Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Fewer Men Now Required to be Tested for Non-Gonococcal Urethritis

1. Summary of the impact (indicative maximum 100 words)

Imperial College researchers have demonstrated the association of the pathogen, *Mycoplasma genitalium*, with symptomatic non-gonococcal urethritis (NGU) and have shown that sexual transmission of infection is unlikely in asymptomatic men. As a result, the NGU national guidelines updated in 2008 recommended discontinuing urethral smears in all asymptomatic men, so reducing a) consultation times in men attending for screening and b) follow-up appointments for men with NGU. This has enabled genitourinary medicine (GUM) departments to release £23 million annually; a cost saving that was directed to seeing more patients in extended clinics and contributed to achieving the government's 48-hour target for accessing GUM departments.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor David Taylor-Robinson, Professor of GU Microbiology and Medicine (1980-96); Emeritus Professor (1996-present)
Professor Myra McClure, Professor of Retrovirology (1992-present)
Dr Patrick Horner, Medical Research Council Clinical Research Fellow and Specialist Registrar (1989-1993); Honorary Clinical Senior Lecturer (2006-2012)

NGU in men is one of the most common conditions managed in GUM clinics, with more than 60,000 cases a year detected prior to 2008. It is diagnosed by performing a genital examination and taking a urethral smear, which is both time-consuming for medical staff and painful for patients. Acute NGU is caused by *Chlamydia trachomatis* in 20-50% of cases. Prior to 1993 it was unclear what other infections caused urethritis, as most men with urethritis responded to antimicrobial therapy (1). Approximately, 10-20% will have symptomatic chronic urethritis post-treatment. A further 20-40% will have persistent asymptomatic urethritis detectable on a urethral smear (2).

A prospective cohort of 110 men with NGU and 50 (control) men without urethritis were recruited between 1993 at St Mary's Hospital London (1-5) to investigate the aetiology of acute and chronic urethritis. It was undertaken by Dr Horner and supervised by Professors Taylor-Robinson and McClure.

An Enzyme Linked ImmunoSorbent assay (ELISA) to detect antibody to the chlamydia heat shock protein 60 (Hsp60) was developed at Imperial College in 1996 (6), on the basis that an immune response to this protein had been associated with a chronic inflammatory response in women infected with *Chlamydia trachomatis*. We further demonstrated that *Mycoplasma genitalium* was associated with acute symptomatic non-gonococcal urethritis, a finding which could not be explained by confounding factors. This association had not been demonstrated previously (1).

We extended this work to show that the persistence and/or recurrence of *Mycoplasma genitalium* and Ureaplasmas were associated with the persistence and/or recurrence of urethritis only in symptomatic men post-treatment (2). Persistent asymptomatic urethritis post-treatment was not associated with persistent/recurrent infection, but with the Chlamydia hsp60 antibody, suggesting that this may be immunologically mediated and these men are not at increased risk of having a sexually transmissable infection. Hence, antimicrobial therapy would not be indicated in such individuals (2, 3, 4).

Further analyses from the NGU cohort demonstrated that the association of Mycoplasma genitalium and *Chlamydia trachomatis* with acute NGU was only in those men with symptoms

and/or signs (5). Thus, men with asymptomatic NGU are not at increased risk of having a sexually transmissable infection (5) and antimicrobial therapy would not be indicated.

There had always been a concern that responding to urethritis (painful smear, antibiotics for patient and partner) could do more harm than good and in 2008, because of the lack of evidence associating asymptomatic urethritis with a sexually transmitted infection, testing for NGU in asymptomatic men was discontinued (1-5).

3. References to the research (indicative maximum of six references)

(1) Horner, P.J., Gilroy, C.B., Thomas, B.J., Naidoo, R.O., Taylor-Robinson, D. (1993). Association of Mycoplasma genitalium with acute non-gonococcal urethritis. *Lancet*, 342, 582-585. DOI. Times cited: 146 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 39.6

(2) Horner, P.J., Thomas, B., Gilroy, C.B., Egger, M., Taylor-Robinson, D. (2001). Role of Mycoplasma genitalium and Ureaplasma urealyticum in acute and chronic nongonococcal urethritis. *Clinical Infectious Diseases*, 32 (7), 995-1003. DOI. Times cited: 78 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 9.37

(3) Horner, P.J., Cain, D., McClure, M., Thomas, B.J., Gilroy, C., Ali, M. et al. (1997). Association of antibodies to Chlamydia trachomatis heat-shock protein 60 kD with chronic nongonococcal urethritis. *Clinical Infectious Diseases*, 24 (4), 653-660. DOI. Times cited: 23 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 9.37

(4) Horner, P.J., Thomas, B., Gilroy, C., Egger, M., McClure, M., Taylor-Robinson, D. (2003). Antibodies to Chlamydia trachomatis heat-shock protein 60 kDa and detection of Mycoplasma genitalium and Ureaplasma urealyticum are associated independently with chronic nongonococcal urethritis. *Sexually Transmitted Diseases*, 30 (2), 129-133. DOI. Times cited: 6 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 2.59

(5) Horner, P.J., Thomas, B., Gilroy, C.B., Egger, M., Taylor-Robinson, D. (2002). Do all men attending departments of genitourinary medicine need to be screened for non-gonococcal urethritis? *International Journal of STD & AIDS*, 13 (10), 667-673. DOI. Times cited: 42 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 1

(6) Horner, P.J., Ali, M., Parker, D., Weber, J.N., Taylor-Robinson, D., McClure, M.O. (1996). Antigen capture ELISA for the heat shock protein (hsp 60) of Chlamydia trachomatis. *J Clin Path*, 49, 642-647. DOI. Times cited: 3 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 2.43

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare, economic, public policy and services, practitioners and services
Main beneficiaries include: patients, NHS, GUM clinics/professionals

The concern in the United Kingdom and Europe was that an unidentified pathogen(s) playing a role in NGU might cause disease in women. No clinical distinction was made between asymptomatic and symptomatic urethritis and the risk of having a sexually transmitted infection. It was assumed that the risk in all men with NGU was similar, irrespective of clinical presentation. Thus, it was common practice in the UK and Europe for all men requesting screening at a GUM or Sexually Transmitted Disease clinic to be tested for urethritis using a urethral smear. Those identified with urethritis, irrespective of symptoms, were informed they had a sexually transmitted disease, given anti-microbial therapy and advised that their partner(s) needed treatment and they needed to re-attend for a repeat smear, after completing treatment. If urethritis was again detected, further treatment was administered and a further visit advised to confirm resolution of infection.

As a result of our work (research references 1, 2, and 5), the 2008 UK and 2009 European NGU guidelines advised that only men presenting to GUM clinics with symptoms or urethritis i.e. discharge, dysuria and penile irritation or testicular pain should be tested for urethritis by urethral smear and that asymptomatic men do not need a urethral smear [1, 2]. Consultations for asymptomatic men are now shorter and can be undertaken by more junior staff (therefore, are less expensive) using non-invasive testing for chlamydia and gonorrhoea by nucleic acid amplification tests, enabling many more men to be seen using existing facilities. The 2008 UK and 2009 European NGU guidelines advised that asymptomatic men post-treatment of NGU are not required to re-attend for a repeat urethral smear and that follow-up can be undertaken over the telephone [1, 2].

Impact on the economy:

In 2007 890,000 men attended GUM clinics of whom 66,000 had urethritis. By 2012, this increased to 1.7 million men, of whom only 2,500 had urethritis [3]. Approximately 50% of men with symptoms have urethritis diagnosed microscopically from a Gram stained urethral smear, thus the total number of men receiving a urethral smear in 2012 was approximately 105,000. The number who potentially would have been offered a urethral smear using the guideline prior to 2008 would have been 1.7 million. If we assume a 75% uptake (conservative estimate) in the remaining 1.6 million, this would equate to an estimated 1.2 million urethral smears that would have been unnecessarily carried out annually. The impacts of this are:

1. Lower cost of a male consultation, as a urethral smear is no longer required. A smear takes 2 minutes for a band 7/8 nurse or a doctor to do at a cost of £1.45 per minute = £2.90. It takes 5 minutes for a band 5/6 nurse to stain and read the slide at £0.75 per minute = £3.75. Costing a total of £6.65, excluding materials, per patient i.e. £7.98 million
2. Fewer men diagnosed with asymptomatic NGU. Previously, they would have been given a diagnosis of a sexually transmitted infection and their partner would have needed to be treated. Before the guidelines were changed in 2008, approximately 66,000 NGU cases in men were diagnosed every year. In 2012, these numbered 52,500, a reduction of 13,500 (18%). By comparison, diagnoses of other STDs in GUM clinics either remained the same or increased. Assuming a partner notification efficacy of 40%, this means that there were 5400 fewer women treated as a result of being in contact with men with asymptomatic NGU. Each new patient costs £150, saving £810,000. Figures calculated from R & D costs.
3. Prevention of pain in men, which likely has contributed to higher attendance, as fewer men are put off attending for screening. A urethral smear can cause pain in some men equivalent to that of childbirth in women [4].

Prior to 2008 66,000 men were diagnosed with acute NGU and all would have been asked to re-attend [3]. In 2012, 52,500 symptomatic men were treated for acute symptomatic NGU of whom 15% would still have symptoms post-treatment [1, 2, 3] i.e. 7875 of the remainder approximately 75% would have returned, if instructed to do so. Thus, approximately 33,500 re-attendances have been avoided which at £100 for a follow-up visit would have saved £3.35 million.

Thus, cost savings now compared to prior to 2008 when urethral smears were carried out on men without symptoms of urethritis:
£7.98 million + £0.81 million + £3.35 million = total £12.14 million

Savings would have been re-invested in GUM services, enabling more people to be seen for a given departmental budget. Thus, the research significantly contributed to helping clinics in the UK achieve and sustain the government's 48-hour access target for GUM clinics (2008) [5].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] Shahmanesh M. UK National Guideline on the Management of Nongonococcal Urethritis: updated December 2008 available from: http://www.bashh.org/documents/1955.pdf. Archived on 7th November 2013.

[2] Shahmanesh, M., Moi, H., Lassau, F., Janier, M. (2009). European Guideline on the Management of Male Non-gonococcal Urethritis. *Int J STD AIDS*, 20 (7), 458-464. DOI.

[3] PHE Table 5 number of STI diagnoses & services in England, 2003-2012 *available at* http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1247816547927. Archived on 7th November 2013.

[4] Apoola, A., Herrero-Diaz, M., FitzHugh, E., Rajakumar, R., Fakis, A., Oakden, J. (2011). A randomised controlled trial to assess pain with urethral swabs. *Sex Transm Infect*, 87 (2),110-113. DOI.

[5] Department of Health. Genitourinary Medicine 48-hour Access: Getting to target and staying there (2008). Available from: http://www.bashh.org/documents/119/119.pdf. Archived on 7th November 2013.