

# Clinical Review

Clinical Review identifies issues in the medical literature of interest to clinicians in Africa. Essential references are given at the end of each section

## STI Review

### *Mycoplasma genitalium*

*Mycoplasma genitalium*, first identified in 1980 as a cause of non-gonococcal urethritis in men, is now emerging as a significant cause of inflammatory reproductive tract infections in women. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the common pathogens associated with cervicitis, urethritis, and pelvic inflammatory disease (PID), but recent studies indicate that *M genitalium* is an important independent cause of sexually transmitted infections (STIs).<sup>1,2</sup>

A recent comprehensive review screened 48 published studies that included over 27 000 women for associations between *M genitalium* and reproductive tract infections.<sup>3</sup> The prevalence of *M genitalium* infection ranged from 2% in low-risk populations to 7.3% in high-risk groups – on a par with general population infection rates for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *M genitalium* was positively associated with urethritis, vaginal discharge, and microscopic signs of cervicitis and/or mucopurulent cervical discharge in 7 of 14 studies. A consistent case definition of cervicitis across studies is needed to better understand these associations.

Because *M genitalium* is very difficult to culture, epidemiological studies of its pathogenicity were limited until the advent of polymerase chain reaction (PCR) technology. It was suspected that *M genitalium* could ascend the reproductive tract through the cervix resulting in infection of the uterus, fallopian tubes, and ovaries, and possibly, infertility. The review finds that several PCR-based studies from geographically diverse populations confirm that *M genitalium* is associated with clinical PID. Among women with PID, infection with *M genitalium* ranged between 13% and 16%. Studies also confirm that *M genitalium* is associated with PID, independently of gonococcal or chlamydial infection. Most studies of PID and *M genitalium* are cross-sectional, making it difficult to determine if the relationship is causal. However, one prospective study in the United States indicated that *M genitalium* was associated with a 13-fold risk of endometritis, and a nested case-control study in Sweden showed a 6-fold increased risk of PID among patients with *M genitalium*.<sup>1</sup>

There is mounting evidence of an association between *M genitalium* and HIV infection. A systematic review of studies prior to 2008 found that patients with

*M genitalium* were twice as likely to be infected with HIV as those not having *M genitalium*. In these largely cross-sectional studies, it was not possible to pinpoint the timing of this association between infection with HIV and *M genitalium*.<sup>4</sup> However, a case-control study nested in a large prospective study in Zimbabwe and Uganda does indicate that *M genitalium* infection increases the risk for HIV acquisition.<sup>5</sup> The study matched 190 women who seroconverted to HIV-1 during follow-up with up to two HIV-negative controls. Prior to HIV-1 detection, *M genitalium* infection was 14.8% among cases and 6.5% among controls. The study found that women infected with *M genitalium* had a greater than two-fold independent risk of HIV-1 acquisition at the visit prior to HIV-1 acquisition, and an estimated 8.7% of incident HIV-1 infections were attributable to *M genitalium*.

Another study of the prevalence of *M genitalium* among female sex workers in Kampala, Uganda found that HIV-positive women were more likely to be infected with *M genitalium* than HIV-negative women.<sup>6</sup> *M genitalium* infection was less prevalent among older women and among those who had been pregnant but never given birth. *M genitalium* was also associated with gonorrhoea, candida, and trichomonas infections.

PID is caused by multiple pathogens, with *N gonorrhoeae* and *C trachomatis* accounting for between one-third and one-half of cases in the US-based PID Evaluation and Clinical Health (PEACH) Study. However, the aetiology clearly varies between subgroups, and in up to 70% of PID cases the cause is unknown.<sup>7</sup> Women with acute PID also test positive for anaerobic and aerobic bacteria common to endogenous vaginal and cervical flora (bacterial vaginosis) and genital mycoplasmas, including *M genitalium*. The US Centers for Disease Control recommends treating acute PID with broad-spectrum antibiotics, either parenterally or orally.<sup>8</sup> Oral therapy is most common, and most appropriate in many African settings, but given the increased antibiotic resistance of *N gonorrhoeae*, especially to quinolones, the choice of effective oral regimens is limited. Ceftriaxone or cefoxitin plus doxycycline have been effective, and adding metronidazole to this treatment improves anaerobic coverage.<sup>9</sup> However, these drugs are not effective against *M genitalium*. In women with suspected PID, the PEACH Study found that *M genitalium* was associated with endometritis and short-term PID treatment failure, as evidenced by persistent endometritis and continued pelvic pain. Azithromycin has been more effective against *M genitalium* than doxycycline, but azithromycin-resistant infections have been reported globally.<sup>10</sup> Additionally, *M genitalium* appears to have increased resistance to tetracyclines.<sup>9</sup> On the positive side, *M genitalium* was found to have variable resistance to fluoroquinolones and was susceptible to macrolides. Newer quinolones, moxifloxacin and gatifloxacin, have recently been shown to be effective against *M genitalium*.<sup>10,11</sup>

Patients with persistent PID or clinically persistent urethritis or cervicitis should be tested for *M genitalium*. Those infected who have not previously been treated with azithromycin can be treated with this drug. Those

whose infection does not respond to azithromycin should receive moxifloxacin.<sup>10</sup> There is clear need for randomised clinical trials to assess the most effective regimens for the treatment of *M genitalium* and PID.

### Drug-resistant *N gonorrhoeae*

*N gonorrhoeae* is especially adept at evolving and developing resistance to antibiotics. While pharmaceutical development has been able to keep ahead of this ever-changing bacteria, *N gonorrhoeae*-resistance now poses a serious threat to STI prevention and treatment programmes worldwide. Prior to the discovery of antibiotics, treatment for gonorrhoea often relied on urethral irrigation and rest. The advent of sulphanilamide in 1935 offered a cure in 80–90% of cases.<sup>12</sup> However, by 1944 many bacteria had developed resistance, and by 1950 over 90% of *N gonorrhoeae* were resistant. From there, treatment moved to penicillins and tetracyclines, especially for those allergic to penicillin. By the 1980s, penicillin and tetracycline resistance among *N gonorrhoeae* isolates was widespread globally. Quinolones, such as ciprofloxacin and ofloxacin, became the next drugs to treat gonorrhoea. However, within a decade, resistance to quinolones was evident in Pacific Asian countries, and soon spread to the United States, Europe, and parts of Africa.<sup>13</sup> Healthcare providers now rely on cephalosporins, including oral cefixime and cefpodoxime. Resistance to oral cephalosporins has been seen in Japan since 2001, and more recently in other western Pacific countries and Europe. Currently, intramuscular ceftriaxone is the only antibiotic that offers a reliable cure for genital gonorrhoea. If *N Gonorrhoeae* develops resistance to this class of drugs, and in the absence of any new therapies, gonorrhoeae may become an untreatable disease.<sup>13</sup> Practitioners need to consider alternative strategies to prolong the effectiveness of current treatment protocols, including higher doses of cephalosporin, multi-dose regimens, and multidrug regimens. There is great need to improve global surveillance of antibiotic resistance by improving laboratory capacity, information sharing and increased funding, especially for research into new therapeutic agents. The World Health Organization is supporting research into controlling both drug resistance and gonorrhoea through the WHO Gonococcal Antimicrobial Surveillance Programme (GASP).<sup>14</sup>

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## Ophthalmology Review

### New WHO estimates for global blindness

As part of the Vision2020 initiative, the World Health Organization publishes its estimates for global blindness every few years. These estimates are derived from population-based surveys, and are generally regarded as the most accurate estimates on which to base programme planning for prevention of blindness. The latest estimates were published in December 2011,<sup>1</sup> and it is worth looking at them in some detail – particularly as they contain good news for Africa.

The previous estimates were published in 2004 and estimated global prevalence of blindness in 2002. Africa was divided into two regions according to mortality statistics, however the prevalence of blindness and visual impairment was assumed to be the same in all African countries. At that time the total population of the WHO African region (which does not include north Africa and the Maghreb) was 715 million people. There were 7.3 million blind (<3/60 best eye) and another 21.3 million with visual impairment (<6/18 but better than 3/60). The prevalence of blindness was approximately 1%, and visual impairment was about 3%.

The latest estimates have a rather different methodology. Firstly, the definition of blindness and visual impairment has changed. In 2002, blindness was defined as the ‘best corrected vision’. This meant that anyone who was blind or visually impaired purely because they needed glasses, but did not have them, was classified as normal even if they could hardly see their hand in front of their face! By definition, uncorrected refractive error could not cause visual impairment, and we all know this to be untrue. The new definition of blindness and visual impairment relies on ‘presenting vision’. This means that if patients have glasses, the vision is tested

with the glasses. If they do not have any spectacles, the uncorrected vision is used. This means that if someone is very short-sighted, but does not have glasses, they will be counted as visually impaired.

The second change is that rather than estimating blindness by geographic region, blindness was estimated for groups of countries according to their economic development. It has been consistently shown that there is a very strong inverse correlation between income per person, and the prevalence of blindness – a country like Ethiopia, with an income per head of less than US\$1000 per year, will have a much higher prevalence of blindness than Sweden, with an income per head of over US\$30000. In practice, most African countries are at a fairly similar stage of economic development, so there were few differences. However, it has made the overall global estimates more accurate.

In 2010, the population of the Africa region had increased to 805 million. The number of blind however, has fallen to 5.9 million, giving a prevalence of 0.73%. The number of people with visual impairment has fallen slightly to 20.4 million. These data are based on no less than 19 different surveys from 12 countries, and I think we can assume that these figures are reliable.

The fall in the prevalence of blindness has been a long time coming, but is not unexpected. The major cause of blindness in Africa is still cataract, and community-based surveys have shown that the cataract surgical coverage is often over 60% (i.e. 60% of patients with blinding cataract have had cataract surgery). The number of cataract operations continues to increase, and, thanks to inexpensive consumables, such as intraocular lenses, produced in India and elsewhere, the unit cost of cataract surgery should continue to fall. There is no room for complacency, but it does seem that the major efforts made by non-government agencies, ministries of health, and eye health workers of all kinds, are having an impact.

In the rest of the world, the numbers of visually impaired people have increased. This is likely to be due to the inclusion of refractive error, which is responsible for about 42% of visual impairment, but only 3% of blindness.

About 21% of blindness has indeterminate or unknown causes. This is because many of the surveys use the rapid assessment method, in which subjects are given a very basic examination in their own home. This is an excellent way of detecting cataract, corneal scar, and refractive error. However, all diseases of the posterior segment – age-related macular degeneration, diabetic retinopathy, and glaucoma are all combined as ‘posterior segment’. This means that the current WHO figures underestimate the proportion of blindness caused by glaucoma and retinal disease – and these are the fastest growing causes of blindness worldwide.

Still on the subject of cataract and public health, did you know that cataract surgery makes you richer? I am not referring to ophthalmic surgeons in private practice who can afford a second Mercedes! A report published at the end of 2010 brought together studies from three countries – Kenya, Bangladesh, and the Philippines – that examined the impact of cataract surgery on

households rather than merely looking at the change in visual acuity of the operated person.<sup>2</sup> In all three countries, a population-based survey identified cataract patients. These were defined as anyone with a vision of less than 6/24 in their best eye, due to cataract. For every cataract patient, an age- and sex-matched control with vision of 6/18 or better was identified. The patients and their households were then interviewed extensively to measure quality of life, time use, and household expenditure and wealth. A total of 599 cases of cataract were identified. They were all offered free or subsidised cataract surgery, and 312 had surgery during the study period.

Not surprisingly, households in which one person was visually impaired were significantly poorer than the control households. This was true in all three countries. Per capita household expenditure, on food, housing, education, etc. was significantly lower if there was a cataract patient in the home.

One year later, the households were re-visited and interviewed again about household expenditure and wealth. There was a substantial change, with the per capita household expenditure rising in the case households but remaining constant in the controls. In all three countries, the differences in expenditure between case and control households were no longer significant. There was relatively less change in asset ownership or self-rated wealth, but this is not surprising as these measures will change more slowly, and one year may be insufficient time to show a significant improvement.

What is particularly striking is that the growth in household expenditure was greatest in the most vulnerable patient groups – those who were poorer, older, female, or unmarried. These are the groups that are most difficult to reach in any healthcare system. Another surprising result was that the improvement in expenditure occurred regardless of the level of visual impairment. Patients who were only visually impaired (3/60 or better) saw a growth in household expenditure that was not significantly different from those who were blind (<3/60). We tend to worry most about the people who are cataract blind (approximately 19 million), but this study shows that even those with visual impairment, who are not yet blind (approx 8 million), suffer economic harm as a result of their disability – and that this harm extends to the entire household in poor countries.

How did the improvement in these households’ circumstances happen? Another study, by the same authors, looked at time use in people who had cataract. Following surgery an additional 1–2 hours per day were spent in productive activities; and fewer of the patients reported needing assistance with daily activities, which freed other family members to be more productive as well.

The study underlines the complex link between poverty and blindness. There is evidence that poverty causes blindness. Poor people are less likely to be able to afford cataract surgery, so they become blind. However, this study also provides evidence that cataract blindness causes poverty. Measures of early life poverty, such as level of education, were not significantly

different between cases and controls, suggesting that the cases were not necessarily born into poverty, but became poorer as a consequence of their disability.

Most of the readers of this column will be struggling with life-threatening diseases, major new challenges, such as multi-drug resistant TB, and utterly inadequate resources. In these circumstances you may feel that cataract surgery is a luxury your healthcare system cannot afford. There is now strong evidence that the provision of cataract surgery is not only cost effective, but that it also lifts households, and even communities, out of poverty, and will do far more than just restore sight to one visually impaired individual. I hope you will make it a priority to ensure that safe and effective cataract surgery is available for all your patients with visual impairment.

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