

# Resistance Issues and Community-Acquired Respiratory Infections

**Daniel F. Sahn, PhD**

Chief Scientific Officer  
Focus Technologies, Inc.  
Herndon, Virginia

Antimicrobial resistance, associated with both excessive and inappropriate use of antimicrobial agents, is a global problem. It is a particular problem in the management of community-acquired respiratory infections, which most often result in the use of antimicrobial therapy. Infections caused by resistant and multiresistant pathogens may also result in high hospitalization rates, long lengths of stay, severe illness, and high mortality, all of which have a great impact on health care costs. The Tracking Resistance in the United States Today (TRUST) Program, the largest longitudinal continuous-surveillance program of its kind, has been conducted every year since 1996 and tracks consecutive respiratory seasons on a year-to-year basis to monitor resistance patterns of respiratory pathogens. This article discusses some of the findings of the TRUST Program, particularly trends in *Streptococcus pneumoniae* resistance. Clinical Cornerstone® Monograph. Copyright © 2004 Excerpta Medica, Inc.

Antimicrobial resistance is a global problem (1). Resistance develops through a range of mechanisms that are often transferable (2) and is associated with both excessive (3) and inappropriate use of antimicrobial agents (4,5). Resistance is a particular problem in the management of community-acquired respiratory infections, which are among the most common types of infections that result in the use of antimicrobial therapy. Therefore, antimicrobial resistance and therapeutic failure are continuous issues for the management of respiratory infections (6). Although overuse and misuse of antimicrobial agents generate antimicrobial resistance, infections caused by resistant and multiresistant pathogens may also result in high hospitalization rates, long lengths of stay, severe illness, and high mortality, all of which have a great impact on health care costs (7–10).

There is an emerging consensus that an overall reduction in prescribing antimicrobial agents will diminish the rising trend of resistance (11). It is also clear that when antibiotics are justified for

the treatment of respiratory and other infections, better prescribing practices and policies will improve recovery and limit the spread of resistance (12). Effective strategies include limiting treatment to infections where bacterial causes are likely and using an appropriate agent based on local patterns of resistance—at sufficient dose and adequate duration—to successfully eradicate the organism (13). Routine surveillance of antimicrobial activity is an important measure for effective empirical treatment (14). Also important is the role of the laboratory,

## KEY POINT

**When antibiotics are justified for the treatment of respiratory and other infections, better prescribing practices and policies will not only improve recovery but also limit the spread of resistance.**

which can identify and test samples for susceptibility from patients who are acutely unwell or from health care workers who may be carrying resistant organisms (15).

### KEY POINT

**TRUST, which was initiated in 1996, is the largest longitudinal continuous-surveillance program of its kind and involves hundreds of institutions that track consecutive respiratory seasons on a year-to-year basis.**

## ANTIMICROBIAL SUSCEPTIBILITIES OF COMMON RESPIRATORY PATHOGENS

Antimicrobial surveillance is a key resource to support appropriate antimicrobial use by providing data for the evaluation of antimicrobial susceptibility trends and patterns. This information is useful for establishing optimal empirical therapy and for evaluating the changing effectiveness of individual agents with time (16–19).

Tracking Resistance in the United States Today (TRUST) is the largest longitudinal continuous-surveillance program of its kind and involves hundreds of institutions that track consecutive respiratory seasons on a year-to-year basis. The TRUST Program has been conducted every year since 1996 to monitor resistance patterns of respiratory pathogens. Information on longitudinal trends in antimicrobial resistance among the key bacterial respiratory pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* between 1998 and 2003 are derived from the TRUST 3 through TRUST 7 reports, respectively (20–22). Because the TRUST database contains information on tens of thousands of strains of *S pneumoniae* and thousands of strains of *H influenzae* and *M catarrhalis*, it is sufficiently robust to provide a variety of important insights into antimicrobial resistance patterns and trends.

**Table I** depicts the in vitro activity of several agents against *H influenzae* (22). With the excep-

tion of ampicillin and trimethoprim/sulfamethoxazole, most agents have maintained high levels of activity. Specifically for the fluoroquinolones, gatifloxacin, levofloxacin, and moxifloxacin have maintained high levels of activity because no fluoroquinolone-resistant isolates were encountered in 2003. Similarly for *M catarrhalis*, almost all agents showed high activity, with the exception of ampicillin, which showed a minimum inhibitory concentration required to inhibit 90% of isolates ( $MIC_{90}$ ) of 8  $\mu\text{g}/\text{mL}$  (**Table II**) (22). To date, no strains have been encountered during the TRUST series that are resistant to fluoroquinolones.

Antimicrobial susceptibilities among *S pneumoniae* in 2003 are shown in **Table III** (22).

Against the fluoroquinolones gatifloxacin, levofloxacin, and moxifloxacin, 99% of the strains were susceptible. Other agents that had substantial activity included ceftriaxone and amoxicillin/clavulanate. The resistance rate was ~17% for penicillin and 20% for cefuroxime, with the macrolide resistance rates approaching 30%.

### Trends in *S pneumoniae* Resistance

Rates of penicillin resistance across the United States were mapped according to geographic source (**Figure 1**) (22). Trending of resistance over time is depicted in **Figure 2** (22). Resistance for penicillin was increasing until 2001 but since then has leveled off or may even be decreasing (20). Similar trends were seen with trimethoprim/sulfamethoxazole and the macrolides. Although resistance may be leveling off, it has done so at an unacceptably high nonsusceptibility rate for penicillin, the macrolides, and trimethoprim/sulfamethoxazole. In contrast, the activity of ceftriaxone remains consistently high. Levofloxacin has the lowest resistance of all the commonly used respiratory antibiotics without any substantial signal that resistance is increasing (20).

### Multiple Drug Resistance Among *S pneumoniae*

Multiple drug resistance (MDR) (ie, resistance to 3 or more agents) is also an important consideration when monitoring trends among *S pneumoniae*.

**Figure 3** (20,21) shows MDR trends from TRUST 3 (1998) to TRUST 7 (2003). For this analysis,

**TABLE I. HAEMOPHILUS INFLUENZAE RESISTANCE — TRUST 7 (2003)**

<i>Agent</i>	<i>MIC<sub>90</sub> (µg/mL)</i>	<i>%S</i>	<i>%I</i>	<i>%R</i>
Amoxicillin/clavulanate	2	99.9	—	0.1
Ampicillin	>8	70.7	0.1	29.2
Azithromycin	2	99.8	—	—
Ceftriaxone	≤0.015	100	—	—
Cefuroxime	2	99.8	0.1	0.1
Gatifloxacin	0.015	100	—	—
Levofloxacin	0.03	100	—*	—*
Moxifloxacin	0.03	100	—	—
Trimethoprim/sulfamethoxazole	>4	77.3	4.5	18.2

n = 1212; TRUST = Tracking Resistance in the United States Today; MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit 90% of isolates; S = susceptible; I = intermediate; R = resistant.

\*National Committee for Clinical Laboratory Standards breakpoints unavailable for categorical interpretation as Susceptible, Intermediate, or Resistant.

**TABLE II. MORAXELLA CATARRHALIS RESISTANCE — TRUST 7 (2003)**

<i>Agent</i> *	<i>MIC<sub>90</sub> (µg/mL)</i>
Amoxicillin/clavulanate	0.25
Ampicillin	8
Azithromycin	0.03
Ceftriaxone	1
Cefuroxime	2
Gatifloxacin	0.03
Levofloxacin	0.06
Moxifloxacin	0.06
Trimethoprim/sulfamethoxazole	0.25

n = 817; TRUST = Tracking Resistance in the United States Today; MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit 90% of isolates.

\*National Committee for Clinical Laboratory Standards breakpoints unavailable for categorical interpretation.

**TABLE III. STREPTOCOCCUS PNEUMONIAE RESISTANCE – TRUST 7 (2003)**

<i>Agent</i>	<i>MIC</i> <sub>90</sub> (μg/mL)	%S	%I	%R
Amoxicillin/clavulanate	2	93.4	2.5	4.1
Azithromycin	16	72.1	0.3	27.5
Ceftriaxone*	1	96.1	2.4	1.5
Cefuroxime	>4	76.1	3.2	20.7
Clindamycin	≤0.25	90.8	0.4	8.8
Erythromycin	>4	71.9	0.3	27.8
Gatifloxacin	0.25	99.1	0.1	0.8
Levofloxacin	1	99.1	0.0	0.9
Moxifloxacin	0.25	99.2	0.4	0.4
Penicillin	2	66.3	16.4	17.3
Trimethoprim/sulfamethoxazole	>4	70.3	5.8	24.0
Vancomycin	0.5	100	–	–

n = 4456; TRUST = Tracking Resistance in the United States Today; MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit 90% of isolates; S = susceptible; I = intermediate; R = resistant.

\*Nonmeningitis breakpoints used: ≤1 μg/mL (S), 2 μg/mL (I), ≥4 μg/mL (R).

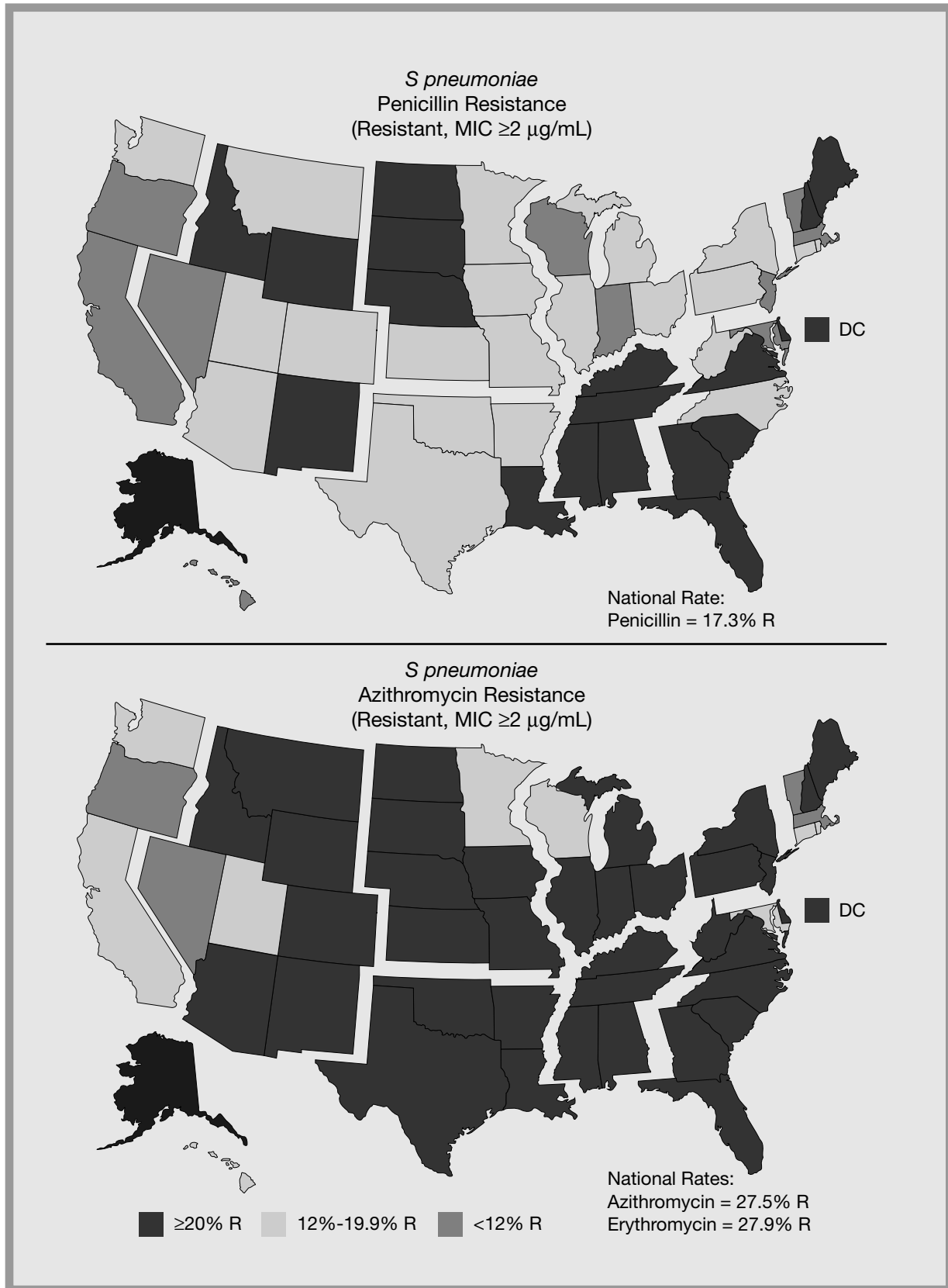
MDR was defined as resistance to 3 or more of the following: penicillin, macrolides (eg, azithromycin), trimethoprim/sulfamethoxazole, ceftriaxone, levofloxacin, and vancomycin. Resistance to 3 drugs was the profile most commonly encountered, with resistance to penicillin, macrolides, and trimethoprim/sulfamethoxazole being the most common phenotype. Since TRUST 6, the rate of MDR strains appears to have leveled off. In TRUST 7 (2003) resistance to 4 drugs occurred among 8% of the MDR strains, and resistance to 5 drugs has rarely been encountered. While the 5-drug resistant strains clearly represent formidable therapeutic challenges, they do not seem to be expanding in numbers from one year to the next but are sporadic in appearance. With regard to the fluoroquinolones, resistance to levofloxacin is rarely a phenotype encountered among the MDR strains.

Associated resistance between penicillin and macrolides is another interesting phenomenon seen with *S pneumoniae* and deserves further examination. When one maps *S pneumoniae* resistance from TRUST 7 (2002–2003) data across the United

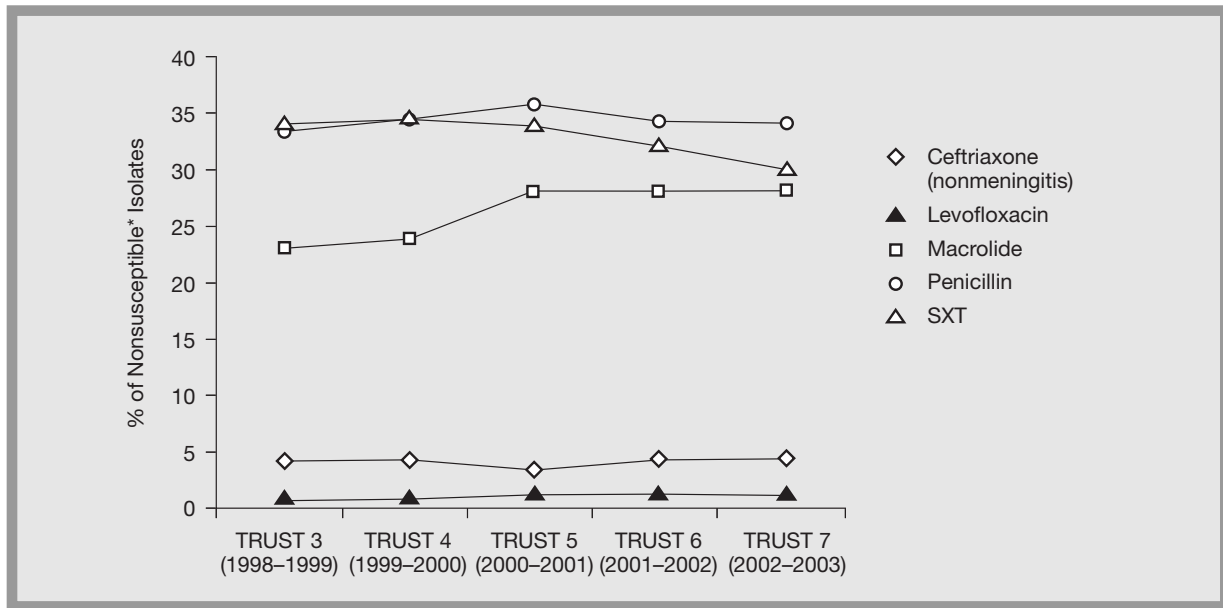
States (Figure 1) and compares penicillin and azithromycin (representing the macrolides) resistance, clearly there are areas where penicillin and macrolide resistance go hand in hand. Among penicillin-resistant strains of *S pneumoniae*, 82% are co-resistant to macrolides.

## CONCLUSIONS

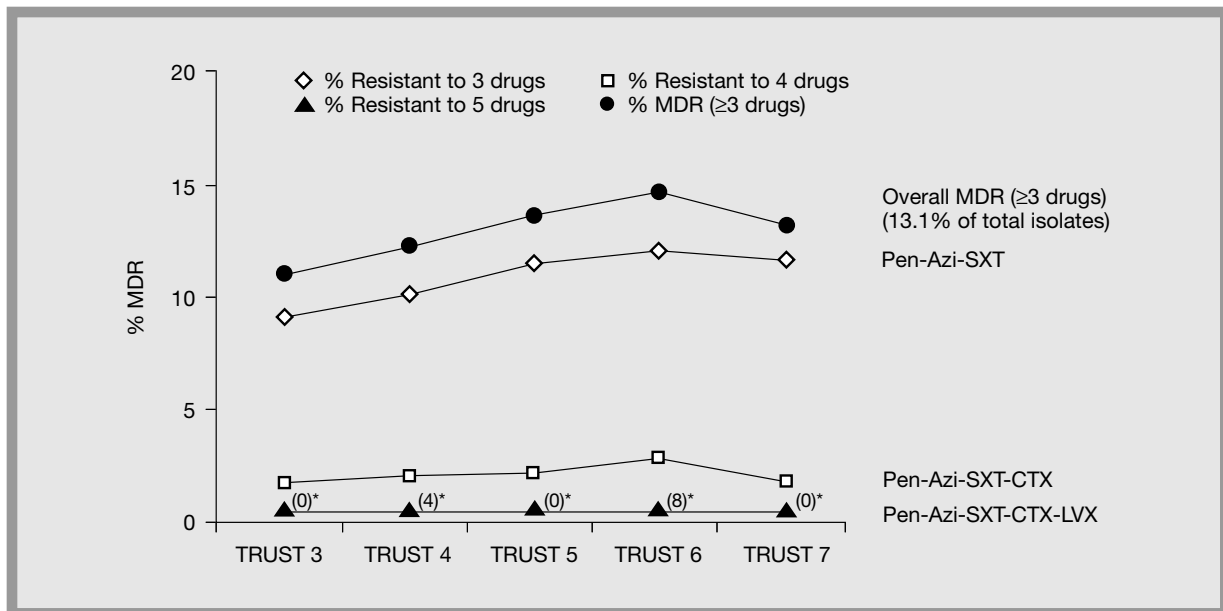
Antimicrobial profiles among key respiratory pathogens are anything but static. The dynamics of resistance are such that continuous monitoring and analysis, as provided by the TRUST initiative for example, is highly recommended. An analysis of such data has demonstrated that, as of 2003, resistance to most agents remains low among *H influenzae* and *M catarrhalis*. In contrast, resistance to single and multiple drugs among *S pneumoniae* is much more problematic and requires careful monitoring. Although agents such as levofloxacin remain highly active, any change in this pattern would substantially impinge on our current therapeutic options for this important pathogen.



**Figure 1.** Streptococcus pneumoniae antimicrobial resistance: TRUST 7 (2002–2003) (22). TRUST = Tracking Resistance in the United States Today; R = resistant.



**Figure 2.** *Streptococcus pneumoniae* antimicrobial resistance trends TRUST 3–7 (1999–2003). TRUST = Tracking Resistance in the United States Today; SXT = trimethoprim/sulfamethoxazole; I = intermediate; R = resistant. \*Nonsusceptible (I and R combined). Reprinted with permission (20,22).



**Figure 3.** *Streptococcus pneumoniae*: Multiple drug resistance (MDR). Azi = azithromycin; Pen = penicillin; SXT = trimethoprim/sulfamethoxazole; LVX = levofloxacin; CTX = ceftriaxone; TRUST = Tracking Resistance in the United States Today. \*Number of isolates encountered (5-drug resistant phenotype). Reprinted with permission (20,21).

### ACKNOWLEDGMENT

Assistance in the writing of this article was provided by Dr. A. Niroshan Siriwardena, MB, MMedSci, PhD, FRCGP, Family Physician and Clinical Senior Lecturer, De Montfort University, Leicester, UK.

### REFERENCES

1. World Health Organization. Overcoming antimicrobial resistance. [www.who.int/infectious-disease-report](http://www.who.int/infectious-disease-report). 2000. 12-9-2003.
2. Kariuki S, Hart CA. Global aspects of antimicrobial-resistant enteric bacteria. *Curr Opin Infect Dis*. 2001;14:579–586.

3. Austin DJ, Kristinsson KG, Anderson RM. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proc Natl Acad Sci USA*. 1999;96:1152–1156.
4. Guillemot D, Carbon C, Balkau B, et al. Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae*. *JAMA*. 1998;279:365–370.
5. Andreumont A. The future control of bacterial resistance to antimicrobial agents. *Am J Infect Control*. 2001;29:256–258.
6. Ben-David D, Rubinstein E. Appropriate use of antibiotics for respiratory infections: review of recent statements and position papers. *Curr Opin Infect Dis*. 2002;15:151–156.
7. Patterson JE. Antibiotic utilization: is there an effect on antimicrobial resistance? *Chest*. 2001;119(Suppl):426S–430S.
8. Holmberg SD, Solomon SL, Blake PA. Health and economic impacts of antimicrobial resistance. *Rev Infect Dis*. 1987;9:1065–1078.
9. Linden PK. Clinical implications of nosocomial gram-positive bacteremia and superimposed antimicrobial resistance. *Am J Med*. 1998;104(Suppl):24S–33S.
10. Niederman MS. Impact of antibiotic resistance on clinical outcomes and the cost of care. *Crit Care Med*. 2001;29(Suppl):N114–N120.
11. File TM Jr. Judicious use of antibiotics to treat respiratory infections. *Curr Opin Infect Dis*. 2002;15:149–150.
12. Gould IM. Antibiotic policies and the control of resistance. *Curr Opin Infect Dis*. 2002;15:395–400.
13. Ball P, Baquero F, Cars O, et al. Antibiotic therapy of community respiratory tract infections: strategies for optimal outcomes and minimized resistance emergence. *J Antimicrob Chemother*. 2002;49:31–40.
14. Pflomm JM. Strategies for minimizing antimicrobial resistance. *Am J Health-Syst Pharm*. 2002;59(Suppl):S12–S15.
15. Low DE. The era of antimicrobial resistance—implications for the clinical laboratory. *Clin Microbiol Infect*. 2002;8(Suppl 3):9–20.
16. Jones RN. Resistance patterns among nosocomial pathogens: trends over the past few years. *Chest*. 2001;119(Suppl):397S–404S.
17. Jacobs MR, Felmingham D, Appelbaum PC, et al. The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. *J Antimicrob Chemother*. 2003;52:229–246.
18. Jones RN. Global epidemiology of antimicrobial resistance among community-acquired and nosocomial pathogens: a five-year summary from the SENTRY Antimicrobial Surveillance Program (1997–2001). *Semin Respir Crit Care Med*. 2003;24:121–133.
19. Davies TA, Goldschmidt R, Pflieger S, et al. Cross-resistance, relatedness and allele analysis of fluoroquinolone-resistant US clinical isolates of *Streptococcus pneumoniae* (1998–2000). *J Antimicrob Chemother*. 2003;52:168–175.
20. Karlowsky JA, Thornsberry C, Jones ME, et al. Factors associated with relative rates of antimicrobial resistance among *Streptococcus pneumoniae* in the United States: results from the TRUST Surveillance Program (1998–2002). *Clin Infect Dis*. 2003;36:936–970.
21. Thornsberry C, Sahm DF, Kelly LJ, et al. Regional trends in antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States: results from the TRUST Surveillance Program, 1999–2000. *Clin Infect Dis*. 2002;34(Suppl):S4–S16.
22. Weaver MK, Sahm DF, Flamm RK, et al. Rates of antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States: results from the TRUST 7 (2002–2003) Surveillance Study. Abstract 201. Presented at the 41st Annual Meeting of the Infectious Diseases Society of America; October 9–12, 2003; San Diego, Calif.