Moving forward in tackling antimicrobial resistance: WHO actions

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Received 4 April 2013
Revised 12 September 2013
Accepted 22 September 2013

ABSTRACT

Although the key focus of this supplement is related to antimicrobial resistance (AMR) in a sexually transmitted infection, *Neisseria gonorrhoeae*, the purpose of this article is to highlight the wider public health impact of AMR and the need for different disciplines of health to coordinate and collaborate in their selection and use of antimicrobial agents. AMR is being detected in health areas ranging from simple drugs used to treat common bacterial infections to the complex formulations used to treat tuberculosis, malaria and HIV infection, and on all continents. Tackling and containing AMR present an ordeal to international and national health authorities on many fronts. In June 2012, WHO launched the WHO Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in *Neisseria gonorrhoeae* with a vision 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. This global action plan is positioned within a long-standing commitment of WHO to the issue of AMR with the launch of the Global Strategy on AMR in 2001 and World Health Day on AMR in 2011.

INTRODUCTION

Antimicrobial resistance (AMR) is among the most important public health threats facing the world today and a crisis which is rising worldwide with the emergence of new multidrug-resistant microorganisms. Although the key focus of this supplement is related to AMR in a sexually transmitted infection (STI), *Neisseria gonorrhoeae*, the purpose of this article is to highlight the wider public health impact of AMR and the need for different disciplines of health to coordinate and collaborate in their selection and use of antimicrobial agents. AMR is being detected in health areas ranging from simple drugs used to treat common bacterial infections to the complex formulations used to treat tuberculosis (TB), malaria and HIV infection, and on all continents. Tackling and containing AMR present an ordeal to international and national health authorities on many fronts. AMR incapacitates the control of infectious diseases, jeopardises progress on health outcomes by increasing morbidity and mortality and imposes huge costs on societies. Increasing AMR also threatens animal health with potential negative impact on food production and global food security. The extensive use of antimicrobial agents in agriculture favours further selection for resistant microorganisms and a potential spread of resistant strains of pathogens. Contamination of the environment from agriculture and aquaculture as well as from hospitals and pharmaceutical industries leads to exposure of the ecosystems to antimicrobial agents and to the increase of pools of resistant bacteria that either can spread or transfer resistant genetic material to other pathogenic bacteria. Of utmost concern is that the emergence of new multiresistant pathogens is fast outpacing available solutions. This is the case with a common STI, *N gonorrhoeae* which has outwitted penicillins, tetracyclines, sulfonamides and fluoroquinolones, all of which can no longer be recommended as first choice drugs for the treatment of gonococcal infections. Following the failure of fluoroquinolones in the treatment of gonorrhoea, third-generation cephalosporins, such as ceftriaxone and cefixime, became the only treatment of choice left for the treatment of gonorrhoea. However, *N gonorrhoeae* has again demonstrated its ability to develop resistance, and reports of reduced susceptibility and treatment failures to both parenteral and oral cephalosporins have been published, heralding a decline of the efficacy of this last treatment option.[1–5]

WHO'S ROLE IN TACKLING AMR

Steps to tackle the growing threat of AMR will require a wide range of comprehensive and coordinated interventions by all countries. Since 2001, when the WHO launched the Global Strategy[6] on AMR, a long-standing commitment to addressing the fears raised by this global health concern has resulted in a number of resolutions being passed by the World Health Assembly and endorsed by all its Member States.[7] Strategies and actions to tackle AMR have evolved in some specific areas such as HIV,[8] malaria,[9] TB[10] and foodborne[11] infections. To reaffirm its commitment, WHO's theme for World Health Day in 2011 (WHD 2011) was on AMR with the launch of a policy package[12] outlining the actions needed to be taken by governments to confront AMR and to stimulate and enhance action by all stakeholders. These areas form the basis of WHO's technical work plan and are summarised as follows:

1. All countries have in place comprehensive, financed national plans to address AMR, with accountability and civil society engagement.
2. Strengthen surveillance and laboratory capacity. WHO's long-term vision is to have an integrated global surveillance capability that operates according to agreed standards and provides timely global reporting on the current state of AMR and of new types and mechanisms of resistance.
3. Ensure uninterrupted access to essential medicines of assured quality. Equitable access to

To cite: Lusti-Narasimhan M, Pessoa-Silva CL, Temmerman M. *Sex Transm Infect* 2013;**89**:iv57–iv59.

antimicrobials is necessary to enable effective treatment, but substandard medicines can contribute to the development of resistance.
4. To reduce AMR emergence and spread by reducing the inappropriate use of antimicrobials (including in agriculture and animal husbandry) and ensure proper patient care.
5. Reduce the spread of antibiotic-resistant organisms in healthcare settings, and ensure patient safety, through enhanced infection prevention and control.
6. Foster innovation and research and development for new treatments, diagnostics and other interventions.

Furthermore, recommendations issued by Ministries of Health at regional meetings confirm the need for concerted action to tackle AMR.[13] Collaboration between agriculture, animal and human health, including coordination with agencies from other sectors such as the World Organisation for Animal Health (OIE) and the Food and Agriculture Organisation of the United Nations (FAO), is critical for success in tackling AMR.[14]

WHO has also made other efforts and progress in advocacy and communication to create high-level awareness and engagement among Member States and other stakeholders, including engagement with key countries in high-level *fora* and WHO governing body meetings. To further develop and coordinate WHO's work on AMR across the Organisation, a Task Force has been established to support Member States in implementing the policies issued on the WHD 2011. In this regard, a country situational analysis has been initiated to foster national comprehensive plans and help inform global strategies.

WHO is in a unique position to convene different groups and promote dialogue and action from different sectors in a complementary manner. Specific action points for different stakeholders which can build on the objectives stated on WHD 2011 have been identified, and in December 2012 WHO convened international technical agencies to identify the objectives, needs and gaps, priorities and next steps for improving global surveillance of antibacterial resistance and to explore opportunities for collaboration.[15] The major emerging threat imposed by Gram-negative Enterobacteriaceae, such as *Klebsiella pneumoniae* and *Escherichia coli*, which are threatening the treatment of serious nosocomial infections and threatening to create species resistant to all currently available agents is one of the areas of focus. For example, approximately 20% of *K pneumoniae* infections and 31% of *Enterobacter* spp. infections in intensive care units in the USA involve strains not susceptible to third-generation cephalosporins.[16] The Gram-negative *N gonorrhoeae*, a commonly encountered sexually transmitted pathogen is also showing decreased susceptibility to third-generation cephalosporins and with anecdotal treatment failures being encountered. Among Gram-positive pathogens, reduction and control of hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) as well as community-associated MRSA are also of high priority as the strains are resistant to the standard first-line antibiotics for staphylococcal infection and patients infected often die in spite of antibiotic treatment.[17] Additionally, and of grave concern, because of the anticipated huge global morbidity and mortality, are diseases such as TB, HIV infection and malaria. The diversity of the problems and pathogens and the commonality of treatment options require an integrated approach for surveillance and containment of AMR.

As much as there is a need for responsible use and enhanced access to existing prevention, new diagnostic tools, innovation, research and development of new tools and treatment options are also an imperative. The strategy to develop new antimicrobials has saved countless lives, but it has also driven the resistance that threatens the gains provided by the advent of antimicrobial agents. There is also a need to invest in new therapeutic options that do not induce resistance and provide long-term solutions. The need for new therapeutic tools includes better antimicrobials as well as new therapeutic options, alternative to anti-infective drugs, and new technologies start to be explored such as the use of nanotechnology and molecular biology to combat bacterial infections.

Currently, there are very few new antimicrobial medicines, diagnostic tools or vaccines in the research and development pipeline. For example, fewer than 5% of drugs currently in the pipeline are new antibiotics. Government, industry and academia should partner to overcome the barriers to research and development. Innovation is also needed to change the current business model in the industry and ideally revert to a scenario where there will be a number of new drugs in the pipeline and simultaneously effective prevention interventions and rational use of medicines.

WHO'S GLOBAL ACTION PLAN TO COMBAT AMR IN *N GONORRHOEA*

Gonorrhoea is among the most frequent of the estimated one million curable STIs occurring daily for which no new therapeutic drugs are in development. Uncontrollable and untreatable gonococcal infections could negatively impact the progress made by countries towards reaching the targets of the United Nations Millennium Development Goals (MDGs) set for 2015, particularly MDGs 4–6, given the impact of this sexually transmitted pathogen on the health of mothers and neonates as well as on people living with HIV. The emergence of AMR is such a complex problem driven by many interconnected factors that a single, isolated intervention will have very little impact. Better linkages with broader health outcomes, particularly with infectious diseases, reproductive, maternal, child health and HIV control interventions, would ensure that countries can move towards attaining their shared national goals and targets.

In June 2012, WHO launched the *WHO Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in Neisseria gonorrhoeae*[18] with a vision 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.

The objective of this global action plan is to control the spread and minimise the impact of AMR in *N gonorrhoeae* through
1. articulating the public health, policy and economic case for urgent, heightened and sustained action to prevent and control *N gonorrhoea* infection and mitigate the emergence and impact of AMR;
2. providing a strategic framework to guide clinical, laboratory and public health actions aimed at minimising the impact of AMR to cephalosporins in *N gonorrhoeae* and
3. providing recommendations for coordinating communication, partnership and advocacy efforts at national, regional and international levels to support the global response.

The United Nations Secretary-General's Global Strategy for Women and Children highlights the need for comprehensive integrated package of interventions and integrated care. This key area of linkage between sexual and reproductive/STI/HIV services provides an opportunity to advocate for and support WHO's gonococcal antimicrobial surveillance programme (GASP). This initiative ensures a successful implementation of

an evidence-based response plan to combat AMR in *N gonorrhoeae* that includes the following:

1. In collaboration with Member States, supporting countries to strengthen laboratory capacities to isolate and culture the pathogens and perform antimicrobial susceptibility tests through retraining of healthcare providers and laboratory technicians.
2. Work with WHO Collaborating Centres and other international and national reference centres to maintain and distribute standardised WHO reference strains of *N gonorrhoeae* to ensure comparability and validity of AMR data.
3. Produce and disseminate standards for performing antimicrobial susceptibility testing.
4. Facilitate an exchange of information and technologies, including mapping of drug resistance patterns to highlight the situation.
5. Given the threat of untreatable gonococcal infections, WHO will collaborate with partners to ensure that the issue 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 on the sexual and reproductive health of women and men, newborns and people living with HIV and underscores the need for research and production of new treatments.

The WHO's GASP aims to ensure a successful implementation of the global action plan through a coordinated approach, and is an example of partnership collaboration and multiregional approach to tackling gonococcal infections and the control of AMR. However, the implementation of the global action plan will require an injection of new money into STI control programmes and interventions. Countries will need to put in place a campaign to increase awareness of the hazards of STIs in general and, in particular, the risk of untreatable gonococcal infections and also increase awareness of the need to use antibiotics judiciously. In addition, effective prevention messages and interventions will need to be disseminated and diagnostic capacities strengthened. In order to monitor the trend of infections and control the upsurge of AMR, an enhanced surveillance system needs to be put in place and sustained. At the international level, an early warning system needs to be established to ensure a rapid exchange of information regarding resistant strains and how they responded to treatment.

The spread of multidrug-resistant *N gonorrhoeae* or other microorganisms 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 (ie, unrelated to the treatment of gonorrhoea or other health conditions with a particular antimicrobial agent). For gonococcal infections, 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, it is critical for effective implementation of this action plan that national-level 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.

Handling editor Jackie A Cassell.

Contributors ML-N and CLP-S contributed to this article with support from MT.

Key messages

- Antimicrobial resistance affects diverse health issues including tuberculosis, malaria, HIV, and gonococcal infections, jeopardizing progress on health outcomes by increasing morbidity and mortality worldwide.
- WHO's *Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in Neisseria gonorrhoeae* supports enhanced, sustained, evidence-based and collaborative multi-sectoral action.
- The implementation of WHO's gonococcal antimicrobial surveillance programme (GASP) will require increased resources to support STI control programmes and interventions worldwide.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

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Sex Transm Infect 2013 89: iv57-iv59 originally published online November 7, 2013
doi: 10.1136/sextrans-2012-050910

Notes