

What is the economic burden imposed by antimicrobial resistance in *Neisseria gonorrhoeae*

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THE DISEASE, IT'S COMPLICATIONS AND SEQUELAE

High rates of gonococcal disease remain in less developed settings and are increasing in marginalised groups in more developed countries. The estimated 60 million new cases of gonorrhoea occurring globally each year¹ themselves constitute a major public health problem. These are mainly mucosal infections, but if left untreated or improperly treated, may be complicated by spread to nearby organs, dissemination via the blood stream or eye infection in the new born. Decreased fertility may result from epididymo-orchitis in men or pelvic inflammatory disease (PID) in women and PID in turn may lead to the occurrence of ectopic pregnancy.

The complication rate in mucosal and, presumably, untreated gonorrhoea, or else where treatment has failed, is difficult to quantify, but some estimates² suggest that for every 100 women with gonorrhoea, of whom 25 are pregnant, one or two will suffer disseminated infection and 25 PID, six will become infertile, one will have an ectopic pregnancy and seven of their new born will have an eye infection. Fertility is also decreased through increased rates of first trimester abortion of up to 20% in pregnant women with gonorrhoea. Ophthalmia neonatorum may cause permanent blindness. Others³ have estimated that PID develops in 20% of women with untreated gonococcal infection, and, in the context of this discussion, presumably also with failed treatment.

To this list of 'traditional' complications, may also be added the amplification of spread of sexually transmitted HIV – up to five fold - that occurs in those with gonorrhoea while exposed to HIV. With regard to HIV transmission and gonorrhoea, the same sources² suggest that the benefits from treating gonorrhoea in a core group of high frequency transmitters extend over time. Thus for every 100 successfully treated cases of gonorrhoea, about 400 HIV infections would be prevented over a decade. These

epidemiologically based estimates were given added credence by field studies in Mwanza, Tanzania⁴ that showed a reduction of HIV rates of 38% in the STI intervention (treatment) arm of matched communities, and biological evidence that showed the reduction in HIV loads in semen (and thus infectious inocula) that followed effective treatment of gonorrhoea⁵. Fleming & Wasserheit⁶ concluded that 'available data leave little doubt that other STDs facilitate HIV transmission ... and that early STD treatment should be part of a high quality, comprehensive HIV prevention strategy.' The reduction in HIV transmission through STI treatment was not seen to the same extent in other studies in Uganda however. Differences in outcomes were attributed to use of intermittent rather than continuous treatment and the different stages of the HIV epidemic in the studies⁷.

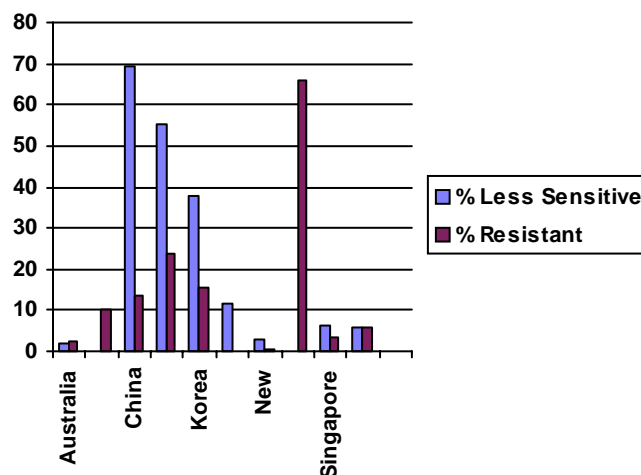


Figure 1
Percentage of *Neisseria gonorrhoeae* less sensitive and resistant to quinolone antibiotics in 10 selected countries in the WHO Western Pacific region in 1996. Less sensitive: ciprofloxacin MICs 0.06 – 0.5 mg/L; Resistant: ciprofloxacin MICs =, > 1 mg/L. (Taken from ref 7)

In any analysis of the costs of gonorrhoea, those attributable to its sequelae and complications must be added to those resulting from primary disease.

THE ROLE OF ANTIBIOTIC TREATMENT AND EFFECTS OF ANTIMICROBIAL RESISTANCE IN GONOCOCCI (AMR in GC)

Control of gonorrhoea and its complications is accomplished by an integrated approach that optimises disease prevention, case finding and appropriate treatment⁷. The interactions between these various components are illustrated when improved diagnostics allow recognition and then treatment of the high proportion of asymptomatic or 'oligosymptomatic' patients who constitute reservoirs of infection and reinfection. The relevance of antibiotic treatment, over and above its benefit to the individual, is interruption transmission chains and removal of these reservoirs - resulting in reduction in disease rates of up to 30%⁸.

The above assumes that treatment is effective. However *Neisseria gonorrhoeae* has a well-developed capacity to develop resistance to those antimicrobials used for treatment of gonococcal disease. The patterns of this resistance have been recently described⁹ and the current situation with regard to AMR in GC is one of considerable and increasing concern. In the past few decades, it has been necessary to discontinue the use of cheap oral agents such as penicillins and tetracyclines because of AMR. More recently fluoroquinolones have been withdrawn as a treatment option in many parts of the world. Those antibiotics that remain available require either unsuitable multi-dose treatments, are injectable rather than orally administered or else are too expensive for use in resource-poor settings. In addition treatment failures have been documented in those other groups of antibiotics also recommended for use (aminocyclitols, macrolides and aminoglycosides). Figures 1 and 2, show the increase in quinolone resistance in gonococci isolated in selected countries in the WHO Western Pacific region GASP network between 19967 and 200310 and demonstrate the rapidity with which AMR in GC may expand. The current threshold of AMR in GC at which removal of an antibiotic from standard treatment regimens is recommended is 5%. Figure 2 shows by how much this 5% level of AMR was exceeded for quinolone antibiotics in the WHO Western Pacific region in 2003.

ESTIMATES OF THE COSTS OF GONORRHOEA IN THE ABSENCE OF ANTIMICROBIAL RESISTANCE

Available cost estimates for gonorrhoea vary in that they may or may not include those attributable for diagnosis and treatment or costs of acute infection as well as sequelae. Some of these data are impossible to derive in those settings where disease is most prevalent. Many infected patients simply do not present for treatment (including the asymptomatic or oligosymptomatic groups) or else obtain treatment in the informal health sector⁷. The use of syndromic management principles usually means that diagnostic testing is not used, but that management algorithms must then include multiple treatments for all possible organisms that may be involved with that syndrome. While these data are simply not available in those settings where disease is most prevalent, some are available from the USA.

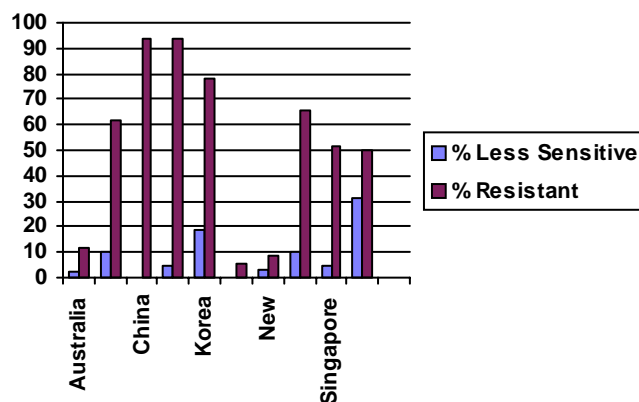


Figure 2.
Percentage of *Neisseria gonorrhoeae* less sensitive and resistant to quinolone antibiotics in 10 selected countries in the WHO Western Pacific region in 2003. Less sensitive: ciprofloxacin MICs 0.06 – 0.5 mg/L; Resistant: ciprofloxacin MICs =, > 1 mg/L. (Taken from ref 10)

The most recent data on the costs of gonorrhoea are contained in estimates in studies by Chesson et al³, Roy et al¹¹ and Ebrahim et al¹². All make assumptions on costs based on North American information. Roy et al¹¹ provided cost estimates for untreated symptomatic and asymptomatic PID (which occurs in around 20% of all cases of gonorrhoea in women³) as lying between \$2000 and \$3500 US dollars (on 2001 values) and the cost of extra cases of transmission

of gonorrhoea to females (per case of gonorrhoea) as about \$US60 and for HIV transmission to males (again per case of gonorrhoea) as about \$US130. The estimated number of cases of gonorrhoea in the US cited in this study was about 800,000. Chesson et al³ estimated the lifetime cost per case of gonorrhoea in women as \$US266.00 and in men as \$US53.00. The total direct estimated cost was \$US77 million among those aged 15-24 years in the USA in 2000. The cost of PID was included and this was about 80% of the cost of gonorrhoea in women. In contrast most costs in men were attributable to acute infection. While it is possible to extrapolate dollar costs from the above data, the general applicability of these numbers outside the USA would be doubtful.

Ebrahim et al¹² applied disability adjusted life years (DALY) estimates to the 1998 USA incidence data on gonorrhoea. About 2600 DALY were attributed to 650,000 gonococcal infections. However not all complications of gonorrhoea, including those of HIV acquisition or neonatal ophthalmia, were included in these estimates. Again it may be difficult to extrapolate directly, but the DALY data may provide some basis for estimating the health and economic burden of gonococcal infections. The global estimate of new cases of gonorrhoea globally is about 62 million per year¹, which would approximate the global DALY generated annually by gonorrhoea at around 250,000.

None of the above estimates capture the full disease cost and are conservative.

ESTIMATES OF COST SAVINGS THROUGH PREVENTION OF GONORRHOEA

As mentioned above, the prevention of sexually transmitted infections requires an integrated approach, which, for gonorrhoea, includes effective antibiotic treatment⁷.

A number of studies in the USA provide estimates of cost savings where integrated prevention programmes have been used over time. It is not possible to estimate the contribution of effective antibiotic treatment to this reduction. The point remains however that effective treatment remains a cornerstone of this integrated approach to disease control and if compromised by AMR, the benefits derived from integrated interventions and set out below would be significantly devalued.

Chesson¹³ estimated the rates of gonorrhoea in the USA that would have existed in 2003 if prevention efforts begun in 1975 had not been in place. While acknowledging that the data were 'crude', without the intervention programme the

number of cases of gonorrhoea in the US would have been substantially higher by 2003 with an estimated 32 million cases averted over 33 years by interventions begun in the mid-1970s. The cost per case averted ranged between recovering only the cost of the intervention programme itself to \$440 USD (2003 value) per case averted. The higher figure was obtained when all benefits were considered such as the prevention of other STDs. (It is not clear if the estimate includes cost savings attributable to prevention of HIV).

Chesson et al¹⁴ also estimated the combined value of reductions in the disease burden due to syphilis and gonorrhoea in the United States between 1990 and 2003. The annual costs associated with primary and secondary syphilis, congenital syphilis and HIV costs attributable to amplification of HIV spread by the two infections decreased from \$589 million in 1990 to \$169 million in 2003 (all in USD 2003 value). Further, 'if the STD rates had remained at 1990 levels through 2003, the total costs... would have been \$8.9 billion' instead of the \$3.8 billion spent because of reductions in disease rates.

COSTS DIRECTLY ATTRIBUTABLE TO ANTIMICROBIAL RESISTANCE IN N. GONORRHOEAE

This is even more difficult to assess. Anecdotally, Meheus (personal communication) estimated that by the late 1980's, after the appearance and spread of penicillinase-producing gonococci, the cost of effectively treating the now penicillin-resistant gonorrhoea in Africa would be greater than the then total health expenditure for all diseases on the continent.

Estimates of the cost of antimicrobial resistance in gonococci may derived in part from the studies by trying to assess the proportion of cases that would fail current standard treatments and then by estimating the direct and consequent monetary burden of this treatment failure. This is also imprecise.

Firstly AMR is not 'absolute' in that resistant strains do not always fail treatment. For example data indicate that with a standard ciprofloxacin regimen, about 6 – 8% will fail when MICs are of the order of 0.12 – 0.5 mg/l, about 40% when MICs are 1 – 2 mg/l and from 4 mg/l and above the failure rate rises exponentially to near 100%. Data also suggest the disease has a natural elimination rate. For example pharyngeal gonorrhoea and endocervical gonorrhoea are said to be eliminated 'naturally' over about one and six months respectively.

Secondly, most treatments for gonorrhoea also include a second agent e.g. for Chlamydia trachomatis as a minimum, and in some syndromic treatments other antimicrobials as well. These other agents may well have an additional anti-gonococcal action that eliminates N. gonorrhoeae even in the presence of resistance to the primary treatment for gonorrhoea. [This addition of other agents comes at a cost too – not only monetary but also in further antimicrobial resistance. The resistance to azithromycin, used for chlamydial co-therapy in cases of gonorrhoea is rapidly increasing¹⁵]. It is also difficult to distinguish a true treatment failure from reinfection in all cases – for a discussion of this issue see⁷.

Within this imperfect framework, the cost of treatment failure can be approximately estimated from known or ‘accepted’ rates of antimicrobial resistance. The higher limit of ‘acceptable’ resistance or failure rates within a general population is currently 5% and zero when found in a population with a high frequency of transmission such as commercial sex workers¹⁴. Roy et al have recently added an estimate of disease prevalence to this assessment¹¹. When prevalence rates in women are 3% or more, the 5% ‘rule’ seems to be appropriate for changing from ciprofloxacin to ceftriaxone. (Roy et al also included in their analysis the cost of antibiotics: that for ciprofloxacin at \$US2 per dose and ceftriaxone at \$US10 per dose. These dollar costs vary widely but the relative cost of ceftriaxone at five times that of ciprofloxacin is not uncommon.)

On this basis, in theory, a standard treatment is kept in place until the resistance rate reaches 5% when it is removed. In practice this rarely happens. In ‘developed’ countries, a treatment would be changed before a 5% rate was reached as, for example, in the USA when penicillins were discontinued as a recommended treatment when a lower, 3% rate was detected. In resource poor settings quite often a much higher treatment failure rate occurs before standard treatments are altered if at all and sometimes evidence for this change is not even sought. However for the purposes of this document, the ‘5% failure/resistance rule’, with all its imperfections, will be used for illustrative purposes of the costs of AMR in GC.

On this highly imperfect assumption, globally there would be a failure of treatment in about 3 million cases of the estimated 62 million new cases of gonorrhoea occurring annually. This translates into a conservative cost of \$US500 million per annum using the model of Chesson et al³ or and

into over 12,000 DALY generated per annum using the model of Ebrahim et al¹². Both of these estimates are from US experience, are themselves imperfect and conservative and may well be unsuited to estimates for other settings. For example, elsewhere the aetiology of PID may be due to other non-sexually transmitted disease – in India for example tuberculosis is a common cause of this condition.

Despite the many qualifications and caveats, the following remain clear:

Gonorrhoea remains a major sexually transmitted disease and in a global context its incidence and prevalence are increasing once more;

There is a significant morbidity associated with sequelae of gonorrhoea particularly in women and their newborn and in the enhanced transmission of HIV that occurs in the presence of gonorrhoea;

The disease and its complications can be readily treated and disease control significantly enhanced through use of a single dose of an effective antibiotic;

The potential gains from use of this single dose antibiotic treatment have been largely eroded through the emergence and spread of antimicrobial resistance in N. gonorrhoeae;

The costs attributable to the increased morbidity and complications that result from ineffective treatment of gonorrhoea can be more than recovered by implementation of an integrated programme of disease control.

The reduction in disease rates itself would be a major contribution to control of antimicrobial resistance gonococci.

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