

# Excessive Antibiotic Use for Acute Respiratory Infections in the United States

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**Estimating the amount and cost of excess antibiotic use in ambulatory practice and identifying the conditions that account for most excess use are necessary to guide intervention and policy decisions. Data from the 1998 National Ambulatory Medical Care Survey, a sample survey of United States ambulatory physician practices, was used to estimate primary care office visits and antibiotic prescription rates for acute respiratory infections. Weight-averaged antibiotic costs were calculated with use of 1996 prescription marketing data and adjusted for inflation. In 1998, an estimated 76 million primary care office visits for acute respiratory infections resulted in 41 million antibiotic prescriptions. Antibiotic prescriptions in excess of the number expected to treat bacterial infections amounted to 55% (22.6 million) of all antibiotics prescribed for acute respiratory infections, at a cost of ~\$726 million. Upper respiratory tract infections (not otherwise specified), pharyngitis, and bronchitis were the conditions associated with the greatest amount of excess use. This study documents that the amount and cost of excessive antibiotic use for acute respiratory infections by primary care physicians are substantial and establishes potential target rates for antibiotic treatment of selected conditions.**

The excessive use of antibiotics in ambulatory practice has contributed to the emergence and spread of antibiotic-resistant bacteria in communities [1–3]. Recent reports estimate that >40% of *Streptococcus pneumoniae* isolates in carriers and a lesser percentage of invasive isolates are nonsusceptible to penicillin [4, 5]. Equally alarming is the development of community-acquired methicillin-resistant *Staphylococcus aureus* infections that led to 4 pediatric deaths [6, 7].

Numerous studies have been performed to characterize the current epidemic of penicillin-resistant *S.*

*pneumoniae* (PRSP). A consistent finding in all reports, summarized by Dowell and Schwartz [1], is that the most important risk factor for transmission of and infection with PRSP is current or recent antibiotic use. Further evidence that the amount of antibiotic use in the community is directly linked to the prevalence of antibiotic resistance can be derived from reports from Finland, where reductions in ambulatory macrolide antibiotic use were associated with a reduction in the prevalence of macrolide-resistant *Streptococcus pyogenes* carriage and infections [8].

In the United States, ~75% of ambulatory antibiotic prescriptions are for the treatment of 5 specific acute respiratory infections (ARIs): otitis media, sinusitis, pharyngitis, bronchitis, and upper respiratory tract infections (URIs) [9]. We have shown, using the same data, that antibiotic prescription rates for colds, URIs, and bronchitis account for a large portion of “unnecessary” antibiotic prescriptions, since these conditions have a predominantly viral etiology and antibiotic treatment of them has not been shown to have a major clinical impact [10, 11]. In the present report, we offer a broader systematic analysis of the prescriptions of

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antibiotics for these conditions by United States ambulatory physicians and provide estimates of the amount and cost of excess antibiotic use for all 5 ARIs, using more current prescribing data. To accomplish this, we determined target (or ideal) antibiotic prescription rates, based on what proportion of patients diagnosed with a specific ARI would be expected to have a bacterial infection, and compared these targets with actual antibiotic prescription rates.

## METHODS

**Calculation of current antibiotic prescription rates.** The National Ambulatory Medical Care Survey (NAMCS), conducted annually by the National Center for Health Statistics, provides national estimates of reasons people seek medical attention, and the diagnoses and prescriptions they receive from a representative sample of United States ambulatory physician practices. A detailed description of the NAMCS and analyses of antibiotic prescribing for adults and children on the basis of the 1992 NAMCS have been reported elsewhere [10, 11].

We used data from the 1998 NAMCS to calculate antibiotic use for all office visits that yielded a principal diagnosis of one of the following ARIs, based on the codes of the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*: otitis media (382.0, 382.4, 382.9), sinusitis (461.0, 461.9, 473.9), bronchitis (466, 490), pharyngitis (including tonsillitis) (034, 462, 463), and URI (460, 465). In order to minimize the likelihood that an antibiotic prescription was unrelated to the principal diagnosis, we included only those prescriptions entered as the principal medication related to the office visit. We further limited our analysis to primary care physicians (general practice, family medicine, pediatrics, internal medicine, and obstetrics/gynecology), because visits to subspecialists were more likely to represent complicated illnesses. The specific antibiotic names (trade and brand) were used for calculating the cost of antibiotic treatment for these conditions.

**Estimation of target antibiotic prescription rates (i.e., for bacterial etiologies).** We searched the MEDLINE database (1966–2000) with use of major subject headings that included “microbiology” and the conditions of interest, and we analyzed references from review articles to identify studies that have examined the microbiology of specific ARIs. We used these studies to estimate what proportion of patients diagnosed with a specific ARI have a bacterial infection (and potentially benefit from antibiotic treatment). Results of bacterial prevalence studies were stratified by age (>17 years [adults] and ≤17 years [children]), and final prevalence estimates were adjusted for age. To increase the similarity between the NAMCS patient population and the population of patients evaluated in the microbiological studies, we limited our selection of microbi-

logical studies to those conducted in nonreferral, nonemergency room, ambulatory settings.

Interpreting the results of bacterial cultures of respiratory tract secretions, especially those from the nasopharynx, throat, and sputum, is complicated by the frequent colonization of the respiratory tract by potential bacterial pathogens such as *S. pneumoniae*, *Haemophilus influenzae*, and group A, β-hemolytic streptococci (GAS). In order to provide the most conservative estimates of potentially treatable acute otitis media [12, 13] and pharyngitis [8, 14–17], we included positive culture results for any pathogenic bacteria in our estimates of bacterial prevalence. These estimates are conservative because the recovery of pathogenic bacteria does not necessarily indicate acute infection. For example, investigators have estimated that ≤50% of recovered GAS represents colonization rather than infection [14]. With regard to sinusitis, we could identify only a single sinusitis study in the ambulatory, nonreferral setting in which most patients (those with any CT abnormality) with suspected maxillary sinusitis had sinus cultures performed [18]. Bacterial prevalence estimates in cases of acute bronchitis are based on serological criteria because culture recovery of atypical bacteria (*Chlamydia pneumoniae* strain TWAR, *Mycoplasma*, and pertussis), the only established bacterial causes of acute bronchitis in otherwise healthy adults, is difficult [19–25].

As noted above, using nasopharyngeal cultures to estimate relevant bacterial prevalence in URIs is difficult, given the high rates of carriage of pathogenic bacteria (*S. pneumoniae*, *H. influenzae*) at this site. Children appear to have high rates of carriage, approaching 50% of children with URIs [26], although a meta-analysis of antibiotic treatment trials did not demonstrate any benefit of antibiotic treatment of URIs [27]. This suggests that recovery of pathogenic bacteria from children is almost always carriage rather than infection. Conversely, 2 studies of adults in Switzerland have shown that ~25% of adults have pathogenic bacteria recovered in cultures of purulent nasopharyngitis specimens, and antibiotic treatment appeared to decrease duration and severity of symptoms in an analysis of the subset of patients whose cultures subsequently yielded pathogenic bacteria [28, 29]. (Most infectious disease experts would not accept isolation of a bacterial “pathogen” from the nose of a patient with a common cold to be an indication of bacterial infection.)

The possibility that some of the purulent nasopharyngitis cases that responded to antibiotics actually were cases of “early” sinusitis could not be excluded, since ≤19% had radiographic evidence of sinusitis (in the absence of major symptoms). Nevertheless, to remain conservative in our estimation of target antibiotic prescription rates, we estimate that one-third of URI visits are by adults, assume all who seek care have purulent nasopharyngitis, and estimate that 25% of these might have a

bacterial infection (i.e., a bacterial prevalence estimate of 8% of total visits for URI).

**Calculating antibiotic cost.** Cost estimates of antibiotic prescriptions were calculated on the basis of 1996 prescription marketing data provided by Source Prescription Database, of NDC Health Information Services (Atlanta), and inflation-adjusted by 0.0755 to 1998 prices with use of the consumer price index for prescription drugs and medical supplies (<http://stats.bls.gov>). These data include estimates of the number of prescriptions dispensed by trade names and generic names for new and refill prescriptions, average quantity (i.e., number of capsules, tablets, etc.) of units per prescription, and average retail price (including patient co-payments). These data were projected to national totals based on prescriptions collected from ~35,000 pharmacies across the United States (representing ~70% of all prescriptions written). Because the NAMCS does not contain data on the strength or quantity of each medication, we computed a weighted average price on the basis of market share for each manufacturer of that same chemical entity. For those medications that are typically administered within physician offices (e.g., injections), we estimated the cost on the basis of the 1996 average wholesale price and adjusted for inflation as above. Weight-averaged medication costs were multiplied by NAMCS sampling weights to obtain national cost estimates.

**Statistical analysis.** National or aggregate estimates of physician visits and antibiotic prescriptions for the selected conditions were obtained with use of the assigned patient-visit weights accompanying the NAMCS database. These weights are derived from the probabilities of being sampled (as a physician practice and as a patient visit), taking into account characteristics such as practice volume and physician, and adjusted for nonresponse. Ninety-five percent confidence intervals (95% CIs) for national estimates were calculated with use of the relative standard error (RSE) of the estimate, with the formula

$$\text{RSE}(x) = (A + B/x)^{1/2} \times 100 ,$$

where *A* and *B* are the coefficients of interest (visits or antibiotic prescriptions) equivalent to the design effect of the NAMCS design, averaged for the physician specialty estimates, and *x* is the aggregate of interest in thousands.

**Sensitivity analyses.** In accordance with accepted methods of economic evaluation [30], we conducted sensitivity analyses to take into account the market share of brand-name product or generic product use. The NAMCS contains data on the prescribed product, which may be different from the actual product dispensed. The primary analysis was conducted on the basis of weight-cost, based upon market share when brand-name products were also available generically. If a brand-name product was not generically available, the estimated cost per prescription was not changed in the sensitivity analyses. Two

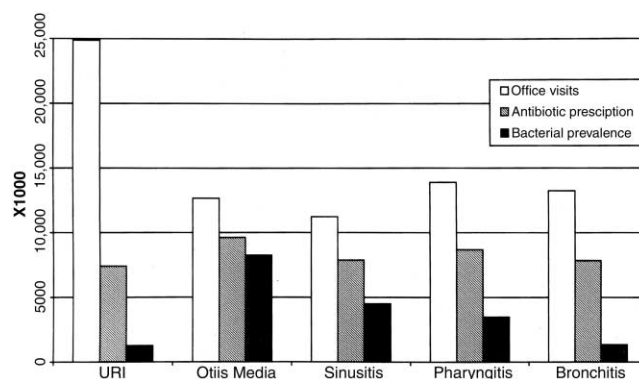
sensitivity analyses were conducted to determine the impact of the brand name versus generic assumption. The first analysis was conducted with cost estimates from generic products only. This represents the minimum possible economic value of the products prescribed. The second analysis was conducted with the higher brand-name-product costs.

## RESULTS

In 1998, an estimated 84 million ambulatory office visits for ARIs resulted in 45 million antibiotic prescriptions in the United States. Primary care physicians (pediatricians, family practitioners, internists, and general practitioners) managed 90% of these visits (76 million) and prescribed 91% of antibiotics for these conditions. The leading conditions accounting for total antibiotic prescriptions by primary care physicians were otitis media and pharyngitis, followed in order by sinusitis, bronchitis, and URIs.

Approximately 25 million patients sought care for URIs in 1998, and 30% were treated with antibiotics (figure 1). Similarly, 76% of 13 million patients who had otitis media, 62% of 14 million patients who had pharyngitis, 59% of 13 million patients who had bronchitis, and 70% of 11 million patients who had sinusitis diagnosed were treated with antibiotics.

To estimate the excess amount of antibiotics prescribed for each specific ARI, we compared bacterial prevalence estimates (derived from population-based studies) with antibiotic prescription rates (figure 1). The bacterial prevalence estimates used for each condition were as follows: otitis media, 65%; sinusitis, 40%; pharyngitis, 25%; bronchitis, 10%; and URI, 5% (table 1). This comparison suggests that ~55% of the total



**Figure 1.** Primary care office visits and antibiotic prescriptions for acute respiratory illnesses in the United States (National Ambulatory Medical Care Survey, 1998). The white bars show estimates of the number of ambulatory office visits for each condition, the shaded bars show the proportion of patients who made an office visit for each condition who were prescribed an antibiotic, and the black bars show estimates of the proportion of cases of each condition likely to be associated with pathogenic bacteria (see table 1 and text).

**Table 1. Estimating the prevalence of bacterial infection in acute respiratory infections.**

[Reference], year	Condition	Location, population, <i>n</i>	Prevalence of pathogenic bacteria, % (predominant species)	Diagnostic standard
[12], 1978	Acute otitis media	United States, 62 children	55 ( <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> )	Tympanocentesis and culture
[13], 1998	Acute otitis media	Multinational, 917 children	62 ( <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i> , others)	Tympanocentesis and culture
[18], 1995	Acute sinusitis	174 adults	40 <sup>a</sup> ( <i>H. influenzae</i> , <i>S. pneumoniae</i> , group A $\beta$ -hemolytic <i>Streptococcus</i> , <i>S. aureus</i> , <i>M. catarrhalis</i> , other)	Sinus puncture and culture
[19], 1990	Acute bronchitis	United Kingdom, 40	8 ( <i>M. pneumoniae</i> )	Serological testing
[20], 1990	Acute bronchitis	United States, 112	3 ( <i>M. pneumoniae</i> )	Serological testing
			4 ( <i>C. pneumoniae</i> TWAR)	Serological testing
[21], 1991	Acute bronchitis	United States, 338	5 ( <i>C. pneumoniae</i> TWAR) <sup>b</sup>	Serological testing
[22], 1992	Acute bronchitis	Norway, 67	3 ( <i>M. pneumoniae</i> )	Serological testing
			0 ( <i>C. pneumoniae</i> TWAR)	Serological testing
[23], 1993	Acute bronchitis	United Kingdom, 203	1 ( <i>M. pneumoniae</i> )	Serological testing
[24], 1994	Acute bronchitis	United States, 247	1 ( <i>M. pneumoniae</i> )	Serological testing
			5 ( <i>C. pneumoniae</i> TWAR) <sup>c</sup>	Serological testing
[25], 1997	Acute bronchitis	Sweden, 113	1 ( <i>M. pneumoniae</i> )	Serological testing
			1 ( <i>C. pneumoniae</i> TWAR)	Serological testing
[16], 1967	Pharyngitis	United States, 715 (85% <12 years)	37 GAS	Throat culture
[14], 1971	Pharyngitis	United States, 624 children (<15 years)	35 GAS	Throat culture
[17], 1975	Pharyngitis	United States, 418 adults	15 GAS	Throat culture
[15], 1989	Pharyngitis	Finland, 106 adults	5 GAS	Throat culture

**NOTE.** GAS, group A  $\beta$ -hemolytic streptococci.

<sup>a</sup> Sinus puncture performed only on patients with mucosal thickening or sinus fluid present on CT scan.

<sup>b</sup> One of 16 serologically defined cases of *C. pneumoniae* (TWAR) infection was positive by culture.

<sup>c</sup> Nine of 12 serologically defined cases of *C. pneumoniae* (TWAR) were positive by PCR.

antibiotics prescribed for ARIs in 1998 ( $n = 22.6$  million prescriptions) are used for infections unlikely to have a bacterial etiology. URIs, pharyngitis, and bronchitis account for the large majority of these excess antibiotic prescriptions.

Using weighted-average estimates, we determined that the total cost of antibiotic prescriptions for ARIs in 1998 was an estimated \$1.32 billion, of which \$726 million was for excess antibiotic prescriptions, on the basis of bacterial prevalence estimates (table 2). If only generic medications are used (when this is an option), the estimated cost is \$1.31 billion. If only brand-name products are dispensed, then the estimated cost of excess medications is \$1.43 billion. Improving the diagnosis of specific ARIs would also have a significant impact on excess antibiotic prescriptions and cost. For example, a 10% reduction (improvement) in diagnosis of acute otitis media and acute sinusitis would result in a decrease of an additional 1.75 million antibiotic prescriptions per year, at an estimated cost savings of \$59 million per year.

## DISCUSSION

Judicious use of antibiotics in ambulatory practice has become increasingly important as antibiotic resistance in community bacterial pathogens continues to accelerate. Analyzing national practice patterns provides useful information to help guide clinicians and health care delivery systems in their efforts to improve antibiotic prescribing practices. Our study results suggest that (1) interventions to decrease total (excess) antibiotic use should focus on URIs, pharyngitis, and bronchitis, and (2) interventions relating to acute otitis media and sinusitis should assess to what degree clinicians use narrow-spectrum and broad-spectrum antibiotics. For either group of conditions, evaluating and improving how clinical diagnoses are assigned is also of paramount importance. Whereas bacterial prevalence estimates used in this study could serve as reasonable antibiotic prescription targets for quality-improvement efforts, in order to promote judicious antibiotic use, final targets and recom-

**Table 2. Estimated annual cost of antibiotic prescriptions for acute respiratory illnesses (ARIs) by primary care physicians in the United States (National Ambulatory Medical Care Survey, 1998).**

ARI diagnosis	No. of prescriptions (in millions)	Cost estimate <sup>a</sup> (in millions)	95% CI (in millions)
Otitis media	9.6	\$280	\$271–\$290
Pharyngitis	8.7	\$215	\$208–\$223
URI	7.4	\$227	\$218–\$235
Sinusitis	7.9	\$310	\$299–\$321
Bronchitis	7.8	\$289	\$279–\$300
Total	41.4	\$1322	\$1290–\$1353

<sup>a</sup> In US dollars, based upon average pharmacy retail price, as provided by Source Prescription Database of NDC Health Information Services. URI, upper respiratory tract infection.

recommendations should take into account local diagnosis and prescribing behavior and bacterial prevalence.

The bacterial prevalence rates we calculated probably overestimate the proportion of patients likely to benefit from antibiotic treatment and likewise the proportion of patients likely to require such treatment. For example, up to 50% of patients with a culture or test positive for GAS will not have serological evidence of an acute infection but will test positive, presumably as a result of carriage [14]. Similarly, although patients with otitis media or sinusitis frequently have pathogenic bacteria present in middle ear or sinus cavity aspirates, a majority of these cases (based on clinical diagnosis) resolve spontaneously without antibiotic treatment, suggesting that a portion of these cases in which pathogenic bacteria are present may not actually involve bacterial infection. Successful drainage of middle ear and sinus cavities through the use of symptomatic therapies (in the context of an adequate host immune response) is often sufficient to achieve clinical resolution without antibiotic therapy.

Finally, antibiotic benefit and/or requirement will also be a reflection of a community's treatment threshold. For example, in the Netherlands, children with acute otitis media are usually not treated with antibiotics unless symptoms have persisted for 3–4 days. As a result, antibiotics are prescribed for only ~30% of children [31, 32].

We should emphasize that these estimates also do not address whether the actual antibiotic prescription rate measured is appropriate. We cannot account for the potential variability in how clinicians assign specific diagnoses of ARIs since we did not have access to clinical information related to each patient visit. We assume that all diagnoses of a given condition in our study population fulfilled reasonable criteria for that diagnosis. However, since the diagnosis of ARI usually depends on clinical criteria rather than a diagnostic test, there is significant het-

erogeneity in how these diagnoses are assigned. For example, whereas one clinician might use the diagnosis of sinusitis only when multiple predictors of acute sinusitis are present (purulent nasal discharge, maxillary toothache, prolonged symptoms), another might use the diagnosis for all patients with prominent sinus symptoms, regardless of other features.

The economic analysis of prescription costs assumes that each prescription written would result in the actual filling of the prescription. However, previous research has shown that up to one-fifth of all new prescriptions are not filled [33]. Theoretically, antibiotic prescriptions are more likely to be filled, because persons with acute illness are seeking prompt resolution of the condition. At present (in 2001), antibiotic costs are also likely to be at least 20% greater, given inflation and the increased use of broad-spectrum macrolides and expanded-spectrum fluoroquinolones in ambulatory practice since 1998.

This study documents that overuse of antibiotics for ARIs is substantial and occurs at a very high price. Reducing excess antibiotic use for URIs and bronchitis is possible through innovative educational intervention strategies that include patient and clinician education and that focus on the lack of benefit of antibiotic treatment of the vast majority of these patients [34]. Reducing total antibiotic use for otitis media, pharyngitis, and sinusitis, however, will require increased use of available diagnostic algorithms and tests, and development of improved diagnostic tests for determining which patients are likely to derive benefit from antibiotic treatment.

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