firstline [1, 3–10]	Pneumonia (including atypical pneumonia), nontuberculosis mycobacteria disease, pertussis, cat scratch disease ( <i>Bartonella</i> ), chancroid ( <i>H. ducreyi</i> ), cervicitis and endocervicitis, urethritis, sexually transmitted infections, babesiosis, other gonococcal or chlamydia infection, infectious diarrhea/traveler's diarrhea, granuloma inguinale, shigellosis, peptic ulcer disease, <i>H. pylori</i> infection, chronic obstructive pulmonary disease exacerbation
Macrolides not firstline [2-4, 11–16]	Pharyngitis, strep throat, scarlet fever, sinusitis, acute otitis media, urinary tract infections, acne, gastrointestinal infections (excluding shigellosis), pelvic inflammatory disease, skin and mucosal infections, and other miscellaneous bacterial infections (eg, syphilis, tuberculosis, Lyme disease)
Antibiotics unnecessary [1, 3, 16–20]	All other conditions, including allergic rhinitis, asthma, acute bronchitis and bronchiolitis, influenza, nonsuppurative otitis media, and viral upper respiratory infection

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**Appendix Table 2. Characteristics of Visits at Which Macrolides Were Prescribed, 2008–2011**

Characteristic	Percentage of Pediatric Visits (95% CI) (n = 869)	Percentage of Adult Visits (95% CI) (n = 1530)
Age, y		
0–2	21 (17–25)	N/A
3–9	38 (34–42)	N/A
0–19	42 (37–46)	N/A
20–64	N/A	78 (74–82)
65+	N/A	22 (18–26)
Region		
Northeast	19 (14–27)	24 (18–32)
Midwest	17 (12–23)	21 (16–27)
South	43 (35–52)	35 (28–42)
West	21 (14–30)	20 (16–26)
Specialty		
Pediatrics	61 (54–68)	N/A
Internal medicine	N/A	28 (23–34)
Family/general practice	28 (22–35)	50 (44–56)
Other specialty <sup>a</sup>	11 (8–15)	22 (17–28)
Sex		
Male	51 (47–54)	37 (34–40)
Female	49 (46–53)	63 (60–66)
Year		
2008	25 (19–31)	22 (18–27)
2009	23 (18–28)	23 (19–28)
2010	26 (20–32)	29 (24–36)
2011	27 (22–32)	25 (20–31)
Metropolitan statistical area		
Nonmetropolitan	11 (6–18)	11 (6–20)
Metropolitan	89 (82–94)	89 (80–94)
Race		
White	83 (79–87)	84 (80–87)
Nonwhite	17 (13–21)	16 (13–20)
Insurance		
Private	66 (61–71)	65 (61–69)
Nonprivate <sup>b</sup>	34 (29–39)	35 (31–39)

<sup>a</sup>Internal medicine visits for children and pediatric visits for adults were classified as Other specialty.

<sup>b</sup>Includes Medicare, Medicaid, Children's Health Insurance Plan, self-pay, and other.



**Appendix Table 3. Average Annual Number, in Millions, of Adult and Pediatric Visits (95% CI) and Percentage of Visits in Which Macrolides Were Prescribed, by Diagnosis, 2008–2011**

Diagnosis	Pediatric Macrolide Prescribing		Adult Macrolide Prescribing	
	No., Millions (95% CI)	Percentage (95% CI)	No., Millions (95% CI)	Percentage (95% CI)
Macrolides firstline	0.6 (0.4–0.9)	7 (5–10)	0.7 (0.5–0.9)	5 (3–6)
Pneumonia	0.5 (0.3–0.8)	6 (4–9)	0.3 (0.2–0.5)	2 (2–3)
Macrolides not firstline	4.7 (3.8–5.6)	53 (48–57)	5.4 (4.5–6.3)	35 (32–39)
Pharyngitis, strep throat, scarlet fever,	1.3 (0.8–1.7)	14 (11–18)	1.3 (0.9–1.7)	9 (7–11)
Sinusitis	1.5 (1.0–1.9)	16 (12–21)	2.9 (2.3–3.5)	19 (16–22)
Acute otitis media	1.4 (1.0–1.9)	16 (12–21)	-	-
Antibiotics unnecessary	3.6 (2.8–4.5)	40 (36–45)	9.2 (7.7–10.8)	60 (56–64)
Asthma, allergy	0.3 (0.2–0.4)	3 (2–5)	0.6 (0.4–0.8)	4 (3–5)
Bronchitis, bronchiolitis	1.2 (0.8–1.6)	13 (10–17)	2.2 (1.7–2.7)	14 (12–17)
Viral upper respiratory infection	0.9 (0.6–1.2)	10 (8–13)	1.8 (1.3–2.3)	12 (9–15)
All remaining codes	1.2 (0.8–1.7)	14 (10–18)	4.7 (3.5–5.8)	30 (25–36)
All conditions (total)	9.0 (7.4–10.6)	100	15.4 (13.2–17.6)	100

Insufficient visits were available to produce reliable estimates of adult macrolide prescribing for acute otitis media.