SURVEILLANCE AND MONITORING OF ANTIMICROBIAL RESISTANCE (AMR)

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Antibiotic resistance is a global problem of increasing significance that takes a costly toll on lives and the health-care economy around the world. It is beyond the ability of any one country to prevent, detect and control antimicrobial resistance (AMR) within its own borders without ongoing engagement of regional and global partners. Challenges to detecting, monitoring and controlling AMR infections are found in all settings and in every country. Improvements are necessary in three areas of surveillance capacity: data collection and data sources, data management, analysis and interpretation; and information reporting, dissemination, communication and use. Focused and targeted international cooperation will be vital to contain and control AMR. A number of ongoing and planned initiatives show a clear path forward to achieve that collaborative success.

Antibiotic resistance is a global problem of increasing significance that takes a costly toll on lives and the health-care economy around the world *(1)*. In May 2014, a resolution passed by the 67th World Health Assembly (WHA) identified antimicrobial resistance (AMR) as "a heavy and growing burden on high-, middle- and low-income countries, requiring urgent action at national, regional and global levels" and called for the development of a draft global action plan to combat antimicrobial resistance to be presented in one year to the 68th WHA *(2)*." In addition to high mortality (multi-drug resistant TB alone killed an estimated 210,000 people *(3)* in 2013), AMR may cost the world's economy as much as 1.6% of global gross domestic product *(4)*.

It is beyond the ability of any one country to prevent, detect and control AMR within its own borders without ongoing engagement of regional and global partners *(5)*. Highly mobile populations, the ease of ever-growing international travel and trade, high density populations, the growth of industrial agricultural practices, environmental changes, continuous pathogen evolution, and increasingly complex health-care treatments have all increased the potential for the emergence and rapid dissemination of new or variant forms of known pathogens, and present an array of new challenges to clinicians, microbiologists and public health officials.

Surveillance and monitoring of antibiotic resistant bacteria is essential for detecting and controlling outbreaks, identifying populations most at risk, designing and evaluating intervention strategies, and focusing the use of scarce resources so that they can be used most efficiently and effectively to prevent illness and save lives *(6, 7)*. However, challenges to detecting, monitoring and controlling AMR infections are found in all settings and in every country.

Awareness of the problem of AMR by medical and veterinary public health officials and clinicians as well as technical capacity for detection and monitoring of these pathogens vary greatly among and within countries. Because AMR can spread widely and rapidly, accurate tracking of infections and resistant strains is of the highest importance. Surveillance data must be comparable – laboratories need to be using valid and reliable testing methods, collection of isolates should be appropriately representative for the purposes of the surveillance activity, and reporting must be complete and consistent from facilities and laboratories which do report. At present, the varied capacity and practices in different countries pose a serious obstacle to the usefulness of international surveillance, particularly from countries with limited resources *(1)*. A coordinated network approach will be a key element to generating AMR data of quality and comparability that would support effective control strategies across countries.

General principles and needs

Surveillance can serve a number of purposes in combating antibiotic resistance. Surveillance serves as an early warning system for the emergence and spread of new forms of resistance, can provide valuable information about geographic variations in incidence and prevalence of resistant pathogens and identify populations at risk. This information is vital to developing public health interventions, prioritizing resistance problems, and efficiently deploying limited resources to implement those interventions. Surveillance then becomes the tool that is used to evaluate the success of those interventions.

Surveillance programmes should be simple, flexible, representative of populations at risk, provide timely information for situational awareness and decision-making, be acceptable to both the data providers and audiences for the analyzed and interpreted information produced by the system, and assure that data is accurate and reliable, and sustainable over time.

Successful global efforts to establish surveillance for TB, malaria and HIV have demonstrated the utility and value of national and international systems and can be used as blueprints and reference points for developing the necessary components of national and international surveillance for antibiotic resistance. *(1)*

Challenges to implementing effective surveillance

Identifying, tracking and monitoring the emergence and spread of antibiotic-resistant bacteria poses a number of challenges in both higher-income as well as in low- and middle-income countries (LMICs). Accessing reliable, accurate data requires recognition of an infection, adequate culturing and handling of specimens, transportation to a laboratory equipped to perform the appropriate testing and an assurance that such tests can be performed correctly and consistently meet quality control standards. Then, the data must be made available in a form that can be transmitted to a central repository of data, aggregated with data from other reporting sites and analyzed and interpreted. Ideally, clinical patient data would accompany microbiologic data to allow for necessary epidemiology assessment. Finally, the analyzed and interpreted information needs to be disseminated in formats that can be easily understood and applied by diverse audiences for both clinical and public health purposes *(6, 7)*. Barriers to even the most basic types of surveillance systems will clearly exist in settings where the health-care and public health infrastructure is inadequate due to limited resources. A lack of resources may result in gaps at more than one stage in the surveillance process – from the inability to obtain appropriate cultures to constraints on processing and laboratory testing to the lack of effective reporting mechanisms. A paucity of trained professionals, including health-care providers, pharmacists, microbiologists and epidemiologists in LMICs is a particular problem in creating a surveillance infrastructure. The ready over-the-counter availability of antibiotics in many countries, combined with the lack of trained health personnel and laboratory capacity encourages self-treatment and at best empirical treatment, at times with drugs which are counterfeit or adulterated *(8)*. Treatment is most likely to be empirical and syndromic where laboratory facilities are most limited.

Data collection and data sources

Effective surveillance and monitoring starts with identifying reliable data sources and optimizing data collection. Both laboratory data, including at a minimum microbial identification and antibiotic susceptibility, and epidemiologic data, including basic demographic, treatment and outcome data on patients, are needed. Data that are used for surveillance purposes are generally obtained from routine clinical laboratory testing patient records. These data are often collected from hospitals and may not be representative of the actual disease burden in a particular community or country. In addition, laboratory methods are often variable, especially in low-resource settings, and the accuracy and reliability of laboratory data has been questioned, even in developed countries. Specific areas to address include:

- **Improving laboratory capacity.** The ability of laboratories to accurately and consistently identify pathogens and their antibiotic susceptibility varies greatly. Trained personnel are the single most important asset in any laboratory. On-site technical assistance, sending staff for off-site training and education, online training courses and laboratory "twinning" are all strategies that have been used to successfully improve laboratory capacity. Ongoing evaluation and testing programmes are important activities to maintain and assure laboratory competence. Not all countries will be able to maintain needed laboratory capacity, suggesting a need for the establishment of regional reference centres to support specialized and reference testing.
- **Prioritize which bacteria are most important to track.** For public health purposes, not every form of bacterial resistance can be monitored with the same level of attention. WHO has identified seven resistant pathogens ("bug-drug combinations") as priorities for surveillance and reporting *(11)*. The CDC has identified 18 pathogens of public health concern in the United States and placed those pathogens into three categories

relative to the need for urgent public health action to combat them *(9)*. Each country may have its own set of priority pathogens, but focusing on an agreed-upon set of priority bacteria with specific resistance profiles will help assure that the data necessary to facilitate collaborative global efforts to prevent and control antibiotic resistance can be integrated and that data collection is sustainable.

- **Prioritize and standardize epidemiologic data collection.** Not all data is of equal value in assessing risks and designing and evaluating interventions to prevent the emergence and spread of bacterial resistance. In areas where electronic data may be available, being parsimonious in selecting key variables to monitor will simplify data management and analyses and enhance the timeliness of reporting. In settings where paper records need to be reviewed and tallied, minimizing the collection burden to those data most relevant for the specific needs of the prevention programme will similarly facilitate sustainability of an efficient and effective programme.
- **Harmonization of standards for identification and susceptibility testing.** Laboratories need to be using common standards and criteria for identification of bacterial resistance. Aggregation of data from different laboratories within a country and comparison of data between countries is vital for effective surveillance but is hampered if definitions or laboratory standards vary. However, due to variations in health systems and regulatory environments, achieving fully harmonized standards can be a challenge even in higher-income countries.
- **Increasing the use of laboratory testing for resistance in clinical specimens.** In order to identify resistant bacteria in the laboratory, doctors and health-care workers must correctly obtain necessary clinical specimens and send them to a laboratory which can perform the testing. The likelihood of this happening varies tremendously among clinical settings, between lower-resource and higher-resource settings and among clinical syndromes. For example, routine susceptibility testing for *Neisseria gonorrhoeae*, the bacteria causing gonorrhea, is rarely done in clinical settings even in higher resource environments. Maximizing the appropriate culturing of clinical specimens will greatly improve the representativeness of surveillance data.
- **Promoting and disseminating innovation.** Developing and promoting the use of new, low-cost technologies to improve laboratory and surveillance capacity to detect, identify and characterize antimicrobial resistance threats. Such technologies can potentially provide comparable information across national and regional boundaries and may include rapid diagnostic tests, kits, and techniques for detecting drug resistant pathogens that can be utilized in developing countries, rural areas, and settings where routine susceptibility testing would normally be unavailable or unreliable. The GeneXpert and related technologies, and the manner in which they have been applied to TB surveillance and control, is one example of the potential value of such innovative approaches *(11)*.

Data management, analysis and interpretation

Within each country, data on antibiotic resistance needs to be centrally stored, managed, analyzed and interpreted to provide the information that will be used for public health purposes. Data needs to be transmitted from the source – the laboratory and the clinical setting where patient information is kept – to a central site and the data may need to be translated into a standard electronic format if it has not been collected and transmitted in that format. The data needs to be analyzed to fulfill the key objectives of antibiotic resistance surveillance – tracking the incidence and prevalence of high-priority pathogens by person, place and time – and making those data available in an easily interpretable form for quick public action as well as for decision-makers to plan medium-term and long-term strategy. Analyzing and interpreting antibiotic resistance data is particularly challenging because of the many different types of bacteria involved and their diverse epidemiology, the variety of different resistance mechanisms and the complexity of integrating and interpreting the clinical, epidemiologic and laboratory data. Focusing on a smaller number of priority resistance threats helps but does not fully solve these difficulties. Specific areas to address include:

- **Taking advantage of rapid technological change to bolster infrastructure for data management and analysis.** The increasing availability of wireless cellphone networks and the enhanced capacities of handheld devices, including smartphones and tablets, offer opportunities to revolutionize data collection, transmission, management and analysis. Cell phone networks have been incorporated successfully in public health initiatives in a number of settings in low-resource countries. It would be good to have the data encrypted if possible to protect confidentiality *(12, 13)*.
- **Increasing the availability of trained personnel to**

manage, analyze and interpret data. Distance learning, on-site technical assistance, training courses and mentoring are all methods which have proven successful in a variety of settings. Collaborations involving individual countries, international partners, and donors are needed to increase capacity for AMR surveillance, to include data collection, analysis and interpretation, and reporting. Also, working with ministries of health and utilizing fellows or residents from the Field Epidemiology Training Program would be helpful to address the availability of trained personnel.

- **Setting up standardized, interoperable IT platforms.** Simplicity is also the key here. The more complicated the software and greater the number of variables involved, the harder it will be to establish easy data sharing and aggregation across countries and regions.

Information reporting, dissemination, communication and use

The value of information derived from public health surveillance depends on the uses to which it is put. Surveillance information needs to be made available to a variety of audiences in ways that those audiences can most readily understand and employ for their needs and purposes. Public officials use surveillance for situational awareness, to target prevention and control efforts where they are most needed, design and evaluate intervention strategies and monitor the success of public health efforts. Of particular importance in LMICs is the need to focus limited resources on the populations most at risk and thus maximize the effectiveness of every public health investment. Health professionals need to know local resistance patterns to make the best antibiotic choices in clinical settings. Decision-makers and legislators need to understand the nature, scope and magnitude of the antibiotic resistance problems within their scope or responsibility or jurisdictions so that they may be more likely to support public health efforts to combat those problems. The general public, as consumers of health care and members of communities affected by resistance problems need to receive information about resistance to enable their participation in prevention and control efforts, such as receiving immunizations and reducing demand for unnecessary antibiotics.

Specific areas to address include:

- **Strengthen systems for international real-time communication of critical health events.** This is consistent with efforts to promote the fulfilment of countries' obligations associated with the International Health Regulations *(14, 15)*. It can also build upon efforts initiated by the Transatlantic Task Force on Antimicrobial Resistance as part of collaborations between the European Union and the United States *(10)*.
- **Leverage and build upon existing international partnerships.** A number of effective global partnerships under the auspices of the United Nations, such as the Codex Alimentarius *(16)* as a collaboration between WHO and the Food and Agriculture Organization (FAO), as well as other organizations such as the World Organisation for Animal Health (OIE) *(17)*, and the Global Fund demonstrate the effectiveness of cooperative efforts to address specific health problems. Many of these groups and others are already engaged in combating antimicrobial resistance. Continuing to promote shared goals and objectives among such groups will increase the likelihood of successful outcomes for the many projects and initiatives underway and planned.
- **Education and information dissemination to the public.** AMR is one of the most complex problems in all of public health and medicine. The threat posed by the emergence and spread of "superbugs" is less well understood than it is for some epidemic and pandemic diseases which spread widely in communities at risk. Health-care professionals around the world often lack the information they need to fully understand the scope and breadth of the problem in their own localities or countries or the interconnectedness of the rising global pandemic of antimicrobial resistance. Communicating the basic biologic and microbiologic facts more broadly and with greater clarity and dispelling misinformation on this topic is a vital step in accelerating and sustaining the permanent global response that will be necessary to contain this threat.

Examples of current activities

A number of activities are underway which address the need for enhancing global surveillance of antimicrobial resistance and offer examples of the wide array of potential solutions to the challenges of tracking and monitoring resistant pathogens.

The recently announced Global Health Security Agenda *(19)* sets forth a series of "Action Packages" to further preparedness and response to infectious disease threats. Several of these Action Packages address needs for combating antimicrobial resistance. One set of activities, specifically targeting antimicrobial resistance *(20)* calls for collaboration among the World Health Organization, the FAO and the OIE to:

"develop an integrated and global package of activities to

combat antimicrobial resistance, spanning human, animal, agricultural, food and environmental aspects (i.e. a one-health approach), including: a) Each country has its own national comprehensive plan to combat antimicrobial resistance; b) Strengthen surveillance and laboratory capacity at the national and international level following agreed international standards developed in the framework of the Global Action plan, considering existing standards and; c) Improved conservation of existing treatments and collaboration to support the sustainable development of new antibiotics, alternative treatments, preventive measures and rapid, point-of-care diagnostics, including systems to preserve new antibiotics."

This effort will also engage countries in "twinning" *(21)* activities, promoting cooperation between higher income and lower and middle income countries. Related packages call for improvements in laboratory capacity and real-time surveillance.

Pilot projects demonstrating the value of international collaboration, which serve as models for implementation of the GHSA Action Packages have been conducted in Uganda *(22)* and Vietnam *(23)*. In both countries, an emphasis on strengthening laboratory capacity and increasing the timeliness of reporting of specified health events showed how strengthening public health infrastructures are necessary and potentially achievable goals. Although not directly aimed at AMR, except for multidrug resistant tuberculosis on Uganda, the principles demonstrated in these projects are directly applicable to the needs of the international network that will be required for detection, prevention and control of the spread of resistant pathogens.

Other examples of successful programmes to enhance laboratory capacity which can serve as models for work in a variety of settings include projects in Guatemala *(24)*, Nepal *(25)*, China (26), and six countries in the Middle East and Central Asia *(27)*.

In addition, CDC's Global Disease Detection Program *(28)*, conducting programmes in 10 countries around the world to develop and strengthen the global capacity to address infectious disease threats. Selected examples of these efforts include:

- In Bangladesh, studying antimicrobial resistance pathogens from patients with diarrheal disease and in environmental samples of river water and hospital effluents.
- In Kazakhstan, collaborating with WHO to produce an antimicrobial resistance toolkit for low- and middle-income countries conduct situation analyses of antimicrobial resistance and its determinants.
- In India, is working with the national Integrated Disease Surveillance Program to initiate routine laboratory surveillance for acute diarrheal disease pathogens (*Salmonella*, *Shigella*, and *Vibrio species*) in two states.
- In Guatemala, studying antimicrobial resistance in blood culture isolates for six key patterns: methicillin-resistant *S. aureus*, vancomycin resistant-enterococci; multi-drug resistant *Acinetobacter*; cephalosporin-resistant *Klebsiella*; and *carbapenem*-resistant *Klebsiella* and *E. coli*.
- In Egypt, working with surveillance programmes for health-care-associated infections and antimicrobial resistance in acute care hospitals for three pathogens of the WHO pathogens of concern: *Escherichia coli* (resistance to 3rd generation cephalosporins and fluoroquinolones); *Klebsiella pneumonia* (resistance to 3rd generation cephalosporins and carbapenems); and methicillin-resistant *Staphylococcus aureus*.

Summary

Efforts to prevent the spread of antimicrobial-resistant bacteria build on the foundation of proven public health strategies: immunization, infection control, protecting the food supply, and preventing person-to-person spread through screening, treatment and education. All of these strategies rely on accurate and reliable surveillance data. The recently released United States National Strategy for Combating Antibiotic-Resistant Bacteria *(5)* has as one of five goals to "Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development". Along with support for the WHO Global Action Plan and the Global Health Security Agenda, this clear recognition of and commitment to international collaboration and cooperation is a cause for optimism in the fight against this ever-growing world-wide threat of antimicrobial resistance. ●

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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