A Primer for Media
Antimicrobial Resistance in the Western Pacific Region
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In order to preserve the miracle of modern medicine, antimicrobials, before it is too late, it is important that containment of antimicrobial resistant is widely recognized as a development agenda issue beyond human health. Given the multi-sectoral nature of the public health concern, actions taken to prevent the emergence and spread of antimicrobial resistance will also directly support achieving the Sustainable Development Goals.

To facilitate a multi-sectoral approach to contain antimicrobial resistance, countries need to develop plans that commit resources to the containment of antimicrobial resistance with efforts by all stakeholders. This must be based on a “One Health” approach, encompassing both human and animal health, in recognition of the fact that human health, animal health and ecosystem health are inextricably linked. Surveillance of antimicrobial resistance and systematic monitoring of antimicrobial use are also key to containing the problem.

WHO is actively working with countries to develop country specific national strategies to combat AMR. At the same time, the scientific community worldwide is working hard to find solutions and, as we leave behind the “golden age” of antibiotics, offer new hope that the disaster of a world completely without antibiotics can be averted.
Antimicrobial resistance is a major public health threat

Antimicrobial resistance is driven by both appropriate and inappropriate use of anti-infective medicines to treat diseases in humans and the widespread use of antibiotics in animal husbandry. Antimicrobial resistance includes antibiotics to treat bacterial infections; antiviral drugs, including antiretroviral therapy to treat HIV, and influenza medications; antiparasitic drugs such as those used to treat malaria; and antifungal medications.

The result is that a growing number of diseases are becoming difficult or even impossible to treat, allowing a common infection to develop into a life-threatening condition. Diseases caused by resistant microbes become harder and more costly to treat. Not only do they require more expensive second- and third-line medications, but the delays in effective treatment ramp up the costs of medical care, increasing mortality as well as heightening the risk of complications and spread of infection.

Antimicrobial-resistant infections extract a high cost at the individual level, in terms of increased suffering and higher mortality, and at the societal level, through increased health-care costs and a less healthy population.

How antimicrobial resistance happens

NATURAL SELECTION
Microorganisms undergo a natural process of adaptation to the antimicrobial agents used to treat them. Through natural selection microorganisms exchange resistant traits, and resistant strains survive and aggregate.

OVERUSE AND MISUSE
The natural process of resistance due to adaptation already means that antibiotics have a limited lifespan, but this process has been accelerated by the overuse and misuse of antimicrobial medicines. Antibiotics are often overprescribed, or used to treat viral infections that they cannot combat. In countries lacking reliable supplies of affordable, quality medicines, antimicrobial resistance – such as resistance to antimalarial medications – is fuelled by supplies of spurious, falsely labelled, falsified or counterfeit medicines often containing too little of the active compound.

ANIMAL HUSBANDRY AND AQUACULTURE
Antibiotics used to treat human diseases are also given to livestock in subtherapeutic doses, not to treat infections, but to promote growth and prevent disease outbreaks among animals kept in factory farming conditions. Both antibiotics and the resistant bacteria make their way into the food chain via contaminated food products and through the water supply system.

ENVIRONMENTAL EXPOSURE
Poorly managed pharmaceutical manufacturing practices and poor water management in some countries lead to antibiotic contamination of water supplies.

The impact
Antimicrobial-resistant infections cause at least 50 000 deaths a year in Europe and the United States of America alone. Reliable data on the global burden are scarce, but a low estimate puts the figure at 700 000 deaths a year (1). If left unchecked, it is estimated that by 2050 the figure will rise to 10 million deaths annually, or 350 million deaths in the coming 35 years (1).

Asia and the Pacific are projected to account for 4.73 million antimicrobial-resistant-related deaths by 2050 (1). There is a large economic cost attributed to drug-resistant infections. Studies commissioned by the Review of Antimicrobial Resistance estimate that at 10 million deaths a year, antimicrobial resistance could cost up to US$ 100 trillion and slice 2% to 3.5% off global gross domestic product (1).

The impact of antimicrobial-resistant infections is expected to affect developing countries most severely. Progress in treating HIV, tuberculosis and malaria, all of which disproportionately affect the developing world, is being jeopardized by the growing threat of antimicrobial resistance. In China, for example, malaria has almost been eradicated, but such gains could be reversed by resistance to current first-line malaria treatments.

Four categories of antimicrobial resistance

ANTIBIOTIC RESISTANCE
Antibiotic resistance is the single biggest category of antimicrobial resistance and refers to antibiotic drugs used to treat bacterial infections. Antibiotic resistance has emerged to drugs that treat a wide range of bacterial diseases, including tuberculosis, gonorrhoea and infections affecting the digestive system, skin, urinary tract and respiratory tract.

The loss of effective antibiotics affects not only the treatment of common diseases, but also large areas of modern medicine: organ transplantation, cancer chemotherapy and major surgery all rely on the use of antibiotics. The antibiotic era, when new drug discoveries more than kept pace with emerging resistance, is over. With a thin pipeline of new drugs, and escalating resistance, these achievements of modern health care are at serious risk, potentially foreshadowing a post-antibiotic era.
In the Western Pacific Region, antibiotic resistance is being fuelled by widespread misuse and overuse, and the faster spread of resistant bacteria as people migrate and travel more. Poor hygiene and lax infection control in hospitals and other health-care settings are also key factors. Insufficient control of antibiotic distribution and sale for both human and animal use plays a part. In Viet Nam, for example, 88% of antibiotics used in urban areas and 91% of those used in rural areas are sold without a prescription (2).

Lack of accountability at government, facility and individual levels is also responsible for the growth of antibiotic resistance.

**ANTIPARASITIC RESISTANCE**

For antiparasitic resistance, malaria is the main disease of concern, followed by helminthiasis (disease caused by intestinal worms).

Malaria is endemic in 10 countries in the Western Pacific Region: Cambodia, China, the Lao People’s Democratic Republic, Malaysia, Papua New Guinea, the Philippines, the Republic of Korea, Solomon Islands, Vanuatu and Viet Nam. Both *Plasmodium falciparum* – one of the most common and most deadly forms of the disease – and *Plasmodium vivax* are prevalent in the Region. There are an estimated 717 million people in the Western Pacific at some risk for malaria, while 41 million people are at high risk, with ethnic minorities and migrant workers disproportionately affected (3).

The first-line treatment is combination therapy containing artemisinin and its derivatives, a group of drugs that are isolated from *Artemisia annua*, or sweet wormwood plant. Although many countries in the Western Pacific Region have been very successful in reducing their malaria burden and several are on course to eliminate malaria, resistance to treatments is a growing threat, and new foci of artemisinin-resistant *P. falciparum* malaria are being detected (4). Resistance to artemisinin has been detected in five countries of the Greater Mekong Subregion: Cambodia, the Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam. In many areas along the Cambodia–Thailand border, *P. falciparum* has become resistant to most available antimalarial medicines.

Artemisinin resistance has emerged partly due to the natural evolution of the parasite but also because the disease is not always treated with the right drug combination in the right dosage, and because of the continued use of artemisinin monotherapy. Also partly to blame are fake and substandard malaria drugs, which fill the gap in the market created when health systems are not robust enough to offer reliable access to the right medications.

Helminthiasis infections of concern in the Western Pacific include lymphatic filariasis (in the Pacific islands) and intestinal schistosomiasis (notably in China, Cambodia, the Lao People’s Democratic Republic and the Philippines).

**ANTIVIRAL RESISTANCE**

**HIV**

Resistance to antiretroviral medications to treat HIV is a potential threat to public health in the Western Pacific Region. Of the estimated 1.4 million people living with HIV in the Region, 520 000 people are receiving antiretroviral therapy (5). Resistance to antiretroviral medications is expected to rise with more people placed on treatment as national HIV programmes push toward treating 90% of all people living with HIV by 2020, or over one million people in the Region. If resistance rises to such an extent that first- and second-line treatment regimens are no longer effective, it could unravel all the successes of national AIDS programmes in getting treatment to people living with HIV.

Globally, in 2010 resistance was estimated at approximately 5% in countries that had not yet begun to scale up treatment access, but since 2010 resistance has been as high as 22% in some areas (6). Indication of antiretroviral resistance in the Region recently arose with Papua New Guinea reporting 16% resistance to antiretroviral drugs used in first line treatment regimens.

**Influenza**

Resistance to antiviral drugs to treat influenza has also become a concern, especially given the pandemic threats that have emerged in recent years. Resistance to frequently used drugs to prevent influenza – has been detected for virtually all influenza A viruses circulating in humans. As antiviral resistance remains a public health threat, the WHO Global Surveillance and Response System monitors the evolution of influenza viruses and provides recommendations for laboratory diagnostics, vaccines, antiviral susceptibility and risk assessment.

**ANTIFUNGAL RESISTANCE**

The fungus *Candida* is a common cause of health-care-associated bloodstream infections, and some types of *Candida* are becoming increasingly resistant to the current first-line and second-line antifungal medications, fluconazole and echinocandins (7).
Tackling the growing threat of antimicrobial resistance needs the active commitment of everyone and there are several key stakeholder groups that must take action:

WHO AND ANTIMICROBIAL RESISTANCE

WHO is playing a leading role in promoting action both globally and in the Western Pacific Region across all sectors. In 2001, WHO launched its Global Strategy for Containment of Antimicrobial Resistance, in which it presented 87 prioritized recommendations for health-care workers, industry, researchers, the media, patients’ representatives and national authorities. It has since been actively supporting Member States to develop their own national strategies and plans.

In October 2014, WHO Member States in the Western Pacific Region endorsed the Action Agenda for Antimicrobial Resistance in the Western Pacific Region. The agenda spells out specific actions that countries can take to develop their national plans, raise awareness of antimicrobial resistance and strengthen their health systems to better contain and monitor antimicrobial resistance.

A Global Action Plan on Antimicrobial Resistance was adopted by the World Health Assembly in May 2015.

When to act? NOW!

We can still change the course of antimicrobial resistance if we act now to preserve the effectiveness of our current antimicrobials for future generations.

References

Since then, antibiotic resistance has emerged in drugs to treat a wide range of bacterial diseases, including tuberculosis, gonorrhoea and infections affecting the digestive system, skin, urinary tract and respiratory tract.

In the Western Pacific Region, antibiotic resistance is being fuelled by widespread misuse and overuse, and the increased spread of resistant bacteria as people migrate and travel more. Poor hygiene and infection control in hospitals and other health-care settings are also key factors. Lack of control over antibiotic distribution and sale for both human and animal use is also responsible for the growth of antibiotic resistance. Table 1 presents information about the main classes of antibiotics and the year resistance was first observed.
Table 1. Antibiotic classes and year resistance first observed

<table>
<thead>
<tr>
<th>ANTIBIOTIC CLASS</th>
<th>EXAMPLE</th>
<th>YEAR OF DISCOVERY</th>
<th>YEAR OF INTRODUCTION</th>
<th>YEAR RESISTANCE OBSERVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfadrugs</td>
<td>Prontosil</td>
<td>1932</td>
<td>1936</td>
<td>1942</td>
</tr>
<tr>
<td>β-lactams</td>
<td>Penicillin</td>
<td>1928</td>
<td>1938</td>
<td>1945</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Streptomycin</td>
<td>1943</td>
<td>1946</td>
<td>1946</td>
</tr>
<tr>
<td>Chloramphenicols</td>
<td>Chloramphenicol</td>
<td>1946</td>
<td>1948</td>
<td>1950</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Erythromycin</td>
<td>1948</td>
<td>1951</td>
<td>1955</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Chlorotetracycline</td>
<td>1944</td>
<td>1952</td>
<td>1950</td>
</tr>
<tr>
<td>Rifamycins</td>
<td>Rifampicin</td>
<td>1957</td>
<td>1958</td>
<td>1962</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Vancomycin</td>
<td>1953</td>
<td>1958</td>
<td>1960</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Ciprofloxacin</td>
<td>1961</td>
<td>1968</td>
<td>1968</td>
</tr>
<tr>
<td>Streptogramins</td>
<td>Streptogramin B</td>
<td>1963</td>
<td>1998</td>
<td>1964</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Linezolid</td>
<td>1955</td>
<td>2000</td>
<td>2001</td>
</tr>
<tr>
<td>Lipopeptides</td>
<td>Daptomycin</td>
<td>1986</td>
<td>2003</td>
<td>1987</td>
</tr>
<tr>
<td>Macrocyclics</td>
<td>Fidaxomicina</td>
<td>1948</td>
<td>2011</td>
<td>1977</td>
</tr>
<tr>
<td>Diarylquinolines</td>
<td>Bedaquiline</td>
<td>1997</td>
<td>2012</td>
<td>2006</td>
</tr>
</tbody>
</table>

* Targeting Clostridium difficile.
Source: Adapted from Lewis (1).

Table 2. Resistance and decreased susceptibility to antibiotics

<table>
<thead>
<tr>
<th>BACTERIUM</th>
<th>YEAR OF INTRODUCTION</th>
<th>YEAR RESISTANCE OBSERVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococci</td>
<td>Infections anywhere in the body, but especially in the intestines, urinary tract and wounds</td>
<td>Many types, especially vancomycin</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Gastroenteritis, urinary tract infections, neonatal meningitis</td>
<td>Third-generation cephalosporins, fluoroquinolones, Carbapenems</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>Pneumonia, infections of the lower biliary tract, surgical wound sites and urinary tract</td>
<td>Carbapenems</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Multidrug-resistant tuberculosis</td>
<td>Isoniazid and rifampin</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Extensively drug-resistant tuberculosis</td>
<td>Isoniazid and rifampin, plus fluoroquinolone and at least one of three injectable second-line drugs: amikacin, kanamycin, capreomycin</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Gonorrhoea</td>
<td>third-generation cephalosporins</td>
</tr>
<tr>
<td>Nontyphoidal salmonella</td>
<td>Salmonella</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Shigella species</td>
<td>Shigellosis</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Pneumonia, soft tissue infections, methicillin-resistant Staphylococcus aureus (MRSA)</td>
<td>Methicillin</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Meningitis, pneumonia, septicaemia</td>
<td>Penicillin</td>
</tr>
</tbody>
</table>

Source: Adapted from Lewis (1).

Empty pipeline

The first antibacterial drugs were introduced in the 1930s, and the pharmaceutical industry went on to develop and bring to market new classes of antibiotics for the following four decades. This was the “golden age” of antibiotics, but from 1968 there was a 30-year-long hiatus in new antibiotic drug discovery. From 1998 to 2012 there were only five new antibiotics brought to market, while resistance to all classes of antibiotics has continued to emerge and spread.

Antibiotic resistance and disease

WHO surveillance data show resistance and decreased susceptibility to a wide range of antibiotics, in some cases to nearly all, or all, available treatments (Table 2).

TUBERCULOSIS

Tuberculosis (TB) is second only to HIV as a killer infectious disease, with 9 million new infections in 2013 and 1.5 million deaths worldwide (2). In the Western Pacific Region there were over 1.3 million newly notified cases in 2013, and 110 000 TB deaths that year (3).

TB drug resistance emerges as a result of improper use of antibiotics to treat TB patients. This includes the use of inappropriate treatment regimens and failure to ensure that patients complete the whole course of treatment.

In the Western Pacific Region, an estimated 4.4% of new and 22% of previously treated TB cases in 2013 were multidrug resistant. Globally, an estimated 9% of patients with multidrug-resistant TB were also resistant to...
second-line antibiotic regiments used to treat it, and were diagnosed with extensively drug-resistant TB (4).

GONORRHOEA
There are over 100 million new cases of gonorrhoea a year worldwide, of which approximately 42 million occur in the Western Pacific Region, by 2008 estimates (5). Resistant gonorrhoea was first identified in 1943, when penicillin became the recommended treatment for sulfonamide-resistant gonorrhoea, less than a decade after sulfonamides were introduced. Penicillin remained the first-line treatment until the mid-1970s, followed by fluoroquinolones by the 1980s. However, resistance to this class of antibiotic emerged in the early 1990s and now only the third-generation cephalosporins remain an effective first-line treatment for gonorrhoea (6). Evidence suggests an increasing trend of treatment failures with drugs currently used for the treatment of gonorrhoea, including the last-line oral cephalosporins, due to gonococcal resistance (7).

The first identified cases of antibiotic-resistant gonorrhoea originated in the Western Pacific. Currently, gonococcal resistance to third-generation cephalosporins given orally has been reported in Japan and in Hong Kong SAR (China), as well as in Norway and the United Kingdom (7).

HOSPITAL-ACQUIRED INFECTIONS
Methicillin-resistant Staphylococcus aureus (MRSA) first emerged as an infection associated with hospitals and other health-care facilities, but it is now also being acquired in the community. Infection can be asymptomatic, but can also lead to pneumonia and soft tissue infections. Hospitals, closed settings such as prisons, and nursing homes have higher rates of MRSA than the general population because they have a high proportion of people with weakened immune systems. Open wounds and treatment with invasive medical devices such as intravenous drips also increase the risk of MRSA infection.

Infection control measures, including screening patients upon admission, separating those who are carrying the strain from those who are not, surface sanitization and proper and consistent hand hygiene, can all help prevent the spread of MRSA. Many countries in the Region have successfully implemented nosocomial (hospital-acquired) infection control measures to combat MRSA and other hospital-acquired infections, such as vancomycin-resistant enterococci and Clostridium difficile.

TYPHOID
Approximately 30 million people a year worldwide contract typhoid. Multidrug-resistant strains of the bacterium Salmonella typhi have spread across Asia and Africa in the past three decades, and the H58 clade of the bacteria is often resistant to the first-line antimicrobials commonly used to treat the disease (8). Resistance is spreading to new regions and populations, and newer antibiotics, such as ciprofloxacin and azithromycin, are also becoming less effective, leading to multidrug-resistant typhoid.

Uses of antibiotics

BACTERIA, NOT VIRUSES!
Antibiotics are mainly used to treat bacterial infections as well as some parasites, but a leading cause of antibiotic overuse and misuse is erroneous prescription to treat viral infections (Table 3). Self-medication by patients in places where antibiotics can be bought over the counter is also a problem, often resulting in using the wrong antibiotic, not completing a full course and sharing antibiotics with family and friends.

Table 3. Distinguishing bacterial from viral infections

<table>
<thead>
<tr>
<th>BACTERIAL INFECTIONS</th>
<th>VIRAL INFECTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonia</td>
<td>Colds</td>
</tr>
<tr>
<td>Sepsis (bloodstream infections)</td>
<td>Most respiratory tract infections</td>
</tr>
<tr>
<td>Wound and skin infections</td>
<td>Influenza (the flu)</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>Viral gastroenteritis</td>
</tr>
<tr>
<td>Bacterial tonsillitis (strep throat)</td>
<td>Measles</td>
</tr>
</tbody>
</table>

Source: ReAct Group (13).

OTHER MEDICAL USES OF ANTIBIOTICS
Antibiotics are not just used to treat common bacterial infections. Many aspects of modern medicine would not be possible without the use of antibiotics. They are widely used for prophylaxis during surgery, including joint replacements, cardiothoracic surgery and caesarean sections. They are also vital to neonatal care and transplant surgery. In the absence of effective antibiotics, it would not be possible to continue to perform these modern miracles of medicine without serious risk of infection.

ANTIBIOTICS IN FOOD PRODUCTION
Antibiotics are widely used in both animal husbandry and aquaculture to prevent and treat disease and to promote faster growth and increased yields (14). Resistant bacteria and antibiotic residues from food production get into the human food chain via meat products, and onto fresh produce through water and soil contamination, and through contamination of the environment with the faeces of antibiotic-treated animals.

Compared to human usage of antibiotics, animal husbandry and aquaculture usage is very poorly regulated. Also, there are no standardized data available on the global use of antimicrobials in livestock, and according to the World Organisation for Animal Health, only 42 countries have a system to collect data on the use of antimicrobials in livestock.

In the United States of America, the Food and Drug Administration data show that 80% of the antibiotics sold are used not by humans but in animal feed, three
with it increased use of antibiotics in animal husbandry and meat. However, in developing countries, rapidly increasing husbandry increases, so does demand for antibiotic-free products. Limited studies of soil and water contamination have shown that these antibiotics are finding their way into the human food chain there (17–19).

In the Western Pacific Region, very few data on antibiotic use in animal husbandry and aquaculture are available, but the limited data available from China, which produces half of the global total of pigs (approximately 500 million a year), suggest that antibiotic use is very widespread. Limited studies of soil and water contamination have shown that these antibiotics are finding their way into the human food chain there (17–19).

Japan’s prevalence of MRSA was among the highest in the world. However, the introduction of infection prevention and control measures in a hospital urology ward, including avoidance and reduction of antimicrobial prophylaxis, improvement of operative procedures and the use of surveillance cultures, successfully reduced the in-hospital transmission of the disease (9, 10).

In Hong Kong SAR (China), proactive infection control measures – including an active surveillance culture, early single room isolation with strict contact precautions, directly observed hand-hygiene practices in health-care workers and patients, and environment disinfection – enabled a major teaching hospital to prevent the spread of multidrug-resistant organisms such as MRSA, bringing the number of cases down from 8.65 per 1000 patient-days in 2002 to 0.79 per 1000 patient-days in 2009 (11).

In 2011, China launched a special campaign for rational use of antibiotics in hospitals, with a grading scheme for all hospitals and clinicians on reporting of antibiotics prescribed. Hospitals in China have implemented antimicrobial stewardship practices, and studies show significant reductions in antimicrobial usage (12).

References
Factors contributing to antimicrobial resistance

Antimicrobial resistance in the Western Pacific Region is driven by a range of interconnecting factors:

**WITHIN THE HEALTH SECTOR:**
- weak regulation and lack of enforcement for good manufacturing practices in the pharmaceutical sector;
- lax control of antimicrobial quality, supply and usage, including over-the-counter availability of antibiotics and other antimicrobials;
- inadequate availability of quality drugs, fuelling demand for spurious, falsely labelled, falsified or counterfeit medicines;
- poor hospital infection prevention and control; and
- lack of awareness among health-care workers.

**BEYOND THE HEALTH SECTOR:**
- poor sanitation and environmental hygiene leading to greater incidence of infectious disease;
- low level of public awareness about antimicrobial resistance and its impact;
- lack of awareness and political commitment at government or policy level; and
- poor awareness and lack of national policies to combat antimicrobial resistance, conduct surveillance of antimicrobial resistance and monitor antimicrobial usage.
- widespread antibiotic usage in animal husbandry and aquaculture against a backdrop of lax or absent regulation and rapidly increasing demand for protein foods.
Table 1. Active surveillance programmes in the Western Pacific Region

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>PROGRAMME</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTIBACTERIAL RESISTANCE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Global Project on Anti-tuberculosis Resistance Surveillance (2)</td>
<td>Data collected by WHO collaborating centres, reference laboratories and other partners. Findings integrated into web-based reporting system. Data from 136 countries analysed and published in the Global Tuberculosis Report.</td>
</tr>
<tr>
<td>Gonorrhoea</td>
<td>WHO Gonorrhoea Antimicrobial Surveillance Programme (GASP) (3)</td>
<td>Global network based in Australia with 64 participating countries. GASP reports from Western Pacific Region published annually in the journal Communicable Diseases Intelligence.</td>
</tr>
<tr>
<td>Foodborne infections</td>
<td>Global Foodborne Infections Network (4)</td>
<td>Established by WHO, Danish Technical University and other partners. Capacity-building programme that promotes surveillance and intersectoral collaboration.</td>
</tr>
<tr>
<td>ANTIVIRAL RESISTANCE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>WHO Global HIV Drug Resistance Surveillance Network (5)</td>
<td>Global network of experts advises WHO on HIV drug resistance. Includes organizations implementing activities to control and monitor the emergence of HIV drug resistance in countries, individual experts, network of designated laboratories that perform quality-assured genotyping to support HIV drug resistance surveys.</td>
</tr>
<tr>
<td>ANTIPARASITIC RESISTANCE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>WHO global database</td>
<td>Summarizes findings from over 4000 studies. WHO standard protocol to assessment of therapeutic efficacy adopted worldwide. Covers all malaria drugs, including artemisinin-based therapies.</td>
</tr>
</tbody>
</table>

*Yes= High, No= Low
Surveillance of antimicrobial resistance

Surveillance, the systematic collection and analysis of health-related data, enables public health decision-makers to know the patterns of use and resistance. WHO has highlighted surveillance as a key component of antimicrobial resistance containment.

Although surveillance alone cannot reduce antimicrobial resistance, it is key to tracking the emergence and spread of resistant strains. It promotes awareness and informs decision-making on policies to reduce antimicrobial resistance in health-care facilities and in the community.

There are numerous mechanisms already in place to measure antimicrobial resistance in the Western Pacific (Table 1). Many are disease specific and comprise a part of disease control programmes focusing on (for example) HIV, tuberculosis or malaria. The Global Antimicrobial Surveillance System (GLASS) to systematically monitor antimicrobial resistance is currently being developed by WHO.

Monitoring antimicrobial use

Monitoring the frequency and volume of antimicrobial usage is essential. Armed with this information, health systems can harvest data on how antibiotics are being used and conduct gatekeeping to ensure that every antibiotic is appropriately prescribed. It is also needed to inform policy-making to contain resistance. However, in the Western Pacific there is little information on the status of antimicrobial use and resistance. WHO has proposed a regional system to monitor antimicrobial use, collecting data on antimicrobial use at all levels of the health system, and initiating collective action on containing antimicrobial resistance in the Region. Most of the WHO regions have such a network in place, although comparable indicators have not been established.

Containing antimicrobial resistance in the Western Pacific

Containing the growing threat of antimicrobial resistance cannot rely on individual, community-level or government effort alone. All sectors of society are affected and can contribute to the solution.

GOVERNMENT-LEVEL ACTION:

• develop and implement a comprehensive national plan to contain antimicrobial resistance and raise awareness in multiple sectors;

• promote awareness, leadership and financial commitment from all affected sectors;

• strengthen surveillance networks and laboratory capacity to monitor trends in usage and resistance;

• monitor human and animal use of antimicrobials and resistance, using globally agreed standards and approaches;

• adapt and institute good practices regarding effective regulation and enforcement to ensure availability of effective, safe and quality antimicrobials; and

• ensure equitable and universal access to prioritized antimicrobials by strengthening financing and procurement mechanisms for antimicrobials.

COMMUNITY-LEVEL ACTION:

• improve water supply, sanitation and basic community-level hygiene to reduce the incidence of infections and thereby reduce demand for antimicrobials; and

• conduct intensified public education campaigns to change social norms around antibiotic use and foster a community-wide approach to tackling antimicrobial resistance.

HEALTH SYSTEM-LEVEL ACTION:

• introduce stringent infection prevention and control measures in health-care facilities, for example, hand hygiene, screening and isolation of inpatients;

• ensure that education for all health-care workers covers rational use of antimicrobials, health facility infection prevention and control and other measures to contain antimicrobial resistance; and

• set up a mechanism for reporting community-acquired and hospital-acquired infections associated with antimicrobial resistance to ensure accurate data collection.

INDIVIDUAL-LEVEL ACTION:

• always finish a prescribed course of antibiotics;

• don’t self-prescribe or buy antibiotics over the counter; and

• practise good hand and food hygiene to reduce risk of infection.

National plans in the Western Pacific

AUSTRALIA

In 2015, Australia launched its first National Antimicrobial Resistance Strategy 2015–2019 (7). The strategy acknowledges the costs of antimicrobial resistance and the need for a “One Health” approach, encompassing human, animal and ecosystem health. It is based on a vision of “a society where antimicrobials are recognized and managed as a valuable shared resource, maintaining their efficacy so that infections in humans and animals remain treatable and communities continue to benefit from the advances that antimicrobials enable”. The plan lays out seven clear objectives and will be supported by a separate implementation plan with guidelines for monitoring and evaluation.
CAMBODIA
Cambodia has also developed a national policy to combat antimicrobial resistance, with a 2015–2017 national strategy launched in 2014. The strategy details seven components:
• commit to a master plan to combat antimicrobial resistance;
• strengthen laboratory capacity;
• strengthen antimicrobial resistance surveillance;
• ensure uninterrupted access to essential medicines of assured quality;
• regulate and promote rational use of medicines;
• enhance infection prevention and control; and
• foster innovations and research and development of new tools.

FIJI
During the first WHO-promoted antibiotic awareness week in 2015, Fiji launched its National Antimicrobial Resistance Action Plan. The five strategic objectives of the plan are:
• improve awareness and understanding of antimicrobial resistance through effective communication, education and training;
• strengthen nationally coordinated surveillance systems;
• reduce the incidence of antimicrobial resistance events through improved infection prevention and control, sanitation and hygiene, measures and implementation of wellness;
• optimize the use of antimicrobial medicines in human and animal health; and
• establish and ensure governance, sustainable investment and actions to combat antimicrobial resistance.

In addition, a national antimicrobial resistance committee was formed with the first task to develop an operational plan for the national action plan.

PHILIPPINES
In 2014 the Philippines Government issued Administrative Order No. 42, signed by the President, for the creation of an “interagency committee for the formulation and implementation of a national plan to combat antimicrobial resistance in the Philippines”. The order recognized the need for a government-led, interagency response, based on the WHO six-point health policy agenda for containing antimicrobial resistance. The committee will be co-chaired by the Department of Health and the Department of Agriculture, and members will include the Department of the Interior and Local Government, the Department of Science and Technology and the Department of Trade and Industry. In November 2015, the Philippines Action Plan to Combat Antimicrobial Resistance: One Health Approach was launched at the first Philippine Antimicrobial Resistance Summit.

VIET NAM
Viet Nam launched its Action Plan on Antimicrobial Resistance 2013–2020 to “promote activities to prevent drug resistance, contribute to improving the quality and effectiveness of the prevention and control of epidemics, and treatment to protect, care for and improve people’s health” (8).

It sets out six main activities to achieve this:
• raise awareness of the community and health workers on drug resistance;
• enhance and improve capacity of the national surveillance system for antibiotic use and antimicrobial resistance;
• ensure adequate supply of quality essential drugs;
• improve safe and rational use of medicine;
• strengthen infection control; and
• strengthen safe, appropriate antibiotic use in livestock, poultry, aquaculture and cultivation.

In June 2015, the country’s Ministry of Health, Ministry of Agriculture and Rural Development, Ministry of Industry and Trade, and Ministry of Natural Resources and Environment signed an aide-memoire on antimicrobial resistance, together with Viet Nam-based development partners including WHO, the Food and Agriculture Organization of the United Nations, the United Nations Children’s Fund, the United States Agency for International Development and the United States Centers for Disease Control and Prevention.

References
WHO'S RESPONSE

WHO has identified antimicrobial resistance as a global public health threat that calls for immediate containment efforts at the local, national, regional and global levels.

Global and regional policy guidance

2001: WHO GLOBAL STRATEGY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance was first recognized as a serious threat to public health in the late 1990s, and by 2001 WHO had developed its Global Strategy for Containment of Antimicrobial Resistance (1). This presented 87 prioritized recommendations for health-care workers, industry, researchers, media, patients’ representatives and national authorities. WHO has since been actively supporting Member States to develop their own national strategies and plans.

2011: WORLD HEALTH DAY

The theme of World Health Day 2011 was “Antimicrobial resistance: no action today, no cure tomorrow” (2). WHO introduced a six-point policy package to combat the spread of antimicrobial resistance:

1. commit to a comprehensive, financed national plan with accountability and civil society engagement;
2. strengthen surveillance and laboratory capacity;
3. ensure uninterrupted access to essential medicines of assured quality;
4. regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care;
5. enhance infection prevention and control; and
6. foster innovations and research and development for new tools.
In October 2014, Member States in the sixty-fifth session of the WHO Regional Committee for the Western Pacific endorsed the Action Agenda for Antimicrobial Resistance in the Western Pacific Region (Box 1) (3, 4). The agenda spells out specific priority actions that countries should take to strengthen their national plans, raise awareness of antimicrobial resistance and strengthen their health systems to better contain and monitor antimicrobial resistance.

The agenda also stresses the need for regional collaboration to share evidence, strengthen access to quality antimicrobial agents and improve infection prevention and control.

### 2014: ACTION AGENDA FOR ANTIMICROBIAL RESISTANCE IN THE WESTERN PACIFIC REGION

In October 2014, Member States in the sixty-fifth session of the WHO Regional Committee for the Western Pacific endorsed the Action Agenda for Antimicrobial Resistance in the Western Pacific Region (Box 1) (3, 4). The agenda spells out specific priority actions that countries should take to strengthen their national plans, raise awareness of antimicrobial resistance and strengthen their health systems to better contain and monitor antimicrobial resistance.

The agenda also stresses the need for regional collaboration to share evidence, strengthen access to quality antimicrobial agents and improve infection prevention and control.

### 2015: GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

The Sixty-eighth World Health Assembly passed a resolution adopting the Global Action Plan on Antimicrobial Resistance (5).

The action plan is based on five strategic objectives:

- to reduce the incidence of infection;
- to optimize the use of antimicrobial agents; and
- to ensure sustainable investment in countering antimicrobial resistance.

### Key WHO publications

**THE EVOLVING THREAT OF ANTIMICROBIAL RESISTANCE: OPTIONS FOR ACTION**

The evolving threat of antimicrobial resistance: options for action (6), published in 2012, examines the experiences with interventions that address the growing threat of antimicrobial resistance, describes the lessons learnt along the way and highlights the gaps still remaining. It draws attention to areas where knowledge is lacking and where urgent action is still needed.
ANTIMICROBIAL RESISTANCE: GLOBAL REPORT ON SURVEILLANCE
WHO’s first major global report on antimicrobial resistance (7), including antibiotic resistance, was published in 2014, and revealed that this serious threat is no longer a prediction for the future.

It is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country. Antibiotic resistance in particular was highlighted as a clear and present danger to public health.

The report, while noting that resistance is occurring across many different infectious agents, focuses on antibiotic resistance in seven different bacteria responsible for common serious diseases such as bloodstream infections, diarrhoea, pneumonia, urinary tract infections and gonorrhoea. The results are cause for high concern, documenting resistance to antibiotics, especially “last-resort” antibiotics, in all regions of the world.

WORLDWIDE COUNTRY SITUATION ANALYSIS: RESPONSE TO ANTIMICROBIAL RESISTANCE
The 2015 report, Worldwide country situation analysis: response to antimicrobial resistance (8) outlines the findings of a survey of WHO Member States, which reveals that while much activity is under way and many governments are committed to addressing the problem, there are major gaps in actions needed across all six WHO regions to prevent the misuse of antibiotics and reduce spread of antimicrobial resistance.

It summarizes current practices and structures aimed to address the issue, and shows there are significant areas for improvement.

ANTIMICROBIAL RESISTANCE IN THE WESTERN PACIFIC REGION: A REVIEW OF SURVEILLANCE AND HEALTH SYSTEMS RESPONSE
This 2015 publication (9) details how antimicrobial resistance is reaching alarming levels in the Western Pacific Region. The document provides an in-depth situational review and technical discussion on surveillance, monitoring of antimicrobial use and the health systems response, for the containment of antimicrobial resistance in the Region.

References
Efforts to contain antimicrobial resistance are gathering pace around the world, and there is also much work under way on the development of new antibiotics, alternatives to antibiotics and diagnostic testing.

This field offers much cause for optimism, particularly given the rapid advances in genetics, genomics and computer science. Research into better and faster diagnostic tests to ensure antibiotics are targeted to where they can be most effective is another active area.

There are growing calls for changes in animal husbandry and aquaculture practices, from both the public and the scientific community. On a more fundamental level, sanitation, water supply and basic public health measures and health care are improving in many lower- and middle-income countries, which should lead to reductions in infectious disease incidence.
New antibiotics

Despite being a highly profitable market, with estimated global sales of US$ 40 billion, the antibiotics market does not incentivize research and development (1). The faster resistance emerges, the less profitable it is to invest in new antimicrobial drug development. The commercial return on a new class of antibiotics is also to some extent dependent on the resistance of existing generations of drugs (1). According to data from the Pew Charitable Trusts, as of December 2014, there were an estimated 37 new antibiotics that have the potential to treat serious bacterial infections in clinical development for the United States of America market. However, given the typical success rate for drug development, it is likely that only one fifth will progress to clinical testing in humans and approval for patient use (2).

For those drugs that do make it to market, the current market mechanism contributes to the growth of antibiotic resistance by incentivizing manufacturers to sell large quantities of new antibiotics. One suggestion is the creation of a global antimicrobial research innovation fund to provide funding for blue-sky research into drugs and diagnostics and delink drug profitability from sales volume (1).

Even though the current market environment is not especially favourable to new antibiotic development, research and development continues. For example, researchers at the University of Queensland in Australia are working to find antibiotics capable of combating superbug bacteria through the Community for Open Antimicrobial Drug Discovery (3). The initiative, funded by the Wellcome Trust, invites chemists to submit their existing compounds for free screening for antimicrobial activity. As of June 2015, the initiative aimed to screen over 50 000 compounds in the following 18 months.

Alternatives to antibiotics

PREDATORY BACTERIA AND PHAGES

Phages are viruses that attack bacteria. They have been in clinical use since phage therapies were developed by scientists in the Soviet Union in the 1920s, and they continue to be used in former countries of the Eastern bloc. The United States National Institute of Allergy and Infectious Diseases considers phages to be one of the priority areas of research to counter antibiotic resistance (4).

Researchers are investigating phages in animal models and cell culture. Examples include Bdellovibrio bacteriovorus (found in soil), Micavibrio aeruginosavorus and an engineered version of the gut bacterium Escherichia coli to prey on pneumonia-causing Pseudomonas aeruginosa. The field has attracted US$ 16 million in funding under the Pathogen Predators programme of the United States Defense Advanced Research Projects Agency (5).

ANTIMICROBIAL PEPTIDES

Small proteins (peptides) that destroy bacteria are found in all plants, animals and fungi, and those found in amphibians and reptiles, animals that are particularly resistant to infection may lead to new therapeutic compounds for use in humans. One compound, pexiganan, based on a peptide from frog skin, has gone into phase III clinical trials to treat diabetic foot ulcers (5).

Other new developments to combat antimicrobial resistance

DRUGS TO WEAKEN BACTERIA

In 2013, IBM Research and the Institute of Bioengineering and Nanotechnology announced the development of an antimicrobial hydrogel that destroys drug-resistant bacteria such as MRSA. Hydrogels are typically used in household cleaners such as alcohol and bleach, but so far have not been suitable for therapeutic use. The researchers developed a molecular structure such that materials can remain in place under typical physiological conditions while still demonstrating antimicrobial activity (13). This means the same antimicrobials can be used in hydrogels that can break through diseased biofilms on, for example, medical equipment, bed rails and other surfaces in a hospital environment. They can also be used in creams and other therapeutic products applied directly to contaminated parts of the body (14).

BETTER RAPID TESTING FOR INFECTIONS

In everyday clinical situations it can be difficult for doctors to distinguish between viral and bacterial causes of, for example, upper respiratory tract infections or infections of the ear canal during a patient consultation, and one of the main abuses of antibiotics is prescription for viral infections. A new blood test under development can distinguish between bacterial and viral infections, with results available in a few hours. The test has not yet been released but has already been approved for use in the European Union (15).

CHANGES TO ANIMAL HUSBANDRY AND AQUACULTURE PRACTICES

In the face of mounting evidence of antimicrobial resistance due to use in food production, there are also growing calls for radical changes in the way meat and fish are produced. Tyson Foods, the single largest producer of poultry in the United States, announced in April 2015 that it would stop using human antibiotics in poultry rearing by 2017 (16). This followed a pledge from McDonald’s Corporation that by March 2017 it would no longer buy chicken fed with human antibiotics (17).

UNIVERSAL HEALTH COVERAGE AND HEALTH SYSTEMS STRENGTHENING

All countries in the Western Pacific Region have made a commitment to strive for universal health coverage – ensuring that all people can use the promotive, preventive,
curative, rehabilitative and palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship. This requires countries to work hard on health systems strengthening, a process that can help in the fight against antimicrobial resistance. Moreover, most countries in the Region are experiencing rapid economic and social development, with standards of sanitation, public hygiene and infrastructure undergoing significant improvements. This should lead to lower levels of infectious disease.

DISCLAIMER: WHO does not endorse any products or organizations mentioned in the text.
With the emergence and spread of multidrug- and pandrug-resistant microorganisms, urgent action is needed across all sectors to contain antimicrobial resistance in the Western Pacific Region.

Stories to watch

UNTREATABLE DISEASES
There are already emerging cases of multidrug-resistant, extensively multidrug-resistant and completely resistant diseases. Cases to watch include tuberculosis and gonorrhoea. In addition, what were previously only hospital-acquired infections are now also found in the community, a trend that is likely to continue.

Diseases to watch: tuberculosis, gonorrhoea, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and *Clostridium difficile*.

CHANGES IN ANIMAL HUSBANDRY
The bad news is that contamination of meat, poultry, fish and seafood with resistant bacteria (for example, MRSA, *Escherichia coli* and *Salmonella* spp.) and antibiotic residue is likely to continue and even escalate as antibiotic use continues to rise. The good news is that there are increasing demands by the food industry and consumers for antibiotic-free food.

NATIONAL ACTION
Building on WHO’s support for national-level action to contain antimicrobial resistance, more countries in the Western Pacific can be expected to formulate national policies, strategies and plans. Other stories to watch include the development and implementation of existing plans, notably: Viet Nam’s new political commitment; antimicrobial stewardship in China; and Australia’s new antimicrobial resistance programme.
BETTER SURVEILLANCE
The Japan Nosocomial Infections Surveillance (JANIS) programme uses a sophisticated system to provide basic information on the incidence and prevalence of hospital-acquired infections and antimicrobial-resistant bacteria in Japanese medical facilities. Launched in 2000, its membership (which is voluntary) includes more than 1000 hospitals across Japan, which enables it to provide representative national-level epidemiological data.

Useful links

ANTIMICROBIAL RESISTANCE
WHO page on antimicrobial resistance: http://www.who.int/topics/drug_resistance/en/

Review on antimicrobial resistance: http://amr-review.org/

ANTIBIOTICS AND ANTIBIOTIC RESISTANCE

Alliance for the Prudent Use of Antibiotics: http://www.tufts.edu/med/apua/


US Centers for Disease Control and Prevention Get Smart Program: http://www.cdc.gov/getsmart/


ANIMAL HUSBANDRY AND FOOD PRODUCTION
WHO page on food safety and antimicrobial resistance: http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/en/


World Organization for Animal Health information for the media: http://www.oie.int/for-the-media/amr/

Institute for Agriculture and Trade Policy: http://www.iatp.org

PRESENTATIONS


VIDEOS AND TED TALKS
Misuse of antibiotics: the consequences. Otto Cars, founder of ReAct and Professor of Infectious Diseases at Uppsala University in Sweden: https://vimeo.com/84578072

Antimicrobial resistance: antibiotics in the livestock sector and their impact on public health. FAO: https://www.youtube.com/watch?v=N06gmbzs-Pc

What do we do when antibiotics don’t work any more? Maryn McKenna: https://www.ted.com/talks/maryn_mckenna_what_do_we_do_when_antibiotics_don_t_work_any_more?language=en


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