Antimicrobial resistance – a global epidemic

Prepared by the Secretariats of WHO, WIPO and WTO

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What is antimicrobial resistance?

Antimicrobial resistance (AMR) occurs when bacteria, parasites, viruses and fungi become resistant to antimicrobial drugs that are used for treating the infections they cause. Every time an antimicrobial medicine is used, it diminishes the effectiveness for all users, because its usage increases the possibility for the bacteria to become resistant. Antimicrobial resistance threatens the effective prevention and treatment of an increasing range of infections, including blood poisoning, pneumonia, diarrhoea, gonorrhoea, tuberculosis, HIV/AIDS and malaria.

Resistance against antibiotics (medicines used to prevent and treat bacterial infections) is an urgent problem because antibiotics are a cornerstone of modern medicine and most medicinal procedures in human and animal health rely on functioning antibiotics.

What causes antimicrobial resistance?

Antimicrobial resistance is mainly driven by inappropriate use. Global antibiotic consumption in humans has increased by 36% between 2000 and 2010.[1] Half of this increased use is regarded as unnecessary, e.g. when antibiotics are used to treat illnesses like common colds that are caused by viruses, where antibiotics have no effect. In many countries, antibiotics can be bought without prescription or do not have underlying standard treatment guidelines. These factors increase antibiotic resistance because of a lack of knowledge of proper antibiotic use.

The problem of resistance is not only evident in human medicine consumption. Antibiotics are also used in veterinary medicine, for growth promotion in animals and disease prevention in agriculture, aquaculture and horticulture. In the US, for example, more than 70% of antibiotics are used in agricultural production, primarily for growth promotion and prophylaxis.[2] Worldwide consumption in animals is estimated to rise by 67% from 63,151 tons in 2010 to 105,596 tons in 2030.[3]

How does resistance develop?

Resistant bacteria can be transmitted to humans through various channels such as the food chain, animal-to-human contact, and the environment.[4]

Globalization fuels the spread of antimicrobial resistance where transmission is facilitated by increased trade, travel and both human and animal migration. Travellers often carry home resistant bacteria from holidays or business trips. An example of globalization fuelling the spread of antimicrobial resistance is seen in the antibiotic-resistant strain of colistin. Colistin is widely used in Chinese livestock which has likely led the bacteria to evolve, gain resistance and transmit from livestock to humans through food. This strain was reported earlier this year in the US[5] and Europe.[6] This example shows that antimicrobial resistance cannot be tackled in isolation by individual countries but needs global cooperation.

Why is antimicrobial resistance a problem?

Antimicrobial resistance affects high-, low- and middle-income countries. There are particular diseases that have higher rates of antimicrobial resistance such as tuberculosis and gonorrhoea. Recent global estimates in 2013 reveal 480,000 new cases of multidrug-resistant tuberculosis (MDR-TB) with extensively drug-resistant tuberculosis (XDR-TB) present in 100 countries. Further, there are treatment failures as a result of resistance to treatments of last resort for diseases such as gonorrhoea. Consequently, there is a risk that gonorrhoea may become untreatable if no vaccines or new treatments are being developed.[7]

A reliable estimate of the global burden of antimicrobial resistance is difficult to obtain as data is not systematically and consistently collected. However, estimates from Europe indicate that the excess mortality due to resistant bacteria in hospital infections exceeds 25,000 annually, with annual costs of at least €1.5 billion. Outpatient data from the US indicates more than 63,000 deaths annually due to resistant bacterial infections.[8]

A combination of having less developed health systems, higher rates of infectious diseases and low quality and improper use of antibiotics, among other factors, increases the burden of antimicrobial resistance in low- and middle-income countries. For example, the crude infectious disease mortality rate in India is 416.75 per 100,000 persons[9] with bacterial resistance increasing over time. Between 2008 and 2013, E. coli resistance to a type of antibiotics – a third-generation cephalosporins – increased from 70% to 83%. This highlights the increasing burden of antimicrobial resistance in developing countries.[10]

Additionally, antimicrobial resistance causes extra health care cost and leads to loss of productivity. Patients with resistant infections are more expensive and difficult to treat and are more likely to require longer hospitalisation than patients infected with drug susceptible strains. As a consequence, antimicrobial resistance has major economic costs, estimated at $55 billion annually in the US alone.[11] The World Economic Forum annual risk report has been listing the spread of infectious diseases – including the rise of resistant pathogens – among the high-impact risks to the global economy.[12]

Although resistant strains of bacteria are not a new phenomenon, increased speed of resistance to antimicrobial medicines and especially to last resort antibiotics for some bacterial infections has turned antimicrobial resistance into one of the greatest threats for human health. In a post-antibiotic era, common infections and minor injuries can be fatal. This is far from being an apocalyptic fantasy, but a very real possibility for the 21st Century.

What are measures against antimicrobial resistance?

There are a number of possible measures against antimicrobial resistance including improvement of hygiene, infection control to prevent spread of resistant bacteria, development of new antimicrobials against which bacteria are not resistant, improved conservation efforts to maintain the effectiveness of new antimicrobials and of existing drugs.

Stewardship, innovation and access are three key objectives in addressing antimicrobial resistance.

Stewardship, innovation and access – a delicate balance of conflicting goals

Stewardship to maintain the effectiveness of new and existing antimicrobials. However, stewardship can constrain access and undermine current innovation.

Innovation for new anti-microbials. However, innovation needs to be accessible, and innovation without conservation is wasteful.

Access to antimicrobials for the millions of people without them. However, increased access without conservation and innovation will speed up resistance.

Source: Adapted from John-Arne Røttingen, based on Hoffman et al. (2015)

Stewardship

Stewardship describes the careful and responsible management of resources entrusted to one's care. With respect to antimicrobials, stewardship refers to appropriate antimicrobial treatment to improve patient outcomes while minimizing the development and spread of resistance.

Core considerations in determining a stewardship framework for appropriate use of antimicrobials include:

- the type of antimicrobials that should be included in the framework;
- the type of antibiotics that should be subject to a conservation scheme; and
- identification of actors and responsibilities of all stakeholders from manufacturers of antimicrobials to the end users of antimicrobials such as clinical staff and patients.

A range of stewardship measures can be used to appropriately use and distribute antimicrobials. These measures along with many other measures can include:

- better diagnostics in health care facilities in order to facilitate appropriate use of antibiotics;
- avoiding unnecessary use of antibiotics;
- prescription and distribution of antibiotics through adequately trained personnel;
- improving education and training of all people who work with antibiotics: health care workers, pharmacists and other dispensers, patient, national governments and others;
- appropriate distribution of antibiotics that facilitates access to, but does not lead to excessive use of antibiotics;
- quality assurance audits to support antimicrobial stewardship embedding into practice.

Addressing the rising threat of AMR requires a holistic and multi-sectoral (One-Health) approach[13] because antimicrobials used to treat various infectious diseases in animals may be the same or be similar to those used in humans. Resistant bacteria arising either in humans, animals or the environment may spread from one to the other, and from one country to another.

While access to effective antimicrobials is a prerequisite for productive and sustainable agriculture, in particular in relation to animal husbandry, antibiotics have to be used with more responsibility. Therefore, effective stewardship in tackling antimicrobial resistance requires a global multidisciplinary collaborative effort across industries.

Innovation

There is a severe lack of investment in new medicines against microbes. The market-based innovation system has insufficient incentives because the return on investment in antibiotic research is too small to attract the required R&D investments. The low return on investment can be explained by a number of factors. Antibiotics have a short treatment course compared to medications for chronic diseases which leads to lower treatment costs. Additionally, while new antibiotics are needed, they will face competition with existing generic products. Fostering appropriate use can also mean that new antibiotics are only used very conservatively to delay resistance building as much as possible which will diminish the revenue that the inventor can generate. These and other factors have led to minimal antibiotics breakthroughs since the 1980s and increased on-going concern about the lack of new products in the pipeline.

New innovative and comprehensive incentive initiatives are needed to complement the existing innovation model to foster the development of new antibiotics. This could include a mixture of push mechanisms (e.g. grants for basic research and clinical trials, product development partnerships), pull incentives (e.g. milestone prizes or market entry rewards) and regulatory measures (e.g. specific regulatory pathways). All these market measures have to factor in the public health objectives of antibiotic conservation and access.

Many of these initiatives build on the concept of delinkage,[14] where the income from the sales of a product is untied from the cost of its development. This is highly relevant for antimicrobial resistance because delinkage removes the need for recouping the costs of developing a product by requiring high prices or selling large volumes.

Several national and regional innovation initiatives have already been implemented in the past years, including the Biomedical Advanced Research and Development Authority in the United States of America; the Innovative Medicines Initiative in Europe; the EU Joint Programming Initiative on Antimicrobial Resistance; and various prize funds for diagnostics, such as the Longitude Prize.

In 2016, WHO and DND*i* have launched the Global Antibiotic Research & Development Partnership.[15] The aim is to develop new antibiotic treatments addressing antimicrobial resistance and promote their responsible use for optimal conservation, while ensuring equitable access for all. The Partnership will stimulate innovation for global needs in the area of antibiotics by ensuring that any new products are also suitable for resource-limited settings. It will work closely with all stakeholders, including pharmaceutical and biotechnology companies, other product development partnerships, academia, civil society, and health authorities from countries of all income levels.

Access

The problem of infectious diseases and antibiotic use plays out very differently across the globe. Certain countries are less exposed to the problem than others because of successful infection control programmes in hospitals. Further, while some countries experience overuse, many people still lack access to antibiotics, and more people die because of this lack than of resistant infections. Despite an increase in worldwide antibiotic consumption, lack of access even to affordable generics remains a huge problem in many countries.

Pneumonia accounts for 15% of all deaths of children under 5 years old, killing an estimated 922,000 children in 2015. Only one-third of children with bacterial pneumonia receive the antibiotics they need.[16]

Antibiotics protected by patents will often have a higher price, which constrains access. One option to overcome this barrier is using delinkage in the development of new antibiotics as described above. Voluntary licensing agreements have emerged as a tool that has helped improve affordable access to patented medicines for HIV/AIDS and hepatitis.

The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) provides WTO Members with policy space within which they can put in place and apply a domestic intellectual property regime that is responsive to their particular needs in the health sector. This includes using existing flexibilities to foster access to antibiotics.

In the long run, building strong health systems is the most sustainable approach to ensuring affordable access to good-quality essential medicines, including antimicrobial medicines and vaccines, as well as diagnostics and other vital interventions.

Antimicrobial resistance and trade

Given that no country is self-sufficient in the supply of medicines, trade in general is essential to ensure access. Eliminating trade barriers such as high tariffs, unnecessary custom formalities and other obstacles contribute to ensuring access to affordable medicines.

Certain measures to incentivize appropriate use of antibiotics can impact international trade of antibiotics or products that have been manufactured using antibiotics or that are carriers of resistant bacteria. Such measures would likely be measured against the WTO Agreements on Technical Barriers to Trade (TBT), or the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS). Both agreements allow WTO Members to take measures to protect human health or the environment. They encourage WTO Members to base any trade restrictive measures on international standards, guidelines or recommendations where applicable. Therefore, WTO trade law ultimately can support the implementation of international standards for appropriate use of antibiotics, including in the area of animal husbandry and/or good manufacturing practice, for example, through the inclusion of environmental standards that prevent spill-over of antibiotics into the environment from factories by wastewater.

Increased international attention

WHO adopted the Global Action Plan on Antimicrobial Resistance (GAP-AMR) in 2015. The plan focuses on a comprehensive approach meaning that actions in all relevant sectors should be implemented synergistically. To tackle antimicrobial resistance, the global action plan sets out five strategic objectives:

- to improve awareness and understanding of antimicrobial resistance;
- to strengthen knowledge through surveillance and research;
- to reduce the incidence of infection;
- to optimize the use of antimicrobial agents; and
- to develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

The GAP-AMR has been endorsed through resolutions by both the Food and Agriculture Organization of the United Nations (FAO)[17] and World Organisation for Animal Health (OiE).[18]

In addition to the GAP-AMR, the World Health Assembly in 2016 discussed options for a global development and stewardship framework on antimicrobial resistance. The purpose of such a possible framework would be to add value and achieve strategic objectives identified in the GAP-AMR focusing on:

- preservation of antimicrobial medicines through a stewardship framework covering control, distribution and appropriate use;
- development of new health technologies for preventing and controlling antimicrobial resistance; and
- promotion of affordable access to existing and new antimicrobial medicines and diagnostic tools.

Antimicrobial resistance will be discussed at the United Nations General Assembly's 71st session in September 2016 in New York.

While antimicrobial resistance affects every country, each country should take actions that address the needs and capabilities of their health system to preserve global antibiotic resources.

Antimicrobial resistance is a multi-faceted global issue requiring a shared responsibility by all countries to protect citizen health and combat the global threat posed by AMR.

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