Antibiotic Resistance in \textit{Neisseria gonorrhoeae}

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The incidence of gonorrhea is increasing in developed countries and remains high elsewhere. This untenable disease burden, the complication rate in women and newborns, and the amplification of human immunodeficiency virus transmission that accompanies gonorrhea makes control of gonococcal disease a priority. However, antibiotic resistance in \textit{Neisseria gonorrhoeae} has severely compromised the successful treatment of gonorrhea. Older therapies are ineffective, whereas those that remain efficacious are unaffordable in many high-incidence settings. Penicillins, tetracyclines, and newer macrolides have limited utility, and spectinomycin (and in many parts of the world, quinolones) have been withdrawn because of resistance. Of the usually recommended treatments, only the third-generation cephalosporins, and most notably ceftriaxone, have retained their efficacy, but decreased susceptibility to these antibiotics has also appeared. A sustained decrease in gonococcal disease requires an integrated approach combining improved prevention, better diagnosis, and effective treatment. Without continued commitment and effort, gonorrhea may well become untreatable.

\textbf{GONORRHEA: THE DISEASE AND THE PATHOGEN}

Gonococcal disease is defined by the demonstration of the presence of \textit{Neisseria gonorrhoeae} in clinical samples. The gonococcus is an organism found only in humans and is highly adapted to its ecological niche. Most often it infects mucosal surfaces, causing sexually transmitted urethritis in men and endocervicitis in women. Anorectal and pharyngeal infections, which are more difficult to treat, may occur in both sexes, and in neonates,ophthalmic infection is acquired during passage through an infected birth canal during delivery. Endocervical, anorectal, and pharyngeal infections are commonly asymptomatic, so that clinical presentation is delayed and reservoirs of infection and transmission are established.

\textbf{COMPLICATIONS}

Complications particularly affect women, their fertility, and their newborns and include amplification of HIV transmission in both sexes. Extension of mucosal infection to contiguous areas may give rise to epididymoorchitis in men or pelvic inflammatory disease in women, both of which may result in infertility, and eye infection. The latter may lead to corneal perforation and blindness. In a small proportion of gonococcal infections, mainly in women, gonococcemia may occur and may result in tenosynovitis, septic arthritis, or even endocarditis and meningitis. Salpingitis, causing pelvic inflammatory disease and infertility, may also give rise to the serious complication of ectopic pregnancy. Gonorrhea is also a significant cause of first-trimester abortion, again decreasing fertility.

It is also now recognized that gonorrhea is, along with genital ulcer disease, a potent amplifier of the spread of sexually transmitted HIV \cite{1}. Rates of HIV transmission in those with gonorrhea may be as much as 5 times that in persons without gonorrhea. The biological basis of this amplification of HIV transmission is related to the increased load of HIV in semen and vaginal fluid in persons with both gonorrhea and HIV, compared with that in persons with HIV alone. This arises from recruitment of HIV-infected inflammatory cells to the mucosal surfaces infected with the gonococcus, thereby increasing the infective inoculum of HIV transmitted by up to 8 times. Those with gonorrhea are also more susceptible to acquisition of HIV.
infection. These situations are reversed by treatment [2].

The sheer numbers of gonococcal disease alone—estimated to be ~60 million new cases per year globally—make it an important public health issue. The distribution of disease is, however, uneven, and gonorrhea is described as a "disease of the disadvantaged" [3]. Less developed countries have significantly higher rates of gonorrhea than do Western industrialized nations, but in all countries, those lower on the socioeconomic scale have disproportionately high disease rates. Precise incidence rates are difficult to determine because resources are most lacking where the disease is concentrated [4]. Estimates of disease rates among those aged 15–49 years (per 1000 population per year in men and women, respectively) include 57 and 67 in sub-Saharan Africa, 30 and 31 in South and Southeast Asia, and 27 and 29 in Latin America and the Caribbean. These high rates of gonorrhea currently are either stable or increasing, despite control efforts. High disease rates are observed in indigenous populations, in homosexually active men, in women, and in the urban poor. Disease rates are now rising substantially in former Eastern Block countries and in homosexually active men in developed countries [5].

TRENDS IN AND MAGNITUDE OF ANTIMICROBIAL RESISTANCE IN GONOCOCCI


Regional data. A number of regional surveillance programs for antimicrobial resistance in gonococci have existed at various times. One long-term program (Gonococcal Antibacterial Surveillance Program [GASP]) has continuously monitored antimicrobial resistance in gonococci in the WHO Western Pacific Region since 1992 [7]. Similar programs exist in Latin America and Southeast Asia but are less developed. A West African GASP has produced some early data. The Western Pacific Region historically has particular difficulty with regard to development of antimicrobial resistance in gonococci, and resistance to penicillins, spectinomycin, tetracyclines, quinolones, and now, third-generation cephalosporins has been documented in long-term quality-controlled studies.

In the past decade, the emergence and spread of gonococci resistant to the quinolone group of antibacterials in the Western Pacific Region has been dramatic. The quinolone group includes the widely used, relatively cheap, orally administered ciprofloxacin. A seemingly inexorable and exponential increase in quinolone-resistant *N. gonorrhoeae* each year resulted in more centers reporting this resistance, a higher proportion of these resistant gonococci in each center, and organisms with increasing MICs, so that currently this group of agents is totally ineffective for treatment of gonorrhea in many parts of the Western Pacific Region. Figures 1 and 2 illustrate the current situation and rapid evolution of quinolone-resistant *N. gonorrhoeae* in the Western Pacific Region. Rates of resistance to quinolones exceed 50% in most of the countries in the region and, in some instances, approach or exceed 90% [8]. Similar figures apply to penicillins and tetracyclines. Failures of treatment with oral third-generation cephalosporins for infection with gonococci with raised MICs have been documented in Japan. Gonococci with raised ceftriaxone MICs have been seen in low numbers in Singapore, Brunei, Japan, China, Korea,
Gonococcal Resistance to Antimicrobials

Evolution of quinolone resistance in selected countries in the World Health Organization Western Pacific Region, in 1992–2000. A, Vietnam (Vn); B, Australia (Aus) and Singapore (Sing); C, China (Ch) and Hong Kong Special Administrative Region (HK). Int, intermediate, less susceptible to ciprofloxacin (MIC, 0.12–0.5 mg/L); Res, resistant to ciprofloxacin (MIC, ≥1 mg/L). The number and proportion of quinolone-resistant isolates increased progressively over time, and MICs became progressively higher, as shown by the shift from intermediate to resistant.

New Zealand, and Australia in the past 2 years. Spectinomycin resistance is limited in extent but has been documented as long ago as the 1980s and is linked to usage.

Country-based data. There are a number of programs within various countries for surveillance of antimicrobial resistance in gonococci. Probably the oldest of these are in Australia (Australian Gonococcal Surveillance Programme [AGSP]), which began in 1979, and the United States (Gonococcal Isolate Surveillance Program [GISP]). Other programs include those in Canada, the United Kingdom (Gonococcal Resistance to Antimicrobials Programme [GRASP]), Sweden, Denmark, Singapore, China, Hong Kong, Bangladesh, and France. These programs have all shown a progressive increase in resistance over time. The current data from AGSP, GISP, and GRASP reveal loss of utility of penicillins and, increasingly, quinolones [9–11]. In Scandinavian surveys, the problems of multiresistant gonococcal infections acquired overseas are a feature of the data. Chinese, Hong Kong, and Bangladeshi data all point to major problems with multiply resistant gonococci. Individual country-based data have been published periodically from a number of countries in Central and South America, Southern Africa, Central Asia, Europe, and elsewhere, either as intermittent analyses or as individual studies. The data available from Africa and Latin America show that quinolone resistance is not as pronounced as it is in Asia, but penicillin and tetracycline resistance is at a high level.

**IMPLICATIONS FOR PUBLIC HEALTH**

Control of gonorrhea, a major public health issue requiring an integrated approach in which provision of effective treatment is an essential component. The importance of gonorrhea as a public health issue is such that availability of effective treatment of gonorrhea is essential for the individual patient, to interrupt transmission chains and to reduce the overall disease burden.

It has long been recognized that a comprehensive program is required for the control of gonococcal disease (and indeed all sexually transmitted infections) [6]. This integrated approach has as a central component the requirement of early and effective treatment. The treatment strategies recommended [12] are for single-dose therapy on first presentation or diagnosis. This treatment should, as a minimum, cure ≥95% of cases. The rationale behind this approach is to achieve compliance rates not possible with multidose treatments and to reduce any further disease transmission as quickly as possible. (Gonococci are no longer viable 12 h after effective antibiotic treatment.)

Use of laboratory and antimicrobial resistance data in tailoring treatments for gonorrhea. Most treatments, and especially those provided in less developed settings, rely on syndromic management principles, rather than identification of an etiologic agent, as the basis for therapy [6]. The reasons for this have much to do with the cost and reliability of laboratory services and access to diagnostic facilities as well as the difficulties associated with in vitro cultivation of gonococci. Although nucleic acid amplification assays improve this diagnostic capacity, they remain too expensive for routine use in resource poor areas. Nucleic acid amplification assays are not currently capable of producing reliable antimicrobial resistance data. Thus, the single-dose treatments recommended for gonorrhea must be predetermined, and knowledge of patterns of antimicrobial resistance in gonococci is a major factor in ar-
riving at a suitable standard treatment regimen. Disaggregated local information, as opposed to pooled country-based information, is relevant to tailoring treatment schedules to particular geographic regions. The GISP and AGSP data have, over time, provided examples of significant spikes in resistance rates in their jurisdictions. For example, Hawaii [13] and Sydney [9, 14] (figure 3) have had significant problems with quinolone resistance, necessitating a change in treatment schedules that is not yet required in other parts of the respective countries. The treatment regimens in Sydney were adjusted to account for problem by substituting ceftriaxone for ciprofloxacin as the recommended therapy in public sexually transmitted disease clinics. In contrast, penicillins remained suitable for use in remote settings in rural Australia because of low rates of resistance.

**Antibiotic resistance in** *N. gonorrhoeae*, **a major and increasing obstacle to effective treatment and disease control.** The single-treatment-dose approach presupposes that the antibiotic treatment provided is effective. *N. gonorrhoeae*, however, has a formidable ability to develop resistance. One manifestation of the effects of antimicrobial resistance in gonococci has been the progressive loss of inexpensive and effective treatments and the need for use of more-expensive agents. In many settings with high disease prevalence, high rates of resistance to penicillins, tetracyclines, and quinolones have necessitated the use of injectable cephalosporins. In many situations in which antimicrobial resistance is a problem, effective agents are costly and thus cannot be reliably supplied. Inappropriate or inadequate treatments continue to be used, with unsatisfactory outcomes for disease treatment, rates, and complications.

**Local and international concerns surrounding antimicrobial resistance in gonococci for public health.** The potential for emergence and spread of antimicrobial resistance in gonococci to compromise effective treatments is emphasized by the events that occurred after the appearance of quinolone-resistant *N. gonorrhoeae* in the Western Pacific Region. It parallels earlier experience with penicillins, in which antimicrobial resistance mediated by penicillinase production arose in this region. In both examples, antimicrobial resistance, due to these separate mechanisms, spread rapidly and widely. First, from the 1980s onward, penicillins had to be withdrawn from use in many countries. Then, quinolone-resistant *N. gonorrhoeae* strains from the Western Pacific Region had an adverse impact initially on countries in the Pacific Rim and subsequently more generally, so that progressive removal of quinolones from treatment schedules is occurring. Examples of the spread of quinolone-resistant *N. gonorrhoeae* affecting treatment regimens include data from Australia (figure 3), Sweden, Denmark, the United Kingdom, and Hawaii. It has recently (April 2004) been recommended that quinolone treatment be discontinued in some subgroups of patients in the United States [13].

![Figure 3. Ciprofloxacin-resistant *Neisseria gonorrhoeae* (MIC, ≥1 mg/L) as a percentage of all gonococcal isolates isolated in Sydney, Australia, over the course of 20 years, 1984–2003.](image)

The importance of international travel as a means of spread of antimicrobial resistance is well illustrated by the data on penicillinase-producing *N. gonorrhoeae* and quinolone-resistant *N. gonorrhoeae*. Those infected in one part of the world will often spread the infection to those elsewhere. If ineffective treatment is used, not only is the patient not cured, but the spread of the resistant strain will continue. It is therefore important to know where a patient contracted the infection, in addition to knowing both the local and the global patterns of antimicrobial resistance. Also, attempts to prevent emergence of antimicrobial resistance and contain it in all settings may help keep one country’s current problem from becoming another’s.

**Quality and use of the data.** Surveillance of antimicrobial resistance in gonococci is predicated by the need to detect levels of resistance of ~5%, because at this level of treatment failure, consideration should be given to alteration of recommended treatment regimens and programmatic treatments [12]. A surveillance program for antimicrobial resistance in gonococci should thus ideally be comprehensive, active (i.e., linked to clinical data), continuous, and long-term [15]. However, limited resources often result in intermittent examination of selected isolates. Less satisfactory, but often the only thing possible, is the generation of antimicrobial resistance data from 1-time surveys. Interpretation of data may be further compromised by small sample sizes or by isolates obtained from specialized populations. For example, some sexually transmitted disease clinics manage a disproportionate number of difficult cases, and a preponderance of treatment failures may be included. Some comparability of data within a country or program can be attained by use of internationally agreed-on quality control strains and by participation in an external quality control program [7]. Standardization of methods is helpful but not essential to this process. The volatile nature of antimicrobial resistance in gonococci means that a sufficiently large and representative sample of isolates must be examined longitudinally.
If a reliable antimicrobial resistance surveillance system is in place, it is also essential to disseminate the data to decision makers, who in turn must have sufficient knowledge and authority to make necessary changes to treatment schedules. **Limitations of data quality being addressed by the International Collaboration on Gonococci quality assurance and quality control.** To act on antimicrobial resistance data at a public health level, there must be reassurance of the validity and robustness of the information. Particular problems exist for surveillance of antimicrobial resistance in gonococci. Many of these limitations are resource-based, but these problems are compounded by the difficulties associated with isolating and testing an organism with fastidious growth requirements. These considerable difficulties can lead to generation of doubtful data. Requirements for laboratory quality control and external quality assurance systems, which exist for validation of susceptibility testing of more readily cultivatable pathogens, are even more important for gonococci. This has been addressed by the International Collaboration on Gonococci, a group initially formed by the relevant groups from the WHO and US Centers for Disease Control and Prevention and with membership of interested parties from all continents. In 2005, it is anticipated that a new set of international control strains will become available. These have been tested in 6 participating laboratories, and their categorization has been agreed on by consensus. They will supplement existing WHO controls, which are less applicable to gonococci with newer forms of antimicrobial resistance.

**Control of antimicrobial resistance in gonococci.** Control of antimicrobial resistance in gonococci relies, to a significant extent, on control of the disease itself—a monumental task that involves continuing commitment and a multidisciplinary approach [6]. Other relevant factors involved in containment of antimicrobial resistance in gonococci are those factors generally applicable to control of antimicrobial resistance in other organisms and diseases [16, 17]. Antimicrobial resistance in gonococci rarely arises first in settings with an established regulatory framework that oversees drug evaluation and approval, enforcement of prescription-only drug access, reliable drug delivery systems, an informed prescriber base, and laboratory systems with good and evaluative diagnostic standards. Rather, antimicrobial resistance in gonococci most often arises, and resistant gonococci spread most frequently, in situations in which antibiotics are readily available (often in the informal health sector), drug quality is suspect (as a result of poor manufacturing, adulteration, or degradation), and compliance with standard treatment regimens is poor—the latter often because of the unaffordability of the recommended dose [6].

All of the above factors (and some others) must be continuously addressed for antimicrobial resistance in gonococci to be contained. In summary, there needs to be access to demonstrably reliable antibiotics as part of a comprehensive program of disease control.

**Outcome indicators.** The outcome indicators for control of antimicrobial resistance in gonococci are difficult to measure, because of both the technical and the logistical reasons outlined above. The more sophisticated antimicrobial resistance surveillance systems are capable of detecting deterioration in antimicrobial resistance. However, implementation of programs to contain antimicrobial resistance rarely reverses an already existing problem. Thus, “improvement” in the situation is really gauged by a slowing in the rate of emerging resistance—a concept difficult to measure and to promote as a positive achievement.

Some have suggested that antimicrobial resistance in gonococci is a measure of disease control itself, such that when the rates of disease are falling, antimicrobial resistance may be perceived to be less of a problem. Others have suggested that, as an indicator of the incidence of disease, rates of complications of gonorrhea, such as pelvic inflammatory disease, are useful surrogates for disease rates. However, these indicators are also difficult to measure. The best compromise in the current circumstances is to try to monitor appropriate drug use, drug quality and availability, and levels and trends in antimicrobial resistance [17].

**Future directions.** Gonorrhea attracts little in the way of priority funding—it is an old problem. Despite gonorrhea’s high global incidence and prevalence, its high rate of complications, and the decreasing capacity to treat gonococcal diseases, efforts aimed at its eradication are minimal. In these circumstances, the prospects for diminution in antimicrobial resistance in gonococci and for control of gonorrhea are not hopeful.

The general requirements for control of antimicrobial resistance in gonococci are well established and are inextricably linked to disease control itself [6]. The operational needs, with regard to those who have the disease, are the ability to identify symptomatic and asymptomatic persons infected with gonococci quickly and cheaply and to provide simple, inexpensive, and effective treatments at the time of diagnosis. Specifically, there is a need for rapid, reliable (i.e., sensitive and specific), affordable, and simple near-patient diagnostic testing facilities and for assurance of the effectiveness of treatment through monitoring of antimicrobial resistance. The issues of prevention are more complex. In the area of sexually transmitted infection, a major obstacle is effecting behavioral change, which is a prerequisite for improved outcomes. Vaccine prospects are bleak. The nature of the organism is such that it owes its existence to its ability to avoid immune mechanisms of the host through continual adaptation [6].

There are, however, positive developments. The WHO is developing systems of cheap diagnostics with sufficient predictive value to underpin currently used syndromic manage-
ment algorithms for sexually transmitted infections. It has been
demonstrated that effective surveillance systems for antimicro-
bial resistance in gonococci can function reliably in settings
with few resources at relatively little cost [7]. The WHO is also
developing ready access to color-density maps, which show the
distribution, by region and country, of antimicrobial resistance
to those agents most often used for the treatment of gonorrhea.
These data are available at the WHO drug resistance Web site
[18] and are updated periodically.

Molecular approaches to the diagnosis of gonorrhea have
e ncoun tered some problems of sensitivity and specificity but
have been particularly valuable in helping to define disease
incidence in special surveys. It is possible that enhancements
or modifications to nucleic acid amplification assays will also
allow determination of antimicrobial resistance patterns in the
medium term. Such a development would facilitate assessment
of antimicrobial resistance patterns and would greatly enhance
the ability to recommend appropriate treatments.

Gonorrhea rarely kills directly, yet the morbidity and suf-
f ering it causes are substantial, although not readily quantifiable
in dollar terms. Nonetheless, some estimates of the benefits of
effective treatment have been gathered. One calculation suggests
that, for every 100 women treated successfully for gonorrhea
(among whom 25 are pregnant), 25 cases of pelvic inflam-
atory disease, 7 cases of ophthalmia neonatorum, and 6 in-
stances of infertility will be prevented. Over and Piot [19] have
estimated the cumulative impact of treating gonorrhea suc-
cessfully in a core group. For every 100 cases treated, 425 cases
of HIV are prevented every 10 years. These benefits are sub-
stantial and would more than repay any investment in disease
control.

The means to achieve proper treatment for gonorrhea are
available, as are the processes by which the disease can be
controlled. What is lacking are the means to continue the task.

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