Antibiotic-resistant *Streptococcus pneumoniae*

Implications for medical practice

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ABSTRACT

OBJECTIVE To review the definition and prevalence of antibiotic-resistant *Streptococcus pneumoniae*, its links with antibiotic prescribing, data on antibiotic prescribing and prescribing appropriateness, and evidence-based treatment guidelines for common respiratory tract syndromes.

QUALITY OF EVIDENCE Primary studies consist of cross-sectional surveys and case-control studies. Treatment guidelines are based on clinical trials, meta-analyses, and cohort studies. Study designs were appropriate for the specific study questions.

MAIN FINDINGS The increasing prevalence of penicillin-resistant *S pneumoniae* is concurrent with increasing antibiotic prescribing. Individual patients show a twofold to ninefold increase in nasopharyngeal carriage of resistant bacteria or invasion with resistant bacteria (among those who have received antibiotics in the preceding 3 months). Cross-sectional data as well as data from medicaid and drug databases attest to overprescribing of antibiotics for respiratory tract infections. Physician surveys and focus groups blame this on parental pressure for antibiotic prescriptions. However, parents in focus groups and surveys deny they pressure their physicians and indicate their main purpose for office visits is to obtain a diagnosis and to seek reassurance that their children are not seriously ill. Evidence-based guidelines suggest treatment strategies that would reduce antibiotic prescribing.

CONCLUSIONS The few antibiotics that can be used with resistant organisms are expensive and are increasingly being needed. To control the rise of antibiotic resistance, it is important to limit antibiotic overprescribing.

RÉSUMÉ

OBJECTIF Examiner la définition et la prévalence du *Streptococcus pneumoniae* résistant aux antibiotiques, ses liens avec la prescription d'antibiotiques et l'indication de cette ordonnance, ainsi que les lignes directrices sur le traitement fondé sur des données probantes des infections communes des voies respiratoires.

QUALITÉ DES PREUVES Les études primaires consistent en des sondages transversaux et des études de cas témoins. Les directives sur le traitement sont fondées sur des essais cliniques, des méta-analyses et des études de cohorte. La conception des études convenait aux questions précises de ces dernières.

PRINCIPAUX RÉSULTATS La prévalence accrue du *S pneumoniae* résistant à la pénicilline coïncide avec la hausse de la prescription d'antibiotiques. Chez les patients, on a détecté de deux à neuf fois plus d'incidence d'hébergement rhinopharyngien de la bactérie résistante ou d'envahissement à cette dernière (chez les personnes qui avaient pris des antibiotiques au cours du précédent trimestre). Les données transversales, ainsi que celles tirées de medicaid et des bases de données sur les médicaments, confirment une prescription abusive d'antibiotiques pour les infections des voies respiratoires. Dans les sondages et les groupes de discussion avec des médecins, on blâme la situation sur les pressions exercées par les parents pour obtenir une ordonnance. Par ailleurs, les parents, dans les sondages ou les groupes de discussion, nient avoir exercé des pressions sur leur médecin et indiquent que les principaux motifs de la consultation était le prononcé du diagnostic et l'assurance que leurs enfants n'étaient pas gravement malades. Les lignes directrices fondées sur des données probantes suggèrent des stratégies de thérapie qui auraient pour effet de réduire la prescription d'antibiotiques.

CONCLUSIONS Les rares antibiotiques qu'on puisse utiliser pour des organismes résistants sont coûteux et leur besoin se fait de plus en plus sentir. Pour contrôler l'augmentation de la résistance aux antibiotiques, il importe de limiter la prescription excessive d'antibiotiques.

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This article summarizes current knowledge about contributors to and implications of increasing antibiotic resistance. A MEDLINE search was performed in June 1997 using the explode command for the search terms "Drug resistance, Microbial" and "Epidemiology," and the terms "*Streptococcus pneumoniae*" or "Antibiotics" and "Prescriptions, Drug." Results from this and an earlier search were combined with studies in the authors' personal files and with data to which the authors had access that have not been published in peer-reviewed journals.

Quality of evidence

Data describing antibiotic susceptibility were derived from surveys involving large numbers of laboratories. Studies examining risk factors for resistant organisms were case-control studies or cross-sectional surveys, which examined presence or absence of outcome and risk concurrently in a total population, and cohort studies.[1] Data about antibiotic prescribing comes from case series; surveys, such as the United States Ambulatory Medical Care Survey; or administrative databases, such as the Saskatchewan Drug Database. Evidence about interventions listed in practice guidelines is based predominantly on randomized clinical trials or meta-analyses. Thus, the evidence included in this review is of high quality.

Definition of problem

Streptococcus pneumoniae is the leading bacterial cause for illness and death in young children, as it is the most common cause of bacteremia, otitis media, pneumonia, and meningitis.[2] It accounts for $4 billion US in expenditures each year in the United States.[3]

In general, *S pneumoniae* has displayed exquisite sensitivity to penicillin despite a case report of a resistant isolate from Australia as early as 1964.[4] Unlike resistance due to β-lactamase production, where bacteria produce an enzyme that breaks down the β-lactam ring, penicillin resistance among the pneumococci occurs by alterations in one or more of six known penicillin-binding proteins (PBPs) located in the *S pneumoniae* cell membrane. The normal function of these PBPs is to promote cross-linking of bacterial cell wall precursors, an integral step in cell wall development. This action is inhibited when PBPs are bound to penicillin.

Resistance to penicillin (and to other β-lactam antibiotics) occurs when target PBPs become physically altered so that penicillin binds with reduced affinity. These alterations occur as a result of chromosomal mutation.[5,6] Intermediate- or high-level resistance to penicillin develops once at least three PBPs have been altered.[7] Resistance to cephalosporins occurs when just two PBPs have been altered.[7] Resistance to other antimicrobial agents is mediated by transposons or chromosome alterations, which also generally result in altered binding sites.[5,6]

Fully sensitive isolates of *S pneumoniae* are defined by a minimal inhibitory concentration (MIC) of <0.1 mg/mL.[8] Intermediate resistance to penicillin is defined by an MIC of 0.1 to 1.0 mg/mL and high-level penicillin resistance is defined by an MIC of 2.0 mg/mL or more. Susceptibility is not tested between the 1- and 2-mg/mL concentrations, so that all organisms can be classified into one of the three groups. Intermediate- and high-level resistance to other antibiotics are also defined according to MICs.[8] For the sake of clarity, and to distinguish the more clinically relevant high-level resistant strains, changes to the nomenclature have recently been suggested.[9] All *S pneumoniae* with an MIC of 0.1 mg/mL or more are considered unsusceptible (PNSP), and the subgroup with MIC of 2.0 mg/mL or more are considered penicillin-resistant pneumococci.[9] However, definitions in the literature continue to overlap as new definitions are adopted. Approximately three quarters of the PNSP strains in Canada have had MICs in the 0.1 and 1 mg/mL range.[10]

Prevalence

The first clinically significant infection caused by a penicillin-resistant strain of *S pneumoniae* was reported from Australia in 1967.[4] Between 1974 and 1984, penicillin resistance rates of 10% or higher were reported from Israel, Papua New Guinea, Poland, South Africa, Spain, and some areas in the United States.[11] In 1977 multiresistant isolates were first found in South Africa.[12]

Antibiotic-resistant *S pneumoniae* could emerge rapidly over 2 or 3 years. This has been well documented in the United States (**Table 1**[2,9,13-16]). Worldwide, there is considerable variation in the inci-

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dence of PNSP. Surveys have reported the highest prevalence of PNSP in Korea[17] (70%), Hungary[18] (59%), South Africa[19] (45%), and Spain (44%)[20] and moderately high rates in Hong Kong[21] (29%), Japan[22] (26%), the United States[23] (25%), and Bulgaria[24] (24%). In some cases, adjacent countries have very different rates of resistance. For example, the rate of PNSP in Hungary[18] is very high (59%), while in Italy[25] and Austria,[26] the rates are low (7% and 6%, respectively).

In 1979, two cases of PNSP disease were reported from Canada.[27,28] Several Canadian surveys on penicillin-resistant pneumococci have been published or presented. Until recently, the rate of PNSP was 3% or less.[27,29,30] Since 1994, however, increased resistance has been reported in different regions. Seven percent of clinical isolates from community and hospital laboratories in Toronto during 1993 and 1994 were PNSP.[31] A later survey of clinical isolates obtained from 39 hospital and community laboratories across the country during 1994 and 1995 found that 12% of isolates were PNSP.[10] Interestingly, 20% of invasive isolates were PNSP (95% CI 13%, 27%), compared with 11% of noninvasive isolates (95% CI 9%, 13%).[10] Three percent of invasive isolates obtained from 10 pediatric hospitals across Canada from 1991 to 1994 were PNSP.[32] In 1996, however, the proportion of PNSP isolates increased to 8% (personal communication from Dr D. Scheifele, Principal Investigator for IMPACT and Professor of Pediatrics at the University of British Columbia). Thus Canada could be experiencing a period of rapid increase in PNSP rates as occurred earlier in the United States and elsewhere.

Simor and colleagues[10] have observed significantly higher frequency of resistance to other classes of antibiotics, such as quinolones, macrolides, tetracyclines, chloramphenicol (eg, Chloromycetin), and trimethoprim-sulfamethoxazole (eg, Septra), among penicillin-resistant pneumococci.[33] Because the mechanism of action and resistance are different for these drugs, multidrug resistance could be related to the bacteria's exposure to antibiotic selection pressures. In other words, penicillin exposure is correlated with exposure to other antibiotics.

Risk factors for resistance

Several epidemiologic studies have identified risk factors for carriage of resistant organisms and invasive disease due to resistant organisms. These factors include recent hospitalization, recent receipt of antibiotics, and day-care attendance.

Antibiotic exposure presumably acts as a selection process whereby antibiotics inhibit the growth of susceptible bacteria, providing a competitive advantage to resistant organisms. Antibiotic exposure increases the risk of nasopharyngeal carriage twofold to fivefold[34-39] and the risk of invasive disease with resistant pneumococci twofold to 10-fold.[40-45] Rates of carriage of PNSP in those receiving no recent antibiotics ranged from 9% to 21% and increased to 39% to 67% among antibiotic recipients.[34-39] Percentage of antibiotic use before invasive infection with penicillin-susceptible and unsusceptible pneumococci ranged from 4% to 39% and 30% to 77%, respectively.[40-45] In addition, transmission of resistant organisms can occur where many children are in contact with each other, such as in day-care centres. The problem of transmission in such settings is compounded by the high frequency of antibiotic exposure among children attending day-care centres.[46]

This rise in antibiotic resistance with antibiotic exposure has been demonstrated among individuals as well. Three cohorts of children, two of whom were receiving antibiotic prophylaxis for recurrent ear infections, were studied.[47] At the time prophylaxis was initiated and at the equivalent time in those not receiving prophylaxis, all pneumococcal isolates from nasopharyngeal specimens were fully penicillin susceptible. Five months after prophylaxis was initiated, 25% of pneumococcal isolates from the group receiving amoxicillin prophylaxis versus none in the sulfisoxazole (Pediazole) and control groups were unsusceptible to penicillin. Four months after discontinuing prophylaxis, only 5% of pneumococci in the amoxicillin group were unsusceptible. Thus, the association of carrying penicillin-resistant organisms after

Table 1. Emergence of antibiotic-resistant *S pneumoniae* in the United States

REFERENCE	PERIOD	PENICILLIN-UNSUSCEPTIBLE PNEUMOCOCCI (%)	PENICILLIN-RESISTANT PNEUMOCOCCI (%)
Spika et al[13]	1979-1987	5	0
Breiman et al[2]	1991-1992	8	1
Butler et al[9]	1993-1994	14	3
Hofmann et al[14]	1994	25	7
Doern et al[15,16]	1994-1995	25	10

Penicillin unsusceptible—minimal inhibitory concentration is 0.1 mg/mL or more; penicillin resistant—minimal inhibitory concentration is 2.0 mg/mL or more.

amoxicillin exposure appears to be reversible when the exposure is taken away. This study did not examine levels of sulfisoxazole resistance after prophylaxis using this antibiotic.

Antibiotic use

Most information about antibiotic prescribing comes from the United States. In the most definitive study, a random sample of 35 000 to 72 000 charts were reviewed from 2500 to 7200 physicians primarily engaged in patient care activities at four times: 1980, 1985, 1989, and 1992.[48] During that period, use of antibiotics stayed stable, but there was a shift of antibiotics from penicillin and ampicillin to amoxicillin and cephalosporins. Respiratory tract infections accounted for three quarters of the prescriptions during 1992.[48]

Data on the proportions of antibiotic prescription by clinical syndrome would be helpful. In a multiphysician pediatric clinic, 98% of children with otitis media, 43% with uncomplicated upper respiratory tract infection or asthma, 100% with sinusitis, 82% with bronchitis, and 81% with pharyngitis received antibiotic prescriptions.[49] In another study using the Kentucky Medicaid claims database, 57% of children with uncomplicated nasopharyngitis were prescribed antibiotics.[50] This rate is only slightly lower than the rate of antibiotic prescribing of 68% for otitis media and 62% for sinusitis. Considering that most upper respiratory infections, bronchitis, and asthma are related to viral infections, gross overprescribing is taking place for respiratory tract infections.

Canadian data on proportions of antibiotics by specific indication are generally unavailable. In Canada, antibiotics were the second most commonly prescribed drug class (after cardiovascular agents), accounting for 26.3 million prescriptions in 1996.[51] The Compuscript database provides some interesting information about the types of antibiotics, the patients who receive antibiotics, and the medical specialty of prescribing physicians. The number of prescriptions increased by 10% between 1992 and 1993; use has been stable since then.

Amoxicillin is the most frequently prescribed antibiotic, accounting for approximately 25% of all antibiotic prescriptions (6.8 million prescriptions). This is followed by cephalosporins (3.3 million prescriptions) and erythromycin (2.7 million prescriptions). Children 9 years and younger receive proportionately more prescriptions for amoxicillin, cephalosporins, erythromycin (eg, Eryc), and trimethoprim than older individuals.

Three quarters of all antibiotic prescriptions are written by general or family practitioners. Five percent are written by pediatricians, the next largest group of prescribers.

Data on prescriptions for children 5 years and younger were also obtained from the Saskatchewan drug database for the year 1995 (personal communication from Mary Rose Stang, PhD, Saskatchewan Health, August 19, 1997). During that year, 94 077 visits for respiratory tract infections took place for 34 381 children. Of these visits, 40 516 (43%) resulted in antibiotic prescriptions. The most common diagnosis was acute upper respiratory infection (43 160 visits), for which 38% of children received antibiotics. Of 4743 visits for the common cold, 1052 (22%) resulted in antibiotic prescriptions. Because these conditions are caused by viruses, there should be no role for antibiotic treatment.

Most patients with tonsillitis, pharyngitis, and bronchitis received antibiotics. Because group A streptococci account for only 13% of pharyngitis or tonsillitis and because bronchitis in children is viral in origin, antibiotics are also overprescribed for these conditions. The high costs of antibiotics for respiratory tract infections among children younger than 5 years in this small population should also be stressed; in 1995 more than $547 000 or $16 per child in that age group was spent on antibiotics in Saskatchewan.

One of the few published Canadian studies examined antibiotic prescription for croup, a viral illness for which antibiotics are not indicated.[52] In this study, a significantly higher rate of antibiotic prescription was observed in a rural hospital staffed by family practitioners (63%) than in a community hospital staffed by both pediatricians and family practitioners (38%) and a tertiary care hospital staffed by pediatricians only (6%).

Physicians sense pressure from parents of ill children for antibiotic prescriptions.[53-56] The difficulty in absolutely differentiating a bacterial from a viral infection, lack of perceived risk of adverse effects from antibiotic prescriptions, lack of concern about costs when insurance companies will pay for antibiotics, and the perception that antimicrobial resistance is a risk at a population level not at a patient level, all predispose physicians to prescribe antibiotics.[56] Furthermore, some physicians believe that antibiotics prevent secondary bacterial infection in the setting of a preceding viral infection, although a meta-analysis has shown that this is not the case.[57]

When parents are questioned about their reasons for bringing their children to physicians, most state

that they are seeking a diagnosis[58] or reassurance that the illness is not serious.[53,54] The lack of parental satisfaction with a physician diagnosis of a viral infection has also recently been highlighted.[59] The contradictions between parent and physician perceptions could be related to inadequate communication or miscommunication. Certainly it takes less time to explain why an antibiotic is not needed than to write a prescription for an antibiotic. In this age of increased antibiotic resistance, however, parents must be educated about the advantages of withholding antibiotics.

Practice guidelines

Evidence-based guidelines have been developed recently by the US Centers for Disease Control and Prevention, American Academy of Pediatrics, and American Academy of Family Practice[60] to help physicians curb antibiotic use in managing common respiratory infections. After reviewing the evidence, they have provided guidelines on management of otitis media,[61] cough or bronchitis,[62] the common cold,[63] and pharyngitis[64] (**Table 2**).

In adults with severe *S pneumoniae* pneumonia, penicillin G or ampicillin treatment of penicillin-resistant *S pneumoniae* was not associated with greater mortality.[65] This finding is likely related to the high concentrations of penicillin achievable in the blood and lung relative to MICs. These data suggest no change in empiric therapy for community-acquired pneumonia.

Because achievable antibiotic concentrations are lower in cerebrospinal fluid, vancomycin (Vancocin) should be added to ceftriaxone (Rocephin) as empiric therapy when pneumococcal meningitis is suspected based on the presence of positive smear results.[66] Antibiotic coverage can be narrowed once susceptibility results are available. Because of concerns about the rising frequency of high-level penicillin resistance, similar empiric therapy has been suggested to manage critically ill children with suspected sepsis.[66]

Potential for reversal of antibiotic resistance

The development and dissemination of guidelines has fortunately been successful in reversing high levels of antimicrobial resistance in community-acquired infections.[67,68] A study in Iceland[66] showed lowered pneumococcal resistance rates to penicillin in conjunction with widespread dissemination of guidelines to physicians, a public health campaign directed at the general population, and elimination of government financial support for antibiotics to make consumers bear the full cost of most such agents. A Finnish study showed a halving of erythromycin resistance among group A streptococci after dissemination of practice guidelines related to macrolide use.[68]

Brook and Gober[47] have demonstrated reversal of nasopharyngeal colonization with penicillin-resistant pneumococci 4 months after amoxicillin prophylaxis

Table 2. Evidence-based treatment guidelines for respiratory tract infections

SYNDROME	EVIDENCE	RECOMMENDATION
Acute otitis media	Antibiotics reduce failure rate compared with placebo. No antibiotics superior over others. Meta-analysis, randomized trials	Amoxicillin (first-line antibiotic) recommended if acute otitis media confirmed by presence of symptoms and bulging eardrum with effusion on insufflation
Cough illness, bronchitis	No difference between antibiotics and placebo. Reduction of pertussis transmission with antibiotics. Randomized trials, cohort studies	Antibiotics are not indicated for usual coughs or bronchitis unless pertussis is suspected.
Common cold	• No difference between antibiotics and placebo in duration of purulent nasal discharge. Randomized trials • No differences between antibiotics and placebo in secondary bacterial infections. Meta-analysis	Antibiotics are not indicated for shortening illness duration or preventing secondary bacterial infections.
Pharyngitis	• Most acute pharyngitis is viral (85%). Cannot differentiate group A streptococcal infection from viral infection. Cross-sectional surveys. • Antibiotics prevent rheumatic fever if used to treat group A streptococcal pharyngitis and marginal clinical improvement. Randomized trials	Group A streptococcal pharyngitis must be confirmed by culture or antigen detection. Penicillin is first-line agent.

Data from US Centers for Disease Control and Prevention, American Academy of Pediatrics, and the American Academy of Family Practice.[59-63]

Key points

- Antibiotic resistance has increased alarmingly in Canada and other countries, largely because of inappropriate prescribing.
- Antibiotics are used too often to treat viral illnesses, and second- and third-generation drugs are overused in preference to simpler ones.
- Family physicians write about 75% of all antibiotic prescriptions.
- Reducing use of antibiotics for viral conditions and reserving newer antibiotics for serious bacterial infections can reverse this trend.

was discontinued. These three studies[47,67,68] support discontinuing or restricting antibiotics to reverse trends of increasing antibiotic resistance in the community. The effect of aggressive use of guidelines in community practice mirrors previous experience with hospital guidelines and nosocomial infections, provided baseline resistance rates have not already reached too high a level.[69]

For guidelines to be effective, however, they need to be incorporated into everyday practice. To achieve this goal, the problem must be important and guidelines must be convincing and acceptable to primary caregivers. Recommendations must reflect the conditions of general office practice. Thus, an important implementation strategy requires that primary caregivers review and debate these guidelines and modify them for their specific practices.

A recent example is the work by McIsaac et al,[70-72] who have developed a clinical method to score group A streptococcus throat infections. This scoring method has been shown to reduce unnecessary antibiotic prescribing for this common condition.

Conclusion

The frequency of antibiotic resistance has reached worrisome levels. This frequency has been attributed, at least in part, to widespread, often inappropriate, antibiotic use. Physicians acknowledge overprescription of antibiotics and indicate that they do bow to parental pressure for antibiotic prescriptions.[53] The rise in antimicrobial resistance among pneumococci has already resulted in changes to recommendations for empiric therapy, leading to increased cost and toxicity. Thus, a two-pronged approach must be taken to manage infectious diseases: prudent use of wide-spectrum antibiotics for serious disease but, more importantly, avoidance of antibiotics for viral infections and use of narrow-spectrum antibiotics for less serious bacterial infections.

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References

1. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research. Principles and quantitative methods.* 1st ed. Belmont, Calif: Lifetime Learning Publications; 1982.
2. Breiman RF, Butler JC, Tenover FC, Elliott JA, Facklam RR. Emergence of drug-resistant pneumococcal infections in the United States. *JAMA* 1994;271:1831-5.
3. Gable CB, Holzer SS, Engelhart L, Friedman RB, Smeltz F, Schroeder D, et al. Pneumococcal vaccine: efficacy and associated cost savings. *JAMA* 1990;264:2910-5.
4. Hansman D, Bullen M. A resistant pneumococcus. *Lancet* 1967;2:264-5.
5. Neu HC. The crisis in antibiotic resistance. *Science* 1992; 257:1064-73.
6. Klugman KP. Pneumococcal resistance to antibiotics. *Clin Microbiol Rev* 1990;3:171-96.
7. McDougal LK, Rasheed JK, Biddle JW, Tenover FC. Identification of multiple clones of extended-spectrum cephalosporin-resistant *Streptococcus pneumoniae* in the United States. *Antimicrob Agents Chemother* 1995;39:2282-8.
8. National Committee for Clinical Laboratory Standards. *Performance standards for antimicrobial susceptibility testing.* Villanova, Penn: National Committee for Clinical Laboratory Standards; 1997.
9. Butler JC, Hofmann J, Cetron MS, Elliott JA, Facklam RR, Breiman RF. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the Centers for Disease Control and Prevention's pneumococcal sentinel surveillance system. *J Infect Dis* 1996; 174:986-93.
10. Simor AE, Louie M, Low DE. Canadian national survey of prevalence of antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 1996;40:2190-3.
11. Appelbaum PC. World-wide development of antibiotic resistance in pneumococci. *Eur J Clin Microbiol* 1987;6:367-77.
12. Jacobs MR, Koornhof HK, Robins-Browne RM, Stevenson CM, Vermaola ZA, Freiman I. Emergence of multiply resistant pneumococci. *N Engl J Med* 1978;299:735-40.
13. Spika JS, Facklam RR, Plikagtis BD. Antimicrobial resistance of *Streptococcus pneumoniae* in the United States, 1979-1987. *J Infect Dis* 1991;163:1273-8.
14. Hofmann J, Cetron MS, Farley MM, Baughman WS, Facklam RR, Elliott JA. The prevalence of drug-resistant

Streptococcus pneumoniae in Atlanta. *N Engl J Med* 1995; 333:481-6.

15. Doern GV, Brueggemann A, Holley HP, Rauch AM. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994 to 1995: results of a 30-center national surveillance study. *Antimicrob Agents Chemother* 1996;40:1208-13.
16. Doern GV. Trends in antimicrobial susceptibility of bacterial pathogens of the respiratory tract. *Am J Med* 1995; 99(Suppl 6B):3S-7S.
17. Lee HJ, Park JY, Jang SH, Kim JH, Kim EC, Choi KW. High incidence of resistance to multiple antimicrobials in clinical isolates of *Streptococcus pneumoniae* from a university hospital in Korea. *Clin Infect Dis* 1995;20:826-35.
18. Marton A. Pneumococcal antimicrobial resistance: the problem in Hungary. *Clin Infect Dis* 1992;15:106-11.
19. Friedland IR, Klugman KP. Antibiotic-resistant pneumococcal disease in South African children. *Am J Dis Child* 1992; 146:920-3.
20. Garcia-Leoni ME, Cercenado E, Rodeno P, De Quiros JCLB, Nartubez-Hernandez D, Bouza E. Susceptibility of *Streptococcus pneumoniae* to penicillin: a prospective microbiological and clinical study. *Clin Infect Dis* 1992;14:427-35.
21. Kam KM, Luey KY, Fung SM, Yu PP, Harden TJ, Cheung MM. Emergence of multiple antibiotic resistant *Streptococcus pneumoniae* in Hong Kong. *Antimicrob Agents Chemother* 1995;39:2667-70.
22. Yoshida R, Kaku M, Kohno S, Ishida K, Mizukare R, Takemura H, et al. Trends in antimicrobial resistance of *Streptococcus pneumoniae* in Japan. *Antimicrob Agents Chemother* 1995;39:1196-8.
23. Drug-resistant *Streptococcus pneumoniae*—Kentucky and Tennessee, 1993. *MMWR Morb Mortal Wkly Rep* 1994;43:23-6.
24. Setchanova L. Clinical isolates and nasopharyngeal carriage of antibiotic-resistant *Streptococcus pneumoniae* in the Hospital for Infectious Diseases, Sofia, Bulgaria, 1991-1993. *Antimicrob Drug Resist* 1995;1:79-84.
25. Marchese A, Debbia EA, Arvigo A, Pesce A, Schito GC. Susceptibility of *Streptococcus pneumoniae* strains isolated in Italy to penicillin and ten other antibiotics. *J Antimicrob Chemother* 1995;36:833-7.
26. Mittermayer H, Jebelean C, Binder L, Haditsch M, Watschinger R. Antibiotic susceptibility of pneumococci isolated in Austria over a four-year period. *Eur J Clin Microbiol Infect Dis* 1996;15:817-20.
27. Ahronheim GA, Reich B, Marks ME. Penicillin-insensitive pneumococci. *Am J Dis Child* 1979;133:187-91.
28. Pabst HF, Nigrin J. Penicillin resistance of pneumococci and immunodeficiency. *Lancet* 1979;2:359-60.
29. Dixon JMS, Lipinski AE, Graham MEP. Detection and prevalence of pneumococci with increased resistance to penicillin. *Can Med Assoc J* 1977;117:1159-61.
30. Jette LP, Lamothe F, The Pneumococcus Study Group. Surveillance of invasive *Streptococcus pneumoniae* infection in Quebec, Canada, from 1984-86: serotype distribution, antimicrobial susceptibility, and clinical characteristics. *J Clin Microbiol* 1989;27:1-5.
31. Simor AE, Rachlis A, Louie L, Goodfellow J, Louie M. Emergence of penicillin-resistant *Streptococcus pneumoniae* in southern Ontario, 1993-94. *Can J Infect Dis* 1995;6:157-60.
32. Scheifele D, Gold R, Talbot J, Members of the IMPACT surveillance network. *A national survey of invasive pneumococcal infections in children, 1991-1994.* San Francisco: Infectious Disease Society of America; 1996.
33. Matsumura S, De Azavedo J, Fletcher A, et al. *An* in vitro *study of new and old antimicrobials in the treatment of penicillin-resistant* Streptococcus pneumoniae. In: American Society for Microbiology. Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. 17-20 Sep 1995; San Francisco. Washington DC: American Society for Microbiology, 1995. p. 88.
34. Boken DJ, Chartrand SA, Goering RV, Kruger R, Harrison CJ. Colonization with penicillin-resistant *Streptococcus pneumoniae* in a child-care center. *Pediatr Infect Dis J* 1995;14:879-84.
35. Reichler MR, Allphin AA, Breiman RF, Schreiber JR, Arnold JR, McDougal LK. The spread of multiply resistant *Streptococcus pneumoniae* at a day care center in Ohio. *J Infect Dis* 1992;166:1346-53.
36. Robins-Brown RM, Kharsany ABM. Antibiotic-resistant pneumococci in hospitalized children. *J Hyg* 1984;93:9-16.
37. Radetsky MS, Istre GR, Johansen TL, Parmlee SW, Lauer BW, Wiesenthal AM. Multiply resistant pneumococcus causing meningitis: its epidemiology within a day-care centre. *Lancet* 1981;2:771-3.
38. Duchin JS, Breiman RF, Diamond A, Lipman HB, Block SL, Hedrik JA. High prevalence of multidrug-resistant *Streptococcus pneumoniae* among children in a rural Kentucky community. *Pediatr Infect Dis J* 1995;14:745-50.
39. Zenni MK, Cheatham SH, Thompson JM, Reed GW, Batson AB, Palmer PS. *Streptococcus pneumoniae* colonization in the young child: association with otitis media and resistance to penicillin. *J Pediatr* 1995;127:533-7.
40. Amitai Y, Rotenberg M, Wirtschafter D, Haas H, Michel J. Increasing frequency of penicillin-resistant pneumococci: epidemiological aspects and case-control study. *Isr J Med Sci* 1985;21:340-5.
41. Tan TQ, Mason EO, Kaplan SL. Penicillin-resistant systemic pneumococcal infections in children: a retrospective case-control study. *Pediatrics* 1993;92:761-7.
42. Nava JM, Bella F, Garau J, Lile J, Morera M-A, Marti C. Predictive factors for invasive disease due to penicillin-resistant *Streptococcus pneumoniae*: a population-based study. *Clin Infect Dis* 1994;19:884-90.

43. Block SL, Harrison CJ, Hedrick JA, Tyler RD, Smith RA, Keegan E. Penicillin-resistant *Streptococcus pneumoniae* in acute otitis media: risk factors, susceptibility patterns and antimicrobial management. *Pediatr Infect Dis J* 1995;14:751-9.
44. Jackson MA, Shelton S, Nelson JD, McCracken GH. Relatively penicillin-resistant pneumococcal infections in pediatric patients. *Pediatr Infect Dis* 1984;3:129-32.
45. Pallares R, Gudiol F, Linares J, Ariza J, Rufi G, Murgui L. Risk factors and response to antibiotic therapy in adults with bacteremic pneumonia caused by penicillin-resistant pneumococci. *N Engl J Med* 1987;317:18-22.
46. Kellner JD, Ford-Jones EL, Matlow A, Low DE, Corey M, Watson H. K 17. Nasopharyngeal (NP) carriage of *Streptococcus pneumoniae* (SP) in children in daycare centres (DCC). In: American Society for Microbiology. Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 15-18 Sep 1996; New Orleans. Washington, DC: American Society for Microbiology; 1996. p. 252.
47. Brook I, Gober AE. Prophylaxis with amoxicillin or sulfisoxazole for otitis media: effect on recovery of penicillin-resistant bacteria from children. *Clin Infect Dis* 1996;22:143-5.
48. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. *JAMA* 1995;273:214-9.
49. Arnold KE, Leggiadro RJ, Breiman RF, Lipman HB, Schwartz B, Appleton MA. Risk factors for carriage of drug-resistant *Streptococcus pneumoniae* among children in Memphis, Tennessee. *J Pediatr* 1996;128:757-64.
50. Mainous AG, Hueston WJ, Clark JR. Antibiotics and upper respiratory infection. Do some folks think there is a cure for the common cold? *J Fam Pract* 1996;42:357-61.
51. Consensus conference: controlling antimicrobial resistance. An intergrated action plan for Canadians. *Can Commun Dis Rep* 1997;23(Suppl 7):S1-S32.
52. Pianosi P, Feldman W, Robson MG, McGillivray D. Inappropriate use of antibiotics in croup at three types of hospital. *Can Med Assoc J* 1986;134:357-9.
53. Palmer DA, Bauchner H. Parents' and physicians' views on antibiotics. *Pediatrics* 1997;99:e6.
54. Mayefsky JH, el-Shinaway Y, Kelleher P. Families who seek care for the common cold in a pediatric emergency department. *J Pediatr* 1991;119:933-4.
55. Cowan PF. Patient satisfaction with an office visit for the common cold. *J Fam Pract* 1987;24:412-3.
56. Hamm RM, Hicks RJ, Bemben DA. Antibiotics and respiratory infections: are patients more satisfied when expectations are met? *J Fam Pract* 1996;43:56-62.
57. Gadomski AM. Potential interventions for preventing pneumonia among young children: lack of effect of antibiotic treatment for upper respiratory infections. *Pediatr Infect Dis J* 1993;12:115-20.
58. Sanchez-Menegay C, Hudes ES, Cummings SR. Patient expectations and satisfaction with medical care for upper respiratory tract infections. *J Gen Intern Med* 1992;7:432-4.
59. Kai J. Parents' difficulties and information needs in coping with acute illness in preschool children: a qualitative study. *BMJ* 1996;313:987-90.
60. Dowell SF, Marcy SM, Phillips WR, Gerber MA, Schwartz B. Principles of judicious use of antimicrobial agents for pediatric upper respiratory tract infections. *Pediatrics* 1998; 101(Suppl):163-70.
61. Dowell SF, Marcy SM, Phillips WR, Gerber MA, Schwartz B. Otitis media—principles of judicious use of antimicrobial agents. *Pediatrics* 1998;101(Suppl):165-71.
62. O'Brien KL, Dowell SF, Schwartz B, Marcy SM, Phillips WR, Gerber MA. Cough illness/bronchitis—principles of judicious use of antimicrobial agents. *Pediatrics* 1998; 101(Suppl):178-81.
63. Rosenstein N, Phillips WR, Gerber MA, Marcy SM, Schwartz B, Dowell SF. The common cold—principles of judicious use of antimicrobial agents. *Pediatrics* 1998; 101(Suppl):181-4.
64. Schwartz B, Marcy SM, Phillips WR, Gerber MA, Dowell SF. Pharyngitis—principles of judicious use of antimicrobial agents. *Pediatrics* 1998;101(Suppl):171-4.
65. Pallares R, Linares J, Vadillo M, Cabellos C, Manresa F, Viladrich PF. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *N Engl J Med* 1995;333:474-80.
66. Committee on Infectious Diseases. American Academy of Pediatrics. Therapy for children with invasive pneumococcal infections. *Pediatrics* 1997;99:289-98.
67. Stephenson J. Icelandic researchers are showing the way to bring down rates of antibiotic-resistant bacteria. *JAMA* 1996;275:175.
68. Seppala H, Klaukka T, Vuopio-Varkila J, Maotiala A, Helenius H, Lager K. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *N Engl J Med* 1997;337:441-6.
69. Swartz MN. Use of antimicrobial agents and drug resistance. *N Engl J Med* 1997;337:491-2.
70. McIsaac WJ, Goel V, Slaughter PM, Parsons GW, Woolnough KV, Weir PT, et al. Reconsidering sore throats. Part 1: problems with current practice. *Can Fam Physician* 1997;43:485-93.
71. McIsaac WJ, Goel V, Slaughter PM, Parsons GW, Woolnough KV, Weir PT, et al. Reconsidering sore throats. Part 2: alternative approach and practical office tool. *Can Fam Physician* 1997;43:495-500.
72. McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *Can Med Assoc J* 1998;158(1):75-83.