Continuous surveillance of antibiotic resistant *Neisseria gonorrhoeae*: A tool to forewarn emerging trends in resistance

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A STEADY DECREASE IN THE INCIDENCE OF GONORRHOEA cases has been reported in the past 20 years by several western countries (1-4). Statistics in Canada show this decline starting in the early 1980s, from a peak of 56,336 cases reported in 1981 to an estimated 4500 cases in 1994, a 92% decrease in the total number of cases over a 13-year period.

Although the incidence of gonorrhoea cases is dropping, there is a constant increase in the number of resistant isolates that parallels the introduction of new antibiotics. The ability of the gonococcus to develop resistance to antibiotics has been shown repeatedly over the years. As early as 1976, chromosomally mediated resistance to penicillin and later multiple resistance to other antibiotics were reported along with plasmid mediated resistance to penicillin (1,5-7). As a result, tetracycline was chosen as the alternative treatment for penicillinase-producing *Neisseria gonorrhoeae* (PPNG) until tetracycline resistant strains were characterized in the United States in 1985 and later reported worldwide (8-11). Currently, third-generation cephalosporins and quinolones are the most effective antimicrobials against gonorrhoea (12,13).

The detection of these susceptibility changes and the accurate prediction of upcoming resistance trends are possible only if a continuous surveillance program is in effect.

THE NATIONAL SURVEILLANCE PROGRAM FOR ANTIBIOTIC RESISTANCE OF *N GONORRHOEAE*

The National Laboratory for Sexually Transmitted Diseases (NLSTD), Laboratory Centre for Disease Control in Ottawa has conducted surveillance of antibiotic resistant *N gonorrhoeae* since 1976. In the early stages of the program, strains previously isolated and identified by provincial laboratories were characterized by antibiogram, auxotype, b-lactamase production and plasmid fingerprinting. With the development of new typing techniques the array of parameters for characterization increased to include serotyping with monoclonal antibodies; confirmation of plasmid mediated resistance to tetracycline with DNA probes; ribotyping; pulsed-field gel electrophoresis; and multilocus enzyme electrophoresis (14-17). These techniques generate a measure of variability that, when combined with epidemiological data, allows for the determination of outbreaks. In addition, the NLSTD program provides an extensive and complete database that allows for ongoing analysis of gonococcal resistance trends in Canada.

In 1994 there were 4500 reported cases of gonorrhoea, representing a 47.8% decline in the number of cases compared with those in 1992 (9421 cases) and a 78.3% drop since 1988 (20,736 cases). However, the percentage of antibiotic resistant isolates (plasmid and chromosomally mediated) is increasing. The percentage of resistant isolates

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TABLE 1
Total burden of resistance exhibited by *Neisseria gonorrhoeae* isolates in Canada

	1988	1992	1993	1994
Reported cases	20,736	9421	6820	~4500
Plasmid-mediated resistance	681 (3.3%)	1415 (15.0%)	934 (13.7%)	1206 (26.8%)
Chromosomal resistance*	499 (2.4%)	590 (6.3%)	267 (3.9%)	276 (6.1%)
Total resistance	1094 (5.3%)	1757 (18.6%)	1122 (16.5%)	1386 (30.7%)

*Minimum inhibitory concentration 2.0 mg/L or less to one or more antibiotics

almost doubled to 30.8% in 1994 from 16.5% in 1993, a six-fold increase since 1988 (Table 1).

During this period a shift in plasmid mediated resistance, reflecting the selective pressure of the antibiotics used for treatment, was observed. Until 1992, the majority of isolates tested were PPNG: 77.7% in 1990, 43.9% in 1991 and 40.9% in 1992. Subsequently, most isolates have exhibited plasmid mediated tetracycline resistance (TRNG) alone or in combination with penicillin resistance (PP/TRNG): 43.3% TRNG in 1993, 71.4% in 1993 and 77.9% in 1994 (Table 2). All but six of the 17,225 isolates tested since 1976 were susceptible to spectinomycin (minimum inhibitory concentration [MIC] less than 128 mg/L). This steady level of susceptibility to spectinomycin exhibited by the gonococcus may result from this antibiotic being recommended as alternate and not as first-line treatment.

These data, collected by the NLSTD Surveillance Program, were used to support revisions to the Canadian treatment guidelines for sexually transmitted diseases in 1992 (12). In the revised treatment guidelines, the recommended therapy for gonococcal infections is ceftriaxone, cefixime or ciprofloxacin (spectinomycin alternatively), with tetracycline for possible concurrent chlamydial infection.

Since the implementation of the new treatment guidelines, *N gonorrhoeae* has been closely monitored for any changes in susceptibility patterns to both ceftriaxone and ciprofloxacin. To date all isolates tested are susceptible to ceftriaxone (MIC 0.25 mg/L or less). Among these isolates, there are minor differences in susceptibility levels depending on the strain characteristics. Thus, isolates characterized as chromosomally mediated resistant (CMRNG) to antibiotics have higher MIC₅₀ and MIC₉₀ to ceftriaxone (0.008 and 0.032 mg/L, respectively) compared with isolates characterized as PPNG, TRNG or susceptible to other antibiotics (MIC₅₀ of 0.002 mg/L and MIC₉₀ of 0.004 mg/L).

Currently, there are concerns with the trend towards quinolone resistance; specifically, resistance to ciprofloxacin. Since 1989, 143 *N gonorrhoeae* isolates with reduced susceptibility to ciprofloxacin (MIC 0.125 mg/L or greater) have

TABLE 2
Plasmid-mediated resistant *Neisseria gonorrhoeae* in Canada

Year	%PPNG (% with PP/TRNG)	%TRNG (% with PP/TRNG)
1990	77.7 (95.4)	4.6 (22.3)
1991	43.9 (80.0)	20.0 (56.1)
1992	40.9 (56.7)	43.3 (59.1)
1993	15.9 (28.6)	71.4 (84.1)
1994	8.6 (22.1)	77.9 (91.4)

PPNG Penicillinase-producing *N gonorrhoeae*; TRNG Plasmid mediated tetracycline resistance; PP/TRNG Tetracycline resistance combined with penicillin resistance

been characterized in Canada. Of these, 13 isolates had a ciprofloxacin MIC of 1.0 mg/L or greater. To date, these strains can only be characterized as susceptible or having reduced susceptibility to ciprofloxacin because the definitions for moderate susceptibility or resistance to ciprofloxacin have not been established (18). Eighty-one per cent of these isolates (116 of 143) were also resistant to other antibiotics: 55.2% were CMRNG and 25.9% were PPNG and/or TRNG. The remaining 27 isolates (18.9%) were susceptible to all other antibiotics tested. Similarly, isolates of *N gonorrhoeae* with even higher reduced susceptibility to ciprofloxacin (up to 32 mg/L) have recently been reported worldwide (19-22, unpublished data).

The emergence of *N gonorrhoeae* exhibiting reduced susceptibility to ciprofloxacin, a quinolone recommended as primary therapy for treatment, demonstrates again the effects of selective pressure of antibiotics on the gonococcus. There have already been reports of treatment failure with the recommended doses of ciprofloxacin. Birley et al (21) reported treatment failure in a case of gonorrhoea caused by a strain with a ciprofloxacin MIC of 16 mg/L. This trend of reduced susceptibility to quinolones will likely evolve to total resistance.

Currently, ceftriaxone, cefixime and ciprofloxacin (spectinomycin alternatively) remain the most effective primary treatments for uncomplicated gonorrhoea. The emerging decrease in susceptibility to ciprofloxacin confirms the need for effective surveillance programs. Continued monitoring of antimicrobial susceptibilities is essential for the early detection of emerging resistance, for the formulation of effective treatment guidelines and, finally, to aid in the evaluation of newer antibiotics as possible alternate therapies.

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