abstract

BACKGROUND AND OBJECTIVES: Antimicrobials are frequently prescribed for acute respiratory tract infections (ARTI), although many are viral. We aimed to determine bacterial prevalence rates for 5 common childhood ARTI - acute otitis media (AOM), sinusitis, bronchitis, upper respiratory tract infection, and pharyngitis - and to compare these rates to nationally representative antimicrobial prescription rates for these ARTI.

METHODS: We performed (1) a meta-analysis of English language pediatric studies published between 2000 and 2011 in Medline, Embase, and the Cochrane library to determine ARTI bacterial prevalence rates; and (2) a retrospective cohort analysis of children age <18 years evaluated in ambulatory clinics sampled by the 2000–2010 National Ambulatory Medical Care Survey (NAMCS) to determine estimated US ARTI antimicrobial prescribing rates.

RESULTS: From the meta-analysis, the AOM bacterial prevalence was 64.7% (95% confidence interval [CI], 50.5%–77.7%); *Streptococcus pyogenes* prevalence during pharyngitis was 20.2% (95% CI, 15.9%–25.2%). No URI or bronchitis studies met inclusion criteria, and 1 sinusitis study met inclusion criteria, identifying bacteria in 78% of subjects. Based on these condition-specific bacterial prevalence rates, the expected antimicrobial prescribing rate for ARTI overall was 27.4% (95% CI, 26.5%–28.3%). However, antimicrobial agents were prescribed in NAMCS during 56.9% (95% CI, 50.8%–63.1%) of ARTI encounters, representing an estimated 11.4 million potentially preventable antimicrobial prescriptions annually.

CONCLUSIONS: An estimated 27.4% of US children who have ARTI have bacterial illness in the post-pneumococcal conjugate vaccine era. Antimicrobials are prescribed almost twice as often as expected during outpatient ARTI visits, representing an important target for ongoing antimicrobial stewardship interventions. Pediatrics 2014;134:e956–e965

WHAT’S KNOWN ON THIS SUBJECT: Many pediatric acute respiratory tract infections (ARTI) are viral and do not require antimicrobial treatment. Recent estimates of antimicrobial overprescribing for these infections, defined based on the published bacterial disease prevalence among all ARTI, are not available.

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KEY WORDS: infectious diseases epidemiology, otitis media

ABBREVIATIONS

AOM—acute otitis media

ARTI—acute respiratory tract infections

CI—confidence interval

GAS—group A streptococcal

ICD-9-CM—International Classification of Diseases, Ninth Revision, Clinical Modification

NAMCS—National Ambulatory Medical Care Survey

PCV—pneumococcal conjugate vaccine

URI—upper respiratory infection

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Antimicrobial prescribing for childhood acute respiratory tract infections (ARTI), including acute otitis media (AOM), sinusitis, bronchitis, upper respiratory infection (URI), and pharyngitis, is common in the United States. An estimated 31.7 million visits for respiratory conditions result in antimicrobial prescriptions annually, accounting for >70% of outpatient visits during which antimicrobial agents are prescribed to children.

Recent guidelines exist for AOM, sinusitis, and group A streptococcal (GAS) pharyngitis, and it is widely accepted that pediatric bronchitis and URI are caused by viral pathogens and antimicrobial treatment is unnecessary. Yet previously observed declines in antimicrobial prescribing for ARTI may have been driven primarily by decreased ARTI office visit rates, and antimicrobial prescribing for pediatric URI continues to occur.

Antimicrobial use is associated with increased resistance among bacteria that cause ARTI, posing both individual and community risks. The large number of annual ambulatory ARTI visits and the frequency of antimicrobial prescribing during those visits make ambulatory ARTI an important target for efforts to reduce unnecessary antimicrobial use. Although the introduction of the pneumococcal conjugate vaccine (PCV) in 2000 has altered AOM microbiology specifically over time, no study has comprehensively examined bacterial prevalence rates among uncomplicated ARTI diagnosed in previously healthy children since the introduction of PCV.

Our study had 2 objectives: first, to perform a meta-analysis of studies examining the microbiology of pediatric AOM, sinusitis, bronchitis, URI, and pharyngitis published between 2000 and 2011, to determine expected prevalence rates for bacteria among these conditions; and second, to evaluate estimated current national ambulatory antimicrobial prescribing rates for these 5 ARTI and compare them to those expected based on bacterial prevalence.

**METHODS**

**Meta-Analysis Search Methods**

We were interested in ARTI microbiology changes after PCV introduction in 2000, and wanted to compare those to the most recent available national prescribing data, which were from 2010. We therefore searched Medline, Embase, and Cochrane databases for articles published between January 1, 2000 and January 31, 2012 on the microbial etiology of AOM, sinusitis, bronchitis, URI, and pharyngitis in previously healthy children (Supplemental Figs 3–7). We searched major subject headings including “microbiology” and “acute otitis media;” “sinusitis;” “bronchitis;” “upper respiratory infection” or “URI;” and “pharyngitis,” limited to children <18 years of age. One evaluator (MPK) screened all studies for potential inclusion. We abstracted data from the included full-length articles. We examined references in review articles to identify additional studies for inclusion.

**Inclusion Criteria**

We used a priori inclusion and exclusion criteria. For all ARTI, we included studies conducted in ambulatory or hospital-based ambulatory clinics in which all subjects had sampling to identify bacterial etiologies. We included AOM studies in which >50% of cultures were obtained by tympanocentesis, sinusitis studies in which samples were obtained by sinus puncture or direct middle meatus aspirate, bronchitis and URI studies in which culture samples were obtained by using invasive methods (eg, bronchoscopy), and pharyngitis studies in which all subjects had GAS cultures performed.

**Exclusion Criteria**

We excluded studies by title, then abstract, then full text. We excluded studies that did not include microbiologic data for all subjects, detected pathogens by polymerase chain reaction alone, studied subjects who had chronic symptoms, included subjects who had antimicrobial exposure in the 48 hours before enrollment, enrolled all subjects before PCV licensure in 2000 (for ARTI except pharyngitis), studied inpatients or immunocompromised subjects, and those not published in English.

Because we were interested in determining the bacterial prevalence rate among all subjects who had ARTI, we also excluded studies that only cultured for a single organism. Surface, nasopharyngeal, oropharyngeal, and ototympanum culture methods can collect both normal colonizing flora and pathogens present as colonizing flora. Thus, we excluded sinusitis studies with cultures obtained by nasopharyngeal swab, bronchitis and URI studies with cultures obtained by nasopharyngeal or oropharyngeal swab, and AOM studies in which >50% of microbiologic samples were obtained by culturing spontaneous ototympanum. We also excluded studies that relied only on rapid antigen testing to identify GAS and those that did not discriminate between GAS and other streptococcal species.

**Assessing ARTI Prescribing and Visit Rates Using the National Ambulatory Medical Care Survey**

To determine national estimates for ARTI antimicrobial prescribing, we used the National Ambulatory Medical Care Survey (NAMCS), a survey administered by the National Center for Health Statistics that collects patient visit data from community, non-federally funded, office-based physician practices throughout the United States. The survey uses a multistage probability design in selecting physicians and patients for participation, and can be used to generate national estimates of disease and prescribing patterns.
We analyzed NAMCS 2000 to 2010 data to determine the annual rate of outpatient ARTI visits to pediatricians, general, and family practitioners and antimicrobial prescribing rates during ARTI visits. We used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes to identify subjects who had AOM, sinusitis, bronchitis, URI, and pharyngitis (Table 1). We defined these codes as restrictive, including just those codes for acute ARTIs, or permissive, including both the restrictive codes and additional ICD-9-CM codes for related illnesses used in previous similar studies (eg, 473.9: unspecified sinusitis [chronic]). 10 We identified antimicrobial agents using the proprietary M ultim Lexicon system.

The ARTI visit rate was estimated by the proportion of visits with an ARTI diagnosis both among all outpatient visits and per 1000 population, using US census data to derive population-based visit rates. When more than 1 ARTI condition was present simultaneously, the encounter contributed to visit rates for each condition present.

Assessing Expected Prescribing Rates for ARTI

From the meta-analysis we estimated the prevalence of bacterial infection for ARTI individually, and defined the expected antimicrobial prescribing rate as the bacterial prevalence rate. Antimicrobial prescribing rates were estimated as proportions of ARTI visits with specific antimicrobial agents prescribed among all outpatient ARTI visits. We calculated the expected antimicrobial prescribing rate for ARTI overall as a weighted average of bacterial ARTI rates, by using the estimated national prevalence of each included condition as its weight. We defined potentially preventable prescriptions as the difference between the expected and observed antimicrobial prescribing rates. We additionally performed a sensitivity analysis in which we set the expected antimicrobial prescribing rate at 100% for children <2 years of age who had AOM and for all children who had sinusitis, based on current guideline recommendations, and reassessed the rate of potentially preventable prescriptions.

Based on guidelines, we defined first-line therapy as follows: amoxicillin for AOM, amoxicillin or amoxicillin/clavulanate for sinusitis, penicillin or amoxicillin for GAS pharyngitis, and no antimicrobial agents for bronchitis or URI. We defined all other antimicrobial prescriptions as second-line. When more than 1 ARTI condition was present simultaneously, we used the following hierarchy to attribute antimicrobial prescribing to just 1 of the present conditions and determine if the antimicrobial was first-line: sinusitis with other ARTI > AOM with other ARTI > pharyngitis with other ARTI > URI with bronchitis > bronchitis (see Table 2 for examples). For AOM studies in the meta-analysis, we defined resistant bacterial strains that required second-line therapy as those Streptococcus pneumoniae that were penicillin- or amoxicillin-resistant, β-lactamase producing, Haemophilus influenzae or Moraxella catarrhalis, Staphylococcus aureus, and enteric Gram-negative rods. We additionally examined time trends in first- and second-line therapy for ARTI.

Statistical Methods

For the meta-analysis, we first assessed study heterogeneity by using the I² statistic, and after significant heterogeneity across studies was detected, we applied random effects models to estimate the overall bacterial prevalence and 95% confidence interval (CI). 16 The random effects model for meta-analysis assumes the observed effect sizes can vary across studies because of real differences in the treatment effect in each study as well as sampling variability. This model allows explicit accounting for between-study heterogeneity. 17 All national visit and prescribing estimates accounted for the survey design and were weighted by the sampling weights provided in NAMCS.

We applied linear regression models with year as the main predictor to test whether rates of ARTI visits, antimicrobial prescribing, and first- and second-line prescribing for ARTI changed over time. A paired t test was used to compare prescribing rates identified using restrictive versus permissive diagnosis code definitions. Analysis was performed by using Stata 12.1 (Stata Corp, College Station, TX) and R 3.0.2 (Vienna, Austria). The Seattle Children’s Hospital Institutional Review Board approved this study.

RESULTS

Description of Studies

AOM

For AOM, the search strategy identified 867 articles and examination of review articles identified 1 additional study. We excluded 746 based on title, 49 based on abstract, and were unable to obtain full-text on 2 articles. We reviewed 71 full-text articles, of which 12 were included (Supplemental Fig 3). 12,18,21,30–38,41,43–44
Mean age was available in 6 (50%) studies and averaged 23.1 months. Gender was reported in 8 (66.7%) studies and on average 60.8% of participants were male. The majority of studies (9 out of 12, 75%) were conducted in an outpatient setting, with 3 (25%) recruited from hospital-based ambulatory pediatric (2 studies) or otolaryngology clinics (1 study, Supplemental Appendix 1). The median number of subjects per study was 121 (mean, 295; interquartile range, 92–377). Bacterial samples were obtained by tympanocentesis alone in 5 (42%) included studies, and by tympanocentesis or swab of ear canal contents from those who had spontaneous tympanic membrane perforation of <24 hours’ duration in 7 (58%). Bacteria were isolated during an estimated 64.7% (95% CI, 50.5%–77.7%) of AOM episodes. Among AOM episodes in which bacteria were isolated, S pneumoniae was isolated in 44.1% (95% CI, 34.6%–53.8%), H influenzae in 36.3% (95% CI, 28.3%–44.8%), M catarrhalis in 7.5% (95% CI, 4.5%–11.2%), S pyogenes in 5.5% (95% CI, 0.9%–12.8%), and all other bacteria in 6.6% (95% CI, 0.1%–19.5%). An estimated 35.0% (95% CI, 23.8%–47.0%) of AOM bacterial isolates required second-line therapy.

**Sinusitis**

For sinusitis, the search strategy identified 649 articles. We excluded 579 based on title, 35 based on abstract, and were unable to obtain full-text on 1 article. We reviewed 34 full-text articles, of which 1 article met inclusion criteria (Supplemental Fig 4), precluding meaningful analyses in this group.45 This study included 58 children, among whom 45 (78%) had bacteria isolated. No mention was made regarding subjects’ previous antimicrobial exposure.

**Bronchitis and URI**

For bronchitis, the search strategy identified 706 articles. We excluded 690 based on title and 13 based on abstract. We reviewed 3 full-text articles, of which none met inclusion criteria (Supplemental Fig 5).

For URI, the search strategy identified 347 articles, and examination of review articles identified 1 additional study. We excluded 325 based on title and 6 based on abstract. We reviewed 15 full-text articles, of which none met inclusion criteria (Supplemental Fig 6).

**Pharyngitis**

For pharyngitis, the search strategy identified 836 articles. We excluded 762 based on title, 43 based on abstract, and were unable to obtain full-text on 1 article. We reviewed 30 full-text articles, of which 11 were included (Supplemental Fig 7).46–56 Previous antimicrobial exposure was not mentioned in 4 studies but was assumed to be absent owing to the studies’ prospective nature51,53 and subjects’ acute presentation55,56. Mean age was available in 6 (55%) studies and averaged 75.6 months (Supplemental Appendix 2). Gender was available in 8 (73%) studies and 54% of the participants were male. The majority of studies (8, 73%) were conducted in an ambulatory setting, with 3 recruited through an emergency department, a hospital-based ambulatory otolaryngology clinic, or both an emergency department and an outpatient clinic (1 each). The median number of subjects per study was 454 (interquartile range, 355–568). GAS was isolated during 20.2% (95% CI, 15.9%–25.2%) of all pharyngitis episodes.

**National ARTI Visit and Prescribing Estimates**

Using restrictive diagnosis definitions, overall, the 5 ARTI occurred at an average annual rate of 525 (95% CI, 456–594) per 1000 population and represented a mean of 27.0% (95% CI, 22.8%–31.1%) of all ambulatory clinic visits for US children to pediatricians and general/family practitioners during the study (Fig 1A and B). A mean of 12.8% (95% CI, 9.5%–16.2%) of ARTI visits included ≥2 simultaneous ARTI diagnoses. Population-based visit rates did not change significantly over time for the 5 ARTI overall (P = .76), nor for the proportion of ambulatory visits attributable to ARTI overall (P = .11), AOM (P = .08), bronchitis (P = .15), or pharyngitis (P = .63). Over time there was a significant increase in sinusitis visits (0.05% per year; P = .01) and decrease in URI visits (0.02% per year; P = .04), but these do not represent clinically meaningful visit rate changes. Visit rates for ARTI overall were significantly higher using the alternate permissive diagnosis definitions (difference = 3.1%; P = .002).

Mean annual national prescribing rates for the 5 conditions were as follows: AOM, 85.9% (95% CI, 80.4%–91.4%); sinusitis, 88.8% (95% CI, 86.8%–100%); bronchitis, 71.5% (95% CI, 54.9%–88.1%); URI, 24.4% (95% CI, 16.7%–32.2%); and pharyngitis, 56.9% (95% CI, 48.5%–65.3%). There was no significant linear trend in the overall antimicrobial prescribing rates for ARTI over time (P = .84), nor was there a significant linear (increasing or decreasing) trend in prescribing rates for any individual ARTI.
Adjusting for ARTI frequency, the annual antimicrobial prescribing rate ranged from 51.5% to 61.6% among ARTI visits between 2000 and 2010. A mean of 56.9% (95% CI, 50.8%–63.1%) of ARTI encounters resulted in antimicrobial prescriptions overall (Fig 2). Based on the meta-analysis-derived expected bacterial prevalence rates for the 5 conditions, the expected ARTI prescribing rate as a whole was 27.4% (95% CI, 26.5%–28.3%; Table 3). ARTI prescribing rates overall were not significantly higher using permissive diagnosis definitions (difference, 1.2%; P = .36). In the base-case analysis, we estimated that 11.4 million potentially preventable antimicrobial prescriptions for ARTI occurred annually. In the sensitivity analysis in which all children <2 years of age who had AOM and all children <18 years of age who had sinusitis were expected to receive antimicrobial agents, there were 9.4 million annual potentially preventable prescriptions. Overall, a mean of 59.0% (95% CI, 52.2%–65.8%) of ARTI encounters received first-line therapy (including no antimicrobial therapy for bronchitis and URI). By individual ARTI, first-line therapy rates were as follows: AOM, 46.2% (95% CI, 36.6%–55.8%); sinusitis, 55.0% (95% CI, 17.4%–92.6%); bronchitis, 28.5% (95% CI, 11.9%–45.2%); URI, 75.6% (95% CI, 67.8%–83.3%); and pharyngitis, 58.5% (95% CI, 40.4%–76.6%).

**FIGURE 1**

A. Population-based outpatient visit rates for ARTI using restrictive definitions, both individually and in aggregate, by year. B. Proportion of all outpatient visits accounted for by ARTI using restrictive definitions, both individually and in aggregate, by year. Horizontal lines indicate overall means. Vertical bars represent 95% CI. Red triangles represent subjects of all ages; blue open circles represent subjects <5 years of age; black closed circles represent subjects 5 to 17 years of age.
DISCUSSION

Our study presents the most recent available estimates since PCV introduction for the bacterial prevalence among 5 common ARTI: AOM, sinusitis, pharyngitis, bronchitis, and URI, providing evidence-based target prescribing rates for these conditions. We further demonstrate that national ARTI antimicrobial prescribing rates are almost twice the expected rate based on bacterial prevalence. This represents 11.4 million potentially avoidable antimicrobial prescriptions annually, a number that has not decreased significantly over the preceding decade. Curbing unnecessary antimicrobial use for outpatient pediatric ARTI is a pressing concern; more than half of all outpatient antimicrobial prescribing to children is for ARTI, representing more than 25 million visits annually. However, discriminating bacterial from viral ARTI in the outpatient clinical setting is difficult. Although the rapid streptococcal antigen test is a sensitive and specific way to identify pharyngitis episodes requiring antimicrobial therapy, tympanocentesis and sinus puncture are impractical in routine ambulatory care. Clinicians currently lack tools to distinguish viral and bacterial causes in ARTI other than pharyngitis, so the bacterial prevalence rate may be an unreasonable target rate for antimicrobial prescribing. Nonetheless, our sensitivity analysis, assuming that all children who have sinusitis and all those 2 years of age who have AOM should be prescribed antimicrobial agents, still demonstrated an estimated 9.4 million potentially preventable antimicrobial

FIGURE 1
Continued.

![Graphs showing prevalence of ARTI conditions over time](http://pediatrics.aappublications.org/Downloaded from)
prescriptions annually from among those who had bronchitis, URI, pharyngitis, and those >2 years of age who had AOM. Knowing that antimicrobial agents are often overprescribed for outpatient ARTI may give providers an additional point of reference in their clinical decision-making for whether to prescribe antimicrobial agents for a given patient, and may help providers discuss contingency antimicrobial prescriptions, watch-and-wait strategies, or other approaches with families. Rapid diagnostic tools to discriminate bacterial from viral causes of ARTI other than pharyngitis are urgently needed and could help decrease unnecessary antimicrobial prescribing.

The strengths of our study include our evidence-based identification of ARTI bacterial prevalence rates, use of a nationally representative database, and conservative hierarchical method for assigning antimicrobial prescriptions to visits with more than 1 simultaneous ARTI condition, a strategy not used by other ARTI studies using NAMCS previously. Our study nonetheless has limitations. A single investigator reviewed the literature search results, leading to potential inappropriate study inclusion or exclusion in the meta-analysis. However, any single study would likely not have influenced the point estimate of AOM bacterial prevalence substantially. Further, a meta-analysis of pharyngitis identified

FIGURE 2
Antimicrobial prescription rates in outpatient ARTI visits using restrictive definitions, both individually and in aggregate, by year. Horizontal lines indicate overall means. Vertical bars represent 95% CI. Red triangles represent subjects of all ages; blue open circles represent subjects <5 years of age; black closed circles represent subjects 5 to 17 years of age. No CI is available for the 2009 sinusitis estimate because there was no variation across subjects (100% of subjects received antimicrobial agents).
children.3–5 In addition, a number of studies have focused on the use of antibiotics for acute respiratory tract infections (ARTIs). Among these studies, the American Academy of Pediatrics (AAP) recently published a clinical practice guideline for acute bacterial rhinosinusitis in children.6

Estimates are reported in thousands by convention.58

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<tr>
<th>Condition</th>
<th>Annual Visits in Thousands</th>
<th>Visits With Antimicrobial Prescription in Thousands</th>
<th>Expected Bacterial Pathogen in Thousands</th>
<th>Potentially Preventable Antimicrobial Prescriptions in Thousands</th>
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<tr>
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<td>10 598 (27.4)</td>
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<td>3153 (27.4)</td>
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<th>Condition</th>
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<td>10 598 (27.4)</td>
<td>11 429</td>
</tr>
</tbody>
</table>

Table 3. Estimated Annual Visits and Antimicrobial Prescriptions For ARTI

For 3 conditions (sinusitis, URI, and bronchitis), 1 study met the inclusion criteria, limiting meaningful analysis of bacterial prevalence rates. There are limited studies available to identify the bacterial prevalence rates in acute sinusitis, the best of which significantly antedates PCV introduction in 2000.58 That study nonetheless found that 70% of sinusitis episodes were bacterial in origin, a rate similar to the single more recent study (78%).

CONCLUSIONS

These data provide evidence-based antimicrobial prescribing rate targets for children treated in the outpatient setting for AOM, sinusitis, pharyngitis, bronchitis, and URI. Future interventions are needed to reduce ongoing unnecessary antimicrobial prescribing for these common childhood infections.

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Bacterial Prevalence and Antimicrobial Prescribing Trends for Acute Respiratory Tract Infections
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