Global action plan

to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*

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Abbreviations

AMR	antimicrobial resistance
Ceph-R	cephalosporin resistant
DALY	disability-adjusted life year
GASP	WHO Gonococcal Antimicrobial Surveillance Programme
IUSTI	International Union against Sexually Transmitted Infections
MIC	minimum inhibitory concentration
MSM	men who have sex with men
N. gonorrhoeae	*Neisseria gonorrhoeae*
NGO	nongovernmental organization
PEPFAR	President's Emergency Program for AIDS Relief
STI	sexually transmitted infection
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

1. Introduction

> “ The emergence and spread of drug-resistant pathogens has accelerated. The trends are clear and ominous. No action today means no cure tomorrow. At a time of multiple calamities in the world, we cannot allow the loss of essential medicines – essential cures for many millions of people – to become the next global crisis. ”
>
> Statement of WHO Director-General, Margaret Chan on World Health Day 2011

Gonorrhoea is a major public health challenge today, due to the high incidence of infections accompanied by a dwindling of treatment options. The objective of this global action plan is to control the spread and minimize the impact of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae (N. gonorrhoeae)*. This document is targeted at a number of stakeholders including national- and international-level policy-makers, programme managers, health-care providers, laboratory technicians, multilateral organizations, researchers and donors. The document aims to give guidance on ways to contain the spread of AMR in *N. gonorrhoeae* and it is designed to be implemented in conjunction with broader national and international strategies for the prevention and control of sexually transmitted infections (STIs).

Gonoccocal infections can be prevented through safer sexual intercourse. These infections represent 106 million of the estimated 498 million new cases of curable STIs that occur globally every year. The emergence, in *N. gonorrhoeae*, of decreased susceptibility and resistance to the “last-line” cephalosporins, together with the longstanding high prevalence of resistance to penicillins, sulfonamides, tetracyclines and, more recently, quinolones and macrolides (including azithromycin), is cause for concern. Gonorrhoea has the potential to become untreatable in the current reality of limited treatment options, particularly in settings that also have a high burden of gonococcal infections. The loss of effective and readily available treatment options will lead to significant increases in morbidity and mortality, as the future could resemble the pre-antibiotic era when there was a risk of death from common infections such as a streptococcal throat infection or from a child’s scratched knee.

1.1 Vision

The vision informing this global action plan is to enhance the global response to the prevention, diagnosis and control of *N. gonorrhoeae* infection, and mitigate the health impact of AMR, through enhanced, sustained, evidence-based and collaborative multisectoral action.

1.2 Objective

The objective of this global action plan is to control the spread and minimize 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 and impact of AMR
- providing a strategic framework to guide clinical, laboratory and public health actions aimed at minimizing 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.

1.3 Summary of strategies

To make a sustained difference in the continuing problem of multidrug-resistant *N. gonorrhoeae* infection, two overlapping goals must be met: broad-based control of drug resistance and public health control of gonorrhoea. Both should be approached in the wider contexts of global control of AMR. For gonococcal infections, the public health approach must build upon lessons learnt, and put the following into action:

- advocacy for increased awareness on correct use of antibiotics among health-care providers and the consumer, particularly in key populations including men who have sex with men (MSM) and sex workers
- effective prevention, diagnosis and control of gonococcal infections, using prevention messages, and prevention interventions, and recommended adequate diagnosis and appropriate treatment regimens
- systematic monitoring of treatment failures by developing a standard case definition of treatment failure, and protocols for verification, reporting and management of treatment failure
- effective drug regulations and prescription policies
- strengthened AMR surveillance, especially in countries with a high burden of gonococcal infections, other STIs and HIV
- capacity building to establish regional networks of laboratories to perform gonococcal culture, with good-quality control mechanisms
- research into newer molecular methods for monitoring and detecting AMR
- research into, and identification of, alternative effective treatment regimens for gonococcal infections.

1.4 Role of stakeholders

Successful implementation of the plan to prevent the emergence and spread of drug-resistant gonococci requires an urgent, concerted and sustained effort involving multidisciplinary groups at global, regional and national levels.

At the national level, there needs to be adequate funding, leadership and cooperation among various disciplines working in the area of AMR, particularly with respect to *N. gonorrhoeae*. Support for the plan will require the concerted participation of individuals, organizations and governments. Although there are regional differences in the levels of resistance in *N. gonorrhoeae* and the populations affected, there needs to be a standardized approach to the problem, in terms of surveillance, diagnostic methods and reporting, while recognizing that each country will need to evaluate the scale of its own problem and apply the plan according to the prevailing circumstances.

Most STI-control and -prevention interventions will also benefit the containment of gonococcal AMR. Thus, the plan identifies stakeholders not only as laboratory technicians and clinicians providing care for patients with STIs, but also as policy-

Table 1
Role of stakeholders in preventing the emergence of drug-resistant gonococcal infections

	Policy	Norms	Surveillance	Containment and implementation	Capacity building (clinicians and laboratory technicians)	Communication and education strategy for general public and key populations	Advocacy and political engagement	Drug regulation	Drug rational prescription	Early warning system	Resource mobilization	Research
World Health Organization (WHO)	x	x			x	x	x			x	x	x
Donor agencies	x				x	x	x				x	x
Ministries of health and STI programme managers	x	x	x	x	x	x	x	x		x	x	x
National public health laboratoriess			x			x				x		x
Private sector and NGOs			x	x	x	x			x	x		x
Clinicians			x			x			x	x		x
WHO Gonococcal Antimicrobial Surveillance Programme (GASP) networks			x		x	x	x			x	x	x
Researchers					x					x		x

makers, programme managers and end-users in the community, including the private sector and nongovernmental organizations (NGOs).

At the global level, support is needed from the various international agencies that support countries to fund national plans. For example, support from the Global Fund to fight AIDS, Tuberculosis and Malaria, the President's Emergency Program for AIDS Relief (PEPFAR) as well as other bilateral donors will be critical to ensure the successful implementation of this plan. Given the health implications for reproductive, maternal and child health of untreated gonococcal infections, support from global initiatives such as the United Nations (UN) Strategy for Maternal and Child Health will also be relevant and important. The various roles of key stakeholders, though not exhaustive, are shown in Table 1.

1.5 Key populations

Susceptibility differs widely among populations and, in particular, among people with behaviours that put them at higher or more frequent risk of infections (Table 2). For instance, there is a general lack of STI surveillance among sex workers and MSM, which may signify serious underreporting of data. Additionally, follow-up of sex workers or MSM may be impractical, and treatment of sexual partners an even more difficult task to implement. Strategies for follow-up and treatment of sexual partners will need careful planning and additional human and financial resources.

Appropriate treatment options need to be made available to persons who are allergic to the recommended first-line treatment, and to pregnant women who will need non-teratogenic medication. Although there are no specific recommendations for people living with HIV and who are immunosuppressed, research is needed to understand the interaction of AMR development in *N. gonorrhoeae* and immunosuppression.

1.6 Advocacy and resource mobilization

The WHO World Health Day in 2011 highlighted the global threat of AMR. This recognition provided a strong advocacy message to the world that concrete action by international and national partners, as well as investments for the future, are needed in order to tackle this problem.

The factors that favour the emergence and spread of resistant microbes, and the measures needed to combat AMR are well known, but all the relevant stakeholders must recognize the urgency of the threat that is currently affecting every region worldwide. Sustained advocacy efforts at national and international levels are required, in addition to a realistic assessment of costs to meet needs. There are numerous potential savings from reducing AMR, which need to be highlighted in efforts for resource mobilization.

The spread of resistant *N. gonorrhoeae* is not going to go away and will continue to affect increasing numbers of communities. The rise in rates of resistance to a particular antibiotic may occur over prolonged periods, even in the absence of antibiotic use or misuse (i.e. unrelated to the treatment of gonorrhoea with a particular antimicrobial agent). This phenomenon has been observed in many of the WHO regions, where a high proportion of strains tested continue to exhibit high-level plasmid-mediated resistance to tetracyclines, penicillin and quinolones and their use in treating gonorrhoea has long since been discontinued. Thus,

Table 2
Considerations for key populations

Key populations	Characteristics of population subgroup
Key population at higher risk of STIs – a subgroup of people *experiencing* high rates of exposure to STIs (unprotected sexual intercourse, sexual intercourse with multiple partners); for example: • sex workers • MSM • people who inject drugs	High rates of STIs compared to the general population; high rates of risk behaviour; poorer access to health-care facilities. Resistant strains may appear sooner than in the general population and may require specific treatment modification. Where possible, among MSM, samples should also be obtained from extragenital sites as well as the urethra.
Clients of sex workers STI clinic attendees (usually males) Other subgroups according to the local evidence: • military • police • mobile populations (e.g. transport workers, fishermen)	High rates of STIs compared with the general population; high rates of risk behaviour (sexual contact with key populations); for some subgroups, poorer access to health-care facilities (e.g. mobile populations).
Women	In general, gonococcal isolates for study from women are lacking because of difficulty in collection, poorer positive yield and higher cost than collecting isolates from men. Where possible, samples should also be obtained from women, including from extragenital sites. As women predominantly obtain treatment in gynaecological and related services, opportunities should be taken to test and treat for STIs in these settings. • *Pregnant women*: in pregnant women, suitable treatment alternatives for cephalosporin-resistant strains need to be made available.
Young people	Usually user-friendly services for STIs for young people are lacking. It may, thus, be difficult to set up good surveillance systems for this young population.

it is critical for effective implementation of this action plan that national- and international-level policy-makers and donors support the monitoring of use of antibiotics and resistance trends over time, in order to combat AMR and its public health consequences. This action plan outlines mechanisms to provide adequate health care to patients with persistent gonococcal infections, to strengthen collaborative linkages among regional and international partners for better surveillance of AMR and treatment failures, and to optimize the outbreak response when needed.

1.7 Guiding principles in the implementation of the global action plan

The global action plan is designed to be implemented in conjunction with broader national strategies for STI prevention and control, which will reduce the overall disease burden and minimize the negative impact of multidrug-resistant *N. gonorrhoeae.*

The global action plan will be guided by some of the identified microbiological and non-biological determinants of the emergence and spread of AMR. These determinants include the genetic mutations within the organism, unrestricted access to antimicrobial drugs in some settings, inappropriate selection and overuse of antimicrobial agents, and suboptimal quality of some antimicrobial agents on the market. Furthermore, extragenital – anorectal and especially pharyngeal – infections, particularly affecting key populations such as MSM and sex workers, may also play an important role in the development of resistant strains, as *N. gonorrhoeae* interact and exchange genetic material with other coinfections in these anatomical sites.

Preventing the rapid emergence of drug-resistant gonococci requires a concerted and sustained effort involving multidisciplinary groups. Although new drug classes or synergistic combinations of different antibiotics may be identified for the treatment of multidrug-resistant gonococci, it is critical to prepare for the emergence of untreatable *N. gonorrhoeae* strains in the current reality of limited treatment options, particularly in settings where people cannot afford to use high-quality antibiotics.

This global action plan outlines calls for, and should be implemented within the context of, enhanced STI surveillance to facilitate early detection of the emergence of resistant strains, combined with a public health response to mitigate the impact of cephalosporin-resistant (Ceph-R) *N. gonorrhoeae* on sexual and reproductive health morbidity. Due to the limited current evidence on how and when the Ceph-R gonococcal strains will emerge in significant numbers in different regional and national contexts, the effectiveness of this action plan should be closely monitored and periodically reviewed and revised, based on updated scientific knowledge and data.

2. Background to a global crisis

AMR can kill; it causes longer duration of illness and treatment, often in hospitals; and it increases health-care costs and the financial burden to families and societies. AMR risks taking the world back to a pre-antibiotic era where even minor infections can cause serious morbidity and mortality. AMR occurs when microorganisms such as bacteria, viruses, fungi and parasites develop changes in their genetic coding in ways that make the antibiotic used to cure infection with the microorgansim ineffective. When a particular microorganism becomes resistant to most antimicrobials, it is often referred to as a "superbug". AMR is a global menace that affects not only *N. gonorrhoeae* but also many other important, and sometimes life-threatening, pathogens, including those causing malaria, tuberculosis and hospital-acquired infections such as the multidrug-resistant *Staphylococcus aureus*.

Treatment is one of the key elements in the control of gonococcal infections; control requires the most appropriate and effective treatment for all infected individuals and their sexual partners, and should cure a minimum of 95% of the population infected in any particular setting (*1*).

The prevention and control of gonorrhoea is an important public health intervention because of the magnitude of the problem and related effects, including the following (*2*, *3*):

- the magnitude of new gonococcal infections occurring globally each year is estimated to be 106 million
- the high cost for individuals especially when calculated as disability-adjusted life years (DALYs)
- dwindling treatment options, including the current and last-remaining internationally recommended first-line treatment options – the extended-spectrum cephalosporins
- the long-term sequelae of untreated gonococcal infections, which include persistent urethritis, cervicitis, proctitis and disseminated infections that could lead to pelvic inflammatory disease, infertility, first-trimester abortion, ectopic pregnancy and maternal death. Health consequences to neonates include severe infections that may lead to blindness. In addition, gonococcal urethritis, like many other STIs, significantly increases the risk of acquiring and transmitting HIV infection.

A major cause for concern is that decreasing susceptibility to the "last-line" third-generation cephalosporins is beginning to manifest as clinical treatment failures, particularly with the oral preparation, cefixime. Reports of clinical treatment failures with cefixime have been verified and reported from countries as diverse as Japan (*4*), Norway (*5*) and the United Kingdom of Great Britain and Northern Ireland (*6*). In 2011, the first detected case of high-level resistance to injectable ceftriaxone, which also led to clinical treatment failure, was published (*7*).

N. gonorrhoeae has shown a remarkable ability to acquire novel chromosomal and plasmid-mediated AMR mechanisms over the past 70 years since the advent of antibiotics (*3*). Within 10 years of the introduction of sulfonamides, *N. gonorrhoeae* had become sufficiently resistant to this class of antimicrobials that its use was no longer recommended. Penicillin, which was reserved for sulfonamide-resistant gonococcal infections, became the drug of choice for gonococcal urethritis in 1943, and remained so until the mid-1970s (after the decreasing susceptibility had been repeatedly overcome by increasing the penicillin dose). Tetracyclines rapidly met the same fate as penicillins. Fluoroquinolones, such as ciprofloxacin, became the drug of choice for treating gonococcal infections from the mid-1980s, but the first treatment failures were already being reported by the early 1990s. Resistance to fluoroquinolones is currently so widespread globally that this class of antimicrobials can no longer be recommended as the first-choice treatment for gonococcal infections. Macrolides (including azithromycin) seemed to be the answer, but only for a brief period, because resistance was shown to be rapidly selected. Thus, only the third-generation cephalosporins remain an effective treatment for this multidrug-resistant pathogen (*3*, *8*).

A critical issue with regard to AMR in *N. gonorrhoeae* is that it can occur within and across antibiotic classes, providing this bacterium with the remarkable ability to acquire and retain genetic and phenotypic resistance to several classes of antibiotics at the same time, even when their use has been discontinued. Three important features of the bacterium are at the origin of this resistance:

- the ability of the gonococcal genome to undergo continual mutation and internal recombination, resulting in rapidly evolving gonococcal populations
- acquisition by gonococci of all or part of external resistance or virulence genes from other *Neisseria* species

- the highly transformable nature of the bacterium, which can frequently release DNA and also efficiently incorporate exogenous DNA acquired from other *Neisseria* species and closely related bacteria.

The development of a pool of resistance genes and the ability of the gonococci to maintain these determinants of resistance within their genetic coding is part of the very nature of *N. gonorrhoeae*. Thus, the spread of resistant *N. gonorrhoeae* and increases in rates of resistance to a particular antibiotic may occur over prolonged periods, even in the absence of antibiotic use or misuse (in relation to treatment of gonorrhoea). This phenomenon has been observed in many of the WHO regions, where a high proportion of strains tested continue to exhibit high-level plasmid-mediated resistance to tetracyclines, penicillin and quinolones, despite the fact that their use in treating gonorrhoea has long been discontinued.

The other additional cause for concern is that, in many countries, the diagnosis of gonococcal infections has moved from culture of the pathogen to modern-day, molecular assays using non-invasive specimens such as urine and vaginal swabs. These new technologies cannot, at this stage, be used to determine AMR in *N. gonorrhoeae*, which has created difficulties in identifying the magnitude of AMR in this organism in many parts of the world. Although these diagnostic advances have increased screening and treatment opportunities, they have also resulted in a reduction in routine clinical AMR testing, fewer available gonococcal isolates on which to perform antimicrobial susceptibility testing, and a loss of skills to perform culture by many laboratory technicians and other health-care providers who once had the skills. As isolation and antimicrobial susceptibility testing of *N. gonorrhoeae* is the only reliable method to detect AMR at present, it is necessary to revive the older techniques and skills of culturing the organism in order to rapidly identify AMR.

There is also the concern that most reports of AMR and treatment failures with cefixime and ceftriaxone are coming from countries with good health-care infrastructure and testing and treatment facilities for STIs. This may mean that the extent of the problem, including treatment failures with cephalosporins, is underestimated, as most resource-constrained countries, particularly those with a high burden of STIs, are not performing antimicrobial susceptibility testing in their own settings and surveillance for treatment failures is inadequate. Furthermore, awareness, globally, of potential treatment failures with cephalosporins is low among clinicians and other health-care providers.

Gonorrhoea is among the most frequent of the estimated one million new STIs occurring daily for which no new therapeutic drugs are in development. If gonococcal infections become untreatable with the existing medications, the health implications related to mortality and morbidity of children, women and men are significant. It is, therefore, imperative that the chronically underfunded STI services should be strengthened in order to better detect and respond to emerging AMR. Better linkages with broader health outcomes, particularly with reproductive, maternal and child health and HIV-control interventions, would also ensure that countries can move towards attaining their national goals and targets.

3. Strategies for containing antimicrobial resistance

In order to preserve the effectiveness of cephalosporins, which remain the sole treatment option for gonococcal infections, proper use and close monitoring of the efficacy of these drugs are needed.

The proposed strategies are built upon existing guidance, including:

- Joint United Nations Programme on HIV/AIDS (UNAIDS)/WHO: *Sexually transmitted diseases: policies and principles for prevention and care* (*9*), which outlines the policies and principles for the prevention and care of STIs, to offer guidance to ministry of health officials who have the responsibility of developing and implementing interventions for the control of STIs
- WHO: *Global strategy for the prevention and control of sexually transmitted infections: 2006–2015* (*10*), which outlined methods to promote healthy sexual behaviours, and to upgrade the monitoring and evaluation of STI-control programmes
- WHO: *Policy package to combat antimicrobial resistance* – World Health Day 2011 pack on AMR (*11*), which outlines why AMR is a global concern
- *WHO global strategy for containment of antimicrobial resistance* (*12*), which provides a framework of interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms
- WHO: *Emergence of multidrug-resistant* Neisseria gonorrhoeae – *threat of global rise in untreatable sexually transmitted infections* (*13*), a fact sheet outlining the extensive and urgent problem of AMR in gonococcal infections
- WHO: *Strategies and laboratory methods for strengthening surveillance of sexually transmitted infections* (*14*), which contains relevant appendices and annexes for gonococcal surveillance methods.

3.1 Improving early detection of infection

Early detection and prompt treatment of *N. gonorrhoeae* and other STIs, ideally at the point of the patient's first contact with the health system, is an essential requirement for the public health control of STIs. However, in most developing countries the facilities to make an appropriate laboratory diagnosis at the primary health-care level are not available. Even when laboratory facilities are available, the delays inherent in the reporting of laboratory results hinder timely treatment. In addition, patients presenting with gonococcal infections are more often seen in primary health-care facilities in the public and private sectors rather than in special STI clinics where laboratory services may be available. In all cases, however, the WHO syndromic approach for the management of urethral discharge, which is based on the prevailing causes of the syndrome as well as the antimicrobial susceptibilities of the causative organisms, is recommended as a means to provide immediate treatment (*15*, *16*). AMR epidemiology should, ideally, be obtained from studies carried out locally. If such information is not available, then studies should be carried out, or information should be sought from neighbouring countries, until local studies and established AMR surveillance confirm the status.

3.2 Appropriate and effective treatments for patients and their sexual partners

Single-dose therapy is the recommended treatment for gonococcal infections, to ensure compliance. Treatment of sexual partners is recommended in order to prevent reinfection, and the patient can sometimes be called upon to deliver the prescription to their sexual partner. Following treatment, and in the absence of any recurrent symptoms, no test-of-cure[1] is necessary. However, if existing treatment options fail, clear guidance on alternative options or mechanisms for referral to higher level of expertise is needed. Furthermore, verification and reporting of verified treatment failures are crucial. It is also imperative that all information regarding AMR and treatment failures is used to inform and update the national and international treatment guidelines on a regular basis. Finally, due to the high rates of gonococcal and chlamydial coinfections, patients treated for gonorrhoea may also be treated for chlamydial infection at the same time. In the instance of single-dose cephalosporin treatment for gonorrhoea, patients would also receive concomitant treatment for chlamydial infection, e.g. azithromycin or doxycycline (*17*).

Drugs for STI treatment play a central role in care and STI control. Important considerations when selecting drugs include:

- high efficacy (at least a 95% cure rate)
- low cost (a price that puts little financial burden on individuals, families and the government)
- acceptable toxicity
- microbial resistance that is unlikely to develop or can be delayed
- single dosage (to increase treatment compliance)
- oral administration
- safety for use in women during pregnancy and lactation.

3.3 Good compliance

Inadequate knowledge of health-care providers leads to improper prescription and dispensing practices. In order to promote education of the health-care provider and the client on good compliance to recommended treatment regimen for antimicrobial medicines, it is important to train prescribers and dispensers on how to educate their clients on the correct use of antibiotics and the importance of following the prescribed treatment.

3.4 Educating the client

A person who presents with an STI at a health-care facility needs clear information for preventing reinfection, and counselling on the risks of infection, ways of

1. Test-of-cure is the reculturing or isolation and identification of the pathogen, e.g. *N. gonorrhoeae*, from a site of initial infection to determine whether the patient has been cured following treatment. It should be realized that, in the case of STIs, post-treatment infections result from reinfection caused by failure of sexual partners to receive treatment, or a new infection due to initiation of sexual activity with a new infected partner. Therefore, a careful history and a candid discussion with the patient are essential in order to interpret a test-of-cure procedure.

preventing becoming infected, treatment compliance and notification and treatment of sexual partners.

Health-care-seeking behaviour can be greatly improved through educating the general public about STIs, their complications and the importance of appropriate care. Individuals are more likely to seek appropriate health care if they:

- are able to assess their own risk
- know the effects of untreated STIs on themselves and their seuxal partners and family members
- acknowledge that a change in behaviour will have benefits
- know that their actions will be supported by social norms
- know that high-quality confidential services exist.

3.5 Strengthening surveillance

In order to notify and investigate drug-resistant *N. gonorrhoeae* in a timely manner, strengthened surveillance programmes are needed. STI surveillance, including gonococcal antimicrobial susceptibility surveillance, conducted in a systematic and regular manner, would enable the early detection of resistant microorganisms and monitor their spread among people and geographic areas. This would enable drug-resistant infections to be verified and notified early and allow correct decisions to be taken about treatment of individual patients, as well as informing national and international treatment guidelines. AMR surveillance relies on laboratories that can accurately identify resistant pathogens. Where laboratories exist, methods for AMR testing for STIs are often lacking. Furthermore, there is variation in the methods used for AMR testing. This makes it difficult to compare data between laboratories and between countries. Thus, there is a need to consolidate AMR surveillance, using appropriate epidemiological methods and applying standardized protocols (3, *18*). Quality-assurance systems, including monitoring and supervision of laboratories, are important, as well as continuing education and capacity building for laboratory personnel. Surveillance data must be analysed and reported promptly on a regular basis, and the data used to inform national medicines policy and updating of standard treatment guidelines.

3.6 Laboratory capacity strengthening

Establishing a network of laboratories at national, regional and international levels will support the implementation of AMR surveillance. Actions required to overcome operational difficulties for clinicians, laboratory technicians and local health departments in relation to detection of probable Ceph-R *N. gonorrhoeae* cases include the following:

- building awareness of clinicians about emerging Ceph-R *N. gonorrhoeae*, and the potential occurrence of cephalosporin treatment failures
- inculcating an ethos of verifying and reporting treatment failures
- strengthening health-care providers' skills in collection of clinical samples that are suitable for culture and AMR testing

- addressing logistic and economic constraints to obtaining laboratory supplies for collection and transport of culture specimens (for instance swabs, transport media and candle jars)
- training laboratory technicians and building capacity for performing culture and AMR testing
- increasing the availability of routine laboratory services for gonococcal culture and AMR testing in clinical laboratories
- establishment of a mandatory requirement for laboratory technicians to report AMR testing results to the local and national health authorities.

A mitigation plan could be developed to target symptomatic patients (especially male patients with gonococcal urethritis) seeking treatment at the clinics, to ensure the operational feasibility is a cost-neutral approach. All proposed activities in the plan, apart from the strengthening of gonococcal culture and laboratory capacity-strengthening activities, could be implemented using the existing clinic infrastructure and resources.

With respect to the significant proportion of asymptomatic infections with *N. gonorrhoeae* and the cost of routine tests-of-cure for uncomplicated gonococcal infections, early detection of Ceph-R *N. gonorrhoeae* may not be feasible in populations with high rates of asymptomatic gonococcal infections. Therefore, additional resources are required to expand mitigation activities to accomplish the early detection of Ceph-R *N. gonorrhoeae* in such populations.

3.7 Regulatory mechanisms

Governments must ensure uninterrupted access to the recommended effective treatments. Efficient systems for managing drug procurement and distribution should be put in place, and issues with drug quality need to be tackled through comprehensive drug regulations.

The rational use of antimicrobials is essential for containing AMR. The promotion of national standard treatment guidelines requires proper training and supervision of health-care providers. The lack of appropriate legislation and poor enforcement of the proper use of antimicrobials, such as selling antibiotics over the counter or turning a blind eye to self-medication practices, have resulted in an irrational use of antimicrobial medicines and may have contributed significantly to AMR in *N. gonorrhoeae.* Promotion and enforcement of evidence-based treatment guidelines, and enforcement of prescription-only use of antimicrobials through established pharmacies and outlets, are important actions needed at national levels.

3.8 Advocacy and communication

In order to implement AMR surveillance, there needs to be a mechanism to mobilize political commitment and funds. Communication strategies and messaging that reach target populations are also essential. A key barrier to the prevention, treatment and care of STIs is stigma and the perception of unworthiness attached to stigma, particularly for vulnerable populations such as people living with HIV and young people. In addition, stigmatization associated with STIs also prevents public discussion and community involvement around the issue of their prevention and care.

In order to contain the spread and impact of gonococcal infections and AMR, the following elements need to be advocated:

- strong leadership at all levels
- additional funding through the creation of line budgets for STI control within national strategic plans
- additional funding through donor mechanisms known to fund STI prevention and control such as the Global Fund to fight AIDS, Tuberculosis and Malaria
- creation of partnerships to increase the visibility, momentum and effectiveness of prevention and care efforts
- establishment of advocates and champions to highlight the harmful effects of STIs on individuals and communities.

Communication is needed to support policy with clear messages, through:

- sharing success stories through the media
- communicating prevention messages and raising awareness about the consequences of STIs
- building the capacity of media personnel to understand and communicate effectively about STIs.

4. Specific responses to cephalosporin-resistant *N. gonorrhoeae*

There have been a number of documented treatment failures with oral cephalosporins worldwide, and a highly ceftriaxone-resistant strain of *N. gonorrhoeae* was recently reported from Japan (*7*). The responses to these outbreaks and subsequent follow-up and surveillance have not been sufficiently coherent. Although the strategies for containing AMR outlined above apply generally to cover early detection and management of cephalosporin resistance in *N. gonorrhoeae*, this action plan endeavours to outline more concrete steps to be taken at the clinic and national levels, from the moment a patient presents to the clinic with a persistent gonococcal infection suspected to be due to resistance to cephalosporins. In addition, it outlines the responses and actions needed at the regional and global levels.

4.1 Early detection of cephalosporin-resistant *N. gonorrhoeae* by clinicians and laboratory technicians

Cases of possible antibiotic treatment failure of gonorrhoea are of considerable importance and the verification of such an event requires close collaboration between clinical staff, laboratory staff and public health officials. Thus, two combined approaches of clinical observation and laboratory isolation and identification of the pathogens are required to detect the emergence of Ceph-R *N. gonorrhoeae*. The two approaches provide a reasonable standardization across different health-care settings, to enhance early detection and to initiate recommended public health responses. The specific responses include both a

patient-oriented and a public-health-oriented component, as described below and illustrated in the flowcharts (Figures 1 and 2).

Figure 1 addresses the management of patients with identifiable genital discharge that persists after appropriate treatment with a recommended cephalosporin drug and in whom reinfection has been excluded. In general, gonococcal isolates for antimicrobial susceptibility testing are taken from the urethra in men because sample collection in men is relatively simpler than in women and the chance of a positive yield is higher in men than in women. Thus, to collect sufficient samples on which to base decisions, fewer samples from men are required than would be needed if samples from women were used. However, where necessary and feasible, antimicrobial susceptibility testing should be carried out on cervical samples from women and samples from the rectum in both men and women who practise anal sex, especially if they are symptomatic. It may also be necessary in certain circumstances to test samples from extragenital sites, such as the pharynx (*14*).

Since persistent or recurrent genital discharge can also be due to concurrent infections, it is important to ensure that chlamydial infection has either been adequately treated already or it has been reliably excluded by appropriate laboratory tests. In addition, depending on the epidemiological importance of *Trichomonas vaginalis* and *Mycoplasma genitalium* in the aetiological causes of genital discharge within the particular setting, treatment for these infections should be given while processing investigations for cephalosporin resistance in *N. gonorrhoeae* (*17*).

The entry point for Figure 2 is either an asymptomatic person with a positive test-of-cure for *N. gonorrhoeae* following treatment with a recommended cephalosporin, or an asymptomatic sexual partner of an index person with cephalosporin-resistant *N. gonorrhoeae*.

Clinicians who diagnose *N. gonorrhoeae* infection in a patient with suspected cephalosporin treatment failure should either take samples for culture and susceptibility testing of relevant clinical specimens, or refer the patient for laboratory examination and testing. A patient who fulfils the clinical criteria for "cephalosporin treatment failure" (Figure 1 and Box 1), and whose gonococcal isolates implicated in the episode have shown an elevated minimum inhibitory concentration (MIC) to one or more recommended cephalosporins (Table 3), is defined as a probable case of Ceph-R *N. gonorrhoeae*. Irrespective of the associated clinical correlates (i.e. clinical presentations and treatment outcome), a case is also defined as probable Ceph-R *N. gonorrhoeae* when the gonococcal isolates obtained from the patient have shown an elevated MIC level (i.e. two MIC doubling dilutions higher than the cut-off point value used to indicate decreased susceptibility to cephalosporins).

The MIC break points for cephalosporins for AMR in *N. gonorrhoeae* have yet to be established. The MIC break-point values used in the case definitions are established by using inputs from expert microbiologists, based on laboratory observations.

Figure 1
Flowchart for the management of cephalosporin treatment failure for urogenital infections – symptomatic patients

(Adapted from the WHO *Guidelines for the management of sexually transmitted infections (17)*.)

NAAT = nucleic acid amplification test.

N.B. This flowchart assumes that the patient has received and taken effective therapy for gonorrhoea and chlamydia prior to this consultation OR chlamydial infection has been reliably excluded by appropriate laboratory tests

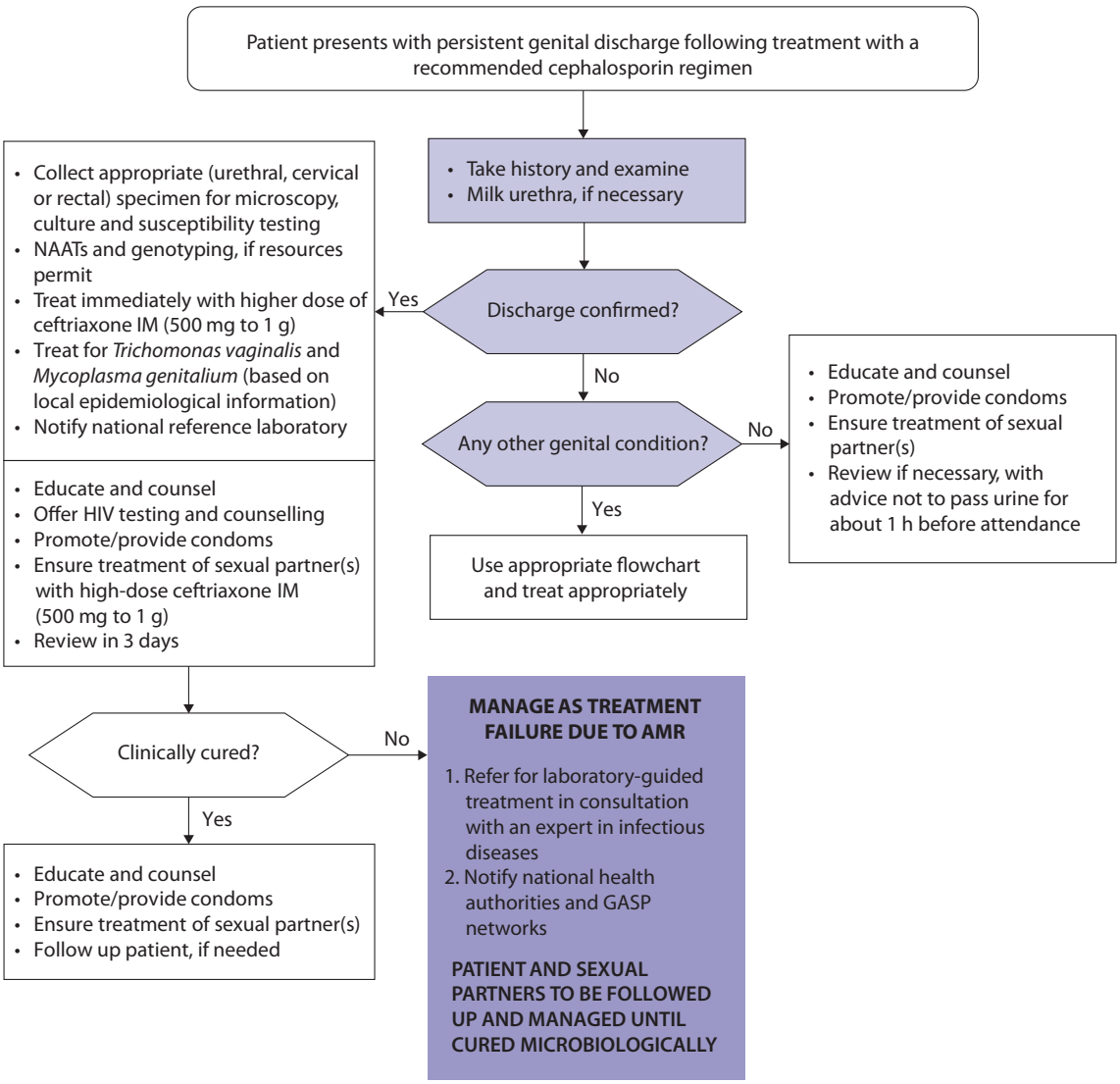
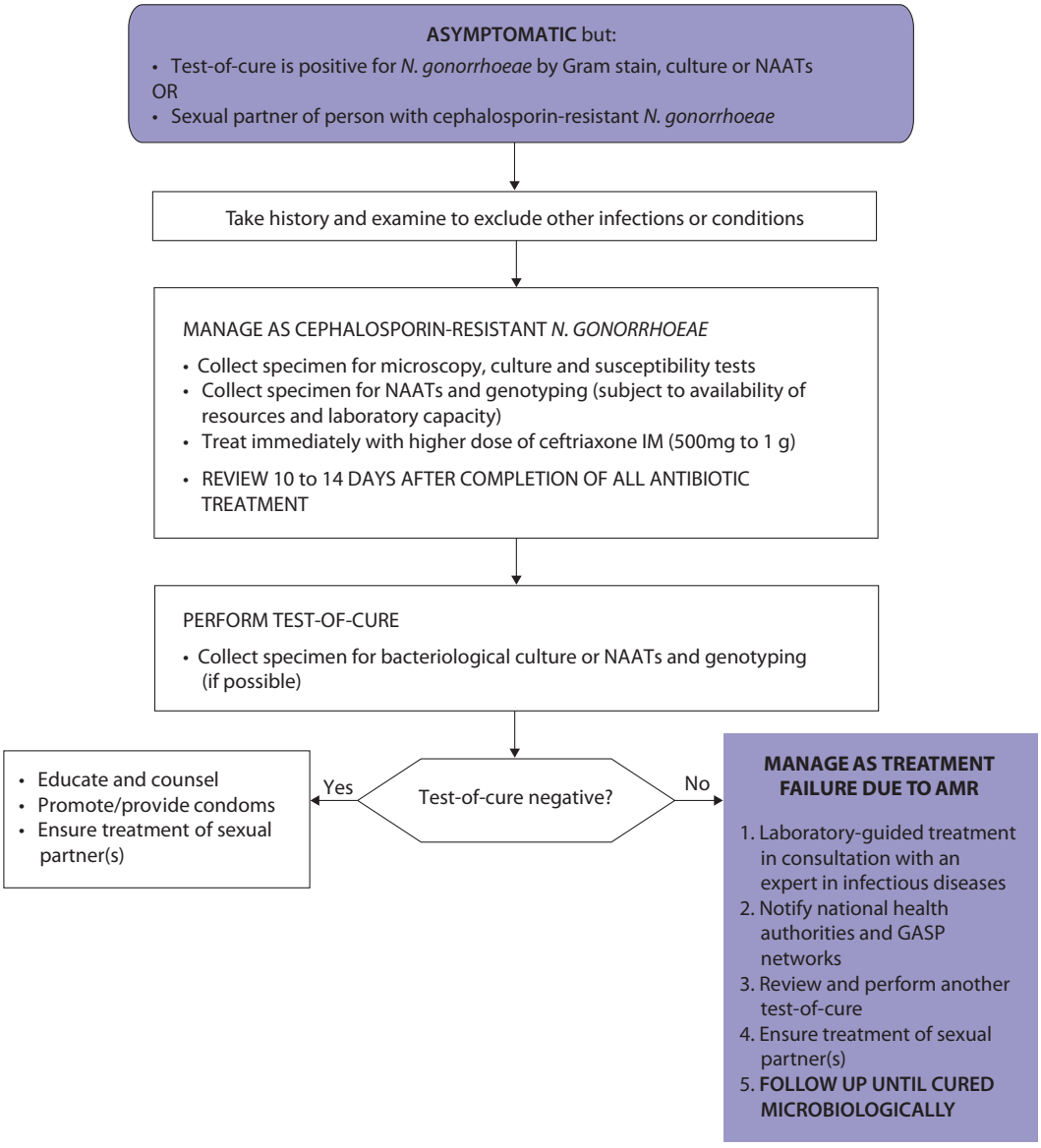


Figure 2
Flowchart for the management of cephalosporin treatment failure for urogenital infections – asymptomatic patients

NAAT = nucleic acid amplification test.



Note: if infection persists after the follow-up test-of-cure, treatment should be guided by antimicrobial susceptibility tests in collaboration with an expert in infectious diseases, and the laboratory results. In the absence of such information, the following combination therapy could be tried:

- 2 g azithromycin single oral dose + gentamicin 240 mg single IM dose OR
- 2 g azithromycin single oral dose + spectinomycin 2 g single IM dose OR
- either gentamicin 240 mg IM or spectinomycin 2 g IM.

Box 1
Case definition – *Neisseria gonorrhoeae* cephalosporin treatment failure

A person who has received appropriate treatment for gonococcal infection with one of the recommended cephalosporin regimens (for example, ceftriaxone or cefixime)

AND

One of the following positive tests for *N. gonorrhoeae*:

- the presence of intracellular Gram-negative cocci on microscopy taken at least 72 h after completion of treatment; or
- isolation of *N. gonorrhoeae* by culture taken at least 72 h after completion of treatment; or
- a positive nucleic acid amplification test (NAAT) taken 2–3 weeks after completion of treatment.

AND

No history of sexual contact reported during the post-treatment follow-up period.

Table 3
Criteria for decreased susceptibility to cephalosporins

Drug	MICs (mg/l)
Cefixime	≥0.25
Ceftriaxone	≥0.125

When a probable Ceph-R *N. gonorrhoeae* case is identified at a clinic, the clinician and local health authority should collect additional clinical and epidemiological information from the index patient and their sexual partners. At a minimum, the following information should be collected from the index patient:

- treatment taken and when
- anatomic site(s) of infection
- demographic and behavioural risk factors:
  - demographic characteristics
  - sexual orientation and practices
  - drug use
  - HIV status
- sources of infection

  - recent travel history of both the index patient and their sexual partner(s)
  - the place and type of sexual contact(s)
- risk of secondary transmission
  - the place(s) and number of recent sexual contacts.

The information should be collected by the local health department using a standard data-collection form. The local health department should also explore the introduction and validation of other novel interview methods such as the mobile phone and web-based interviews, particularly for sexual partners.

The laboratory assessments of probable Ceph-R *N. gonorrhoeae* cases should be performed on relevant clinical specimens (i.e. specimens collected from all possible sites of infection) using culture and susceptibility testing. As recommended in the STI-treatment guidelines for persistent or recurrent urethral discharge, the Ceph-R *N. gonorrhoeae* cases should be followed up and re-evaluated by culture for *N. gonorrhoeae*. Repeat susceptibility testing should be performed on any positive isolates.

Treatment failures for gonorrhoea have occurred with gonococci over a wide range of MIC values, including those classified as *decreased susceptibility* and *resistant*. Where treatment failure is confirmed as defined, the gonococcus should be considered resistant, irrespective of the MIC value.

Clinicians and laboratory technicians should report the probable Ceph-R *N. gonorrhoeae* cases to a centralized surveillance site. Further laboratory evaluation of the Ceph-R *N. gonorrhoeae* isolates should be performed at a gonococcal reference laboratory2. If strains of *N. gonorrhoeae* with unusually high MICs are confirmed by the reference laboratory, an alert should be raised at the regional and global levels.

It is important to maintain reserves of high-efficacy treatment options for patients with probable Ceph-R *N. gonorrhoeae*. Clinicians treating patients with suspected or confirmed treatment failure or persons infected with a strain found to demonstrate in vitro resistance, should conduct culture and susceptibility testing of relevant clinical specimens, or refer to a specialist centre and reference laboratory and re-treat the patients with higher doses of ceftriaxone, in the first instance. Doses of 500 mg to 1 g ceftriaxone, given intramuscularly, should be considered.

4.2 Action for programme managers and STI surveillance staff

All cases of treatment failure with the recommended first-line treatment regimen should be accurately recorded and reported to the district level as soon as possible. These reports will form part of the early warning system and should alert the authorities to the possibility of AMR in the community. A more systematic investigation should be initiated in collaboration with a national reference laboratory and/or the WHO regional or international network of the Gonococcal Antimicrobial Resistance Surveillance Programme (GASP).

2. Information on national, regional or global reference laboratories may be obtained by contacting the GASP network or WHO http://www.who.int/reproductivehealth/topics/rtis/en/index.html.

When cases of treatment failure occur with increased frequency or in large numbers (for example, five separate cases in a month), a more thorough determination of the magnitude of the problem is mandated. The response of the public health system then includes liaising with the laboratory to identify the proportion of isolates that show resistance.

For most AMR surveillance for *N. gonorrhoeae*, the prime objective is to determine the number of resistant gonococci as a proportion of all isolates tested. When the proportion of resistant strains obtained from the tested samples is at a level of 5% or more, or when any unexpected increase below 5% is observed in key populations with high rates of gonococcal infection (for instance in MSM or sex workers), steps should be taken to review and modify the national guidelines for STI treatment and management, while at the same time enhancing gonococcal surveillance.

The figure of 5% has a significant influence on sampling requirements, but it is often difficult to achieve a sample size that is sufficiently large for this purpose. Alternatively, the magnitude of the problem could be estimated by initially testing a smaller number of isolates. For example, only 100 to 200 isolates could be examined initially and if 3–10% of gonococci tested show resistance, surveillance should be boosted to obtain a requisite number of strains to guide the revision of STI-treatment guidelines.

When receiving repeated notifications of Ceph-R *N. gonorrhoeae* or reports of treatment failure from clinicians and/or laboratory technicians, the local health departments should initiate epidemiological assessments to measure the level of spread in affected locations. The proposed activities include the following:

- *review of clinical records* to identify additional cases of treatment failure with cephalosporins reported in the affected areas and determination of whether there are any possible sexual networks among the cases
- *epidemiological assessment* to identify potential demographic and sexual-behavioural risk factors of individuals when clusters of Ceph-R *N. gonorrhoeae* or confirmed treatment failure cases are identified
- *design and implementation* of the following clinic-based activities to enhance case detection:
  - targeted gonorrhoea screening and laboratory examination of samples
  - test-of-cure (using culture) for key populations at high risk of infection
- *enhanced laboratory capacity* to improve gonococcal culture and susceptibility testing
- *enhanced local surveillance* activities to monitor the appearance and magnitude of Ceph-R *N. gonorrhoeae* and confirmed treatment-failure cases in the affected areas. These activities include conducting ad hoc rapid assessment studies (e.g. local GASP) using different sample-collection approaches, such as:
  - prospective collection of gonococcal isolates
  - retrospective review of antimicrobial susceptibility test patterns of gonococcal isolates
  - laboratory evaluation of patients with repeat episodes of gonorrhoea within a short period

- *communication strategies* to increase awareness of local clinicians and laboratory technicians about the presence of Ceph-R *N. gonorrhoeae* cases and/or confirmed cases of treatment failure.

Health departments should prioritize notification of the sexual partners of patients with *N. gonorrhoeae* infection thought to be associated with cephalosporin treatment failure or partners of patients whose isolates demonstrate decreased susceptibility to cephalosporin. It is important to rapidly identify, screen and treat the sexual partners of patients with Ceph-R *N. gonorrhoeae* or confirmed treatment failure, and, ideally, to test any identified isolates for antimicrobial susceptibility.

4.3 Research gaps and needs

Antibiotic use is among the greatest achievements of modern medicine. However, bacteria naturally evolve, mutate and acquire resistance over time. Currently, the speed with which antibiotics are being lost far outpaces the development of replacement drugs.

Drug research and development is expensive and time consuming. The average cost of a new drug is estimated to be between 800 million and 1.7 billion US dollars. There are very few antibacterial drugs in development and 8 of the 15 major pharmaceutical companies that once had antibiotic discovery programmes have left the field, while a further two have reduced their efforts[3]. Despite the financial and often constraining scientific and regulatory processes in place, it is critical to continue research in AMR to understand, prevent and treat new infections.

The lack of publications in this field is affected by the lack of data being shared among research groups, as well as the fact that many scientific journals are reluctant to publish simple data on STI surveillance unless linked to populations of interest or the data are within randomized-controlled trials. Bodies such as the International Union against Sexually Transmitted Infections (IUSTI), WHO and GASP networks should explore channels of publishing short reports online in a timely manner, in order to facilitate information sharing, awareness and greater collaboration.

The research community has a critical role to play in understanding and controlling the threat of untreatable gonorrhoea. Additional initiatives are needed in the areas of laboratory, operational and therapeutic responses to existing and new regimens. Some research needs, though not intended to be comprehensive, are listed next.

Operational research

The following areas of operational research merit investigation:

- the efficacy of new antibiotics or other therapeutic compounds
- combination therapy – which may have synergistic effects in resistant strains
- antimicrobial choices for pregnant women
- treatment choices for gonococcal infections in neonates

3. Fauci T. Video address at the World Health Day 2011, WHO Geneva, April 7 2011.

- geographical patterns of resistance, and links to vulnerable populations, such as sex workers and MSM
- disaggregated data, particularly for key populations
- selection criteria for the use of antibiotics in relation to circumstances such as key populations, sexual orientation, national context, availability and epidemiological data
- microbiological effects (on *N. gonorrhoeae* as well as other affected bystander microorganisms) of combination therapies
- determination of the optimum regimen (antibiotic(s) and dosage) for treating Ceph-R *N. gonorrhoeae*.

Laboratory research

Laboratory research into the following should be conducted:

- identification of factors that contribute to the emergence and spread of AMR in *N. gonorrhoeae*
- newer molecular methods for monitoring and detecting AMR
- increasing culture capacity
- incorporation of new WHO reference strains
- laboratory methods to determine MICs and phenotypes for replicability and comparison
- correlation of genetic phenotypes to MIC and to clinical outcome.

Applied or field research

Applied research should be carried out to investigate:

- local use and misuse of antimicrobials
- how AMR affects infections in extragenital sites
- pharyngeal infections and the efficacy of treatments such as spectinomycin and kanamycin
- barriers to uptake of new guidelines

Research and development

The research and development in this area should include:

- creation and development of new diagnostic methods
- creation and development of new therapeutic options.

Mathematical modelling

Mathematical modelling should be used to:

- study the costing of aspects of AMR and control of the impact of AMR, in order to transfer the knowledge and capacities from one setting to another and better plan for scale-up

- analyse the cost effectiveness, feasibility and acceptability of interventions needed
- determine the impact and pace of spread of AMR and related activities in relation to health and economies
- examine pharmacokinetics and pharmacodynamics of antibiotics, for example, with use of Monte Carlo[4] simulations, especially in relation to treatment of pharyngeal infections (to optimize treatment regimens).

5. Advocacy and action by the World Health Organization, international partners and national stakeholders

Successful implementation of this action plan will require strengthened advocacy and donor support. This global action plan is, therefore, also designed as an advocacy tool to raise awareness of the importance of controlling gonorrhoea and other STIs, and highlight the support needed. The commitment of governments, and support from international donors and agencies, such as the Global Fund to fight AIDS, Tuberculosis and Malaria and PEPFAR, to combat AMR will be critical to ensure the successful implementation and impact of this plan. In addition, strengthened public–private partnerships with broader goals for STI control can act as a stepping stone, particularly for countries with high rates of STIs, including HIV, and of maternal and child mortality.

The emergence of different forms of AMR in *N. gonorrhoeae* is often followed by rapid spread of the disease, both nationally and internationally. Available data on gonococcal AMR and treatment failures with cephalosporins are predominantly from industrialized countries. It could be that these data represent only the tip of the global health burden, as surveillance data from resource-constrained settings are scarce, and a silent epidemic of AMR may be occurring.

5.1 The World Health Organization

Working with international and regional partners and stakeholders, through GASP, WHO will ensure successful implementation of an evidence-based response plan that includes the following elements:

- in collaboration with Member States, supporting countries to strengthen laboratory capacities to take adequate clinical samples, culture *N. gonorrhoeae* and perform AMR testing through retraining of health-care providers and laboratory technicians
- producing and disseminating standards for performing *N. gonorrhoeae* culture and AMR testing
- working with WHO collaborating centres and other international and national reference centres to maintain and distribute standardized and up-to-date WHO reference strains of *N. gonorrhoeae*, to ensure comparability and validity of AMR data

4. Monte Carlo simulation is a problem-solving technique that that uses multiple trial runs of random samples of parameters or inputs to estimate the probability of certain outcomes.

- facilitating an exchange of information, advice and technologies, including mapping of drug-resistance patterns, to highlight the situation
- maintaining a web-based system of posting treatment failures, including mapping and regularly updating the data on emerging resistant strains
- collaborating with partners to ensure that the issue of gonococcal AMR is highlighted within key initiatives such as the Global Health Initiative and the UN Secretary-General's Plan of Action for Women and Children, to stress the consequences of untreatable gonococcal infection for the sexual and reproductive health of women and men, newborn babies and the implications of AMR on people living with HIV, and underscore the need for research and production of new treatments
- ensuring that attention to AMR in *N. gonorrhoeae* and other STIs is maintained by strengthening collaboration with other key public health programmes, including programmes for reproductive health, maternal and child health and HIV
- collaboration with international partners and ministries of health to promote awareness of this important public health issue and mobilize additional human and financial resources for comprehensive mitigation activities and interventions.

5.2 National-level policy-makers

A comprehensive national plan for combating AMR requires leadership, advocacy and resources within the ministry of health, because stewardship and a coordinated response by the national authorities are key to the success of AMR-control programmes. National authorities should identify opportunities for funding STI surveillance, including gonococcal AMR surveillance.

In the case of AMR to gonococcal infections, strengthened collaboration between STI, HIV and reproductive health policies and programmes is essential. The ministries of finance and education must also recognize the need to contribute to the national efforts through sustained funding and sexuality education for young people. Involvement of networks of people living with HIV and other members of civil society, including representatives of key populations at high risk of infection, such as sex workers and MSM, in a meaningful partnership, will also accelerate progress towards controlling AMR in *N. gonorrhoeae*. In order to implement a coordinated response, the involvement and roles of each stakeholder should be identified and put into a framework of action, such as the one illustrated in Table 4.

At the national level, a number of structures need to be put in place to ensure a coordinated and sustained response. The following process, with local adaptation, can be followed to set up such a structure.

1. Establishment of an STI guideline working group, with involvement of relevant government ministries or units, including those that may not actually be responsible for the implementation of new guidance but nevertheless still have a stake in the process, such as:
    - professional bodies and associations (e.g. obstetrics and gynaecology professionals or associations of midwives)

- NGOs involved in delivery of reproductive health service (including family planning associations, safe motherhood programmes, youth organizations and other service-delivery or training NGOs, etc.)
- relevant private-sector representatives (private health-care provider representatives or organizations, social marketing organizations, pharmacists involved in service delivery, pharmaceutical companies, etc.)
- university institutions or experts involved in health service research, epidemiology, service delivery, or provider training
- country or regional WHO or other UN agencies
- reproductive health service delivery donors
- community groups
- clinical experts who will make use of these guidelines (e.g. primary health centre health-care providers, gynaecologists, family planning staff, maternal and neonatal health staff, reproductive tract infection/STI service providers)
- laboratory experts
- health economists or medicine-procurement experts
- pharmacologists
- representative end-users (both providers and patients/clients)
- experts with skills in group process or with guideline-development, writing and editing skills

It is important that stakeholders are involved from the early stage, as this will promote ownership and buy-in. Such a participatory and consultative process will increase the acceptability of the new practices or guidelines.

2. Development, publication and dissemination of a national mitigation plan.
3. Establishment and strengthening of monitoring and evaluation mechanisms based on a clear plan of what is to be achieved, how and by whom, and when, with a clear set of indicators.
4. Advocacy and resource mobilization for Ceph-R *N. gonorrhoeae* mitigation and general prevention and control of gonorrhoea and STIs.
5. Enhancement of local health-care providers' awareness of and participation in the mitigation activities.
6. Effective prevention and control of gonococcal infection, using appropriate treatment regimens.
7. Putting effective drug regulations in place.
8. Development and implementation of laboratory capacity strengthening to support mitigation activities, including regular AMR surveillance (laboratory assessment, training and support).
9. Development and implementation of health service capacity strengthening to support mitigation activities (laboratory diagnosis, treatment, partner outreach services).

10. Conduction of clinical, epidemiological and operational research projects to enhance the mitigation activities.
11. Implementation of the mitigation activities and periodic reviews and updates of the plan with lessons learnt.

5.3 International-level partners and donors

A broad-based approach that engages multiple partners and sectors should be adopted, because prevention and control of STIs can be achieved only by joining forces. It is therefore important to create strategic alliances and coalitions between the private and public sectors, multilateral and bilateral aid agencies, organizations in the UN system, the pharmaceutical industry, the media, professional and civil society organizations, and academic institutions, in order to present consistent, simple and accurate messages regarding the importance of antimicrobial use and AMR and its containment, and to implement strategies to contain the emergence of AMR.

Such partnerships between national and international stakeholders will increase the visibility and effectiveness of interventions. Monitoring and evaluation of the response to the emergence of cephalosporin resistance can be more broadly observed and acted upon in a timely manner. Participation of the various relevant stakeholders will have important outcomes; some of the most important outcomes are outlined next.

- The information derived from the surveillance of antimicrobial use and AMR, including the containment thereof, will be regarded as global public goods for health, to which all governments should contribute.
- Governments, NGOs, professional societies and international agencies will be encouraged to support the establishment of networks, with trained staff and adequate infrastructures, which can undertake epidemiologically valid surveillance of AMR and antimicrobial use, to provide information for the optimal containment of resistance.
- The establishment of international inspection teams qualified to conduct valid assessments of pharmaceutical manufacturing plants will be encouraged.
- An international approach to the control of counterfeit antimicrobials in line with the WHO guidelines will be supported.
- It will encourage innovative approaches to incentives for the development of new pharmaceutical products and vaccines for neglected infections such as gonorrhoea and other STIs.
- An international database of potential research funding agencies with an interest in AMR will be established.
- It will establish new, and reinforce existing, programmes for researchers to improve the design, preparation and conduct of research to contain AMR.

The appropriate lessons learnt from the prevention and control programmes for other pathogens with emerging AMR should also be scrutinized to improve the performance of this action plan.

5.4 Communications strategy

All international partners should strengthen their channels of communication with each other, as well as engaging with international and national media to highlight the issue of STIs in general and AMR in particular. Some of the actions to be pursued include the following:

- building the capacity of media personnel to develop and disseminate accurate, supportive messages for controlling STIs and use of antimicrobials
- improving the public's engagement in prevention and control of STIs and the importance of gonococcal AMR
- mobilization of political will and commitment
- raising awareness about the consequences of untreatable STIs.

Table 5
Proposed framework for implementation of the global action plan to control the spread and impact of AMR in *N. gonorrhoeae* at national level

Activities	Time-frame: Year Q1	Q2	Q3	Q4	Targets – *date*	Indicators	Key responsible	Potential partners	National operational plan targets	Budget
Establishment of an STI guideline working group										
Development, publication and dissemination of a national mitigation plan										
Establishment and strengthening of monitoring and evaluation mechanisms (facilitate the creation of facility- and district-level units, systematically monitor treatment failures by developing standard case definition of treatment failure and regular reporting to GASP surveillance networks)										
Advocacy and resource mobilization for Ceph-R *N. gonorrhoeae* mitigation and general prevention and control of gonorrhoea										
Enhancement of local health-care providers' awareness of and participation in mitigation activities										
Effective prevention and control of gonococcal infection, using appropriate treatment regimens										
Putting effective drug regulations in place										

Activities	Time-frame: Year Q1	Q2	Q3	Q4	Targets – *date*	Indicators	Key responsible	Potential partners	National operational plan targets	Budget
Development and implementation of laboratory capacity strengthening to support mitigation activities (laboratory assessment, training and support)										
Development and implementation of health service capacity strengthening to support mitigation activities (laboratory diagnosis, treatment, partner outreach services)										
Conduction of clinical, epidemiological and operational research projects to enhance the mitigation activities										
Implementation of the mitigation activities and review/update of the plan with lessons learnt										

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