
CANADIAN BACTERIAL SURVEILLANCE NETWORK

December 1999

Decreasing Penicillin and Macrolide Resistance in *Streptococcus pneumoniae* in Canada: Who's Driving Whom?

Dr. D. E. Low

Increasing macrolide use has been associated with increasing macrolide resistance in group A streptococci and it has been suggested that a similar association exists with *S. pneumoniae*. In the last decade in Canada there has been an increase in the prevalence of penicillin-non-susceptible *S. pneumoniae* (PNSP) from <3% in 1988 to 16% in 1998. We have found a significant association between PNSP and resistance to macrolides ($P < 0.001$) suggesting that penicillin resistance might actually drive macrolide resistance. Data from Intercontinental Medical Statistics (IMS) Canada indicates the overall number of anti-infective prescriptions (ARx) has decreased significantly in Canada from 865/1000 pop. in 1995 to 765/1000 pop. in 1998, ($p < 0.001$). From 1995 to 1998, prescriptions for oral penicillins decreased from 424/1000 ARx to 387/1000; tetracyclines decreased from 71/1000 ARx to 62/1000; and TMP/SMX decreased from 113/1000 ARx to 98/1000 while prescriptions for macrolides increased from 144/1000 ARx to 180/1000.

Data from ongoing surveillance showed a significant reduction in PNSP from 1998 to 1999 (15.2% to 11.5%, $P = 0.01$) with a modest concurrent decrease in macrolide resistance (10.4% to 9.2%, NS).

Effectiveness of a Pneumococcal Vaccination Program in Preventing Invasive Pneumococcal Disease

K. Green for Toronto Invasive Bacterial Diseases Network

S. pneumoniae is the most common cause of bacterial pneumonia in adults, and the most common cause of bacteremia, bacterial otitis media and meningitis in infants and children. Although pneumococcal vaccine has been available since 1977 and is recommended for high-risk individuals, the efficacy of the vaccine continues to be questioned.

In 1996, the province of Ontario initiated a publicly funded program to deliver pneumococcal vaccine to all citizens in the high risk groups defined by the National Advisory Committee on Immunization (NACI)¹. The goal of the program was to increase the proportion of eligible persons receiving pneumococcal vaccine from an estimated 7%-15% to 65% over three years. Pneumococcal vaccine was distributed to family physicians in conjunction with the annual influenza vaccine and a focused campaign to educate the public and family physicians.

In 1995, the Toronto Invasive Bacterial Diseases Network (TIBDN), a collaborative group of microbiology laboratories, initiated population-based surveillance for invasive pneumococcal disease in metropolitan Toronto and Peel Region (population 3.4 million). Sterile site isolates of *S. pneumoniae* are reported by all microbiology laboratories serving hospitals and the three largest private laboratories. Clinical data, isolates for serotyping and vaccine history are collected on all invasive cases. The combination of the established surveillance system for invasive disease and the implementation of a publicly funded mass vaccination campaign provided us with a unique opportunity to study the effectiveness of pneumococcal vaccination on the incidence of invasive disease.

The proportion of the population eligible for pneumococcal vaccine were estimated as the sum of the population ≥ 65 years of age and those 2-64 years old with a qualifying medical condition. The proportion of the population with an eligible diagnosis was estimated from the 1991 Ontario Health Survey for the population in metropolitan Toronto and Peel Region. The estimate was adjusted upward to account for patients with other qualifying medical conditions (predominantly HIV infection). The proportion was then applied to overall population estimates for 1995-1998, assuming that the overall proportion of the population with qualifying

INSIDE THIS ISSUE

- 1 Decreasing Penicillin and Macrolide Resistance in *S. pneumoniae* in Canada
- 1 Effectiveness of a Pneumococcal Vaccination Program in Preventing Invasive Pneumococcal Disease
- 2 Macrolide Resistance in Streptococci
- 4 Soft Tissue Infections Due to Group A Streptococci

**CBSN Study Office- Mount Sinai Hospital
600 University Avenue, Room 1460
Toronto, Ontario, M5G 1X5**

Phone: (416) 586-3144/1-800-668-6292 fax: (416) 586-3140

Although the cause of this reduction is unclear, there is a reduction in overall antibiotic use and it is somehow associated with reduction in penicillin resistance in *S. pneumoniae*. This is contrary to what is happening in other countries, particularly the U.S. Recent data has found that in some areas of the U.S., high level resistance has reached 40% (a 60-fold increase during the last 10 years) (*Am J Med* 1999 May 3;106(5A):19S-25S). Surveillance during the next year will allow us to determine if this downward trend is real and whether we are able to determine what's driving what.

There are obviously numerous other factors that may be driving resistance, such as dissemination of a clone(s) or linkage of resistance with non-antibiotic factors, which may select for resistance. From this data, for at least some classes of antibiotics and pathogens, there is no linear association between the volume of antibiotic use and resistance. Recognizing such factors is essential if we are to be successful in controlling resistance. ♦

Macrolide Resistance in Streptococci

Dr. Joyce de Azavedo

Macrolides are frequently used for the treatment of respiratory tract infections and it is consequently useful to monitor resistance trends in common respiratory pathogens. In a previous survey of *S. pneumoniae* strains collected from across Canada from 1993-1996, 147/5,029 (2.9%) were found to be erythromycin resistant and two phenotypes, designated MLS and M, were identified(1). Strains with the MLS phenotype demonstrated resistance to erythromycin and inducible or constitutive cross-resistance to clindamycin and streptograminB type antibiotics. Strains with the the M phenotype showed resistance to erythromycin alone. Genetic characterization by PCR, showed that M phenotype strains possessed the *mef* gene (56% of strains) whereas MLS strains possessed the *ermB* gene (44% of strains). These two phenotypes can easily be distinguished by a Kirby-Bauer disk-diffusion assay where erythromycin and clindamycin disks are placed 1.6 cm apart. MLS inducible resistance is identified by a zone of blunting between the two disks and constitutive resistance by growth \leq 19mm around both disks. Strains with the M phenotype always show complete sensitivity to clindamycin. In the last two years, there has been an increase in macrolide resistance in *S. pneumoniae*. Of 1,137 strains collected in 1998, 10.2% were erythromycin resistant and 4.9% were clindamycin resistant indicating an almost equal proportion of MLS and M phenotype strains. In 1999, 792 strains were tested of which 9.2 were erythromycin resistant and 5.2 clindamycin resistant. It is useful to know the prevalence rates of M and MLS phenotypes since strains with the M phenotype can be treated with clindamycin.

Although group A streptococci (GAS) are still susceptible to β -lactam antibiotics, resistance to the macrolides has emerged. The prevalence of the M and MLS phenotypes is somewhat different in GAS compared with *S. pneumoniae*. Of 3,205 clinical isolates collected in Southern Ontario in 1997,

erythromycin resistance was found in 67 (2.1%) strains. Of these, 47 (70%) showed complete sensitivity to clindamycin and were found to possess the *mef* gene by PCR.

Among the remaining 20 strains, 18 and 2 strains respectively showed inducible and constitutive resistance to clindamycin suggesting the presence of an *erm* gene. However, only a single strain yielded an amplicon using *ermB* primers. A new *erm* gene, *ermTR*, was recently reported in GAS strains isolated in Finland. Further analysis of our strains using primers based on the *ermTR* gene, revealed that all but one of the MLS strains possessed *ermTR*(2). Pulsed-field gel electrophoresis and serotyping demonstrated different patterns among these strains suggesting that they were not clonal in origin. The presence of the *ermTR* gene in the majority of erythromycin, clindamycin resistant isolates of different origin suggests that this gene has spread by horizontal transfer between strains of different clonal origin. GAS strains harbouring the *ermTR* gene are generally inducible and can be identified by the zone of blunting in disk diffusion tests. By comparison, *S. pneumoniae* strains with *ermB* genes tend to show constitutive resistance. Among 422 blood culture isolates of viridans group streptococci, collected from across Canada from May 1995 to March 1997, 121(29%) showed resistance to erythromycin but only 19 (16%) strains also showed resistance to clindamycin. PCR showed that 18/19 strains which were erythromycin and clindamycin resistant (MLS phenotype) possessed an *erm* gene including 2 strains which in addition, harbored a *mef* gene. One *S. milleri* strain possessed the newly described *ermTR* gene which has so far only been identified in Group A streptococci. Of the 102 (84%) erythromycin-resistant, clindamycin-sensitive strains (M phenotype) 101 possessed the *mef* gene and 1 strain lacked both genes. The high prevalence of the *mef* gene in viridans streptococci has implications for the current recommendation of macrolide prophylaxis for endocarditis. ♦

References:

1. Johnston, N.J., J.C. De Azavedo, J.D. Kellner, and D.E. Low. 1998. Prevalence and characterization of the mechanisms of macrolide, lincosamide, and streptogramin resistance in isolates of *Streptococcus pneumoniae*. *Antimicrob. Agents Chemother.* **42**:2425-2426.
2. de Azavedo, J.C., R.H. Yeung, D.J. Bast, C.L. Duncan, S.B. Borgia, and D.E. Low. Prevalence and Mechanisms of Macrolide Resistance in Clinical Isolates of Group A Streptococci from Ontario, Canada. *Antimicrob. Agents Chemother* **43**:2144-2144**43**:2144-2147.



THANK YOU CBSN PARTICIPANTS, INVESTIGATORS, COLLABORATORS, AND SPONSORS

The last couple of years have brought many changes to laboratories across Canada. Despite these changes and increased demands, your commitment and participation have kept the Canadian Bacterial Surveillance Network functioning. We are now at the stage where we are starting to identify some interesting and important trends in antimicrobial resistance patterns across the country. This makes your on-going participation vitally important as we continue to assess these changes and evaluate interventions to improve the use of antimicrobial drugs.

In 1995, the network started with 100 participating laboratories and we have averaged about 60 sites per year since then. We hope that we will get our enrollment back up to the 100 mark in 2000. If you have participated before, but for some reason were unable to continue your commitment to the project, please let us know if we can facilitate your involvement in any way. We would appreciate any suggestions for improving the process wherever possible.

In addition, CBSN information, publications, data, and investigator lists are now available on the web at microbiology.mtsinai.on.ca. CBSN participants can access a password protected data base to query antimicrobial resistance patterns in *S. pneumoniae*. To receive your password, complete the on-line database access request form.

We hope this site will become a useful source of clinical and laboratory information and we welcome your participation as it continues to evolve. To send comments, questions or suggestions about the website, email microweb@mtsina.on.ca.

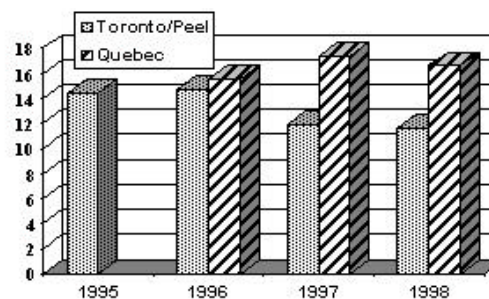
Thank you once again for your continued efforts and support.

Donald E. Low and L. Trpeski for CBSN

underlying conditions was stable over the four years. In addition we conducted an indirect cohort analysis using the methods of Bloome et al² on a subset of patients for whom complete vaccination history and serological typing was available.

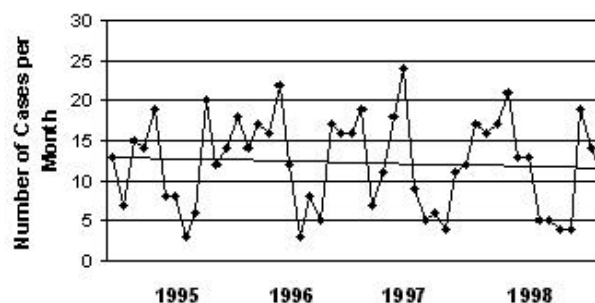
Since the introduction of the vaccination program in 1996, the overall incidence of invasive pneumococcal disease has decreased in metropolitan Toronto/Peel region, in contrast to that in Quebec (Figure 1) where there is no mass vaccination program.

Figure 1. Rates of Invasive Pneumococcal Disease per 100,000 population



While the rate of overall disease is decreasing, the rate in the vaccine ineligible population has remained stable and the rate in the population eligible for vaccine is decreasing, with the most marked decrease in the subgroup of people in which vaccine efficacy is expected to be highest (Shapiro classification of high-efficacy³) (Figures 2, 3 and 4).

Figure 2. Invasive pneumococcal disease, vaccine ineligible population.



REQUEST FOR INFORMATION

In recent weeks, hospitals in Oregon and BC have identified 26 isolates of a yellow pigmented gram positive bacillus tentatively identified as an *Aureobacterium* spp. Pulsed field gel electrophoresis (PFGE) analysis of all 9 Canadian specimens at LCDC shows identical patterns for 2 enzymes, suggesting clonality. Positive specimens have been from both sterile sites and swabs. The working hypothesis is that this is the result of contamination of swabs or media, but the source/mechanism has not yet been identified. If your lab has seen any isolates which may match this description, please contact Dr. David Patrick at the BC Centre for Disease Control (david.patrick@bccdc.hnet.bc.ca).

SOFT TISSUE INFECTIONS DUE TO GROUP A STREPTOCOCCI

Dr. Allison McGeer

Just over half of all invasive GAS infections have a soft tissue focus. Dr. Abdu Sharkawy, a resident in internal medicine, recently completed a review of all the invasive soft tissue disease occurring between 1992 and 1996, in order to better characterize epidemiology, clinical presentations, outcomes and prognostic indicators for this major subset of patients.

Of the 1080 cases of invasive group A streptococcal disease between 1992 and 1996, 524 were identified as soft tissue infections. The incidence of invasive group A streptococcal soft tissue infections increased during the study from 0.62 per 100,000 population in 1992 to 1.03 per 100,000 in 1996 ($p < 0.001$). The median age was 47 with a range between 1 day and 102 years of age, with the highest rates in children and the elderly. The majority of cases (431/524, 82%) were community-acquired. Sixty-six cases (13%) were nosocomial and 27 cases (6%) were reported from nursing homes. Chronic underlying illness was noted in 237 patients (50%). Severe sepsis (hypotension and multiorgan failure) complicated 64 cases (12%) and necrotizing fasciitis was identified in 118 patients (23%). In the setting of severe sepsis, 26% of cases (9/35) involved infection at sites of lymphatic drainage without prior skin break at these sites. The overall mortality rate was 13% (68/520), but was 26% (46/177) in those 64 or older, 23% (53/237) amongst those with underlying illness, 27% (33/119) in necrotizing fasciitis and 49% (23/48) in severe sepsis. The most streptococcal serotypes were M1 (24%) and M3 (9%). Necrotizing fasciitis, severe sepsis and mortality were all associated with infection with M3 serotype. All 194 patients without underlying illness who were not hypotensive at presentation survived, suggesting that such patients may not need to be admitted to the hospital.

One aspect we were particularly interested in is whether taking non-steroidal antiinflammatory agents (NSAIDs, eg. aspirin, motrin) is associated with more severity disease. Overall, 16% of patients (52/316) had taken NSAIDs prior to the onset of illness. The majority of these patients (42, 81%) had been taking NSAIDs regularly for a chronic illness; 10 patients took NSAIDs for relief of symptoms due to GAS. Patients taking NSAIDs regularly prior to illness onset were older than those who did not (median age 70 versus 44 years, $P < 0.001$), and more likely to have a chronic underlying illness (29/43 vs 119/264, $P = 0.007$). They were no more likely to die (9/43 versus 30/270; RR 2.1, 95% CL 0.81, 5.1), to develop severe sepsis (3/41 vs 26/262, RR 0.74, 95% CL 0.21, 2.3), or to develop necrotizing fasciitis (12/43 vs. 60/210, RR 1.3, 95% CL 0.59, 2.9) than other patients. The 10 patients who took NSAIDs after the onset of symptoms were ranged in age from 12-81 years (median 37); and 6 (60%) had an underlying illness. None of the 10 patients died; 2 had severe sepsis, and 5 had necrotizing fasciitis (50% vs. 57/207 others, RR 2.3, 95% CL 1.2, 4.5, $P = 0.04$). Thus, it appears that taking NSAIDs on a chronic basis does not affect your risk of developing either severe sepsis or necrotizing fasciitis. It is possible that taking NSAIDs after the onset of illness makes you more likely to get necrotizing fasciitis; however it is equally likely that the association exists because people with necrotizing fasciitis have severe pain and are thus more likely to take an NSAID before their illness is diagnosed. ♦

Figure 3. Invasive pneumococcal disease, vaccine eligible, low-efficacy group.

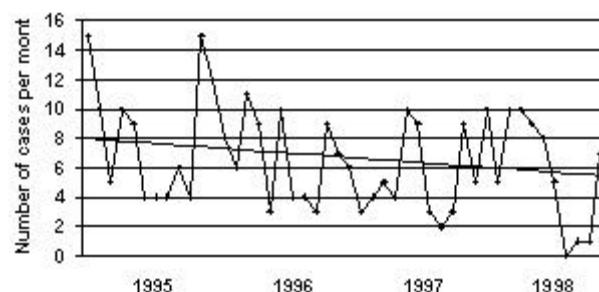
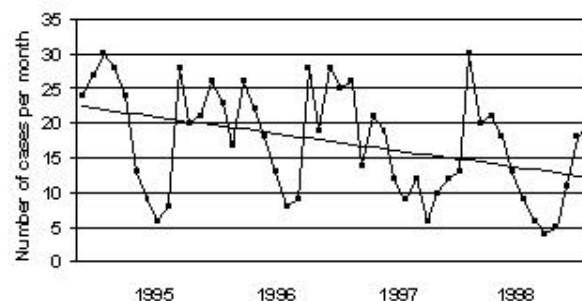


Figure 4. Invasive pneumococcal disease, vaccine eligible, high-efficacy group.



Of the 434 case isolates serotyped in 1995, 396 (92%) of case serotypes were included in the 23-valent vaccine. An indirect cohort analysis comparing the proportion of vaccine type serotypes in vaccinated and unvaccinated cases in 1995, estimates vaccine efficacy for all eligible persons to be 63% (95% CI 13%, 85%; $p = 0.04$) and for eligible immunocompetent (high-efficacy) group to be 89% (95% CI 59%, 97%; $p = 0.003$).

These data suggest that the effectiveness of vaccine in preventing pneumococcal disease is higher than that used by Sisk et al.^{4,5} in estimates of the cost-effectiveness of pneumococcal disease. Publicly funded programs to increase pneumococcal vaccination rates can have a significant impact on the incidence and cost of disease, and are likely to be cost-saving. ♦

References:

1. National Advisory Committee on Immunization. **Canadian Immunization Guide**. Health and Welfare Canada, (Cat No. H49-8/1998E), Ottawa, Canada, 1998, pp140-143.
2. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med* 1991;325:1453-60.
3. Bloome CV, Facklam RR, Fraser DW. Pneumococcal disease after pneumococcal vaccination: an alternative method to estimate the efficacy of pneumococcal vaccine. *New Eng J Med* 1981;303:549-550.
4. Sisk JE, Rigelman RK. Cost effectiveness of vaccination against pneumococcal pneumonia. An update. *Ann Intern Med*. 1986;104:79-86
5. Sisk JE, Moskowitz AJ, Whang W, Lin JD, Fedson DS, McBean AM, Plouffe JF, Cetron AS, Butler JC. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. *JAMA* 1997;278:1333-1339.