
This is the author accepted manuscript (AAM). The final published version (version of record) is available online via SAGE Publications at https://journals.sagepub.com/doi/abs/10.1177/0956462419890526?rfr_dat=cr_pub%3Dpubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Aacrossref.org&journalCode=stda . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/pure/user-guides/explore-bristol-research/ebr-terms/
Diagnosis of some genital-tract infections: part 2. Molecular tests and the new challenges

David Taylor-Robinson, 1 Patrick Horner 2,3,4 and Anna Pallecaros, 5

1Section of Infectious Diseases, Wright-Fleming Institute, Faculty of Medicine, Imperial College London, St Mary’s Campus, Norfolk Place, London W2 1PG, UK
2Population Health Sciences, University of Bristol, UK
3National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Evaluation of Interventions in partnership with Public Health England, University of Bristol, 4Unity Sexual Health, University Hospitals Bristol NHS Trust, Bristol, UK.
5Department of Genito-urinary Medicine, Princess Grace Hospital, 47 Nottingham Place, London W1U 5LZ, UK
Abstract

Promptly and accurately diagnosing genital-tract infections is key to instituting appropriate treatment and control of sexually transmitted infections (STIs). Ano-genital tract testing for STIs in the last two decades has not entirely moved away from insensitive methods but is now at least dominated by highly sensitive molecular methods. These tests can be ordered through the internet for use at home, with self-taken specimens then returned, usually by post, to a clinic or laboratory for testing. The increasing ease of access of the public to this situation, together with increasing online health–seeking behaviour, has resulted in a gap between commercial and NHS management pathways for STIs. Crucially, patients who order multiplex test kits on-line for use at home, and other non-specialists, may not realize that it is worthwhile testing only for *Neisseria gonorrhoeae, Chlamydia trachomatis*, and possibly *Trichomonas vaginalis*, and *Mycoplasma genitalium* if the person is symptomatic or their current partner is infected. The detection and recommended treatment of micro-organisms which to some extent are part of the genital-tract microbiome, such as *Mycoplasma hominis, Ureaplasma* spp. or *Gardnerella vaginalis*, which do not cause symptoms in the majority of those infected, cannot be recommended. We argue that a shift from specialist led to patient and non–specialist led STI management, in the presence of a clinical leadership vacuum, has increased the risk of inappropriate and unnecessary treatment which will drive macrolide, tetracycline and metronidazole antimicrobial resistance. However, in the past 5-6 years several groups have been able to show the value of on-line testing as a consequence of targeting the most important micro-organisms and using molecular tests to allow rapid and appropriately informed treatment. This should herald a brighter future, although there is still a need for leadership to expertly guide commercial and NHS sectors alike. In turn, this requires
dedicated genito-urinary medicine (GUM) commissioning to be maintained at a time when it appears to be most under threat.

**Introduction**

We previously gave an historical account of tests used to diagnose six sexually transmitted bacterial infections, and one protozoal, up to the advent of molecular tests.\(^1\) These have now overtaken almost all others at a time when the digital era has seen a revolution in health-seeking behaviour with an unprecedented growth in the commercial market for STI tests. The public may now seek testing and treatment at home with information and access provided online, sometimes without involvement of a STI specialist or NHS provider. Seemingly, this would appear laudable, but it has some unwanted pitfalls. Here, we consider these together with the molecular tests and the impact that the molecular revolution is having on the sexually transmitted disease (STD) field.

**Observations on molecular diagnostic tests for the microbes under discussion**

**Neisseria gonorrhoeae.** Currently, the molecular tests used most often to detect *N. gonorrhoeae* are those also set up to detect *C. trachomatis* in the same sample. These are the nucleic acid amplification tests (NAATs) based on a polymerase chain reaction (PCR), namely Roche AMPLICOR and COBAS AMPLICOR;\(^2\) one based on strand displacement amplification (BDProb Tec; Becton Dickinson)\(^3\) and one based on transcription-mediated amplification (TMA): APTIMA Combo 2 (Gen-ProbeInc.).\(^4\) The cobas CT/NG v2.0 test (Roche Molecular Systems)\(^5\) behaves comparably to the others mentioned, as does the new Abbott m2000 Real Time CT/NG assay.\(^6\) The GeneXpertCT/NG assay (Cepheid, Sunnyvale, CA), with similar performance to the aforementioned NAATs produces a result within 1.5 hours. All these methods offer excellent sensitivity, usually well above 90%, while maintaining very high specificity. It is recommended that laboratories confirm any reactive
test with an alternative molecular target if the positive predictive value of the initial test for the population tested is less than 90%.\textsuperscript{7}

\textit{Chlamydia trachomatis}. The licensed NAATs for the detection of \textit{C.trachomatis} are those mentioned above for the detection of \textit{N.gonorrhoeae}. All four assays, as said before, are highly specific and sensitive. Furthermore, where resources are limited, pooling of specimens from different individuals can reduce costs without loss of sensitivity.\textsuperscript{8} The formerly often used Abbott LCx ligase chain reaction test\textsuperscript{9} was withdrawn from the market by the manufacturer in 2003.\textsuperscript{10} In 2013, the GeneXpertCT/NG assay (Cepheid, Sunnyvale, CA)\textsuperscript{11} was the first rapid NAAT shown to have attributes equivalent to recognized commercial NAATs. Therefore, it had the potential for use as a point-of-care (POC) test (\textit{vide infra}) and for revolutionizing genitourinary infection diagnostics.\textsuperscript{12, 13} Recent attention has focused on pooling specimens from the pharynx, rectum and urogenital tract of the same individual at risk of infection in all three sites. This may perform better for detecting \textit{C. trachomatis} than \textit{N.gonorrhoeae}, but more data are needed for firm conclusions.\textsuperscript{12, 13}

\textit{Mycoplasma hominis}. Real-time PCR technology for \textit{M.hominis} was described first in 2004\textsuperscript{14} and, although not always of real-time construction, the PCR has subsequently been an integral part of numerous multiplex tests.\textsuperscript{15} Whether they should be used at all is discussed below.

\textit{Gardnerella vaginalis}. Early molecular studies\textsuperscript{16, 17} showed that \textit{G.vaginalis} belongs to a much larger group of bacterial species that are associated with bacterial vaginosis (BV) than was considered in the pre-molecular era. BV is characterised by depletion of key \textit{Lactobacillus} spp., with an increase in bacterial species diversity and load, including that by \textit{Gardnerella vaginalis, Atopobium vaginae} and other BV- associated bacteria (BVAB).\textsuperscript{18-22} \textit{Atopobium vaginae} is more strongly associated with BV than \textit{G.vaginalis}, the latter detectable by a NAAT in many asymptomatic women.\textsuperscript{18-22} Therefore, detecting \textit{G.vaginalis}
without considering its load and changes in the composition of other bacteria in the vaginal microbiome cannot be used to accurately diagnose BV. Becton Dickinson have designed and validated a ‘vaginitis NAAT’ which uses an algorithmic analysis of molecular DNA detection of lactobacilli and four BVAB, including \textit{G. vaginalis, Atopobium vaginae} and \textit{Megasphaera spp.}, to diagnose BV with a sensitivity and specificity of \textgreater90\%, although a study in the UK using the Hay-Ison criteria revealed a specificity of only 79\%.

\textit{Ureaplasma spp.} Thirty-eight or more years after detection and quantification of ureaplasmas by culture, detection, speciation and quantification became possible by using PCR-based tests.\textsuperscript{24-27} Two species can be identified, namely \textit{Ureaplasma urealyticum} and \textit{U.parvum}. \textit{Ureaplasma} spp. are common in the lower genital tract with a greater \textit{U.urealyticum} bacterial load, in some men with non-gonococcal urethritis.\textsuperscript{26, 28} Subsequently, real-time multiplex tests for \textit{Ureaplasma} spp., \textit{M.hominis} and other microorganisms were devised. Whether such tests should be used is considered below.

\textit{Mycoplasma genitalium}. Subsequent to the difficulty in isolating and culturing \textit{M.genitalium}, DNA probes were tried, but these proved insufficiently sensitive. Then in the late 1980s, two groups\textsuperscript{29,30} each developed a PCR test that was much more sensitive. Each amplified different fragments of the MgPa adhesin protein and showed that as little as \(10^{-15}\) g of \textit{M.genitalium} DNA could be detected. This prompted others to use this technique and some
to devise modifications, use a multiplex PCR, target the 16SrRNA gene of *M. genitalium*, and use TMA with success.\textsuperscript{31} Molecular methods have also shown an increase in the prevalence of *M. genitalium* resistance to several antibiotics, particularly macrolides (\textit{vide infra}).\textsuperscript{32} The latter is probably due to extensive use of azithromycin 1g to treat chlamydial infections and non-gonococcal urethritis.\textsuperscript{32} There are now at least two satisfactorily sensitive, FDA-approved, commercial assays, available, namely the Aptima TMA assay (Hologic Ltd) \textsuperscript{33} and the Speedx ResistancePlus MG assay which also tests for macrolide resistance.\textsuperscript{34} The new guidelines \textsuperscript{32} of the British Association for Sexual Health and HIV (BASHH) for *M. genitalium* recommend testing patients with urethritis and pelvic inflammatory disease, and current sexual contacts and, if positive, testing for macrolide resistance-mediating mutations. This will improve clinical outcomes and reduce the risk of resistance to both macrolides and quinolones in the United Kingdom. There is no recommendation to screen asymptomatic individuals.

\textit{Trichomonas vaginalis}. Although some non-molecular diagnostic tests, for example, the OSOM rapid test,\textsuperscript{35} are used for convenience, NAATs out-perform all others.\textsuperscript{36} Thus, the TMA-based APTIMA TV test\textsuperscript{37, 38}, although not the only molecular one,\textsuperscript{39} is highly sensitive, FDA-approved and widely used, particularly as it fits into settings where gonococcal and chlamydial molecular tests are in place. Becton Dickenson have developed a multiplex format for simultaneous detection of *N. gonorrhoeae* and *C. trachomatis* which performs well in accurately detecting all three infections.\textsuperscript{40} The TV assay has also been incorporated in its vaginitis assay with no apparent loss in performance.\textsuperscript{41}

\textbf{Issues around point-of-care (POC) tests}

A POC test has come to mean one in which a specimen is examined in a sensitive and rapid procedure close enough to the patient to let treatment begin with little waiting. We have mentioned before \textsuperscript{1} that efforts to produce a rapid, specific and sensitive non-molecular POC
test for *C. trachomatis* failed, largely due to inadequate sensitivity. Furthermore, the notion by some that a test with a sensitivity less than desired, but allowing rapid treatment, is preferable to a slower NAAT of greater sensitivity belongs firmly to a bygone era. The view that POC tests should increasingly form the diagnostic approach of the future, has gained greater credibility due to the development of rapid NAATs. Modelling suggests that the introduction of such technology in sexual health clinics, including targeted multiplex testing, could be cost effective, and clinical evidence to support this is beginning to emerge. 43-45

Thus, the GenXpert CT/NG molecular test when used on asymptomatic patients attending a rapid testing service (Dean Street Express) provided results, compared with those for patients attending an existing sexual health clinic, that were faster and enabled faster treatment, fewer partner transmissions and reduced clinic costs due to fewer partner attendances. The same molecular test has also been used successfully when conducted routinely as a POC test by clinicians in remote primary healthcare settings. Looking to the future, these POC tests will also be able to detect antimicrobial resistance, enabling diagnosis and individualised treatment at the first health care visit, potentially reducing selection pressure on recommended antimicrobials, reducing transmission of resistant strains and providing a means of surveying resistance. Thus, the introduction of POC testing seems admirable if clinicians are fully aware of the complexities of treatment and can provide it quickly, knowing that it is based on an accurate microbiological diagnosis.

**Multiplex test dilemma**

Outside the NHS, there is increased testing by the public. They are vulnerable to multiplex assays being relatively cheap and to a commercial imperative to do as much testing as possible but, doubtless, bewildered by assays for as many as 12 different microorganisms/conditions. Some companies recommend testing for asymptomatic infections and most suggest treatment for all subjects with positive results. The notion that the public,
without considerable help, can choose the correct tests and receive appropriate treatment is beyond imagination. Several commercial multiplex NAATs, which include detection for gonococcal and chlamydial infections, are available and CE marked. However, it is a concern that there is very limited comparative information in peer reviewed journals for most promoted assays regarding their performance in detecting these infections. Further comments about multiplex tests for Ureaplasma spp., G.vaginalis and other microbes are made later.

**Home on-line screening and treatment**

*Diagnostic and treatment services of apparent merit*

In view of the previous comments, it may seem ironic to say that better involvement of the public in their own care should be a laudable approach to tackling the increasing existence of STDs; home-based tests should empower the individual. Furthermore, it cannot be denied that the increased use of on-line services in the UK and elsewhere. should theoretically help to ease the tension in understaffed and underfunded NHS GUM clinics. In the last dozen years, particularly in the last five to six, there has been a variety of on-line providers that have supported screening and treatment services above and beyond those provided by attending NHS clinics. Success is attributable to the in-put of both physician and laboratory staff and to pin-pointing micro-organisms regarded as the most important. Thus, N.gonorrhoeae and C.trachomatis detection using NAATs has almost always been a feature and, usually, serology to diagnose syphilis and HIV infection. It is imperative that as the provision of on-line testing continues to expand, only appropriate testing and treatment are recommended and that there is a move away from promoting testing for micro-organisms for which there is no evidence that testing does more good than harm, so increasing the risk of antimicrobial resistance. Commercial on-line testing may also compromise an understanding of the true prevalence of infection by public health authorities, unless they are mandated to
contribute anonymised data to the national STI and HIV statistics produced by Public Health England.

New diagnostic NAATs will include POC tests which will enable assessment of antimicrobial resistance, and multiplex options too. The most recent example is that for *M. genitalium* with macrolide resistance testing, the use of which has been shown to prevent the emergence of antimicrobial resistance in this mycoplasma. However, funding for such tests is a major concern, given the decrease in funding for sexual health services (vide infra).

**Screening and treatment services with apparent flaws**

Tests for the micro-organisms detailed above are accessible ‘on-line’ from innumerable commercial web-sites. These can be offered as both screening and diagnostic tests. This easy access to molecular testing for the public has resulted in a gap between the commercial and NHS diagnostic testing pathways. The public who initiate testing on-line should be aware that poorly performing, insensitive, POC tests for *C. trachomatis*, seen repeatedly for close on a decade, still exist. These “CE approved” tests, including that for gonorrhoea, are most often lateral flow immunoassays providing a result within 10-15 minutes. This implies an inferior sensitivity to molecular tests. Promotional material suggests that the accuracy of some tests is >98%, although what limited external validation against a NAAT there is indicates a performance substantially below that stated in the package insert. Such tests can be purchased on-line in the United Kingdom and internationally and are cheaper than the home-based NAATs (see above). The current commercial multiplex assays where specimens are sent to a laboratory for testing may be relatively cheap, but the wide range of different micro-organisms (up to 12) represented in the ‘one size fits all’ test profiles may attract the biggest market, rather than have the best clinical application. The public should be advised that testing is only worthwhile for *N. gonorrhoeae* and *C. trachomatis*, and in women possibly *T. vaginalis*, which has been reported to cause infection only rarely in the UK, although
associated with black minority ethnicity and deprivation in some parts.\textsuperscript{61} \textit{M. genitalium} is also worth testing for \textsuperscript{62}, but only if the patient is symptomatic or their current partner is infected. Screening of asymptomatic men cannot be recommended in the absence of randomized controlled trials demonstrating cost effectiveness. \textsuperscript{63} The need for controlled trials before screening for \textit{M. genitalium} can be advised is also seen, for example, in women with reproductive problems.\textsuperscript{64} This note of caution contrasts with the notion that there is little or no need to test for the presence of some other micro-organisms. Thus, \textit{M. hominis} has never been shown to cause urethritis or other significant disease in men and its recovery from the vagina, cervix or urine is very difficult to relate to any problem in the upper genital tract.\textsuperscript{65} While a strong association with BV is undoubted, it has never been shown to be a cause in itself. Also, a positive test for \textit{Ureaplasma} spp. in asymptomatic men and women does not deserve attention. However, testing for \textit{U.urealyticum} may be appropriate in men with symptoms and signs of urethritis \textsuperscript{66} although only if indisputable pathogens have been excluded and the organism load is large, as this species is probably only causal in 20-60\% when it is associated with a high load.\textsuperscript{28,67} In women, as is the case for \textit{M. hominis}, detection of either \textit{Ureaplasma} spp. in the vagina, cervix or urine has never been related significantly to a problem in the upper genital tract, or to the painful bladder syndrome, the urethral syndrome or infertility.\textsuperscript{68} A positive role for ureaplasmas in chronic lung disease of extremely low birth-weight infants has some support, \textsuperscript{68,69} but evidence for their involvement in preterm delivery is less convincing \textsuperscript{68} despite a report \textsuperscript{70} of a more promising association based on aggressive antibiotic therapy. Nevertheless, in both lung disease and premature delivery nothing has been published to justify routine antibiotic therapy to prevent mother to baby transmission. Whether large, rather than small, numbers of these organisms might be associated with any of the diseases mentioned is a logical but insufficiently tested notion. Hence, until there are definitive answers, there is no logic in screening or testing
asymptomatic or symptomatic men and women for *M.hominis, U.urealyticum* or *U.parvum*, unless, of course, ureaplasmas are being sought as part of a research investigation. Indeed, the expert view \(^{28}\) is that it is unquestionably inappropriate to treat just because these organisms have been detected in the lower genital tract. Nevertheless, there are commercial services currently recommending treatment with doxycycline, azithromycin and both sequentially when these micro-organisms are detected in single assays or as part of a multiplex array. Thus, the virtue of having these tests available on-line must be questioned, particularly as it is known that antibiotics may dramatically change the gut and oral microbiomes \(^{71}\) and doubtless the genital-tract microbiome too. So far as *G.vaginalis* is concerned, there seems little point in having it alone in a multiplex array for diagnosing BV when other bacteria, mentioned above, are more strongly associated with BV. A molecular test \(^{72}\) that takes into account various bacteria encountered in BV would seem to have more merit. Of course, tests on vaginal smears for their cellular composition \(^{73,74}\) is a laboratory undertaking without patient involvement at home.

The issues considered are important because a positive PCR test may fuel fears of infection and infectivity among the public and health professionals alike. This is particularly so if reference is made to sexually transmitted infection / disease \(^{75}\) and when positivity may not mean that the micro-organism in question is responsible for the symptoms and, therefore, may not imply treatment. Antibiotics may offer false assuagement of resultant patient distress. Not understanding what antibiotic is required \(^{76}\) or failing to take heed of management guidelines for non-gonococcal urethritis, \(^{77,78}\) *N.gonorrhoeae* \(^{79}\) or *M.genitalium*, \(^{80}\) and/or a lack of understanding that *M.hominis, U.urealyticum* and *U.parvum* can be difficult to eradicate, may have an untoward outcome, namely over-prescribing or providing a wrong antibiotic when the need for effective antibiotic stewardship is an international priority. The extensive treatment for the latter microbes, mainly commensals,
with suboptimal antimicrobial regimens selects for resistance not only in them, but also in
*N.gonorrhoeae* and *M.genitalium*. Thus, although a novel electronic messaging treatment
service for *C.trachomatis* at a community pharmacy with the use of azithromycin 1g ⁸¹ might
seem attractive, it has to be weighed against fostering macrolide-resistance in *M.genitalium.*
Indeed, the spectre of high-grade resistance by gonococci to macrolides ⁸² and most recently
to both azithromycin and ceftriaxone ⁸³ and *M.genitalium* to macrolides and other
antibiotics ⁸⁴-⁹² is with us. In the case of the latter micro-organism, pristinomycin may be the
only antibiotic effective for some patients.⁹³ It is not surprising to learn that syndromic
management may fail ⁹⁴ and empiric treatment needs to be reconsidered ⁹⁵, ⁹⁶ as a result of
antimicrobial resistance. ⁹⁷ Furthermore, increasingly led by non-specialists, commercial
services may sometimes not involve a GUM specialist until repeated courses of antibiotics
lead to iatrogenic harm, including antibiotic-associated candidiasis. This must not be allowed
to continue. A micro-organism already antibiotic resistant or that has developed resistance
during treatment may not be catered for adequately. Although it is theoretically possible that
prolonged sub-inhibitory concentrations of azithromycin intra- and extra-cellularly after
treatment of a gonococcal infection leads to resistance, evidence that previous exposure leads
to resistance by this means is conflicting.⁹⁸, ⁹⁹ This is in contrast to *M.genitalium*, the
resistance of which, as noted, is influenced in this way.

**What should be done?**

It is imperative that inappropriate and unnecessary testing for sexually transmitted micro-
organisms by commercial on-line companies needs to be regulated to ensure that there is a
move away from promoting increased antimicrobial resistance. Achieving this can be helped
by educating the public, particularly those with self-diagnosis and treatment in mind, as to
what is right and wrong by information provided simply, both on-line and in clinics, and by
maintaining GUM commissioning with a remit to lead and disseminate NICE-accredited
guidance for both the commercial and NHS sectors. The crucial nature of this is emphasized by the fact that on the 13th July 2018 the British Association of Sexual Health and HIV (BASHH) launched new NICE-accredited treatment guidelines for *M. genitalium* in an attempt to prevent it becoming a ‘superbug’ within 10 years. At the same time, however, seven in ten sexual health experts said they could not afford diagnostic tests recommended by the guidelines and only one in ten UK public health commissioners said they were making provisions for testing equipment in their 2019 budget.

**Conclusions**

First, for those who intend that diagnosis should start at home, the aim should be procurement of appropriate specimens that are sent under guided instruction to laboratories equipped with rapid and highly sensitive tests, followed by physician-guided treatment. In some areas in the UK and elsewhere an on-line approach to diagnosis and treatment has been developed to good effect and these ventures should be seen as role models for others in the field. The use of very rapid NAATs must be a virtue, but speed associated with such a POC test may be less important than having a knowledgeable and thoughtful approach to treatment based on the correct laboratory result; the latter should be aided by adherence to the appropriate BASHH guideline.

Second, it might appear that the issues are being discussed without positive action being taken. However, it would be churlish to believe this when one of us (PH) attended a Parliamentary Roundtable meeting on Sexual Health and AMR (3rd April 2019). Nevertheless, further thought should be given to how expert clinical leadership can be improved with a view to regulatory change. There should be a multi-agency approach involving key stakeholders with the remit to guard against the use of insensitive and inappropriate tests and help to maintain further improvements in the diagnostic scene. Thus, it would be laudable to discourage testing for *M. hominis, G. vaginalis*, and *Ureaplasma* spp., when positive results have little or no meaning, unless the person is male and has urethritis and quantitative testing
for *U. urealyticum* is available. Third, it would seem appropriate to develop NHS-accredited information leaflets for providers and the public on the use of molecular tests, the significance of results and the most appropriate treatment. Certainly, on-line self-diagnosis has improved, but pitfalls mentioned here should not go unchecked. There is still an opportunity to further harness molecular diagnostics towards best patient care, good medical practice, improved research and avoidance of further antibiotic resistance. Fourthly, with increasing antibiotic resistance of *N. gonorrhoeae* and *M. genitalium* in mind, efforts should be made to encourage the development and testing of vaccines.\textsuperscript{102, 103} Prevention is better than cure.

**Acknowledgement:** This work was supported by the NIHR Health Protection Research Unit in Evaluation of Interventions at the University of Bristol. PH is a Co-Director of Sexual Health Improvement Programme (SHIP), Bristol Health Partners. The views expressed are those of the authors.

**References**


the multiplex detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in female urine and endocervical swab specimens. *J Clin Microbiol* 2003; 41: 304-309.


gonorrhoea in genitourinary medicine clinics in the UK. BMJ Open 2014; 4 (7).


national guideline for the management of infection with *Mycoplasma genitalium* (2018).


40. Van der Pol B, Williams JA, Fuller D, et al. Combined testing for Chlamydia, Gonorrhea,


64. Wiesenfeld HC, Manhart LE. *Mycoplasma genitalium* in women: current knowledge and research priorities for this recently emerged pathogen. *J Infect Dis* 2017; 216(Suppl 2): 389-395.


74. Ison CA, Hay PE. Validation of a simplified grading of Gram stained vaginal smears for


84. Horner PJ. Azithromycin antimicrobial resistance and *Chlamydia trachomatis* infection: duration of therapy may be the key to improving efficacy. *Sex Transm Infect* 2012; 88: 154-156.

85. Tagg KA, Jeoffreys NJ, Couldwell DL, et al. Fluoroquinolone and macrolide resistance-


94. Maduna LD, Lauman JGE, Radebe O, et al. Failure of syndromic management due to


