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Foreword

The Action Plan has been developed by the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) team at the Health Protection Agency (HPA). The HPA is an independent UK organisation set up by the government in 2003 to protect the public from threats to their health from infectious diseases and environmental hazards. In April 2013, the HPA will become part of a new organisation called Public Health England, an executive agency of the Department of Health.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AMR</td>
<td>Antimicrobial resistant</td>
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<tr>
<td>BASHH</td>
<td>British Association of Sexual Health and HIV</td>
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<td>BSAC</td>
<td>British Society of Antimicrobial Chemotherapy</td>
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<tr>
<td>CLSI</td>
<td>Clinical and Laboratory Standards Institute</td>
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<tr>
<td>EDCD</td>
<td>European Centre for Disease Prevention and Control</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<td>EU</td>
<td>European Union</td>
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<td>EUCAST</td>
<td>European Committee of Antimicrobial Susceptibility Testing</td>
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<td>GRASP</td>
<td>Gonococcal Resistance to Antimicrobials Surveillance Programme</td>
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<td>GUM</td>
<td>Genitourinary medicine</td>
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<td>HPA</td>
<td>Health Protection Agency</td>
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<td>MDR</td>
<td>Multidrug resistant</td>
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<td>MIC</td>
<td>Minimum inhibitory concentration</td>
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<td>MSM</td>
<td>Men who have sex with men</td>
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<td>NAAT</td>
<td>Nucleic Acid Amplification Test</td>
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<td>PHE</td>
<td>Public Health England</td>
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<tr>
<td>STBRU</td>
<td>Sexually Transmitted Bacterial Reference Unit</td>
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<tr>
<td>ST</td>
<td>Sequence type</td>
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<td>STI</td>
<td>Sexually transmitted infection</td>
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<td>TOC</td>
<td>Test of cure</td>
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<td>WHO</td>
<td>World Health Organization</td>
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KEY POINTS

Antimicrobial-Resistant Gonorrhoea: Background

- Public health control of gonorrhoea is dependent of the provision of effective antimicrobial therapy and has been compromised by resistance to successive therapeutic agents over decades.
- Surveillance data has shown a drift towards decreased susceptibility to the third generation cephalosporins currently recommended for therapy — ceftriaxone and cefixime.
- Therapeutic failure to ceftriaxone and cefixime is still rare but is documented.
- The WHO Global Action Plan and ECDC Response Plan have been published to provide strategic advice on the threat of MDR gonorrhoea.
- National guidelines have been published in response to this threat and TOC is recommended.

GRASP Action Plan for England and Wales

- Confirmed and probable treatment failure case definitions have been recommended to inform patient management.
- Maintaining resources for isolation of *Neisseria gonorrhoeae* is essential both to inform patient management and to detect emerging resistance.
- Determination of the MIC is necessary to define decreased susceptibility or resistance to ceftriaxone and cefixime.
- Disc testing can be used for screening for potential decreased susceptibility but the MIC should be confirmed using an Etest® or its equivalent.
- Any isolates exhibiting decreased susceptibility to cefixime or ceftriaxone should be referred to the STBRU at the HPA for confirmation.
- Treatment failures should be reported to the HPA.
- Decreased susceptibility to the cephalosporins requires continued research and development to inform public health interventions.
- Communication of the global problem of AMR gonorrhoea to all healthcare professionals and at-risk groups is essential.
- Gonorrhoea prevention activity should continue to be included within HPA (PHE) funded national sexual health promotion programmes.
- Measurable outcomes from this action plan should be audited on an annual basis.
INTRODUCTION

This Action Plan for England and Wales has been developed by the GRASP team at the HPA. The purpose of the GRASP Action Plan is to raise awareness of the national and global problem of AMR gonorrhoea and to provide advice to appropriate healthcare professionals to limit its spread and extend the useful life of current treatments. This document is intended to inform microbiologists, GUM physicians, GPs and any healthcare professionals working in sexual health.

OBJECTIVES

The objective of the GRASP Action Plan is to advise on a national response to retain gonorrhoea as a treatable infection in England and Wales by:

- Provision of robust and timely surveillance data on AMR gonorrhoea in England and Wales.
- Advising on appropriate changes to the national guidelines for the management of gonorrhoea.
- Giving technical advice to clinical microbiologists on appropriate methods for detection of decreased susceptibility or resistant gonococcal isolates in the laboratory.
- Providing support to allow rapid detection of treatment failures to cefixime, ceftriaxone and azithromycin.
- Communication to relevant healthcare professionals and at-risk groups to raise awareness of the threat of untreatable gonorrhoea.
- Promote prevention messages to enhance public health control of gonorrhoea.
BACKGROUND

Gonorrhoea is the second most common bacterial sexually transmitted infection in England and the UK, with 21,000 and 23,183 cases in 2011, respectively, and is often treated empirically to prevent further transmission of infection before the results of laboratory testing are available. Antimicrobial therapy is essential to the public health control of gonorrhoea, in the absence of any protective immune response, but has been compromised over decades by emergence of resistance to successive antimicrobial agents used [1].

In the UK, choice of therapy is recommended by the BASHH national guidelines, which are informed by data from GRASP for England and Wales. The WHO recommends that any first-line therapy should achieve cure in at least 95% of patients [2]. Consequently, when data from GRASP showed ciprofloxacin-resistant gonorrhoea had risen above 5% in 2002, this informed a change in patient management guidelines regarding the third generation cephalosporins, cefixime and ceftriaxone [3].

Therapeutic failure to these highly effective cephalosporins was not reported at the time of their introduction as first-line therapy but concern that the likelihood that resistance would emerge in *N. gonorrhoeae* was high, as this had occurred to previous therapies, particularly penicillins. Cefixime 400mgs, the oral agent, was used most commonly because of its ease of administration and for patient compliance, although ceftriaxone 250mg was recommended for pharyngeal infection and hence has often been used for gonorrhoea in MSM. Azithromycin or doxycycline were recommended for the treatment of concomitant chlamydial infection unless patients were known not to have chlamydial infection.

In 2010, GRASP data showed that there was a consistent drift in decreased susceptibility to cefixime, and that the burden of infection caused by these isolates was among MSM. There were insufficient supporting data to indicate how this related to the outcome of therapy in patients. At the same time, occasional reports of treatment failure began to be reported in the UK, Europe and Japan [4-10].

In 2011, the GRASP steering group recommended that first-line therapy should be changed before the 5% resistance level was reached for cefixime, in order to delay the accumulation of treatment failure and extend the useful life of the cephalosporins. In June 2011, the BASHH guidelines were changed to ceftriaxone at the increased dose of 500mgs in combination with azithromycin 1gram as first-line therapy. Cefixime was retained as second-line therapy for patients refusing the intramuscular injection [11], although GRASP data shows low uptake of this option.

The threat of MDR gonorrhoea is of global concern, and WHO has published a Global Action Plan to raise awareness and inform policy makers and healthcare scientists alike of the problem (Figure 1) [12]. In a similar manner, the ECDC issued a Response Plan, primarily focused on European Union issues (Figure 2) [13]. While both of these plans share a common goal they address the problem at different levels. The aim of the GRASP Action Plan is to learn from these documents and to tailor a national plan for England and Wales to our local situation to contribute to the global response.
Figure 1: Objective of the WHO Global Action Plan [12]

The objective of the WHO Global Action Plan is to control the spread and minimise the impact of AMR in *N. gonorrhoeae* through:

- Articulating the public health policy and economic case for urgent, heightened and sustained action to prevent and control *N. gonorrhoeae* infection and mitigate the emergence of and impact of AMR
- Providing a strategic framework to guide clinical, laboratory and public health actions aimed at minimising the impact of AMR to cephalosporins in *N. gonorrhoeae*
- Providing recommendations for coordinating communication, partnership and advocacy efforts at national, regional and international levels, to support the global response

Figure 2: Specific objectives of the ECDC Response Plan [13]

- Strengthening the surveillance of gonococcal antimicrobial susceptibility in the EU/EEA Member States to inform national treatment guidelines
- Ensuring that a minimum capacity for culture and susceptibility testing in EU/EEA Member States is either available or developed
- Establishing a strategy to rapidly detect patients diagnosed with gonorrhoea who experience a clinical treatment failure despite treatment with the recommended cephalosporins, including the clinical management of affected patients and their sexual partners
- Outlining a set of recommended public health actions to be implemented at the national level, following the detection of MDR in *N. gonorrhoeae*
- Increasing the awareness of policy makers, clinicians, patients and key populations
SURVEILLANCE DATA

In England and Wales surveillance of AMR gonorrhoea is provided through GRASP, which was piloted in 2000 and has been continuous since 2001. The GRASP network of 26 GUM clinics and 24 laboratories is part of the GUM network (GUMNet), which consists of 29 GUM clinics that participate in sentinel surveillance for STIs. GRASP is a sentinel study that collect isolates from consecutive patients with gonorrhoea over a three-month period, July to September, each year. Reports from each year can be found on the HPA website.

PATIENT MANAGEMENT

Clinicians should follow the current BASHH guidelines when treating gonorrhoea: ceftriaxone at the increased dose of 500mgs in combination with azithromycin 1gram as first-line therapy. The procedure for patient follow-up after treatment with the recommended therapeutic regimen is also outlined in national treatment guidelines, and it is essential to confirm resolution of symptoms, to exclude the possibility of re-infection and to pursue partner notification [11].

While TOC is now recommended in all cases, the guidelines recognise that this approach is resource intensive and recommend criteria for clinics applying TOC selectively [11]. However, it should be appreciated that patient follow-up and TOC are central to identifying potential cases of treatment failure, and failure to apply these universally introduces the risk that some treatment failures may be missed. For cases of treatment failure, effective contact tracing, treatment and TOC for all identified partners are key priorities.

Evidence for the appropriate time for TOC is weak and needs further research but current guidelines recommend:

• For persistent symptoms or signs: testing using culture should be performed at least 72 hours after therapy
• If asymptomatic: NAAT taken two weeks after completion of therapy, followed by culture if NAAT is positive.

It should be remembered that azithromycin has a long half-life and hence TOC should be a minimum of 10 days for culture and three weeks for NAATs after treatment with ceftriaxone and azithromycin.
TREATMENT FAILURES

It is important that treatment failures are confirmed, not just as part of good patient management, but also to inform the relationship between treatment given, laboratory data and response to therapy. The ECDC Response Plan has recommended a working definition of a confirmed treatment failure and a probable treatment failure:

Working case definition for treatment failure: clinical and laboratory criteria

**Confirmed** treatment failure includes rows 1 through to 4.

**Probable** treatment failure includes rows 1 through to 3.

<table>
<thead>
<tr>
<th></th>
<th>Confirmed</th>
<th>Probable</th>
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<tr>
<td>1</td>
<td>A gonorrhoea patient who returns for TOC or who has persistent genital symptoms after having received treatment for laboratory-confirmed gonorrhoea with a recommended cephalosporin regimen (ceftriaxone or cefixime in appropriate dose) AND</td>
<td></td>
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<tr>
<td>2</td>
<td>Remains positive for one of the following tests for <em>N. gonorrhoeae</em>: Presence of intracellular Gram-negative diplococci on microscopy taken at least 72 hours after completion of treatment; OR Isolation of <em>N. gonorrhoeae</em> by culture taken at least 72 hours after completion of treatment; OR Positive NAAT taken two-to-three weeks after completion of treatment AND</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Denies sexual contact during the post-treatment follow-up period AND</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Decreased susceptibility to cephalosporin used for treatment*: Cefixime: MIC&gt;0.12 mg/L** Ceftriaxone: MIC&gt;0.12 mg/L**</td>
<td></td>
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</tbody>
</table>

* Ideally, the pre- and post-treatment isolates should be examined with an appropriate and highly discriminatory molecular epidemiological typing method to establish if isolates are indistinguishable.

** These thresholds are in accordance with EUCAST tentative breakpoints. Reporting of probable treatment failures where MICs are lower than the EUCAST breakpoints will be essential to evaluate if current breakpoints are clinically relevant.
LABORATORY ISSUES

Maintenance of culture

As recommended in national treatment and testing guidelines, it is essential that all primary diagnostic laboratories continue to maintain skills in isolation and culture of *N. gonorrhoeae* from clinical samples, in spite of the increased use of highly sensitive gonorrhoea NAATs. In the absence of reliable molecular tests for detection of AMR, culture remains the only means of determining antimicrobial susceptibility, which is likely to play an increasingly important role in patient management if reports of treatment failures continue to emerge. BASHH guidelines recommend that a culture should be taken in all cases of gonorrhoea diagnosed by NAATs prior to antibiotics being given to provide an isolate for susceptibility testing and identification of resistant strains [11].

Antimicrobial susceptibility testing

Monitoring of susceptibility to therapeutic antimicrobial agents is necessary for individual patient management and in order to identify treatment failures. This remains a challenge because resistance resulting in treatment failure has only been reported intermittently and the true relationship between dosage given, laboratory data and treatment failures is largely unknown.

Tentative MIC breakpoints have been recommended to define decreased susceptibility to cefixime and ceftriaxone but these vary, including >0.125mg/L as recommended by EUCAST and BSAC, and >0.25mg/L as recommended by the CLSI. Recent reports of treatment failures have been associated with isolates that exhibit MICs to cefixime and ceftriaxone of these MICs or above. Definition of azithromycin resistance also does not have a strong evidence base and is often recommended at ≥1mg/l.

Determination of susceptibility to the third generation cephalosporins has also proven to be technically demanding, with frequent discrepancies between laboratories in achieving comparable results. Hence this document aims to give guidance to support all laboratories wishing to monitor susceptibility.

The method of choice for determination of the MIC in diagnostic labs is use of Etest® (bioMerieux) (or their equivalent); agar dilution methods are only appropriate for reference centres undertaking surveillance programmes. The procedure for performing an Etest® is described by the manufacturer and in order to obtain reproducible and comparable results it is essential that this is followed, including use of the specific medium recommended. Each batch of Etest® strips should be quality-controlled using isolates exhibiting both susceptibility and decreased susceptibility. There is a lack of data on the comparison of Etest® with strips from alternative suppliers and, therefore, it is essential that the control strains are used for validation. There is a range of WHO control strains available for this purpose, which can be purchased from the National Collection of Type Cultures (NCTC): NCTC13477 to 83.

In busy diagnostic laboratories disc testing is often preferred and two approaches have been used, either: use of discs of earlier cephalosporins as indicators of possible decreased susceptibility/resistance or; use of third generation cephalosporins, particularly cefixime or ceftriaxone discs for direct detection.

The evidence base for both these approaches is not robust. Recent data from STBRU shows that the use of cefuroxime disc (5μg) on GC agar base containing 1% isoVitalex to test an inoculum equivalent to a MacFarland’s standard of 0.5 gives good correlation between reduced zone size and cefixime MIC. Discs of other cephalosporins, such as cefixime (5μg ), ceftriaxone(5μg) and cefpodoxime (10μg), also show a trend between reduced zone size and decreased susceptibility to cefixime, but this approach is less reliable as the zone size does not reduce significantly to give a clear relationship.
Any isolate exhibiting a reduced zone should be confirmed by cefixime and ceftriaxone Etest®. While erythromycin discs are used in many laboratories to detect macrolide resistance, only azithromycin (15μg) discs distinguish between low/moderate resistance (1-8mg/L) and high-level resistance to azithromycin (>256mg/L) [14].

The range of antimicrobials used for susceptibility testing varies in different diagnostic laboratories but should include the recommended first-line therapies: ceftriaxone, cefixime, azithromycin and spectinomycin. Inclusion of ciprofloxacin is useful as resistance remains high but can be considered in patients with hypersensitivity to the cephalosporins.

It is important that isolates exhibiting decreased susceptibility are confirmed and this is offered as a reference service by the STBRU at the HPA. It is paramount that isolates from treatment failures are referred both for confirmation and to build an evidence base for the laboratory definition of resistance.

**Figure 3: Recommendations for testing**

- Determination of MIC by Etest® or equivalent using manufacturers’ instructions is the recommended method of choice
- Any isolate exhibiting a MIC of >0.125mg/L to cefixime or ceftriaxone should be considered as potentially resistant and TOC recommended
- Screening of gonococcal isolates can be achieved using cefuroxime discs (5μg) and azithromycin discs (15μg), but decreased susceptibility/resistance must be confirmed using Etest®
- Isolates exhibiting decreased susceptibility to cefixime or ceftriaxone should be referred to STBRU at the HPA for confirmation
- Any gonococcal isolate suspected of showing decreased susceptibility or from a treatment failure should be archived at the primary laboratory in addition to referral to STBRU

**REPORTING OF POTENTIAL TREATMENT FAILURES**

Rapid communication of treatment failures will be fundamental to increasing understanding of emerging resistance to the cephalosporins. In May 2011, an online reporting tool was launched by the HPA, available to all GUM clinicians through the GUMCAD portal.

A recent review has shown that 14 cases were reported in the first year. Some issues were identified, particularly the inability to link the clinical information to the microbiological data and to the lack of archived isolates for further study. Subsequent improvements have been made and include provision of contact information for the laboratory. Monthly alerts will be issued to all GUM clinics and reports can be made at the HIV and STI web portal: For clinics in the UK but outside England, this form can be accessed from the GRASP website and sent by email to grasp.enquiries@hpa.org.uk.

Only authorised users are permitted to access this secure website – all GUM clinics have been issued with usernames and passwords. These can be obtained from: www.gumcad@hpa.org.uk.

Communication between the GUM clinician and the microbiologist will be a key factor and discussion regarding potentially important isolates should be encouraged.
COMMUNICATIONS

Regular communications will be made to key audiences, including:

- Members of GUMNet (inclusive of the GRASP network) through email notification and the annual GRASP collaborators meeting
- GUM clinicians through the BASHH newsletter and website and at appropriate scientific meetings
- Microbiologists through the HPA-managed network and appropriate scientific societies, such as BSAC
- Other healthcare professionals through STBRU newsletter and scientific publications
- Factsheets at GUM clinics and other appropriate venues to reach at-risk patient populations.

GONORRHOEA TRANSMISSION PREVENTION

Reducing the burden of gonorrhoea should subsequently lessen the chance of AMR transmission. Therefore, the 25% rise in new gonorrhoea diagnoses seen in England in 2011 is concerning. Latest data also show some populations continue to be at significantly increased risk of gonorrhoea, such as MSM, black African and black Caribbean communities. This section sets out considerations to reduce transmission and undiagnosed infections, to affect the spread of AMR gonorrhoea.

A sustained clinical public health response based on early detection, successful treatment and partner notification is imperative to tackling ongoing transmission. The BASHH standards for the management of gonorrhoea (www.bashh.org/guidelines) should be followed, in particular, the need for multi-site sampling (urethral, rectal and pharyngeal) for both symptomatic and asymptomatic MSM. National recommendations on partner notification should be followed with all patients identified with gonococcal infection, preferably delivered by a trained health adviser in GU medicine. Sexual partners should be offered testing and treated epidemiologically for gonorrhoea.

From April 2013, local authorities will be responsible for providing comprehensive, open access sexual health services. The prioritisation and provision of appropriate services will be shaped by local Joint Strategic Needs Assessments, guided by the Public Health Outcome Framework. Local epidemiological STI data, available from the HPA Sexual Health Profiles, should be employed to make the case for the prioritisation of gonorrhoea prevention and control, either as a stand-alone campaign or in synergy with other HIV and STI prevention interventions in populations most at risk.

Alongside the clinical response, promoting safer sexual and health-care seeking behaviour among individuals is also vital. Gonorrhoea is transmitted through unprotected vaginal, oral or anal intercourse or genital contact with an infected sexual partner. As such, safer sex programmes promoting condom use and regular STI testing remain crucial. Every effort should be made to eliminate barriers to testing, available free and confidentially at services such as STI clinics.

Prevention messages should continue to be promoted to all sexually active men and women to reduce their risk of getting and transmitting gonorrhoea. These messages include:

- Always using a condom, correctly and consistently, when having sex with new and casual sexual partners until all partners have had a sexual health screen.
Avoiding overlapping sexual relationships and reducing the number of sexual partners.

Prevention programmes engaging specific groups at higher risk of STI infection should also continue, with a focus on gonorrhoea. Clinicians should take every opportunity to offer testing to MSM and black African and Caribbean groups:

- MSM should have an HIV and STI screen at least annually, and every three months if having unprotected sex with new or casual partners.
- Black Africans and black Caribbeans should have regular HIV/STI screening if having unprotected sex with new or casual partners.

RESEARCH AND DEVELOPMENT PRIORITIES

Research and development should aim primarily to focus on areas that will improve understanding of development and dissemination of decreased susceptibility/resistance. This in turn could facilitate development of targeted intervention strategies to improve individual patient management and control spread of resistance.

Key areas to prioritise include:

- Molecular epidemiological surveillance of a representative sample of the whole gonococcal population to explore associations between antimicrobial susceptibility and type. The current method of choice for this is *N. gonorrhoeae* Multi Antigen Sequence Typing (NG-MAST). This approach will also allow investigation of the dissemination of strains exhibiting decreased susceptibility/resistance to therapeutic agents
- Characterisation of a representative sample of the whole gonococcal population by next generation sequencing to identify markers of antimicrobial resistance and susceptibility
- Characterisation of the mechanisms of any new emerging strains exhibiting decreased susceptibility/resistance (as identified by a novel ST or a higher MIC in an existing ST)
- Greater discrimination within large clonal groups, for example by next generation sequencing, to improve understanding of their dissemination
- Determining fitness of different STs exhibiting decreased susceptibility/resistance to examine relationship between fitness and incidence of ST
- Development of a buffer that could support gonococcal viability for culture and be used for downstream gonorrhoea NAAT testing
GRASP ACTION PLAN FOR ENGLAND AND WALES: MEASURABLE OUTCOMES

GRASP team:

• To review treatment failures reported through the GUMCAD portal, and their compliance with the GRASP Action Plan case definitions, on a quarterly basis and prepare an annual report for dissemination to all GUM clinics.

• To collate quarterly the number of isolates referred to the STBRU from diagnostic laboratories for confirmation of decreased cefixime and/or ceftriaxone and/or azithromycin resistance, with publication of an annual report.

• To monitor the number of isolates referred to GRASP from sentinel sites each year.

• To monitor the number of patients in the annual GRASP data that received the recommended antimicrobial treatment.

HPA (PHE) STI department:

• To document publications and communications to healthcare professionals regarding AMR gonorrhoea.

• To ensure and monitor the inclusion of gonorrhoea prevention activity within PHE-funded national sexual health promotion programmes.
REFERENCES

1. Lewis DA. The gonococcus fights back – is this time a knock out? Sex Transm Infect. 2010; 86:415-421.


