WHO Policy Perspectives on Medicines

10

Containing antimicrobial resistance

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The problem of antimicrobial resistance

Antimicrobial resistance (AMR) is one of the world's most serious public health problems. Many of the microbes (bacteria, viruses, protozoa) that cause infectious disease no longer respond to common antimicrobial drugs (antibacterial drugs including antibiotics, antiviral and antiprotozoal drugs). The problem is so serious that unless concerted action is taken worldwide, we run the risk of returning to the pre-antibiotic era when many more children than now died of infectious diseases and major surgery was impossible due to the risk of infection. The major infectious diseases kill over 11 million people per year. Box 1 shows some AMR prevalence rates, which can vary widely between and within countries, and over time.

Box 1 AMR global prevalence rates

Malaria
- chloroquine resistance in 81/92 countries

Tuberculosis (TB)
- 0–17% primary multi-drug resistance

HIV/AIDS
- 0–25% primary resistance to at least one antiretroviral drug

Gonorrhoea
- 5–98% penicillin resistance in *Neisseria gonorrhoeae*

Pneumonia and bacterial meningitis
- 0–70% penicillin resistance in *Streptococcus pneumoniae*

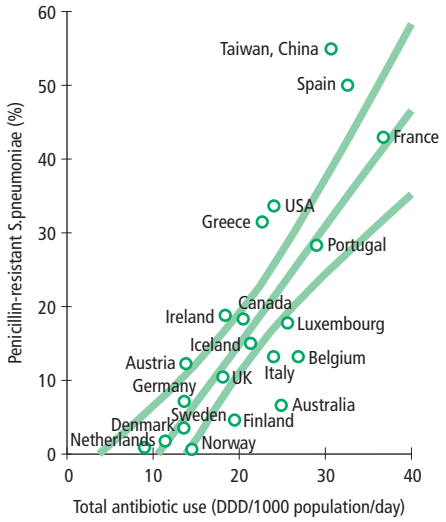
Diarrhoea: shigellosis
- 10–90% ampicillin resistance, 5–95% cotrimoxazole resistance

Hospital infections
- 0–70% resistance of *Staphylococcus aureus* to all penicillins and cephalosporins

Source: WHO country data, 2000–03

Emergence of AMR is a natural phenomenon that follows use of antimicrobials but it is being accelerated by inappropriate antimicrobial use. Higher consumption is associated with higher resistance levels (Fig.1). Estimates suggest that perhaps half of all antibiotic consumption may be unnecessary. In many countries, antimicrobials are bought directly from drug outlets without a prescription or advice from a trained health professional.

Figure 1 Correlation between penicillin-resistant (non-susceptible) pneumococci and out-patient antibiotic use (showing bands with 95% confidence intervals)

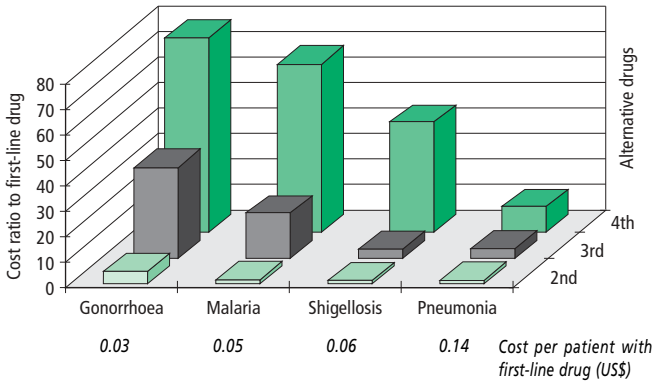


Source: Albrich WC, Monnet DL and Harbarth S, Emerg Infect Dis.; 2004; 10(3):514–7

Doctors' response to AMR has been to switch patients from older antibiotics to newer ones, but new development of these is declining as the pharmaceutical industry has shifted from antibiotics to developing other medicines with potentially larger markets (e.g. for chronic non-infectious illness). Even if new antibiotics are developed, resistance to them would also develop; so prudent use of antibiotics is essential to maintain their effectiveness for future generations.

Serious clinical and financial consequences result from AMR. Morbidity and mortality are increased by delays in administering effective treatment for infections caused by resistant microorganisms. Prolonged illness and hospitalisation are costly and the use of drugs other than first-line drugs may increase costs 100-fold (Fig. 2) making them unaffordable for many

Figure 2 Cost ratio of alternative drugs to first-line antimicrobials for common acute infections



Source: Adapted from WHO Model Formulary, WHO clinical guidelines and Management Sciences for Health's 2004 International Drug Price Indicator Guide

governments and patients especially in developing countries.

Measuring the problem through surveillance

Surveillance is critical to containing the problem of AMR and requires monitoring over time the magnitude and trends in AMR and antimicrobial use and using the data to design interventions and measure their impact.

Epidemiological surveillance of antimicrobial resistance

Resistance varies widely with geographical location, type of community and level of health facility. Therefore local surveillance data should be used to guide clinical management and update clinical guidelines, educate prescribers and guide infection control policies. Data should distinguish between hospital nosocomial and community-acquired infections and should exclude duplicate isolates from the same patient.

A national antimicrobial surveillance system should consist of:

- national reference microbiology laboratory facilities to coordinate epidemiologically sound surveillance of AMR in common pathogens in the community, hospitals and other health care facilities;
- a network of laboratories, all with adequate internal and external quality assurance, that regularly collect and report relevant resistance data and provide quality microbiological diagnostic services.

Surveillance of antimicrobial use

Antimicrobial use should be monitored in terms of the type and degree of irrational use and several well-established methods exist. Aggregate antimicrobial drug consumption data can be used to identify the most expensive and highly used antimicrobials, or to compare actual consumption with expected consumption (from morbidity data). Anatomical Therapeutic Classification (ATC) / Defined Daily Dose (DDD) methodology can be used to compare antimicrobial consumption across institutions, regions and countries. Indicators can be used to investigate antimicrobial use in primary health care, e.g.:

- % patients prescribed antibiotics;
- % of upper respiratory tract cases (usually viral) treated with antibiotics;
- % of diarrhoeal cases (usually viral) treated with antibiotics;
- % cases with infections treated in accordance with clinical guidelines.

Focused antimicrobial use evaluation (drug utilization review) can identify problems concerning the use of specific antimicrobials or the treatment of specific infections, particularly in hospitals.

Reasons underlying inappropriate use should be investigated intermittently and include diagnostic insecurity, prescriber knowledge and habit, unrestricted availability of antimicrobials, overwork, inappropriate promotion of antimicrobials, profit motives and fear of litigation. Understanding such reasons allows appropriate, effective corrective strategies to be chosen.

Core national strategies to contain AMR

Core national strategies to contain AMR are summarised below, based on WHO's *Global Strategy for Containment of AMR* and *Promoting Rational Use of Medicines: Core Components.*

1. Mandated multidisciplinary national task force to coordinate policies and strategies to contain AMR

Many factors contribute to how antimicrobials are used. Therefore, a multidisciplinary approach is needed to develop, implement and evaluate interventions to promote optimal use of antimicrobials and improve infection control programmes.

An adequately resourced task force is needed to coordinate policy and strategies at national level, in both the public and private health sectors. The form of the task force may vary, but it should always involve government (ministry of health), the national reference microbiology laboratory, the health professions (doctors, pharmacists, nurses), academia, the national drug regulatory authority, pharmaceutical industry, consumer groups and NGOs involved in health care. The impact on AMR and use is better if multiple interventions are implemented in a coordinated way. Single interventions are likely to have little impact.

The task force should liaise with all the stakeholders involved in non-human use (including the ministry of agriculture) to develop a national containment programme (see section 10). In addition, the task force should liaise with those responsible for implementing and monitoring population-wide infection control programmes. Such programmes include:

- safe water and sanitation;
- immunization – if people do not contract infectious diseases they do not need antibiotics;
- public education on hygiene and prevention, e.g. hand washing, bed nets, condoms;
- TB, HIV and malaria control programmes;
- cross-infection control in hospitals.

Knowing how well these programmes are being implemented is essential in deciding where to focus efforts to contain resistance.

2. National reference microbiology laboratory coordinating a network of reliable diagnostic microbiology laboratories

Epidemiologically sound surveillance of AMR in key pathogens, using standardised microbiological methods, can be developed on the basis of existing laboratories undertaking diagnostic services and surveillance. To ensure reliable, good quality, epidemiologically sound data, a coordinating national reference laboratory is needed. This laboratory should establish standardised methods, provide external quality assurance for all the participating laboratories and take part in external quality assurance.

Many antimicrobials are prescribed unnecessarily because prescribers are unsure of the diagnosis. Diagnostic procedures help to ensure that antimicrobials are prescribed only when needed. For example, using malaria blood smears in hospitals helps to ensure that patients with malaria are treated with antimalarials and not with unnecessary antibiotics. Sputum microscopy for TB helps to ensure that TB patients are treated with anti-TB drugs and not with inappropriate antibiotics. Quality control for diagnostic procedures, including microscopy, is vital, or false diagnoses will be made or true diagnoses missed, and prescribers will not trust the laboratory.

3. Public education on preventing infection and reducing transmission

People should have the skills and knowledge to make informed decisions about how to prevent infection and reduce transmission of infectious diseases through simple, cheap and effective measures. Such measures include prevention of:

- diarrhoeal disease through hand washing, using safe water sources and containers, boiling unsafe water and using latrines;
- malaria through the use of bed nets impregnated with insecticide;
- sexually transmitted infections through the use of condoms;
- certain infectious diseases through routine childhood vaccination (diptheria, measles, pertussis, Haemohilus influenzae, pneumococcus) and epidemic vaccination (meningitis, typhoid);
- HIV/AIDS and hepatitis B and C through the avoidance of injections (unless oral medicines cannot be used, in which case a sterile needle and syringe must be used).

Governments have a responsibility to provide unbiased information to the community. They can run targeted public education campaigns, taking into account cultural beliefs and the influence of social factors. The important message is that antimicrobials should only be used to treat certain specific diseases; their use in other contexts is ineffective and counterproductive, since they can accelerate the emergence of AMR. Education on preventive measures can be introduced into school health education or into adult education, e.g. literacy and antenatal programmes.

4. Provider education on diagnosis and management of common infections, antimicrobial use, containment of AMR, disease prevention, infection control

All providers, including doctors, pharmacists, nurses, paramedical workers, and drug sellers, should be taught about the issues surrounding AMR. Topics include accurate diagnosis and management of common infections, antimicrobial use, infection control and disease prevention. This education should be provided through:

- undergraduate training for pre-service students;
- postgraduate training and continuing professional development (CPD) programmes for all cadres of in-service personnel including intern doctors.

Unfortunately, relevant AMR topics are often omitted in education programmes, opportunities for CPD are limited, and CPD is not a compulsory licensure requirement. Also, CPD activities are often heavily dependent upon pharmaceutical companies, which may be more interested in promoting their own antimicrobial sales. Governments should therefore support financially efforts by universities and national professional associations to give independent CPD covering AMR issues; promote the provision of unbiased information to prescribers; and regulate drug promotional activities.

5. Development, updating and use of essential medicines lists and clinical guidelines

Evidence-based, regularly updated essential medicines lists and clinical guidelines, for each level of care,

are vital for promoting rational use of medicines. Antimicrobial guidelines and treatment algorithms for infectious diseases may further aid rational use of antimicrobials. If there are reliable data, local AMR trends for infectious diseases should be considered when deciding upon inclusion of each antimicrobial. Governments should ensure that:

- public sector medicine procurement is based on the national medicines list;
- all training institutions include the national clinical guidelines in their training programmes;
- public sector reimbursement policies are based on the national essential medicines list or clinical guidelines.

When possible the shortest effective course of antimicrobial therapy (as indicated by the evidence) should be adopted in the guidelines. Shorter courses of antimicrobial therapy are associated with the development of less resistance than longer courses. The use of fixed-dose combinations, particularly for HIV, TB and malaria is associated with increased patient adherence and will be less likely to stimulate AMR emergence as compared to single-drug treatments.

6. Infection Control Committees to implement infection control programmes in hospitals

Hospitals and nursing homes are breeding grounds for the development and spread of AMR due to the close proximity of patients who have infections and are receiving antimicrobials. An Infection Control Committee (ICC) is responsible for administering infection control programmes in hospitals. The ICC should include, as a minimum, an infection control nurse in small hospitals and a clinical microbiologist, infectious disease specialist and surgeon in larger hospitals. The ICC should liaise closely with the Drug and Therapeutics Committee (DTC) or its antimicrobial sub-committee. An ICC should undertake:

- active surveillance of infections and AMR in order to detect, and manage, outbreaks of nosocomial (hospital-acquired) infection; this requires regular collation and assessment of resistance data from a microbiology laboratory;
- investigation and management of outbreaks or clusters of susceptible and resistant infections;
- interventions to prevent infections, including health worker and patient education;
- development and implementation of policies and procedures to prevent the transmission of infections (Box 2).

7. Drug and Therapeutics Committees and antimicrobial subcommittees to promote the safe, effective use of antimicrobials

Drug and Therapeutics Committees (DTCs) and their antimicrobial sub-committees have been successful in industrialised countries in promoting more rational, cost-effective use of medicines and antimicrobials in hospitals (Box 3). Governments may encourage hospitals and local health authorities to have DTCs by making it an accreditation requirement. Members should represent all the major specialities, the pharmacy and the administration, and declare any potential conflict of interest (such as shares in a wholesaler supplying the hospital). A clinical microbiologist and infectious disease specialist should sit on both the antimicrobial subcommittee (or DTC) and the ICC.

8. Restriction of availability of antimicrobials

This reduces misuse and may be done in two ways.

(1) Restricting antimicrobial availability to prescription-only from licensed outlets

Misuse of antimicrobials may be curbed by enforcing regulations to limit their availability to licensed

Box 2 Preventing transmission of infections in hospitals

1. Hand washing or alcohol-based rinses by staff between patients and before undertaking any procedures e.g. injections.
2. Use of barrier precautions, e.g. wearing gloves and gowns for certain agreed procedures.
3. Adequate sterilization and disinfection of supplies and equipment.
4. Use of sterile techniques, together with protocols, for medical and nursing procedures, e.g. bladder catheterization, administration of injections, insertion of intravenous cannulas, use of respirators, sterilization of equipment, other surgical procedures.
5. Maintenance of appropriate disinfection or sanitary control of the hospital environment, including:
   - adequate ventilation;
   - cleaning of the wards, operating theatre, laundry, etc.;
   - provision of adequate water supply and sanitation;
   - safe food handling;
   - safe disposal of infectious equipment, e.g. dirty needles;
   - safe disposal of infectious body fluids, e.g. sputum.
6. Isolation of infectious patients from other non-infected patients, e.g. separation of suspected and proven sputum-positive TB cases (particularly from HIV-positive patients).
7. Visiting policies such as preventing visitors with infections from visiting patients who may be immuno-compromised, e.g. patients with AIDS or leukaemia or premature babies.
8. Training of health-care staff in appropriate sterile techniques and infection control procedures.

Box 3 Responsibilities of the DTC or antimicrobial committee

- developing, adapting, or adopting clinical guidelines for infectious diseases and antimicrobial guidelines, using local AMR data if possible;
- selecting cost-effective, safe antimicrobials for the formulary, using local AMR data if possible;
- monitoring antimicrobial consumption and use patterns;
- developing policies on the use of antimicrobials by level of prescriber; this includes limiting certain antimicrobials to use only with approval by the DTC or senior prescriber;
- implementing and evaluating strategies to improve antimicrobial use (including drug use evaluation, and liaison with the ICC);
- providing on-going staff education on antimicrobial use (training and printed materials);
- liaising with the ICC with regard to assessing and using local AMR data.

outlets upon receipt of a prescription written by a licensed prescriber. If the availability of all antimicrobials cannot be controlled by this method, certain ones (e.g. vancomycin for methicillin-resistant *Staphylococcus aureus* and the newer cephalosporins and fluoroquinolones) should be restricted in this way.

(2) Classification of antimicrobials by level of prescriber and based on local conditions

Classification of antimicrobials is applicable at all levels of health care. In primary health care facilities and hospitals without laboratories, it may not be possible to distinguish between "restricted" and "very restricted" and the two categories may be treated as one.

Antimicrobials for non-restricted use by any prescriber are safe, effective and reasonably priced, e.g. amoxicillin, and may be prescribed without approval by senior prescribers or the antimicrobial and infection control subcommittees.

Restricted antimicrobials may be more expensive and/or have a wider spectrum of activity, e.g. ceftriaxone or vancomycin. They should only be used for (1) specific infections known to be sensitive to the antimicrobial (after culture and susceptibility testing), or (2) empirical emergency treatment of suspected serious or life-threatening infections pending the result of culture and sensitivity testing. Use of these antimicrobials would require countersignature by a senior physician who has the approval of the DTC for such an activity.

Very restricted antimicrobials are those such as linezolid or meropenem that should be reserved for life-threatening infections where culture and sensitivity testing has indicated resistance to other effective and less expensive antimicrobials. Approval for use in each individual patient must be given by the clinical microbiologist or the DTC itself.

9. Granting marketing authorisation only to antimicrobials meeting international standards of quality, safety and efficacy

Poor quality antimicrobials may result in under-dosage, leading to poor patient outcome and increased AMR through the selection of resistant organisms. The increasing quantity of counterfeit and substandard antimicrobials available worldwide requires vigilance by governments, importers, retailers, the pharmaceutical industry and health professionals. Ensuring quality through enforced regulation, good procurement practice and post-marketing surveillance is essential to containing AMR.

10. Controlling non-human use of antimicrobials

Only about half of all antibiotics are consumed by humans. Most of the rest are added to animal feed

Box 4 Controlling non-human use of antimicrobials

(1) Surveillance by data collection from manufacturers, distributors including feed mills, pharmacies, veterinarians, farmers, and animal producers. The data should cover:
- AMR in animals;
- antimicrobial use in food animals for infections, prophylaxis and as growth promoters;
- national import and export of bulk chemicals with potential antimicrobial use;
- levels of antimicrobial agent residues in food from animal sources.

(2) Reducing and eventually stopping use of all antimicrobial growth promoters in food animals by:
- banning growth promoters used in human therapeutics, or known to select for cross-resistance to antimicrobials used in humans, as soon as possible;
- replacing all growth promoters with safer non-antimicrobial alternatives (e.g. improved animal hygiene) as soon as possible.

(3) Establishing an effective regulatory and control system for all antimicrobials used in agriculture:
- registration of all antimicrobial products used for food animals and in agriculture;
- ensuring that all antimicrobial products used for food animals and in agriculture are of adequate quality and are manufactured according to good manufacturing practices;
- licensing of manufacturers, distributors, and personnel selling or prescribing any antimicrobial products used for food animals or in agriculture.

(4) Education of all stakeholders in the agricultural sector on AMR and the appropriate use of antimicrobial products.

(particularly pigs and poultry) for mass treatment against infectious diseases or for growth promotion. Antimicrobials are also added to water to treat fish diseases and sprayed on to food crops to treat disease (e.g. fire blight in apples). Most antimicrobials registered for human use are also registered for animal use but regulation, such as licensing of prescribers, dispensers and outlets, is much less stringently applied in the agricultural sector. Although the majority of human AMR results from human use, there is evidence of significant spread of certain resistant bacteria (e.g. *salmonella, campylobacter, enterococcus)* from animals to humans. Box 4 lists the major recommendations to control non-human use.

Conclusion

A national programme is needed to undertake surveillance of antimicrobial use and resistance and, based on this data, to develop, implement and evaluate strategies to contain AMR. Critical to success are:

1. an adequately funded, mandated, multidisciplinary, national task force to coordinate strategies to contain AMR;
2. a national reference microbiology laboratory to coordinate a network of reliable diagnostic microbiology laboratories;
3. government investment in the health system infrastructure to ensure the controlled availability of appropriate antimicrobials, and adequately trained personnel to prescribe and dispense them.

Key Documents

World Health Organization. *How to Investigate Drug Use in Health Facilities: Selected Drug Use Indicators.* Geneva: WHO; 1993 (WHO/DAP/93.1).

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All documents available on http://www.who.int/medicines

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