Tropical Medicine and International Health

VOLUME 5 NO 9 PP 640–647 SEPTEMBER 2000

Cost-effectiveness of management strategies for acute urethritis in the developing world

François Crabbé[1], Bea Vuylsteke[1], Miguel de Clerck[2] and Marie Laga[1]

1 *Institute of Tropical Medicine, Antwerp, Belgium*
2 *Médecins sans Frontières, Belgium*

Summary

OBJECTIVE To recommend a cost-effective approach for the management of acute male urethritis in the developing world, based on the findings of a theoretical study.

METHODS A model was developed to assess the cost-effectiveness of three urethritis management strategies in a theoretical cohort of 1000 men with urethral syndrome. (1) All patients were treated with cefixime and doxycycline for gonococcal urethritis (GU) and nongonococcal urethritis (NGU), respectively, as recommended by WHO. (2) All patients were treated with doxycycline for NGU; treatment with cefixime was based on the result of direct microscopy of a urethral smear. (3) All patients were treated with cotrimoxazole or kanamycin for GU and doxycycline for NGU. Cefixime was kept for patients not responding to the first GU treatment. Strategy costs included consultations, laboratory diagnosis (where applicable) and drugs. The outcome was the rate of patients cured of urethritis. Cost-effectiveness was measured in terms of cost per cured urethritis.

RESULTS Strategy costs in our model depended largely on drug costs. The first strategy was confirmed as the most effective but also the most expensive approach. Cefixime should cost no more than US$ 1.5 for the strategy to be the most cost-effective. The second strategy saved money and drugs but proved a valuable alternative only when laboratory performance was optimal. The third strategy with cotrimoxazole was the least expensive but a low follow-up visit rate, poor treatment compliance or lower drug efficacy limited effectiveness. Maximizing compliance by replacing cotrimoxazole with single-dose kanamycin had the single greatest impact on the effectiveness of the third strategy.

CONCLUSION Our model suggested that a cost-effective approach would be to treat gonorrhoea with a single-dose antibiotic selected from locally available products that cost no more than US$ 1.5.

keywords urethritis, treatment, cost-effectiveness, syndromic approach

correspondence Marie Laga, STD/HIV Research and Intervention Unit, Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium. Fax: 32 3 247 6333; E-mail: mlaga@itg.be

Introduction

Urethritis in men is primarily caused by gonococcal and chlamydial infection (Holmes *et al*. 1999). It is well known that prompt and effective treatment of urethritis not only prevents complications and sequelae, but also reduces the risk of HIV transmission (Grosskurth *et al*. 1995; Holmes *et al*. 1999). Syndromic management of urethritis following WHO guidelines recommends concurrent antibiotic therapy for gonococcal and chlamydial infection (WHO 1994). The treatment of gonococcal urethritis used to be straightforward. However, gonococcal resistance to several antibiotics in different parts of the world has made treatment recommendations for gonococcal infection somewhat more complicated. At present there is no single drug for the treatment of gonorrhoea in the developing world that combines efficacy and low price. Cefixime, ceftriaxone, and spectinomycin are recommended by WHO as first-line drugs for the treatment of gonococcal urethritis, because they remain highly efficacious all over the world (Moran & Levine 1995). However, their main drawback is their high cost. Ciprofloxacin, also recommended by WHO, has become cheaper in some countries, but resistance in South and South-east Asia means that it can no longer be universally recommended (WHO 1997; Bhalla *et al*. 1998; Ng *et al*. 1998; Tapsall *et al*. 1998; Bhuiyan *et al*. 1999; Klausner *et al*. 1999). Kanamycin and above all cotrimoxazole are still widely used in Africa where they remain efficacious and are considerably less

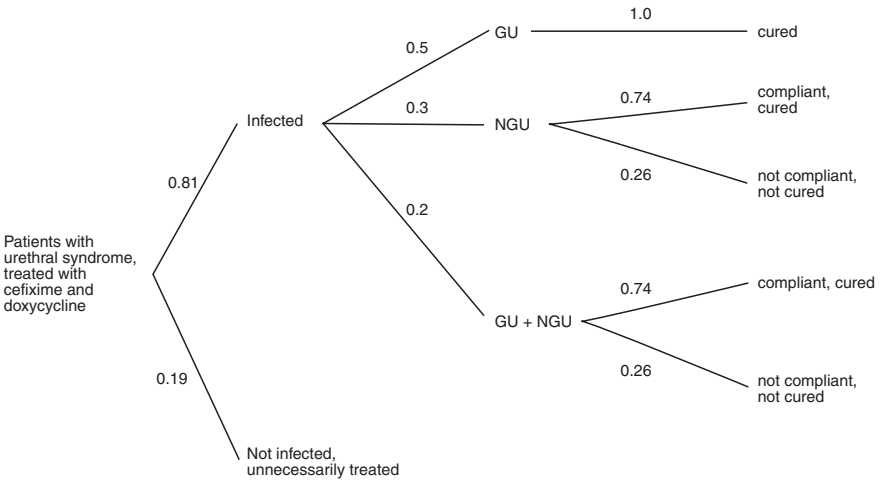

Figure 1 Strategy 1. The gold standard.

expensive. Rather than readily endorsing the recommendation for the most efficacious (and expensive) drugs, public health professionals in the developing world may want to identify the most cost-effective approach towards treatment of gonococcal infection.

Basically, STD programme managers face three options for the treatment of gonococcal urethritis, depending on their priorities. The first option focuses on treatment efficacy, with patients being systematically administered the most efficacious antibiotic. It is the gold standard[1] in terms of drug efficacy. A second option aims for diagnosis specificity and drug saving, with gonococcal infection first confirmed by direct microscopy before treatment. The third option sets the priority on financial accessibility, by having gonococcal infection treated in the first place with an inexpensive drug. The debate between defenders of each management strategy has usually focused either on pharmaceutical efficacy *or* financial accessibility rather than cost-effectiveness. Our objective was to assess the cost-effectiveness of the three options by means of a simple model.

Materials and methods

The three management strategies

The first strategy in our model, which focused on treatment efficacy, had all male patients treated for gonococcal infection with a single oral dose of 400 mg cefixime. Ceftriaxone and spectinomycin, the other first-choice drugs according to WHO, require intramuscular administration and are usually even more expensive than cefixime (Management Sciences for Health 1999). The second strategy, focusing on specificity, had patients treated with cefixime depending on the presence of intracellular diplococci on a Gram-stained urethral smear. The third strategy, focusing on financial accessibility, had all subjects treated with cotrimoxazole, 10 tablets of 480 mg daily for 3 days or kanamycin 2 g IM stat, following WHO's recommendations (WHO 1991). Cefixime was kept for those who failed to respond to first-line treatment. Our model also had all subjects systematically treated for nongonococcal urethritis with doxycycline 100 mg bd. for 7 days, following WHO's recommendation (WHO 1994). While the first strategy was the gold standard, the other two were potential alternatives to be evaluated.

The model

Decision trees were developed to model the management of gonococcal and nongonococcal infection following the three strategies in a hypothetical cohort of 1000 male patients with symptoms and/or signs of urethritis (Figures 1,2,3). The model was kept simple by leaving aside the costs associated with complications in men and in their female partners. Transmission and complication rates were indeed assumed to remain constant in the absence of any intervention. Two additional assumptions were made to limit the complexity of the decision trees. First, patients not infected with gonorrhoea were considered correctly diagnosed by microscopy (i.e. no false positives) and therefore not treated. Secondly, patients not compliant with multidose antibiotic therapy, be it for gonococcal or chlamydial infection, were considered lost and not cured.

The cost of each strategy included consultations, microscopic examination where applicable, and antibiotics for gonococcal and chlamydial infection. The costs of

[1] 'Gold standard' refers to the generally preferred strategy.

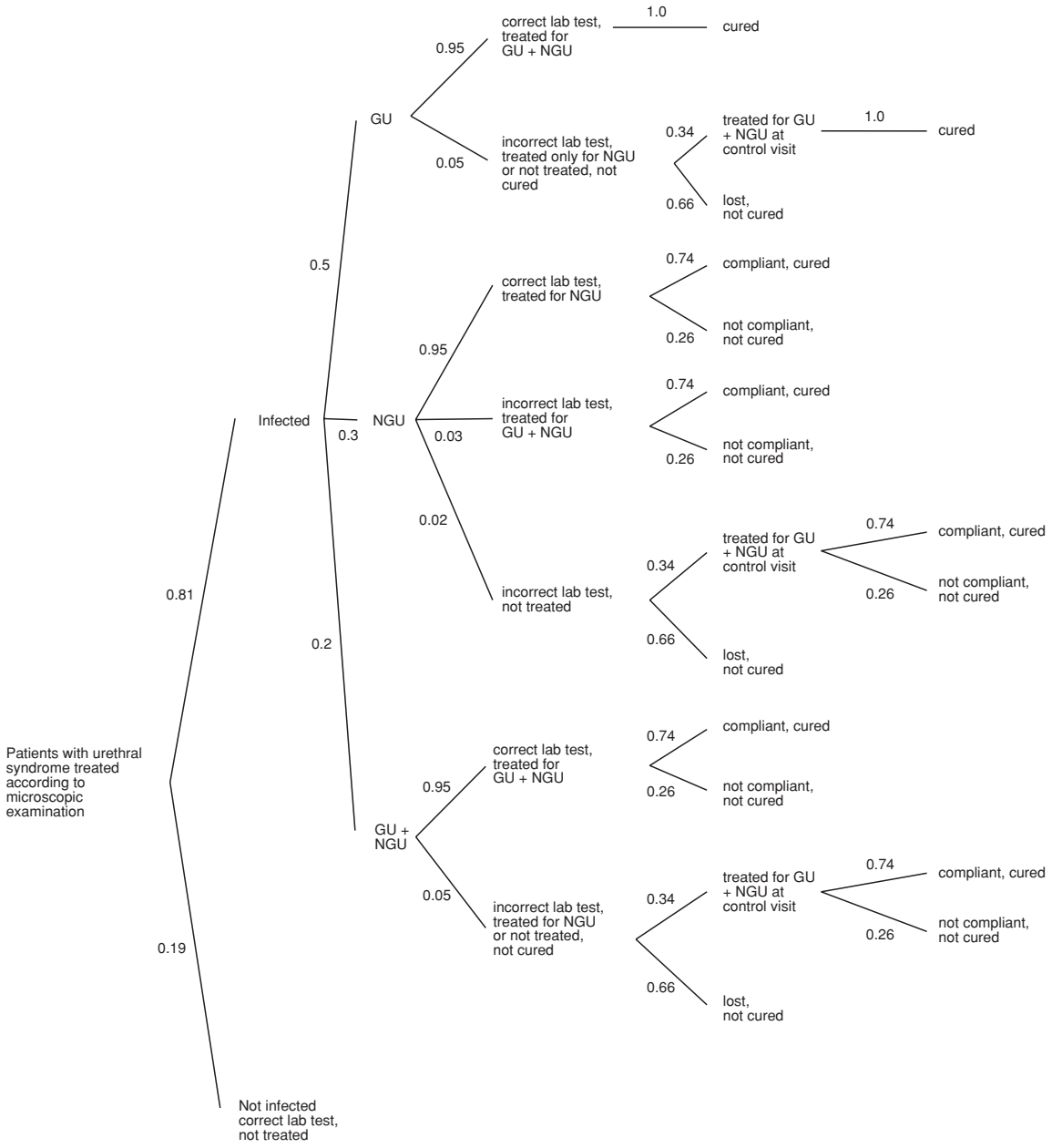

Figure 2 Strategy 2. Based on microscopic examination of a urethral smear.

consultation and laboratory were based on government sector's salaries and workload in several of the poorest countries in sub-Saharan Africa, Latin America and Asia[2].

[2] African countries from which data were obtained included Burkina Faso, Congo, Ghana, Mali and Tchad. Latin American countries included Ecuador, Haiti, and Nicaragua. Asian countries included Bangladesh, Cambodia, China, Laos and Vietnam.

Healthcare provider and laboratory technician's salaries were set at US$ 75 and 100, respectively, for 460 consultations per month. Laboratory costs, including consumables and reagents, were US$ 0.51 per test. Unit costs thus amounted to US$ 0.16 for the medical consultation and US$ 0.73 for laboratory testing. The average cost of generic antibiotics was obtained from the International Drug Price Indicator Guide (>Management Sciences for Health 1999), and that of

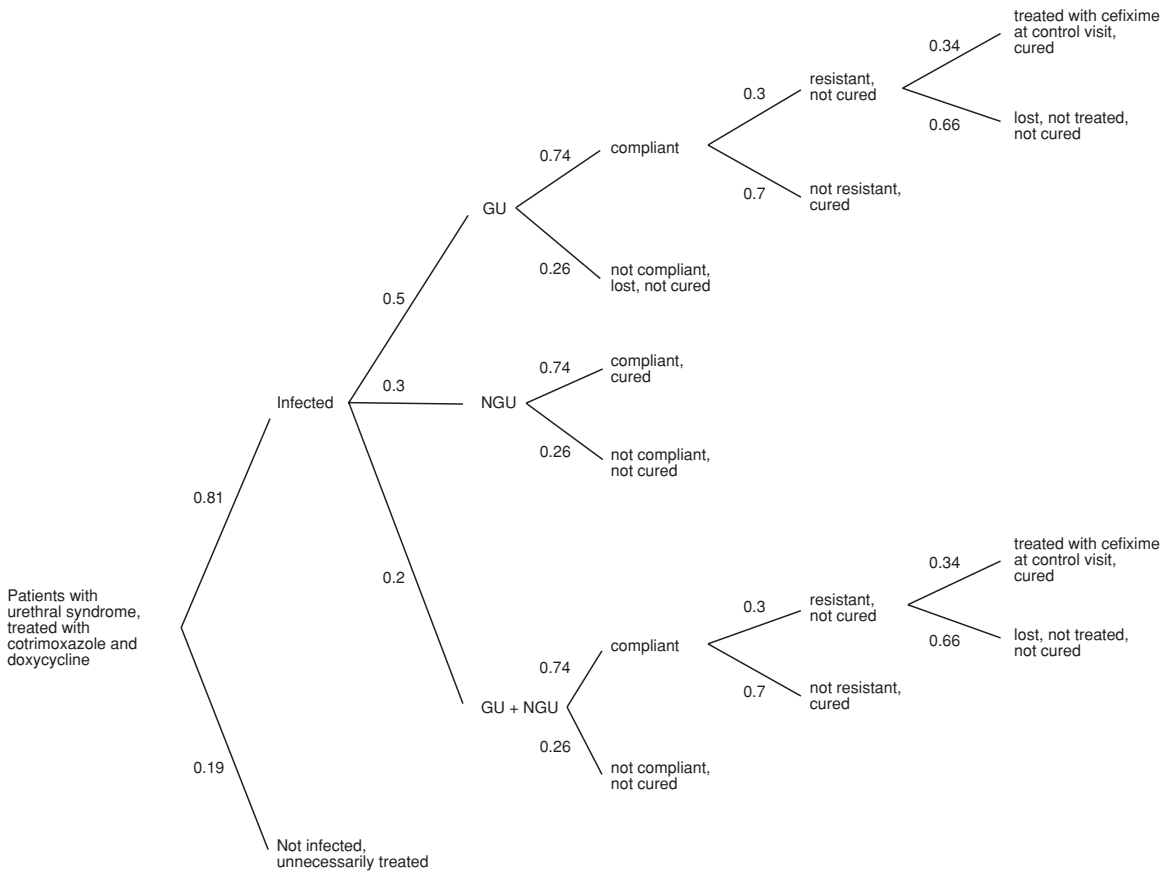

Figure 3 Strategy 3. First treatment with cotrimoxazole. Cefixime reserved for returning failure cases.

cefixime was provided by an international nonprofit drug distributor in the Netherlands. Drug costs were increased by 30% to include transport and handling. Thus the values used in the model were US$ 4.0, 0.9, 0.7 and 0.6, respectively, for a full course of cefixime, kanamycin, cotrimoxazole and doxycycline. The outcome indicator for each strategy was the *rate of patients cured of urethritis*. The *cost per cured urethritis* was obtained by dividing the management cost for 1000 patients by the number of cured patients.

Rates and sensitivity analysis

Table 1 lists the rates ascribed to some of the variables in the model. These were found in the published literature. The follow-up visit rate was estimated by Delphi survey performed for this study. Factors likely to vary widely across countries or types of setting, such as follow-up visit rate, laboratory performance and antimicrobial resistance were submitted to a sensitivity analysis to assess their impact on the model.

Results

Baseline performance

The baseline performance of the three strategies is shown in Table 2. Strategy costs depended largely on the cost of drugs. The gold standard strategy yielded the highest outcome at the highest cost. Following our model the total cost of the strategy was US$ 4800 to effectively treat 87% of the 810 infected patients, or US$ 6.8 per cured urethritis. The 105 subjects (13%) not cured were those who had 'failed' to comply with their doxycycline treatment. Strategy 2 was nearly as effective when laboratory performance was optimal. Despite the additional cost of microscopic examination, limiting the use of cefixime resulted in a total cost of US$ 4000 to cure 85% of infected patients. Strategy 3 was the least expensive option, with a total cost of US$ 1,700, but the rate of cured patients did not exceed 64%. Table 3 shows the influence of changing some of the variables on the cost-effectiveness of strategies 2 and 3.

Table 1 Values at baseline and for sensitivity analysis

	Baseline (%)	Sensitivity analysis (%)		
Subjects with symptoms and/or signs of urethritis, not infected	19*			
Infected patients with				
gonococcal infection	50			
nongonococcal infection	30			
both	20†			
Compliance with				
multidose treatment	74‡			
single-dose treatment	100			
Follow-up visit rate	34	50	70	90
Validity of the Gram stain§				
sensitivity	95	80	60	
specificity	95	85	70	
Gonococcal resistance to antibiotics				
cefixime	0			
cotrimoxazole	30	20	10	0
kanamycin	30	20	10	0

* Kuvanont *et al*. (1989); Mayaud *et al*. (1992)
† Louis *et al*. (1993)
‡ Jordan (1989); Katz *et al*. (1991); Homedes & Ugalde (1993)
§ Goodhart *et al*. (1982); Landis *et al*. (1988)

Influence of laboratory performance on cost-effectiveness

The performance of strategy 2 clearly depended on the quality of microscopic examination. Both the effectiveness and total cost decreased, though not markedly, when the sensitivity and specificity were arbitrarily set at 80% and 85%, then 60% and 70%, respectively. However, the cost per individual patient increased since the number of cured patients dropped faster than the total cost.

Influence of the follow-up visit rate

Keeping the gold standard in mind, we first modified the follow-up visit rate in strategy 3 to observe its effect on cost-effectiveness. Even after almost tripling the follow-up visit rate, the effectiveness only increased from 64% to 72%. While the total cost rose as a consequence of the greater number of patients treated with cefixime, the cost per cured urethritis was only marginally increased.

Table 2 Baseline performance of the three strategies

Strategy	N (%) of cured urethritis *	Total cost (US$)	Cost ($) per cured urethritis
1	705 (87)	4800	6.8
2	688 (85)	4000	5.8
3	516 (64)	1700	3.3

* Percentages are calculated from a total of 810 patients considered really infected.

Influence of drug efficacy

When cotrimoxazole efficacy was maximized (the other variables being unchanged), 599 patients (74%) were cured at an individual cost of US$ 2.5. In the 100%-efficacy scenario, the effectiveness was basically limited by the 74% compliance with the multidrug regimen. We also looked at the consequence of replacing cotrimoxazole with single-dose kanamycin. At a 70% efficacy kanamycin cured 74% of the cohort at a cost of US$ 3.2 per cured patient. As the efficacy of the drug went up, the percentage of cured patients went up and the costs went down. With kanamycin efficacy at 100%, strategy 3 matched strategy 1 in terms of efficacy but at one third of the cost.

Our findings remained unchanged even after raising the unit costs for consultation from US$ 0.16 to 0.48, and for laboratory testing from US$ 1.17 to 1.66. This actually meant tripling labour costs or dividing workload by three. Only when labour costs were multiplied by six did strategy 1

Table 3 Impact on model outcome of performance of microscopic examination, follow-up visit rate and gonococcal antimicrobial resistance

Strategy 2 Performance of microscopic examination Sensitivity	Specificity	N (%) cured cases	Total cost (USUS$)	Cost (US$) per cured urethritis
95	95	688 (85)	4000	5.8
80	85	638 (79)	3850	6.0
60	70	572 (71)	3650	6.4
Strategy 3 Impact of follow-up visit rate Return rate	N (%) of cured urethritis	Total cost (USUS$)	Cost (USUS$) per cured urethritis	
34%	516 (64)	1700	3.3	
50%	535 (66)	1800	3.4	
70%	562 (69)	1950	3.5	
90%	587 (72)	2050	3.5	
Impact of cotrimoxazole efficacy Drug efficacy	N (%) of cured urethritis	Total cost (US$)	Cost (US$) per cured urethritis	
70%	516 (64)	1700	3.3	
80%	544 (67)	1650	3.0	
90%	572 (71)	1600	2.8	
100%	599 (74)	1500	2.5	
Impact of kanamycin efficacy Drug efficacy	N (%) of cured urethritis	Total cost (US$)	Cost (US$) per cured urethritis	
70%	601 (74)	1950	3.2	
80%	635 (78)	1900	3.0	
90%	670 (83)	1800	2.7	
100%	705 (87)	1700	2.4	

become less expensive than strategy 2, as labour costs associated with strategy 2 surpassed drug savings. Likewise, our findings were unaffected by modifying the rates of gonococcal, chlamydial or mixed infection in the model.

Finally, we calculated the price cefixime should ideally not exceed in order to have strategy 1 comparing favourably in terms of cost with the least expensive strategy. At US$ 1.5 per cefixime treatment, the total cost of the first strategy dropped to the baseline cost of the third strategy, i.e. US$ 2,300, or slightly less than US$ 3.3 per cured urethritis.

Discussion

In short, the gold standard strategy was, as expected, both the most effective and the most expensive approach. Strategy 2 matched the gold standard only when laboratory performance was optimal. Falling laboratory performance led to effectiveness falling similarly. Strategy 3 using cotrimoxazole was the least expensive, but was limited by treatment compliance even at the highest drug efficacy. With kanamycin, the effectiveness of strategy 3 depended mainly on drug efficacy. At 100% drug efficacy, it matched the gold standard in terms of effectiveness, at a much lower cost.

These findings confirm what most public health decision-makers already knew intuitively, but they pointed to a few additional facts. The gold standard strategy is expensive when third-generation cephalosporins have to be recommended. At US$ 4 per treatment with cefixime, drug costs dwarf labour costs. In a country like Cambodia, a reasonable estimate of the cost of procuring drugs for the syndromic management of STDs at primary encounter level nationwide amounted to nearly US$ 3 million per year, with cefixime representing most of it. The national government is obviously unable to face such an enormous cost. Since patients are equally unable to afford treatment, the best drug for the treatment of gonococcal infection remains

inaccessible to most. However, in some African countries, such as Côte d'Ivoire or South Africa where the efficacy of quinolones remains and where national governments have managed to obtain them at around US$ 1.5, strategy 1 with quinolones is definitely the preferred option.

Strategy 2 seems to offer an attractive alternative to the gold standard especially where labour costs (and thus the cost of laboratory work) are much lower than imported drugs. However, our model showed that this option is valid only when laboratory performance is optimal. Its advantages become marginal when the quality of laboratory work falls below this level.

When increasing the follow-up visit rate in Strategy 3 we were surprised that its impact was so limited. However, our model revealed that only 90 patients with gonorrhoea and 36 with mixed infection were likely to return for a follow-up visit. Thus increasing the follow-up visit rate from 34 to 90% added only 71 subjects to the total number of cured patients. Our model clearly suggested that efforts to bring patients back to the consultation would have limited benefit. Improving the efficacy of cotrimoxazole in Strategy 3 resulted in increased effectiveness and lower costs. However, our model highlighted the importance of treatment compliance. Even at maximum efficacy, the total rate of cured patients with cotrimoxazole as the first line drug (599) was just under the rate obtained with a single administration drug such as kanamycin at 70% efficacy (601). Our model suggested that the multiple-dose cotrimoxazole regimen, however efficacious and inexpensive, should no longer be recommended when there is a single administration alternative that does not cost more than US$ 1.5.

Which single-dose products could be used to treat gonococcal infection at an acceptable cost in the developing world? Unfortunately there is no single inexpensive drug. Since gonococcal resistance to antibiotics varies extensively across countries, local assessment of drug efficacy has become mandatory and options vary. For example, the single administration of amoxycillin and clavulanic acid is currently the preferred option in Kenya. Gentamycin is recommended in Malawi and kanamycin in Zimbabwe.

Our theoretical exercise has limitations. Only a few variables were considered in the model. In order to keep it simple, patients not compliant with multiple-dose drug regimens (cotrimoxazole or doxycycline) were considered lost and not cured. The rate of transmission of infection to female partners as well as the rate of complications were deemed constant and not taken into account. Costs included only drugs, consultations and microscopic examination where applicable. Extra costs associated with improving the follow-up visit rate or with monitoring gonococcal antimicrobial resistance were not considered. Low labour costs are representative of many countries in the developing world, but do not necessarily apply worldwide. Finally the issue of intramuscular administration *vs*. oral intake was not considered.

Nevertheless, by translating concepts into numbers our model emphasized the advantages and limitations of the three strategies, and suggested the following two conclusions. First, the simplest and most cost-effective approach for public health decision-makers might be to negotiate the purchase of WHO's recommended drugs at around US$ 1.5 per treatment. Alternatively, they might try to identify an efficacious single-dose product from among inexpensive antibiotics, based on local gonococcal resistance findings. Secondly, cotrimoxazole should be abandoned for the treatment of gonococcal infection, especially if there is a single administration alternative that does not cost more than US$ 1.5.

References

Bhalla P, Sethi K, Reddy BS & Mathur MD (1998) Antimicrobial susceptibility and plasmid profile of *Neisseria gonorrhoeae* in India (New Delhi). *Sexually Transmitted Infections* **74,** 210–212.

Bhuiyan BU, Rahman M, Miah MR *et al*. (1999) Antimicrobial susceptibilities and plasmid contents of *Neisseria gonorrhoeae* isolates from commercial sex workers in Dhaka, Bangladesh: emergence of high-level resistance to ciprofloxacin. *Journal of Clinical Microbiology* **37,** 1130–1136.

Goodhart ME, Ogden J, Zaidi AA & Kraus SJ (1982) Factors affecting the performance of smear and culture tests for the detection of *Neisseria gonorrhoeae*. *Sexually Transmitted Diseases* **9,** 63–69.

Grosskurth H, Mosha F, Todd J *et al*. (1995) Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* **346,** 530–536.

Holmes KK, Sparling PF, Mårdh PA *et al*. (1999) *Sexually Transmitted Diseases* 3rd edn. MacGraw-Hill, New York, pp. 833–845.

Homedes N & Ugalde A (1993) Patients' compliance with medical treatments in the third world. What do we know? *Health Policy & Planning* **8,** 291–314.

Jordan WC (1989) Doxycycline *vs*. tetracycline in the treatment of men with gonorrhea: The Compliance Factor. *Sexually Transmitted Diseases* **8,** 105–108.

Katz BP, Caine VA, Batteiger BE & Jones RB (1991) A randomized trial to compare 7- and 21-day tetracycline regimens in the prevention of recurrence of infection with *Chlamydia trachomatis*. *Sexually Transmitted Diseases* **18,** 36–40.

Klausner JD, Aplasca MR, Mesola VP, Bolan G, Whittington WL & Holmes KK (1999) Correlates of gonococcal infection and antimicrobial-resistant *Neisseria gonorrhoeae* among female sex workers, Republic of the Philippines. 1996–97. *Journal of Infectious Diseases* **79,** 729–733.

Kuvanont K, Chitwarakorn A, Rochananond C *et al*. (1989) Etiology of urethritis in Thai men. *Sexually Transmitted Diseases* **16,** 137–140.

Landis SJ, Stewart IO, Chernesky MA *et al*. (1988) Value of the

gram-stained urethral smear in the management of men with urethritis. *Sexually Transmitted Diseases* **15,** 78–84.

Louis JP, Migliani R, Trebucq A *et al*. (1993) Prise en charge des maladies sexuellement transmissibles au Cameroun, en milieu urbain, en 1992. *Annales de la Société Belge de Médecine Tropicale* **73,** 267–278.

Management Sciences for Health (1999) *International Drug Price Indicator Guide*. Arlington.

Mayaud P, Changalucha J, Grosskurth H *et al*. (1992) The value of urine specimens in screening for male urethritis and its microbial aetiologies in Tanzania. *Genitourinary Medicine* **68,** 361–365.

Moran JS & Levine WC (1995) Drugs of choice for the treatment of uncomplicated gonococcal infection. *Clinical Infectious Diseases* **20** (Suppl. 1), S47–S65.

Ng PP, Chan RK & Ling AE (1998) Gonorrhoea treatment failure and ciprofloxacin resistance. *International Journal of Sexually Transmitted Diseases and AIDS* **9,** 323–325.

Tapsall JW, Limnios EA & Shultz TR (1998) Continuing evolution of the pattern of quinolone resistance in *Neisseria gonorrhoeae* isolated in Sydney, Australia. *Sexually Transmitted Diseases* **25,** 415–417.

WHO Western Pacific Region Gonococcal Antimicrobial Surveillance Programme (1997) Surveillance of antibiotic susceptibility of *Neisseria gonorrhoeae* in the WHO western pacific region 1992–94. *Genitourinary Medicine* **73,** 331–332.

World Health Organization (1991) Management of patients with sexually transmitted diseases. *Technical Report Series 810.* WHO, Geneva.

World Health Organization (1994) *Management of Sexually Transmitted Diseases*. WHO, Geneva.