Trends in Medical Research

ISSN 1819-3587

Academic Journals Inc.

www.academicjournals.com

Trends in Medical Research 10 (4): 106-113, 2015
ISSN 1819-3587 / DOI: 10.3923/tmr.2015.106.113

Surveillance for Antibiotic Resistance in Nigeria: Challenges and Possible Solutions

[1]Idris Abdullahi Nasir, [2]Adamu Babyo, [3]Anthony Uchenna Emeribe and [1]Noel Ochada Sani
[1]Department of Medical Microbiology, University of Abuja Teaching Hospital, P.M.B. 228, Gwagwalada, FCT Abuja, Nigeria
[2]Department of Medical Microbiology, Abubakar Tafawa Balewa University Teaching Hospital, P.M.B. 0117, Bauchi, Bauchi State, Nigeria
[3]Department of Medical Laboratory Science, College of Medical Sciences, University of Calabar, P.M.B. 1115, Calabar, Nigeria

Corresponding Author: Idris Abdullahi Nasir, Department of Medical Microbiology, University of Abuja Teaching Hospital, P.M.B. 228, Gwagwalada, FCT Abuja, Nigeria Tel: +2348030522324

ABSTRACT

There is no doubt that antibiotics have saved the human race from a lot of suffering due to bacterial disease burden. Without these drugs, millions of people would have succumbed to infectious diseases. Regrettably, antibiotic resistance (ABR) threatens the effective treatment of these pathogens. The incidence of ABR and the emergence of multidrug-resistance bacteria are on the increase and has been considered a major public health issue. In view of this, we conducted this review of relevant published articles using extensive literature search made through PubMed, Google scholar, Scopus and HINARI on the emergence and spread of ABR, challenges and possible solutions to ABR surveillance especially in Nigeria. Findings from our review revealed that surveillance for ABR in pulmonary tuberculosis was the only system in good function in Nigeria. Regrettably, most hospitals have poor ABR systems for other bacteria. This setback was found to be linked to multifactorial reasons. Urgent and coordinated action is required at all levels to ensure preservation of these life-saving drugs for future utility. Detection of resistance and monitoring its spread requires appropriate laboratory-based surveillance. In addition, there is need to sustain the efficiency of diagnostic laboratories, improved surveillance, better regulation and education of the public, clinicians/prescribers in the appropriate use of antibiotics.

Key words: Antibiotic resistance, laboratory, surveillance, Nigeria

INTRODUCTION

The very first antibiotic was penicillin, discovered by Sir Alexander Fleming in 1929. He put disease causing bacteria in a petri dish and found that penicillium mould inhibited their growth. During World War II, penicillin saved literally thousands of people from death from wound infections. Over the next decades, penicillin and subsequent antibiotics significantly improved the life expectancy of millions, more by effectively treating a wide variety of formerly lethal diseases, such as pneumonia and tuberculosis (McGeer *et al*., 2001).

Antibiotics are used to treat diseases or infections caused by bacteria. They work by interfering with one of the processes vital to the survival of invading bacteria, such as the formation or integrity of the cell wall (McGeer *et al*., 2001).

During the past six decades antimicrobial agents have played a critical role in reducing the burden of infectious diseases all over the world (Finch *et al*., 2003). The emergence of resistance and its rapid spread is negating the impact of these drugs. When a microbe can withstand the effects of an antimicrobial medicine, it is considered to be resistant. As a result of resistance, many antimicrobial medicines are losing their ability to treat infectious diseases. Resistance to antimicrobial agents typically occurs as a result of four main mechanisms namely enzymatic inactivation of the drug, alteration of target sites, reduced cellular uptake and extrusion by efflux (Davies, 1994; Spratt, 1994; Nikaido, 1994; Smith, 2004). It has been reported that chemical modifications could be significant in antibiotic resistance, though exclusion from the cell of unaltered antibiotic represents the primary means in denying the antibiotic access to its targets and this is believed to enhance resistance even in cases where modification is the main mechanism (WHO., 2013).

Inappropriate and irrational use of antibiotics is a major factor that promotes the spread of resistance (Ndihokubwayo *et al*., 2013). Antibiotic resistance is a phenomenon where microbes acquire genes that enable them withstand the effects of antimicrobial agents. Antibiotic resistance threatens the success of medical interventions at all levels of health care and creates a set of specific challenges for clinical, therapeutic and public health interventions with local, national and global dimensions (WHO., 2001a).

Bacteria that belong to the normal flora in humans become indiscriminately exposed to antibiotic compounds every time antibiotics are used. Therefore, the most significant resistance has been emerging among these microorganisms (WHO., 2001a). Since most of them are truly opportunistic pathogens, the most vulnerable segment of societies i.e. the young, elderly and immune-compromised are likely to face infections and the consequences of failing antibiotic effectiveness. Moreover, the trajectory of antibiotic resistance is rather predictable. Still, no surveillance system exists that would allow measuring the magnitude of antibiotic resistance as a threat to global health. The laboratory is the most important arena where investigations into appropriate use of antimicrobial drugs can be done (WHO., 2001b).

Public health surveillance is the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation and evaluation of public health issues. Laboratory-based surveillance is one of the pillars of monitoring trends of infectious diseases and their antimicrobial resistance pattern (WHO., 2001b). This surveillance relies on data produced in clinical and/or public health laboratories.

A lot of antimicrobial assays exist; most of these assays can help in tracking emergence and spread of resistant pathogens. Rational testing choices, when combined with strict adherence to recommended methodology and quality control can generate meaningful epidemiologic data for rational therapeutic policies and identifying antibiotic resistance pattern (WHO., 2001b). Besides direct care of patients, the results of diagnostic microbiology testing are used to inform local, regional and national surveillance systems. Surveillance of bacterial resistance generates essential information, which promotes and directs stewardship activities.

The scarcity of quality-assured microbiology laboratories in low resource settings and lack of priority given in the past decades to sustained bacterial surveillance have led to large empty areas

on the worldwide resistance maps, especially for sub-Saharan Africa and rural Asia. Quality-assured microbiology services and routine bacterial resistance surveillance are urgently needed in most of these areas. The addition of antibiotic resistance to death registers might help to raise awareness of antibiotic resistance on the priority agenda of policy makers (Diekema and Pfaller, 2013; ECDC., 2013).

Here conducted this extensive review of relevant published articles using extensive literature search made through PubMed, Google scholar, Scopus and HINARI on the concepts of antibiotic resistance, antibiotic susceptibility testing for surveillance, components of standard antibiotic resistance (ABR) surveillance programs, with special interests on challenges of ABR surveillance in Nigeria and possible solutions.

EMERGENCE OF ANTIBIOTIC RESISTANCE

The emergence of ABR is determined by a complex (and largely uncertain) interaction of environmental, epidemiological, clinical and behavioral factors (Coast and Smith, 2003). There is overwhelming evidence that the use and overuse of antibiotics has been a powerful selector of resistance (Coast and Smith, 2003).

Antibiotic resistance occurs when antibiotic levels that would normally prevent the growth of or kill a particular bacterium become ineffective because of a change in the bacterium. An antibiotic is no longer clinically effective when this occurs at a therapeutic dose for treatment of infection.

There are two stages in the emergence of antibiotic resistant bacterial strains:

- **Genetic mutation or gene acquisition:** Resistance arises due to a mutation(s) in the DNA sequence of the relevant gene(s) in the bacterial chromosome, or because the existing antibiotic resistance gene is transferred into the bacterium from another resistant bacterium (gene acquisition or horizontal gene transfer)
- **Selective advantage:** Once a resistance gene or mutation is present (and expressed), the cells containing it are able to grow in the presence of the antibiotic and therefore increase in numbers at the expense of susceptible cells. Naturally resistant organisms are also favoured. The total amount of antibiotic used is a general indicator of the selection pressure and continuous exposure to an antibiotic provides the strongest selection pressure (Taiwo, 2011; Wernli *et al*., 2011)

SPREAD OF ANTIBIOTIC RESISTANCE

Resistant bacteria can move from one environment to another (e.g. animal to human or vice versa). Such spread can occur through direct contact (e.g. between animal and human) or indirectly (e.g. in food or water). The global spread of resistant organisms is well documented and presumably due to movement of hosts or contaminated products between locations (including between continents) (Wernli *et al*., 2011).

Resistance due to mutations in the bacterial genome is spread by transmission of the bacterium, whereas horizontal gene transfer allows for resistance to be spread between commensal and pathogenic bacteria and vice versa and also between different species of bacteria. The most frequent mechanism underpinning ABR is horizontal gene transfer between a resistant bacterium and a susceptible one, this occurs in the absence of selection (Wernli *et al*., 2011).

COMMON ANTIBIOTIC RESISTANT PATHOGENS IN NIGERIA

- Methicillin resistant *Staphylococcus aureus* (MRSA)
- Vancomycin resistant *Staphylococcus aureus* and Enterococci
- Multidrug resistant gram negative bacteria such as those with extended spectrum beta-lactamase (ESBL) resistance and carbapanem resistant enterobacteriacae
- Multi drug and extensive-drug resistant *Mycobacterium tuberculosis* (MDR-TB and XDR-TB)

ROLES OF CLINICAL MICROBIOLOGY LABORATORY IN ANTIBIOTIC RESISTANCE SURVEILLANCE

A key partner in the surveillance of AMR is the microbiology laboratory. Healthcare workers and public health authorities rely on the work and expertise of medical laboratory professional to determine what organism is causing infection in a patient and the antimicrobials that would be effective treatment options. Surveillance system for ABR is driven by laboratory data. To ensure that data is comparable, two approaches are taken:

- Send isolates to a limited number of reference laboratories for analysis and reporting
- Standardize protocols across the participating laboratories and enforce participation in external quality assurance programs

PATHOLOGY DATABASE

In developed nations, laboratories invariably use Laboratory Information Systems (LISs), which may capture data directly from testing equipment, or data may be entered manually. Two approaches are common for the storage of laboratory testing data:

- Each laboratory or network has a proprietary or commercial LIS
- Data is captured into a WHONET database at the local site

Unfortunately, these LISs for ABR surveillance are not functional in Nigeria and most developing countries.

LABORATORY INVESTIGATIONS

It is worthy to note that antibiotic susceptibility tests results are not limited to therapeutic purpose but could be used surveillance of antibiotic resistance pattern. Laboratory investigations for ABR can be performed on:

- Pure colonies of known pathogen to determine their minimum inhibition concentration thereby determining the antimicrobial susceptibility/resistance pattern
- Target special gene packet carrying resistance trait by using molecular assays

ANTIBIOTIC SUSCEPTIBILITY TESTING (AST)

These are conducted mainly to determine the susceptibility and resistance pattern of antibiotics on pathogen. This can be achieved through the following methods:

- Dilution susceptibility tests
- Disk diffusion tests (e.g. Kirby Bauer and Stokes method)
- The E-test and E-test based automated testing systems (e.g. Vitek analysers)

- **Molecular techniques:** It has been encouraged that laboratory surveillance should rely mainly on molecular and sequence-based typing data (WHO., 2011). This is because it can be applied to clinical specimens where culture confirmation of infection is not possible (e.g. slowing growing and fastidious bacteria)

SURVEILLANCE OF ANTIBIOTIC RESISTANCE

Surveillance of antimicrobial resistance tracks changes in microbial populations, permits the early detection of resistant strains of public health importance and supports the prompt notification and investigation of outbreaks. Surveillance findings are needed to inform clinical therapy decisions, to guide policy recommendations and to assess the impact of resistance containment interventions.

The WHO Global Strategy for Containment of Antibiotic Resistance recognized laboratory-based surveillance of antibiotic resistance as a "fundamental priority" for the development of strategies to contain antibiotic resistance and for assessment of the impact of interventions. In face of the above mentioned dimensions of antibiotic resistance as a threat to public health, many countries have established national and regional surveillance collaborations, others have not. Furthermore, there is no formal framework for collaboration among surveillance programs worldwide. This lack of a global framework for collaborative surveillance of antibiotic resistance hobbles efforts to track emerging resistance challenges; to identify, characterize and contain new threats and to systematically compare and evaluate the value of national resistance containment activities (WHO., 2011).

SCOPE OF ANTIBIOTIC RESISTANCE SURVEILLANCE

A concerted effort is required to bring all laboratories under the umbrella of quality practice to meet national standards. Antibiotic resistance surveillance can be achieved through:

- Creating awareness and training in good clinical laboratory practice to follow standard operating procedures, quality control and quality assurance
- Standard practice on antimicrobial testing must be strictly adhered to in the laboratory
- Results must be interpreted using international guidelines
- Standard documentation of procedures and timely dissemination of results into the surveillance database must be followed
- Networking of laboratories within states and across the country will build the capacity of testing laboratories through technology transfer, training and inter-laboratory comparison of results (WHO., 2011)

ANTIBIOTIC RESISTANCE SURVEILLANCE DATABASE

- Results/data generated from individual laboratories are compiled and sent to national reference laboratory for action
- These are eventually fed into an antimicrobial resistance database network
- These data depicts the analysis of trends in the occurrence of antimicrobial resistance pattern of various bacteria over time and between different laboratories within country

ANTIBIOTIC RESISTANCE SURVEILLANCE SYSTEMS IN NIGERIA

Nigeria is a developing country with the largest population size in Africa of approximately 165 million. The Nigeria health system comprises a set of public and private service providers

in multiple settings, supported by a variety of legislative, regulatory and funding arrangements (Federal Ministry of Health, 2014).

Responsibilities for healthcare costs are distributed across the three levels of government, nongovernment organizations and individual Nigerians. Public-sector service provision is the responsibility of state and territory governments for public hospitals and a mixture of Nigerian federal, state and local governments for community and public health services. From 2003 onwards there has been extensive health system reform in Nigeria, affecting the way services are delivered and funded. Overall coordination of the public healthcare delivery system is the responsibility of Nigerian government supported by the Federal ministry of health.

Nigeria has been fairly served by medium-quality, few accredited medical/pathology laboratory services in both the public and private sectors, which generate key information on bacterial isolates and their antibiotic resistance patterns. Such data is critical to coordinated ABR surveillance systems (MLSCN., 2014).

Nigeria, however, has no national coordination of these data. Existing national and state-based ABR surveillance activities are often voluntary and they operate without systematic oversight and functional leadership at the national level. Although, several tertiary institutions has an Antimicrobial Resistance Standing Committee, there had been no national coordination of activities, comprehensive national reports on antibiotic use and resistance, or capability to readily link antimicrobial usage and resistance data at a national level. However, there is only a single entity that fulfils such a role at a national level; the National Tuberculosis and Leprosy Control Programme (NTBLCP) in Zaria, Nigeria. This programme has four reference laboratories providing services for drug resistant TB in Nigeria. Recently, the introduction of nested PCR equipment called the GeneXpert® that could detect rifampicin resistance has aided availability of molecular-based anti-TB resistance testing in several healthcare facilities in Nigeria (WHO., 2014).

Based on available facts, Nigeria has been keeping pace in tracking antibiotic resistance to first-line anti-tuberculosis; however, prompt switch to second-line drugs whenever MDR-TB is detected is usually less achieved. This might invariably lead to poor prognosis or emergence of another deadlier resistant strain (XDR-TB).

CHALLENGES ASSOCIATED WITH ANTIBIOTIC RESISTANCE SURVEILLANCE IN NIGERIA

Although progress has been made in gathering and using ABR data in TB, however, challenges still remain. Major challenges include lack of a comprehensive policy and plan to address ABR, weak medicines regulatory capacity and circulation of substandard/counterfeit antibiotics, lack of ABR surveillance strategies, weak laboratory capacity on ABR testing and reporting, lack of essential laboratory reagents and consumables and limited quality assurance and control protocols (Frean *et al*., 2012).

The medicines supply and distribution systems in most part of Nigeria are fragmented and weak. This situation increases the opportunities for infiltration of substandard/counterfeit medicines into the supply chain. Inadequate access to basic health services coupled with shortages and frequent stock-out of essential medicines including antibiotics in public health facilities could lead patients to look for other sources usually through illicit sources of supply, which usually deal with substandard/counterfeit medicines.

The WHO Global Strategy for Containment of Antibiotic Resistance recognized laboratory-based surveillance of antibiotic resistance as a “fundamental priority” for the development of

strategies to contain antibiotic resistance and for assessment of the impact of interventions. However, laboratories are perhaps the most neglected of all hospital departments in Nigeria and other developing countries and have been termed the "Achilles' heel" of global efforts to combat infectious diseases.

The lack of inter-laboratory framework for collaborative surveillance of antibiotic resistance seriously hampers efforts to track emerging resistance challenges; to identify, characterize and contain new antibiotic threats and to systematically compare and evaluate the value of national resistance containment activities (CDC., 2009).

SOLUTIONS AND RECOMMENDATIONS

In order to prevent and combat ABR, comprehensive national ABR policies, strategies and plans should be developed and implemented involving policymakers, partners and stakeholders in public health. Targeted capacity building activities in various domains including ABR surveillance, laboratory services, quality control of test reagents and protocols, effective medicines regulation and rational use of medicines are urgently needed. Furthermore, establishment of national and/or regional policy platforms for management of antibiotic resistance could play crucial role.

In establishing a multi-disease drug resistance surveillance network, the regional health community can build on a range of existing efforts. In order to initiate change, a detailed national/regional analysis of the situation on ground by a multidisciplinary group including the agriculture and animal sectors is required (Shaban *et al*., 2013).

Understandably, the majority of surveillance programs are laboratory-based. Strategies for ensuring and maintaining the quality of laboratory test results are critical to the value of surveillance initiatives. All facilities should have procedures for ongoing assessment of the quality of test reagents and test performance by medical laboratory scientists. In addition to internal quality control practices, laboratories should also participate in national and/or External Quality Assurance (EQA) programs. Building clinical laboratory capacity will enable the generation of adequate and reliable ABR data that can guide policy actions to combat ABR. Nigeria should therefore strengthen their capacity for early detection and identification of resistant bacteria that cause diseases of public health importance. Antibiotic resistance surveillance data help monitor the susceptibility patterns of bacteria to antimicrobial agents. An active antibiotic resistance surveillance committee should be introduced, it should comprise of all major departments and professionals of hospitals e.g. consultant microbiologists, medical laboratory scientists, physicians, surgeons, nurses and pharmacists.

ACKNOWLEDGMENT

We would like to appreciate Pharmacist Ibrahim Abdulkadir of Ahmadu Bello University Teaching Hospital, Zaria, Nigeria for proof-reading the final draft manuscript before submission.

REFERENCES

CDC., 2009. Laboratory accreditation program to strengthen health systems. Centers for Disease Control and Prevention, Atlanta, GA., USA. http://www.cdc.gov/globalaids/Success-Stories/lab-accreditation.html.

Coast, J. and R.D. Smith, 2003. Antimicrobial resistance: Cost and containment. Expert Rev. Anti-Infect. Ther., 1: 241-251.

Davies, J., 1994. Inactivation of antibiotics and the dissemination of resistance genes. Science, 264: 375-382.

Diekema, D.J. and M.A. Pfaller, 2013. Rapid detection of antibiotic-resistant organism carriage for infection prevention. Clin. Infect. Dis., 56: 1614-1620.

ECDC., 2013. Antimicrobial resistance surveillance in Europe 2012. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden, November 15, 2013.

Federal Ministry of Health, 2014. Mission and vision. Federal Ministry of Health, Nigeria. http://www.health.gov.ng/index.php/about-us/mission-and-vission.

Finch, R., D. Greenwood, S.R. Norrby and R.J. Whitley, 2003. Antibiotic and Chemotherapy: Anti-Infective Agents and their Use in Therapy. 8th Edn., Churchill Livingstone, USA., ISBN-13: 978-0443071294, pp: 45-49.

Frean, J., O. Perovic, V. Fensham, K. McCarthy and A. von Gottberg *et al*., 2012. External quality assessment of national public health laboratories in Africa, 2002-2009. Bull. World Health Organiz., 90: 191-199.

MLSCN., 2014. Laboratory external quality assurance assessment. Medical Laboratory Science Council of Nigeria, Asokoro, Nigeria

McGeer, A., C.A. Fleming, K. Gree and D.E. Low, 2001. Antimicrobial resistance in Ontario: Are we making progress? Laboratory Proficiency Testing Program Newsletter No. 293, Toronto, Ontario, Canada, January 9, 2001, pp: 1-2.

Ndihokubwayo, J.B., A.A. Yahaya, A.T. Desta, G. Ki-Zerbo and E.A. Odei *et al*., 2013. Antimicrobial resistance in the African region: Issues, challenges and actions proposed. Afr. Health Monit., 16: 27-30.

Nikaido, H., 1994. Prevention of drug access to bacterial targets: Permeability barriers and active efflux. Science, 264: 382-388.

Shaban, R.Z., M. Cruickshank and K. Christiansen, 2013. National surveillance and reporting of antimicrobial resistance and antibiotic usage for human health in Australia. Antimicrobial Resistance Standing Committee, Canberra, Australia, June 2013, pp: 1-138.

Smith, A., 2004. Bacterial Resistance to Antibiotics. In: Hugo and Russell's Pharmaceutical Microbiology, Denyer, S.P., N.A. Hodges and S.P. Gorman (Eds.). Blackwell Science, Massachusetts, USA.

Spratt, B.G., 1994. Resistance to antibiotics mediated by targ*et al*terations. Science, 264: 388-393.

Taiwo, S.S., 2011. Antibiotic-resistant bugs in the 21st century: A public health challenge. World J. Clin. Infect. Dis., 1: 11-16.

WHO., 2001a. Strategy for containment of antimicrobial resistance. WHO/CDS/CSR/DRS/2001.2, Department of Communicable Disease Surveillance and Response, WHO., Geneva, Switzerland, pp: 1-105.

WHO., 2001b. WHO global strategy for containment of antimicrobial resistance. WHO/CDS/CSR/DRS/2001.2, World Health Organization, Geneva, Switzerland, pp: 1-99. http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf.

WHO., 2011. Establishment of national laboratory-based surveillance of antimicrobial resistance. SEA-HLM-415, WHO Regional Office for South-East Asia, New Delhi, India. http://apps.searo.who.int/PDS_DOCS/B4692.pdf.

WHO., 2013. WHONET software. http://www.who.int/drugresistance/whonetsoftware/en/.

WHO., 2014. Nigeria: Tuberculosis profile. World Health Organization, Switzerland.

Wernli, D., T. Haustein, J. Conly, Y. Carmeli, I. Kickbusch and S. Harbarth, 2011. A call for action: The application of the international health regulations to the global threat of antimicrobial resistance. PLoS Med., Vol. 8. 10.1371/journal.pmed.1001022