Antimicrobial Use in Defined Populations of Infants and Young Children

Jonathan A. Finkelstein, MD, MPH; Joshua P. Metlay, MD, PhD; Robert L. Davis, MD, MPH; Sheryl L. Rifas-Shiman, MPH; Scott F. Dowell, MD, MPH; Richard Platt, MD, MS

Background: Antimicrobial overprescribing contributes to bacterial resistance, but data on use in infants and young children are limited.

Objectives: To assess antimicrobial use in a defined population of infants and young children and to determine diagnosis-specific prescribing rates for common infections.

Design and Setting: Retrospective cohort study of children served by 44 practices affiliated with 2 managed care organizations.

Patients: Children aged 3 months to 72 months enrolled in either health plan between September 1, 1994, and August 31, 1996.

Analysis: Rates of antimicrobial use were calculated as the number of pharmacy dispensings divided by the number of person-years of observation contributed to the cohort in 2 age groups (3 to <36 months and 36 to <72 months). Other outcomes included the distribution of diagnoses associated with antimicrobial dispensing and population-based rates of diagnosis of common acute respiratory tract illnesses.

Results: A total of 46,477 children contributed 59,710 person-years of observation across the 2 health plans. Rates of antimicrobial dispensing for children aged 3 to 36 months were 3.2 and 2.1 dispensings per person-year in the 2 populations. A substantial fraction of younger children (35% in population A and 23% in population B) received 4 or more antimicrobial prescriptions in a single year. For children aged 36 to 72 months, the dispensing rates for the 2 populations were 2.0 and 1.5 antimicrobials per person-year. We found significant differences in rates between the populations studied and a decrease in use at all sites from 1995 to 1996. The diagnosis of otitis media accounted for 56% of antimicrobial drugs dispensed to children aged 3 to 36 months and 40% of those dispensed to children aged 36 to 72 months. Antimicrobial prescribing for colds and upper respiratory tract infections, bronchitis, and sinusitis was less frequent than previously reported but accounted for 10% to 14% of antimicrobial drugs dispensed.

Conclusions: In these populations, otitis media accounted for the largest number of antimicrobial agents dispensed to children younger than 6 years. Clearly inappropriate indications such as cold, upper respiratory tract infection, and bronchitis accounted for smaller fractions of antimicrobial use but may be most amenable to change. However, interventions that encourage use of strict criteria for diagnosis and treatment of otitis media will likely have the greatest impact on overall antimicrobial exposure. Monitoring defined populations longitudinally will allow assessment of the effectiveness of such national and local initiatives.


Editor’s Note: I’m still waiting for the study that will provide clear indication for the use of antimicrobial drugs in otitis media, but I’m not holding my ears.

Catherine D. DeAngelis, MD

The increasing prevalence of antimicrobial-resistant microorganisms is widely viewed as a significant emerging threat to public health. Penicillin resistance in previously sensitive organisms, such as Streptococcus pneumoniae, has been detected in 16% of isolates from 19 states, and rates as high as 41% have been reported for children. Recent data from the SENTRY surveillance program showed the percentage of penicillin-resistant pneumococcus from 27 US hospitals to be 44%, with 16% being highly resistant. A core recommendation of the Centers for Disease Control and Prevention for minimizing the impact of drug-resistant S pneumoniae is the reduction of unnecessary antimicrobial use. Because children have the highest rates of antimicrobial use, specific principles for use in pediatric populations have been developed and disseminated.
PATIENTS AND METHODS

SETTING

We performed a retrospective cohort study in defined populations of children served by 2 large MCOs: Harvard Pilgrim Health Care in eastern Massachusetts (population A) and Group Health Cooperative of Puget Sound in northwest Washington State (population B). We included data from pediatric practices caring for more than 100 children aged 3 to 72 months enrolled in the health plans. Population A included patients from 20 network group practices with a total of 86 pediatricians and 23 pediatric nurse practitioners, with 7 family physicians providing a small fraction of pediatric care. Population B included patients cared for in health centers of an integrated staff model organization; the 1995 data are drawn from 24 practice sites, 2 of which were closed during the study period, with their patients absorbed by the remaining practices. Clinicians for population B included 28 pediatricians, 18 nurse practitioners, 181 family physicians, and 68 physician assistants.

PATIENTS

Children aged 3 months to 6 years were studied from September 1, 1994, to August 31, 1996. We used enrollment files of the MCOs to calculate the number of days each child was enrolled and then aggregated them as the denominator for population-based rates. Contributed time began on the first day of the study period, at enrollment in the health plan, or at 3 months of age (whichever came last) and ended at the end of the study, at disenrollment, or at their sixth birthday (whichever came first). We specified 2 age groups before the analysis: 3 months up to 36 months and 36 months up to 72 months; published guidelines for care of febrile children use 36 months as the cutoff value. Some children contributed less than a full year of observation time and others contributed observation time to both age groups.

We examined 2 separate time periods, September 1, 1994, to August 31, 1995, and September 1, 1995, to August 31, 1996. For our analysis of the frequency of antimicrobial use in individual children (Figure 1), we limited the sample to those who were covered by the plan and remained in one age group for an entire year.

To be included, enrolled children must have received pharmacy benefits through the health plans. We excluded children nominally enrolled in each health plan (4% in population A and 14% in population B) who had no record of any ambulatory visits (including well-child care) and no antimicrobial dispensing during the observation period. We believe that this most often occurred because of dual sources of health insurance.

DATA SOURCES AND ANALYSIS

We used automated ambulatory claims and pharmacy dispensing data routinely collected by MCOs. The claims systems allowed identification of diagnoses using International Classification of Diseases, Ninth Revision (ICD-9), codes. We created diagnostic categories that included the following ICD-9 codes and their subcodes: otitis media (381-382); pharyngitis (including tonsillitis and scarlet fever) (462, 463, 034.0, and 034.1); sinusitis (461 and 473); bronchitis (466 and 490); URI and common cold (460 and 465); and a composite group including sepsis, pneumonia, and urinary tract infection (including 030-041, 480-486, 590, 595, and 599). Remaining diagnoses, including well-child care visits, were categorized as “other.” In the 17% of encounters for which more than 1 diagnosis was recorded, we assigned a primary diagnosis giving priority to a respiratory tract illness and, when present, to a potential bacterial source (eg, if common cold and otitis media were coded, the latter was designated “primary”). Follow-up visits (eg, for otitis) are also included in visit counts for each diagnosis.

Pharmacy claims records, which include original prescriptions and refills, were linked with the most recent ambulatory encounter if one occurred within the 3 days preceding the dispensing. We excluded antituberculosis drugs, antihelminthics, topical antimicrobials, and other antimicrobial agents rarely used in ambulatory pediatric care.

Data were analyzed using SAS statistical software (SAS version 6.12; SAS Institute Inc, Cary, NC). Confidence intervals for rates of dispensing were calculated using approximate Fisher intervals for Poisson variables in person-time data (Computer Programs for Epidemiological Analysis; USD Inc, Stone Mountain, Ga). All comparisons of person-time incidence rates assumed 2-tailed \( \alpha = .05 \).

The frequency distributions of antimicrobials dispensed to each child were compared using the Wilcoxon rank sum test for nonparametric data.

The ambitious goal of changing antimicrobial prescribing practices for children requires accurate data on current patterns of use. In some countries, such data are available for identified geographic districts or the nation as a whole. In the United States, the 1992 National Ambulatory Medical Care Survey (NAMCS) estimated an annual average rate of antimicrobial prescribing of 928 per 1000 children younger than 13 years. The 1995-1996 NAMCS estimated an annual average rate of 1150 per 1000 children younger than 5 years (Linda F. McCaig, MPH, e-mail communication, November 24, 1998). The NAMCS sampled physician visits in representative practices and extrapolated the results to the entire US population. For children younger than 18 years, antimicrobial agents were prescribed for colds, upper respiratory tract infections (URIs), and bronchitis in 44%, 46%, and 75%, respectively, and accounted for 21% of all antimicrobials prescribed. Although these represent the best US estimates of antimicrobial use to date, data on the number of patients served by these practices are not directly available. Such visit-based studies yield direct estimates of prescription rates per visit but do not allow characterization of antimicrobial use for a cohort of children over time. Finally, no published analyses of the NAMCS specifically address prescribing to infants and young children, the highest users of antimicrobial agents. Others have contributed useful data on the rates and patterns of diagnosis of otitis media and antimicrobial prescribing using Medicaid claims files, but these might not be generalizable to non-Medicaid populations. Although it is difficult to obtain complete data on geographically defined communities in the United States,
managed care organizations (MCOs) care for reasonably large populations in which patterns of antimicrobial use can be studied. Data from MCOs that allow tracking medication use for a specific population base will be useful to gauge the effectiveness of initiatives to decrease antimicrobial exposure. We therefore studied antimicrobial prescribing in children enrolled in MCOs in 2 cities to determine the rates and distribution of antimicrobial use among infants and young children, to assess diagnosis-specific prescribing, and to determine the frequency with which diagnoses of common respiratory tract infections are assigned.

RESULTS

The cohort included 46,477 children who were observed for 59,710 person-years. The gender distribution was similar for both populations (population A, 48.5% female and population B, 48.3% female). Dispensing rates were higher for children aged 3 to 36 months than for those aged 36 to 72 months ($P < .001$) (Table 1). The rates were also significantly higher in 1995 than in 1996 ($P < .001$). Both these effects were evident in each of the health plans, which also differed significantly from one another; overall, children in population A received 2.56 antimicrobial drugs per person-year and those in population B received 1.82 ($P < .001$).

Figure 1 shows the distribution of antimicrobial drug dispensings per year. More than one quarter of the children in both age groups received no antimicrobials. There were also substantial proportions (11%-35% depending on age and site) who received 4 or more dispensings in a year, with such frequent dispensing more common among younger children ($P < .001$). First-line penicillins accounted for 57% of all antimicrobials dispensed, trimethoprim-sulfamethoxizole for 17%, cephalosporins for 12%, erythromycins for 7%, and amoxicillin-clavulanate for 4%.

Primary diagnoses linked to antimicrobial agents are presented in Figure 2. Approximately 80% of antimicrobial drug dispensings could be linked to an ambulatory visit in the preceding 3 days. Fifty-six percent of all antimicrobials dispensed to younger children were associated with a diagnosis of otitis media. A diagnosis of cold or URI accounted for 3% of antimicrobials dispensed. The combined fraction of antimicrobials dispensed for colds and URIs, bronchitis, and sinusitis (illnesses with overlapping symptoms and signs) was 10% in children aged 3 to 36 months and 14% in those aged 36 to 72 months.

### Table 1. Rates of Antimicrobial Drug Use of the Study Population*

<table>
<thead>
<tr>
<th>Patient Age Group</th>
<th>Antimicrobials Dispensed per Person-Year† of Observation, Mean No. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population A (n = 13,694)</td>
</tr>
<tr>
<td>3 to &lt;36 mo</td>
<td>3.34 (3.29-3.40)</td>
</tr>
<tr>
<td>36 to &lt;72 mo</td>
<td>2.19 (2.15-2.23)</td>
</tr>
<tr>
<td>All children</td>
<td>2.75 (2.72-2.78)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.
†The mean number of person-years contributed was 1.4 for population A and 1.2 for population B.
visits; visits for otitis media with effusion were associated with an antimicrobial in 36% and 40% of patients in populations A and B, respectively. Although visits for colds and URIs were frequent, the proportion treated with antimicrobials was low, from 8% to 17% depending on site and age group. Together, prescriptions for colds and URIs, bronchitis, and sinusitis accounted for fewer than 0.3 antimicrobial drug dispensings per person-year.

Among infants and young children, respiratory tract illness (especially otitis media) is common, diagnosis is challenging, and pressures to treat with antimicrobial agents may be intense. The overall rates of antimicrobial use we report are somewhat higher than those estimated by the 1992 NAMCS.10 However, our rates of antimicrobial use...
for otitis media of 1.24 to 1.68 dispensings per person-year for children aged 3 to 5 years older than those reported by Berman et al in a population-based study using Medicaid claims in Colorado. As with other medical practices, we can learn a great deal by studying variation among geographic areas and patient groups.

Our data also show that a substantial fraction of children receive no antimicrobials, whereas others receive several prescriptions each year. This likely reflects person-to-person variation in occurrence of disease and differences in care-seeking behavior by parents and responses to perceived parental expectations by physicians. Some investigators have suggested that clinicians frequently prescribe antimicrobial agents for viral URI in response to parental demand or to shorten explanation time during office visits. In a recent survey, 48% of physicians reported parental pressure to prescribe unnecessary antimicrobial agents, and one third reported at least occasionally complying. Recent identification of predictors of high-prescribing rates among individual physicians adds another dimension to our understanding of what drives overuse.

Colds and bronchitis accounted for fewer than 10% of prescriptions in these health plans, a figure lower than the 21% reported from NAMCS data for children younger than 15 years. The proportion of visits for colds and URI that were treated in these populations was also lower—8% to 1%—compared with the 44% to 46% previously reported. Although bronchitis was often treated with antimicrobial drugs, this indication accounted for 5% or less of all prescriptions. Physicians in these 2 MCOs might choose different diagnostic codes for the same illnesses than the broader sample of physicians in the NAMCS. They might also be more attentive to coding diagnoses that are consistent with treatments prescribed. Alternatively, methodological differences in studies of antimicrobial prescribing might account for some differences in reported results. For example, the NAMCS used a visit-based instrument to capture primary and additional diagnoses. If URI was listed first and otitis media second, an antimicrobial, if present, was linked to the diagnosis of URI. In this study, we used an algorithm that gave priority to a presumed bacterial infection as the primary diagnosis when more than 1 was recorded.

Like other investigators, we included commonly used ICD-9 codes to focus on specifically diagnosed respiratory tract infections. Among visits linked to an antimicrobial drug and categorized as “other,” some carry another diagnosis consistent with viral upper respiratory tract illnesses. To investigate the impact of our a priori selection of ICD-9 codes, we reviewed diagnoses for the 12% of antimicrobial drugs linked to visits categorized as “other” in population A. Of these, 1.8% of all antimicrobials were linked with viral respiratory tract infections, 1.1% with unspecified or nonrespiratory viral illnesses, 2.2% with possible bacterial infections, 3.0% with noninfectious diagnoses, and 3.7% with well-child care. The latter group is likely to represent children who present for well-child care with an intercurrent illness and shows that use of diagnoses from claims will misclassify some of the reasons antimicrobial agents are prescribed.

The potential impact of variability in assigning diagnostic codes, although small, makes overall antimicrobial use rates particularly important study outcomes.

In this study, the diagnosis of acute otitis media was the most common reason for antimicrobial drug prescribing. If acute otitis media is being overdiagnosed, it would likely account for the largest fraction of antimicrobial overuse. The literature regarding the reduction of antimicrobial prescribing often ignores diagnostic uncertainty in respiratory tract infections, which may be another important factor in overprescribing; visualization of the tympanic membrane is rarely optimal in a febrile, squirming young child. Interventions that promote the use of strict criteria for diagnosis of otitis media, or even a “watchful waiting” approach in some patients, may make the greatest impact.

The substantial differences between the 2 populations studied illustrate the importance of understanding local patterns of disease and management in designing interventions to improve care. The antimicrobial dispensing rates reflect differences in rates of presentation for illnesses and smaller differences in diagnosis-specific treatment rates. These 2 plans differ in geographic location (Northeast vs Northwest), delivery system structure (staff vs network model), and the frequency of family physicians as providers of care to children. Although there were no concerted efforts to decrease antimicrobial prescribing during the observation period, practice-specific education from the health plan or other sources might have occurred. Demographic differences in the populations served may also be important. Additional work is needed to determine which, if any, of these factors contribute to the differences in results between the 2 sites.

The decrease in antimicrobial use we observed from 1995 to 1996 emphasizes the importance of suitable comparison groups for assessing the impact of interventions to decrease antimicrobial use. It is difficult to rule out random year-to-year variation, but these data might be evidence of a secular trend in the direction of lower antimicrobial treatment rates. This change antedated the Centers for Disease Control and Prevention guidelines promoting judicious antimicrobial use but might have occurred in response to increased awareness by professionals and the public regarding the risks of antimicrobial overuse during this period.

As attempts are made to reduce antimicrobial prescribing, we will need to watch carefully for changes in coding among competing diagnoses. For example, if physicians reduce their antimicrobial treatment of bronchitis but increase the diagnosis and treatment of sinusitis, no progress will be made. Conversely, if public education reduces the frequency of physician visits for upper respiratory tract symptoms, overall exposure to antimicrobial drugs might decrease even if the proportion of visits with treatment remains high. Monitoring defined populations over time will allow analysis of complex changes in care-seeking and prescribing behavior.

The generalizability of this study depends on the extent to which physicians and patients in these MCOs are representative of those in their communities. Studies in other settings will help determine the extent of the varia-
tion in prescribing practices across the United States. Although administrative pharmacy databases have the advantage of capturing actual medications dispensed, rather than merely prescribed, they have limitations as well. A substantial fraction (19%) of antimicrobials dispensed could not be linked to an office visit in the preceding 3 days; reasons might include providers prescribing (or refilling prescriptions) by telephone or delayed filling of prescriptions by patients. Although we limited our cohorts to patients with prescription drug coverage, it is possible that a small number of medications were purchased “out of pocket” with no claim submitted to the health plan or were submitted to another insurer. Likewise, these databases would not include records of medication samples given directly to patients. Finally, analysis of automated data sources cannot assess the appropriateness of diagnoses made or treatments prescribed.

The public health community, physician groups, and the lay press are increasingly delivering the unified message that major change in the use of antimicrobial agents is warranted. Data from Iceland support the correlation between community antimicrobial use rates and bacterial resistance and the premise that decreasing prescribing may have a substantial impact on resistance. If we do not know what magnitude reduction in antimicrobial prescribing will affect the prevalence of antimicrobial resistance among community pathogens in the United States. Although continued efforts to eliminate antimicrobial prescribing for colds, URIrs, and bronchitis are warranted, use of more stringent criteria for the diagnosis of acute otitis media will likely have the greatest impact on overall antimicrobial exposure for infants and young children. Monitoring defined populations during the next several years will help us assess progress toward the intermediate goal of reducing antimicrobial use and the ultimate goal of preventing resistance.

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From the Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, Mass (Dr Finkelstein and Platt and Ms Rifas-Shiman); The Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital, Boston (Dr Platt); the Philadelphia Veterans Affairs Medical Center and the Division of General Internal Medicine, University of Pennsylvania School of Medicine (Dr Metlay); the Department of Pediatrics, University of Washington School of Medicine, Seattle (Dr Davis); and the Respiratory Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Ga (Dr Dowell).

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Corresponding author: Jonathan A. Finkelstein, MD, MPH, Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, 126 Brookline Ave, Suite 200, Boston, MA 02215.

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