

The antimicrobial resistance containment and surveillance approach — a public health tool

Gunnar S. Simonsen,¹ John W. Tapsall,² Benedetta Allegranzi,³ Elizabeth A. Talbot,⁴ & Stefano Lazzari⁵

Abstract Antimicrobial drug resistance (AMR) is widely recognized as a global public health threat because it endangers the effectiveness of treatment of infectious diseases. In 2001 WHO issued the Global Strategy for Containment of Antimicrobial Resistance, but it has proved difficult to translate the recommendations of the Global Strategy into effective public health actions. The purpose of the Antimicrobial Resistance Containment and Surveillance (ARCS) approach is to facilitate the formulation of public health programmes and the mobilization of human and financial resources for the containment of AMR. The ARCS approach highlights the fundamental link between rational drug use and containment of AMR. Clinical management of human and animal infections should be improved through better disease control and prevention, high quality diagnostic testing, appropriate treatment regimens and consumer health education. At the same time, systems for supplying antimicrobial drugs should include appropriate regulations, lists of essential drugs, and functional mechanisms for the approval and delivery of drugs. Containment of AMR is defined in the ARCS approach as the continuous application of this package of core interventions. Surveillance of the extent and trends of antimicrobial resistance as well as the supply, selection and use of antimicrobial drugs should be established to monitor the process and outcome of containment of AMR. The ARCS approach is represented in the ARCS diagram (Fig. 2) which provides a simplified, but comprehensive illustration of the complex problem of containment and monitoring of AMR.

Keywords Drug resistance; Drug resistance, Microbial; Anti-infective agents/supply and distribution/pharmacology; Prescriptions, Drug; Patient compliance; Legislation, Drug; Communicable diseases/diagnosis; Practice guidelines (*source: MeSH, INSERM*).

Mots clés Résistance aux médicaments; Résistance microbienne aux médicaments; Antiinfectieux/ressources et distribution/pharmacologie; Ordonnance médicale médicament; Observance prescription; Législation pharmaceutique; Maladie transmissible/diagnostic; Ligne directrice pratique médicale (*source: MeSH, NLM*).

Palabras clave Resistencia a las drogas; Resistencia microbiana a las drogas; Agentes antiinfectivos/provisión y distribución/farmacología; Prescripción de medicamentos; Cooperación del paciente; Legislación de medicamentos; Enfermedades transmisibles/diagnóstico; Pautas prácticas (*fuentes: DeCS, BIREME*).

Arabic

Bulletin of the World Health Organization 2004;82:928-934.

Voir page 932 le résumé en français. En la página 933 figura un resumen en español.

Introduction

Antimicrobial drug resistance (AMR) jeopardizes the effectiveness of the treatment of bacterial, viral, fungal and parasitic infections worldwide (1). The emergence and spread of AMR are the result of the selective pressure exerted by use of antimicrobial agents and the transmission of resistant microorganisms both in hospitals and in the community. Antimicrobial resistance has become a global public health problem. Resistance to antituberculosis drugs is spreading widely in countries of Africa, the Americas, Asia and Europe causing a serious threat to public health (2). Following the global dissemination of chloroquine and sulfadoxine-pyrimethamine resistance, the treatment of *Plasmodium falciparum* malaria in most countries has had to rely on combination therapy with or without artemisinin and

its derivatives (3). The rapid selection of resistant mutant strains in human immunodeficiency virus (HIV)-positive patients undergoing treatment with antiretrovirals (ARVs) often leads to therapeutic failure and is a serious concern at a time when a major global effort is under way to increase access to these drugs in developing countries (4). Community-acquired respiratory pathogens, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*; sexually transmitted microorganisms such as *Neisseria gonorrhoeae*; and enteric pathogens such as *Shigella* spp. and *Salmonella* spp., frequently become resistant to first-line antibiotics making treatment much more complicated and costly (5–7). In hospitals, the emergence and dissemination of methicillin-resistant staphylococci; vancomycin-resistant enterococci; and multidrug-resistant Gram-negative bacilli,

¹ Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM), Department of Microbiology, University Hospital of North Norway, N-9038 Tromsø, Norway. Correspondence should be sent to this author (email: gunnar.skov.simonsen@unn.no).

² WHO Collaborating Centre for STD and HIV, The Prince of Wales Hospital, Sydney, Australia.

³ Department of Infectious Diseases, University of Verona, Verona, Italy.

⁴ Division of TB Elimination, Centers for Disease Control and Prevention, Atlanta GA, USA.

⁵ Director, CSR, Lyon, France.

Ref. No. 03-009100

(Submitted: 29 October 2003 – Final revised version received: 31 May 2004 – Accepted: 8 June 2004)

including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, are seriously limiting the options for treatment with antimicrobials, especially in critically ill patients (8–11).

Although many factors contribute to this deteriorating situation, the use of antimicrobials is the single most important determinant of resistance. Overuse and misuse result from poor prescribing behaviour, uninformed patient demand and lack of adherence to the treatment regimen prescribed. Low-quality drug formulations, inadequate dosage regimens and insufficient duration of therapy are also important contributors to AMR. The aggregation of highly susceptible patients, the intensive and prolonged use of antibiotics and the lack of implementation of standard practices for infection control are often responsible for the emergence, selection and spread of multi-resistant pathogens in hospitals and other health-care settings. Inappropriate use of antimicrobials also extends to the veterinary and agricultural fields. Large volumes of antibiotics (50% of the total global consumption) are administered to food-producing animals for prophylaxis, treatment and growth promotion purposes. About 80% of these administrations have been reported to be unnecessary and this practice may affect human health both because of the presence of drug residues in foods and the selection of resistant bacteria in animals (12).

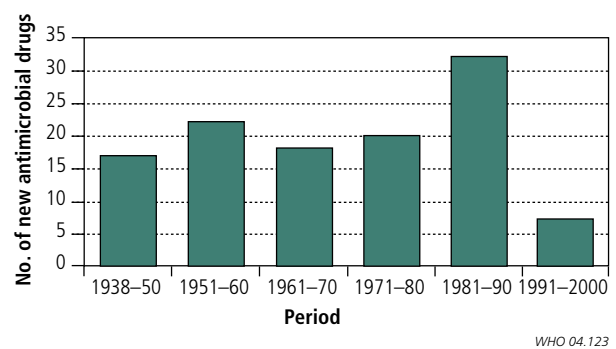
In 2001, in response to this threat, WHO released the *Global Strategy for Containment of Antimicrobial Resistance* (13). The Global Strategy includes 14 priority interventions and 67 recommendations in the areas of advocacy, education, management and regulation of drug use. However, the effective management of AMR in a public health context is challenging because AMR is a group of problems involving diverse pathogens transmitted in unique ways that cause a wide range of clinical syndromes. As a consequence there is no single intervention likely to be completely effective in preventing and containing AMR and it has proved difficult to develop integrated public health programmes for this purpose. Furthermore, difficulties in documenting both the impact of AMR and the results of isolated or grouped interventions to control it have hampered the identification of simple strategies and targets for containment programmes. In addition, powerful market forces influence the development, distribution and use of antimicrobial drugs in human and veterinary medicine. These forces have the potential to stimulate the development and distribution of new drugs, but may at the same time promote overuse and misuse of antimicrobials and thus act counter to AMR containment programmes. Finally, in recent years, the lack of economic incentives combined with increasing development costs has led to a decreased interest in the development of new antimicrobial drugs (Fig. 1) (14). The Antimicrobial Resistance Containment and Surveillance (ARCS) approach addresses some of these challenges by proposing a practical implementation “package” of effective interventions for the containment of AMR.

The ARCS approach

The ARCS approach (Fig. 2) illustrates the essential link between infections in humans and animals, and the need for appropriate treatment with quality antimicrobial drugs and containment of antimicrobial resistance. The ARCS approach is a generic one, applicable to different geographical or socioeconomic settings, and to different infectious diseases, regardless of availability of resources and organization of health-care systems.

The fundamental axiom is that if the use of antimicrobials inevitably leads to the development of AMR, inappropriate drug use will accelerate and exacerbate its emergence

Fig. 1. New antimicrobial drugs licensed from 1938–2000, per 10-year period, excluding antiviral drugs



and spread. Containment of drug resistance is therefore based on rational drug use, defined as the cost-effective use of antimicrobials that maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of resistance to antimicrobials. The use of antimicrobial drugs is influenced by determinants related to the infection, the patient or the prescriber, and also by determinants related to the availability and quality of antimicrobial drugs. These determinants are illustrated by the “arcs” of the diagram; on one side are: the burden of disease, diagnostics, prescriber behaviour, and consumer expectations and adherence, and on the other side: the drug regulatory framework, procurement, management and quality assurance systems. For each of these main determinants, effective public health interventions do exist. On the infection side, the principal interventions are: disease prevention and control, quality diagnostic testing, appropriate treatment regimens and consumer health education. For the antimicrobial drugs, the elements are: appropriate drug regulations, lists of essential drugs, and functioning mechanisms for the approval and delivery of drugs. The success of the ARCS concept requires the continuous application of this package of core interventions because piecemeal, limited implementation is unlikely to achieve the desired results. Finally, a monitoring system for both the implementation process and the outcome of AMR containment programmes is required to guide ongoing activities, assess their impact and provide data for advocacy (15).

Components of the ARCS diagram

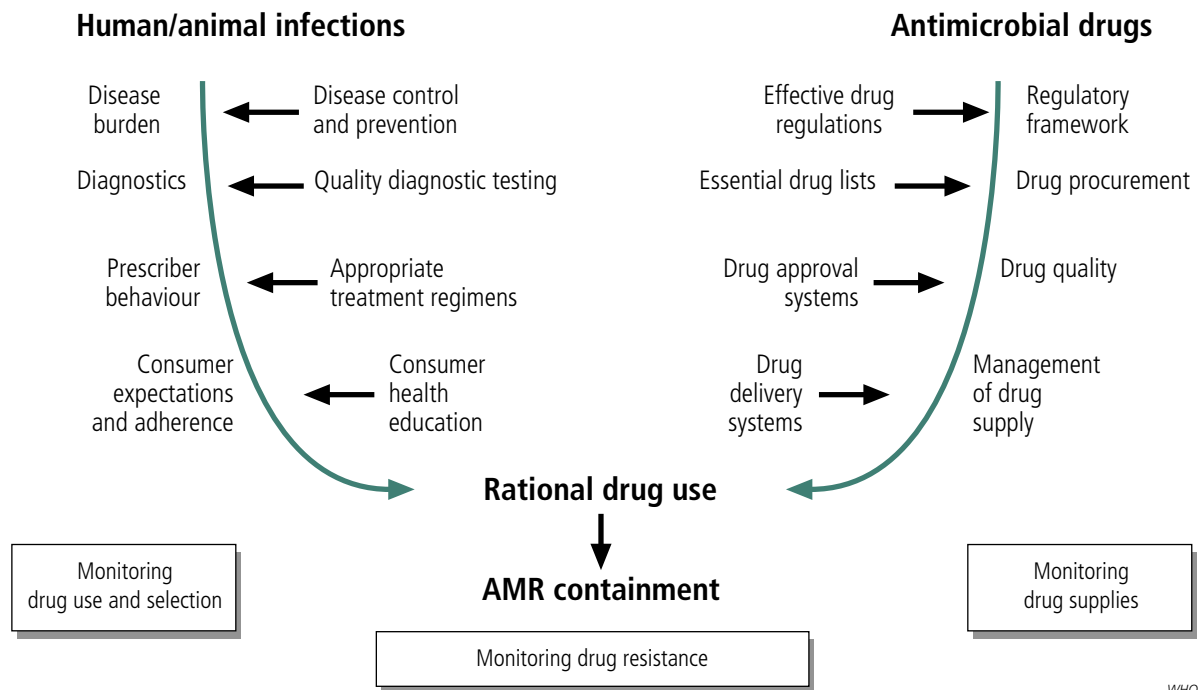
Human/animal infections

“Human/animal infections” refers to any situation in which the use of an antimicrobial drug is contemplated. The prescription is often made by a professional and is fully justified based on the needs for prophylaxis or treatment. In other situations, the need for antimicrobial medication may be assessed by a non-professional, or by the patients or animal owners themselves. In some cases, antimicrobials may be administered to asymptomatic individuals as a preventive measure or as part of a mass-treatment strategy. Antimicrobials may also be used for reasons that have no clear link to human or animal infections, as is the case with use of growth promoters in animal husbandry and the use of food preservatives.

Disease burden/disease prevention and control

The burden of infectious diseases requiring treatment is one of the main determinants of antimicrobial use. Reducing the

Fig. 2. Diagram of ARCS – Antimicrobial Resistance Containment and Surveillance



incidence and prevalence of infectious diseases is consequently a core intervention for containment of AMR. “Disease prevention and control” covers a wide range of preventive activities such as provision of clean water and safe food, control of hospital infections, community education on preventive practices (i.e. use of condoms and bednets, improved sanitation, etc.) and the development and use of vaccines. Effective treatment of infectious diseases will in itself constitute an important intervention that leads to reduced transmission to contacts and to possible animal reservoirs. However, a reduction in disease burden alone is not sufficient to reduce the impact of resistance as the proportion of patients infected with resistant strains may remain stable or even increase.

Diagnosics/quality diagnostic testing

Diagnostic testing is a powerful tool in the evaluation and management of infectious diseases in individual patients as well as for public health purposes (e.g. for developing standard treatment guidelines). A wide variety of technologies is now available ranging from biochemical markers of infections to the specific determination of causative agents. The susceptibility to antimicrobial drugs is now more easily detectable by traditional and molecular-based systems. Three inter-related problems must be dealt with in order to derive the full benefit from these diagnostic techniques. Firstly, the cost of testing is prohibitive in many settings, and low-cost alternatives are urgently needed. Secondly, diagnostic testing should be available at the point of patient care to improve the quality of patient management. Finally, the quality of diagnostic tests must be assured as erroneous results will jeopardize the quality of treatment. False-positive laboratory results may lead to unnecessary antimicrobial treatments, whereas false-negative results will fail to make the correct etiological diagnosis and often lead to

inappropriate treatment or excessive use of broad-spectrum antibiotics. Both types of error will contribute to the development of resistance.

Prescribers’ behaviour/appropriate treatment regimens

Certified prescribers have a clear responsibility for prescribing antimicrobial drugs appropriately. This responsibility not only affects the well-being of the individual patient or animal, but also has an impact on society in general. Educational efforts should target prescribers in all sectors of human and animal health care. Because the treatment of acute infections often requires administration of medications on an empirical (syndromic) basis, implementation of standard treatment guidelines and essential drug lists are powerful mechanisms to improve prescription practices. In some settings the personal economic interests of prescribers are linked to drug sales. Where it exists, this link must be broken because it is incompatible with the concept of rational and judicious drug prescription.

Consumer expectations and adherence/consumer health education

The decision to prescribe an antimicrobial drug will depend not only on the education of the professionals, but also on the perceptions and expectations of patients and animal owners. Rational drug use cannot be achieved if the patients and animal owners remain convinced of the need for antimicrobial drugs and simply move from prescriber to prescriber until they obtain them. The education of the general public is particularly urgent in countries where antimicrobials are freely available over the counter or in the informal health system. Patient adherence to treatment is also essential for rational drug use, particularly in the case of prolonged treatment regimens (e.g. for patients with

tuberculosis or HIV) as nonadherence e.g. through interruption of treatment, reduced or irregular dosage or frequent treatment changes, contributes to the emergence of AMR (16).

Antimicrobial drugs

Antimicrobial drugs include all pharmaceutical formulations used in the treatment of infectious diseases that are specifically aimed at the infecting microorganism. The term does not normally include antiseptics and similar substances used to suppress microbial growth on body surfaces even though many of the problems encountered with antimicrobials do also apply to these substances.

Regulatory framework/effective drug regulation

A regulatory framework must be in place for AMR containment activities to succeed. This framework must be administered through a national regulatory authority, which is fully empowered to discharge its core functions. Although drug regulation alone cannot ensure their rational use, systems that ensure pre-marketing evaluation and approval of drugs; regulation of drug manufacture, importation and distribution; capacity to effectively enforce mandatory prescription for antimicrobial drugs; and independent drug information aimed at prescribers, are a prerequisite for any successful public health programme for the containment of AMR.

Drug procurement/essential drug lists

A system for drug procurement is needed to allow the population to gain access to necessary drugs, and this is often achieved through essential drug lists. In the context of containment of AMR, essential drug lists should be used to encourage adherence to recommended standard treatment guidelines by promoting drugs and indications as detailed in the guidelines. However, in most countries essential drug lists only apply to the public sector and separate systems for regulation and monitoring of procurement of antimicrobials in the private sector may be required.

Drug quality/drug approval systems

Ineffective regulation results in drugs of inferior quality reaching the market, and in many countries this is a major obstacle to rational drug use. Treatment with low-quality drugs can be ineffective and result in poor outcome. In addition, the extensive use of formulations with an inadequate content of antimicrobial substances contributes to the selection of resistant strains. Containment of AMR requires effective quality assurance systems with proper market control and enforcement capacity.

Management of drug supply and drug delivery systems

A drug supply system should be developed to regulate and monitor management of drug distribution by both the public and private sectors. For some infectious disease programmes this function includes direct procurement, storage, transportation and distribution of antimicrobials. Providing a continuous supply of appropriate antimicrobial drugs is an essential element in ensuring patient adherence and prescribers' use of standardized regimens. Cost is also an important element: by making treatment affordable it is possible to reduce the risk of inadequate treatment regimens or insufficient duration of treatment on economic grounds.

Monitoring aspects of the ARCS approach

Measuring the success or failure of containment of AMR is a difficult exercise that presents major methodological and logistical challenges. The ARCS approach suggests three broad areas of activity:

- monitoring drug quality and availability;
- monitoring drug use; and
- monitoring levels and trends in AMR.

An assessment of the systems for drug selection, quality assurance, and distribution and supply is essential for an evaluation of the ARCS programme. A minimum requirement for monitoring drug use is a list of the antimicrobial substances that are available on the market and an indication of the per capita consumption. A more comprehensive system would also monitor the use of different antimicrobials for specific clinical indications using internationally recognized standards (i.e. the Anatomical Therapeutic Chemical (ATC) Classification and the Defined Daily Dose (DDD) units) as well as assessing both prescribers' behaviour and patients' expectations and adherence.

Monitoring the extent and trends in AMR should always use valid laboratory practices and epidemiologically sound sampling methods. Resistance testing can be based on *in vitro* laboratory tests (e.g. for tuberculosis (TB)), clinical assessment of treatment failure (e.g. for malaria) or genetic sequencing (e.g. testing for resistance to ARVs). In some settings, data from routine diagnostic AMR tests are available, whereas in other situations it will be more appropriate to conduct targeted studies of specific resistant pathogens. The selection of a limited number of indicator diseases or pathogens, based on regional or national priorities, may facilitate the implementation of a surveillance system. An ongoing system for integrated AMR surveillance of microbes from humans, food and animals intended for human consumption is recommended where resources are available (17). It should be noted that it is difficult to achieve the level of sophistication of AMR surveillance systems needed to directly measure the impact of the individual components of containment programmes. AMR surveillance should therefore focus on continuous generation, analysis and interpretation of data for advocacy and evaluation of the AMR strategy, and for answering specific questions related to empirical (syndromic) treatment protocols (18).

Discussion

AMR is the expression of the ability of microbes to resist the actions of naturally occurring or synthetically produced compounds inimical to their survival. In a clinical context, AMR refers to a reduction in clinical efficacy so that either the benefits for the individual of treatment with an antimicrobial drug or the benefits to general public health are compromised. In the public health context, AMR reduces the efficacy of standard drug regimens, resulting in an increased disease burden and higher costs (13).

Containment of AMR requires the continuous application of accepted and documented interventions that slow the rate of emergence and spread of AMR and limit its consequences for individual case management and/or public health. Although measuring the effect of each recommended intervention presented in the ARCS approach may not be feasible, their combined impact is believed, on the basis of evidence or consensus, to have a positive influence on the multiple factors that

contribute to AMR. Promoting rational use of antimicrobial drugs is considered to be the most important element in AMR containment (19) and implies that the decision to prescribe drug(s) should be based entirely on medically sound rationale, and that therapy must be effective and safe. Drugs should be selected on the basis of an assessment of the actual need for an antimicrobial together with considerations of efficacy, safety, suitability and cost. Finally, all patients should be provided with relevant, accurate and clear information regarding their condition and the medication(s) prescribed, and on this basis they should accept and adhere to the treatment. A set of core interventions to promote more rational use of medicines has recently been defined by WHO (20).

The complexity of the AMR problem and of the interventions required to contain it makes an assessment of the impact of the ARCS approach very challenging. However, empirical evidence shows that the interventions outlined in the approach, where implemented consistently and in an integrated manner, can contain the development of AMR. The best example comes from the DOTS strategy, the currently recommended approach to TB control and the containment of multidrug-resistant TB, whose main elements are listed in Box 1. These elements closely match the main interventions defined in the ARCS strategy, including standardized and supervised practices for patient management, regular provision of quality drugs and an efficient monitoring system. The emergence and spread of multidrug-resistant TB has been monitored by WHO and international partners for more than 10 years in many countries. The available data suggest that the consistent implementation of the DOTS strategy, which results in high cure rates is associated with low levels of multidrug-resistant TB, an indication of the efficacy of the DOTS package as an AMR containment strategy (21). Additional evidence comes from the experience in selected European countries which has shown that appropriate legislation combined with high quality drugs, education efforts and prescribing standards can maintain a low level of AMR.

Box 1. Elements of DOTS strategy for treatment of tuberculosis

- Political commitment
- Case detection by microscopical examination of sputum smears
- Standardized treatment regimen with directly observed therapy
- A regular, uninterrupted supply of all essential anti-tuberculosis drugs
- A standardized recording and reporting system

Conclusions

The ARCS approach appears to have several advantages when advocating concrete approaches to translating the general principles of AMR containment into functional public health programmes. It provides a simplified but comprehensive illustration of the complex challenge of AMR containment and surveillance as detailed in the Global Strategy and it identifies the package and range of interventions required to improve rational drug use. It clarifies the importance of an integrated “package” approach, which must include all the elements that would lead to the rational use of available antimicrobial drugs. Finally, its generic framework can be adjusted to fit different local situations and can be applied to specific diseases or syndromes, including TB, HIV and malaria. ■

Acknowledgements

The authors would like to thank Dr K. Holloway, Dr V. Reggi, Dr A. Aidara-Kane, Dr A. Defelici, Dr H. Sobel, Dr A. Wright, Dr M. Aziz and Dr P. Ringwald of the World Health Organization, Geneva, Switzerland, and Dr D.M. Bell of the Centers for Disease Control and Prevention, Atlanta, GA, USA, for their helpful comments and discussions during the development of the ARCS concept and the preparation of this manuscript.

Conflicts of interest: none declared.

Résumé

La maîtrise et la surveillance de la résistance aux antimicrobiens comme outil de santé publique

La résistance aux antimicrobiens est largement reconnue en tant que menace pour la santé publique dans le monde entier car elle met en péril l'efficacité du traitement des maladies infectieuses. En 2001, l'OMS a publié une stratégie mondiale pour la maîtrise de la résistance aux antimicrobiens, mais il s'est révélé difficile de traduire les recommandations de cette stratégie en actions de santé publique concrètes. L'approche ARCS (*Antimicrobial Resistance Containment and Surveillance*) de maîtrise et de surveillance de la résistance aux antimicrobiens a pour but de faciliter la formulation de programmes de santé publique et de mobiliser les ressources humaines et financières nécessaires pour endiguer la résistance aux antimicrobiens. L'approche ARCS souligne le lien fondamental entre l'usage rationnel des médicaments et la maîtrise de la résistance aux antimicrobiens. La prise en charge clinique des infections humaines et animales doit être améliorée grâce à de meilleurs moyens de prévention

et de lutte contre les maladies, des tests diagnostiques de bonne qualité, des schémas thérapeutiques appropriés et une éducation des consommateurs dans le domaine de la santé. Par ailleurs, les systèmes d'approvisionnement en antimicrobiens devront intégrer des réglementations appropriées, des listes de médicaments essentiels et des mécanismes efficaces d'autorisation et de distribution des médicaments. La maîtrise de la résistance aux antimicrobiens est définie dans l'approche ARCS comme l'application permanente de cet ensemble d'interventions de base. Une surveillance de l'étendue et des tendances de la résistance ainsi que de la fourniture, de la sélection et de l'utilisation des antimicrobiens devront être mises en place pour suivre le processus d'endiguement et ses résultats. L'approche ARCS est représentée par un diagramme (figure 2), qui illustre de façon simplifiée mais complète la complexité du problème posé par la maîtrise et la surveillance de la résistance aux antimicrobiens.

Resumen

El enfoque de contención y vigilancia de la resistencia a los antimicrobianos: una herramienta de salud pública

Está ampliamente admitido que la resistencia a los antimicrobianos (RAM) constituye una amenaza para la salud pública mundial, dado que pone en peligro la eficacia del tratamiento de las enfermedades infecciosas. En 2001 la OMS lanzó la Estrategia Mundial para la Contención de la Resistencia a los Antimicrobianos, pero se ha podido constatar que es muy difícil traducir las recomendaciones de esa estrategia mundial en iniciativas de salud pública eficaces. La finalidad del enfoque de Contención y Vigilancia de la Resistencia a los Antimicrobianos (ARCS) es facilitar la formulación de programas de salud pública y la movilización de recursos humanos y financieros para contener la RAM. El enfoque ARCS resalta la gran relación existente entre el uso racional de los medicamentos y la contención de la RAM. El manejo clínico de las infecciones humanas y animales debe mejorarse mediante un mayor control y prevención de las enfermedades, unas pruebas

diagnósticas de alta calidad, unos regímenes terapéuticos apropiados y la educación sanitaria de los consumidores. Al mismo tiempo, los sistemas para el suministro de antimicrobianos deben incluir reglamentos apropiados, listas de medicamentos esenciales y mecanismos funcionales para la aprobación y administración de los medicamentos. La contención de la RAM se define en el marco del enfoque ARCS como la aplicación continua de ese paquete de intervenciones básicas. A fin de vigilar el proceso y los resultados de la contención de la RAM, es necesario establecer sistemas de vigilancia de la magnitud y las tendencias de la resistencia a los antimicrobianos, así como del suministro, selección y uso de esos medicamentos. El enfoque ARCS se ha representado mediante el diagrama de la figura 2, que ilustra de forma simplificada pero completa el problema complejo que supone la contención y el monitoreo de la RAM.

Arabic

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