Anti-Microbial Resistance

Ibukun F. Ifedayo
Clinical III, Medicine, OAU

Introduction

Evolution of species is a constant process of nature that ensures the survival of the fittest. The ability of a species to adapt to changes in its environment is needed for survival and proliferation. This is true for all organisms. The human species has successfully adapted to the earth over years albeit with the aid of technology.[1] The situation is not the same for bacteria which since the advent of the earliest antimicrobials have been involved in a constant battle for survival. Bacteria and other infective microorganisms have undergone changes in their structure to withstand antimicrobials; this is detrimental to man.

Antimicrobial resistance (AMR), also known as drug resistance, is the resistance of a microorganism to a drug to which it was previously sensitive i.e. drugs used to cure infections by such microorganisms become ineffective.[2,3] Using clinical outcome, antimicrobial resistance can be defined as a failure of a drug to kill a microbe following standard course of treatment.[4] Resistant organisms which include bacteria, viruses and some parasites are able to withstand attacks by antimicrobial drugs including antibiotics, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist and may spread to other individuals.[2]

The discovery of antimicrobials was one greatest medical achievements of the 20th century. Most of the currently used antibiotics or their parent compounds were discovered in that century.[4] Following the introduction of antimicrobials into medical practice, (sulphonamides in the 1930s, penicillin and streptomycin in 1940s and others in later years) was the emergence of antibiotic resistant bacteria populations.[4] Gonococci, Meningococci and Staphylococci developed resistance to sulphonamides and penicillin few years after their use for treatment of such infections.[5,6]

Over the years, AMR developed as a consequence of the use, and particularly the misuse, of antimicrobial drugs, to such an extent that some microorganisms (TB and enterococci) became resistant to multiple drugs.[2,4,6] Microorganisms resistant to most antimicrobials were dubbed "superbugs".[3]

Antimicrobial resistance is a major public health concern because resistant infections may prolong illness, can spread to others, and imposes huge costs on individuals and society.[3] The World Health Day in 2011 was tagged "Combat Antimicrobial resistance: No Action today, No cure tomorrow" in realization of the implications of AMR. On this day, the World Health Organisation (WHO) issued an international call for concerted action to halt the spread of antimicrobial resistance.[2]

Origin and Mechanism of Antimicrobial Resistance

The origin of antimicrobial resistance can be non-genetic and genetic. Non-genetic origin of AMR is due to the phenotypic characteristics of the microorganism. Non-multiplying organisms may be phenotypically resistant to drugs because active replication is required for most

antibacterial drug actions. Dormant mycobacteria may remain inactive with tissues for many years following drug therapy. Microorganisms may also become resistant to drugs when infection occurs at sites where antimicrobials are excluded or inactive. For example, intracellular organisms require drugs that can enter cells effectively. When microorganisms have lost a specific target structure for a drug for several generations, they are resistant until another generation possessing such target structure is encountered (e.g. penicillins and cell wall deficient L-form organisms).[6,7]

However, AMR develops mainly as a result of genetic change and subsequent selection methods by antimicrobials. Chromosomal resistance emerges as a result of spontaneous mutation in the genetic material coding for susceptibility to a particular drug in a given organism. The genetic material may code for a specific target structure for a drug. This drug places a *selective pressure* on such organisms by killing the susceptible population, leading to the survival and growth of a mutant population in which that target structure is absent. This new mutant population is resistant to the drug and they propagate that resistant gene in the subsequent generation. An example is the loss of penicillin binding protein in staphylococci and streptococci.[4,6,7] Extra-chromosomal resistance is carried by structure called plasmids in bacteria. Plasmids may carry genes for resistance to one or several antimicrobials. This genetic resistance can be transferred across species by mechanisms of transduction, transformation and conjugation; leading to spread of resistance across various species. Cross-resistance occurs when an organism is resistant to a group of different drugs that share a similar mode of action, or are chemically related, for example macrolides and lincomycins.[6,7]

Mechanisms of antimicrobial resistance by microorganisms are diverse. Microorganisms may produce enzymes that destroy the active drug (beta-lactamase and penicillins), they may change their permeability to the drug (tetracycline), develop an altered structural target (penicillins) or an altered metabolic pathway (sulphonamide). These mechanisms may be *intrinsic* or *acquired*, depending on the origin of resistance.[4,6,7]

Epidemiology of Antimicrobial Resistance

AMR is a problem of epidemic proportions. Facts about the incidence and prevalence of diseases caused by drug resistant microorganisms show clearly that AMR is a global public health problem. The WHO reported that about 440 000 new cases of multi drug-resistant tuberculosis (MDR-TB) emerge annually, causing at least 150 000 deaths. Extensively drug-resistant tuberculosis (XDR-TB) has been reported in 64 countries to date.[2]

In most malaria-endemic countries, resistance to earlier generation antimalarial drugs such as chloroquine and sulfadoxine-pyrimethamine is pervasive. Plasmodium falciparum species resistant to artemisinins are emerging in South-East Asia and these infections show delayed clearance after the start of treatment (indicating resistance).[2] A large percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci.[2,8] Ciprofloxacin remains the only antibiotic recommended by WHO for the treatment of dysentery due to Shigella organisms, following widespread resistance to other previously effective antibiotics.[2,10] However, rapidly increasing spread of resistance to ciprofloxacin is reducing the options for safe and effective treatment of shigellosis, particularly for children.[2]

Antimicrobial resistance has become a serious challenge for the management of gonorrhea. Widespread resistance necessitated the replacement of drugs previously used in the treatment of gonorrhea namely penicillin, tetracycline and azithromycin. Now resistance has been reported to involve ciprofloxacin and even "last-line" oral cephalosporins, and is increasing in prevalence worldwide. Untreatable gonococcal infections would lead to increased rates of illness and death, thus reversing the gains made in the control of this sexually transmitted infection.[2,8] New resistance mechanisms, such as the beta-lactamase NDM-1, have surfaced among several gram-negative bacilli. This can make powerful antibiotics, which are often the last defence against multi-resistant strains of bacteria, ineffective.[2]

The developing countries are not spared of this problem because infectious diseases are prevalent in these parts of the world; multiple studies have reported that AMR may be increasing in these countries. The developing countries share the global pattern of AMR described earlier and Nigeria is not an exception.[4,8,10,11,12,14,16] In addition to this, AMR to enteric pathogens causing diarrhoeal diseases which are prevalent in developing countries has been reported.[8,13] Global emergence and spread of multidrug-resistant *Samonella typhi* (resistant to ampicillin, chloramphenicol, and co-trimoxazole) has been a major public-health challenge for developing countries. This has been linked with an increase in disease severity, higher morbidity, mortality and case fatality rates; which is compounded by delay in administering appropriate treatment.[8] Reports from Africa suggest a varied pattern in which multidrug-resistant *Samonella typhi* is common in some areas and absent in others.[8] Resistance of shigella to ampicillin, tetracycline, co-trimoxazole, and chloramphenicol has also become widespread in Africa, even though these drugs are still used for first-line treatment of dysentery in many parts of the continent.[10] This situation is similar in Nigeria and the rest of developing world.[10] Emergence of resistance of shigella to ciprofloxacin is a new cause for concern.[2,8] Antimicrobial-resistant Vibrio cholera strains are becoming more common.[8,15] This resistant strains compound cholera and bacillary dysentery outbreaks, rendering management problematic, resulting in increased mortality rate, as reported among Rwandan refugees.[5,8]

Drug resistant strains of *Streptococcus pneumoniae* has evolved over the years, making the management of acute respiratory bacterial infection more problematic. This evolution of resistance trailed each drug that was used to treat pneumonia. S. pneumoniae strains resistant to

penicillin, tetracycline, chloramphenicol, macrolides, co-trimoxazole have increased worldwide; there has now emerged resistance to fluoroquinolones.[8,17,18,19]

HIV infection generally worsens the problem of AMR. Resistance is a burgeoning concern for treatment of HIV infection, following the rapid expansion in access to antiretroviral drugs in recent years. Apart from the emergence of HIV drug resistant strains, the need for prophylaxis against infections in HIV/AIDS patients and increased frequency of infections and hospitalization in such patients amplifies the problem of AMR. HIV compounds tuberculosis and is partly responsible for increasing drug resistance to tuberculosis.[2,4,8]

Factors That Encourages Antimicrobial Resistance

Several factors aid the continued increase in AMR. One of these is misuse of antimicrobials by physicians in clinical practice. The use of antibiotics for diseases that do not require them creates a selective pressure favoring resistant bacterial strains. Such inappropriate use increases the risk of selection and spread of resistant strains. Unnecessary prescription of antibiotics is seen particularly in cases of acute infantile diarrhea and viral respiratory tract infections. This clinical misuse may be more common among private practitioners who charge higher fees, as their patients demand for antibiotics. Antibiotics misuse is also common the Intensive Care unit (ICU) of hospitals where there is heavy antibiotic use; this has become a breeding ground for drug resistant hospital acquired infections (HAIs) which is later disseminate into the community.[2,4,5,9]

Another factor is the misuse of antimicrobials by unskilled practitioners and the general public. Well-trained medical professionals are scarce in developing countries and there is uneven distribution of such personnel between urban and rural areas, such that rural areas are worse off. A lot of untrained practitioners and self-trained quacks parade themselves as doctors in rural areas. These individuals are hardly aware of harmful effects of inappropriate antibiotic use. Unqualified "chemists" and drug peddlers in Nigeria prescribe antibiotics for headaches, dyspnea, and for prevention of sexually transmitted diseases among prostitutes. In developing countries, drugs are available without prescription over the counter in pharmacies, market stalls and are hawked along roads. Even some traditional healers have been reported to mix antibiotics with herbal preparations. Cultural beliefs that a particular antibiotic can cure a myriad of illnesses perpetuate antibiotic misuse. These practices consequently make individuals use sub-optimal doses of antibiotics or purchase sub-standard drugs, and drugs denatured by weather without any active substance. This is encourages AMR development.[4,5]

The poor quality of antibiotics available in developing countries is another factor that promotes AMR. Lack of quality compliance and monitoring of drug quality, even though there are stipulated standards, enhance the proliferation of "fake" drugs in developing world. Substandard ampicillin, ampicillin/cloxacillin, tetracycline, and oxytetracycline capsules have been detected in Nigeria. These antibiotics produce sub-inhibitory concentrations in vivo, with therapeutic failure as the obvious outcome. This increases the selection of resistant strains. Degraded antibiotics would also produce the same result. Expired antibiotics produced in industrialized countries are shipped to developing world as donations to decrease the cost of liquidation; this has a resultant effect of promoting AMR. The problem of counterfeit drugs and adulterated drugs also persists in the "third" world.[4,5] Related to these; is the issue of bio-inequivalent antibiotics and bio-pharmaceutic interactions which affects the concentration of active metabolite of drugs in the bloodstream due to various drug formulations. There is accumulation of poor absorbed oral antibiotics in the gut which facilitates the selection of resistant organisms. This would promote AMR in enteric organisms.[5,20]

Unnecessary use of antibiotics in animal husbandry, especially for supposed benefits in disease prevention and growth promotion also enhances AMR.[2,4,5,8]

The factors that promote the dissemination of resistant organisms include crowding and unhygienic conditions, inadequate hospital infection control practices, inadequate surveillance, susceptibility and lack of laboratory capacity for guided antibiotic choice. Inadequate momentum in research and development of the essential technologies to combat AMR e.g. drug, diagnostics and vaccine, also affects the spread of infections and aids the proliferation of resistant organisms.[5,8]

Economy and politics play a role in AMR development. In developing countries, political corruption and mismanagement of public funds, personnel, and development programs have created large populations living in abject poverty and at high risk of acquiring infections. The medical expenses, days absent from work, and transportation costs account for substantial economic loss. Many patients cannot afford the cost of good medical treatment in hospitals. Thus, individuals with infectious diseases, unable to pay for medical treatment, serve as a reservoir to infect others. Poverty also affects patient drug compliance, as individuals cannot afford the cost of drugs for the total duration of treatment, promoting the development of AMR during short-term therapy of acute infections and long-term therapy of chronic infections, such as tuberculosis. Lack of resources hinders implementation of most strategies against antibiotic resistance. As a result of such gross underfunding of the health sector, the drug supply is chronically inadequate or at best erratic in health facilities in many countries, including Nigeria.[5,8]

SIX MAJOR FACTORS THAT DRIVE AMR:

- Inadequate national commitment to a comprehensive and coordinated response, ill-defined accountability and insufficient engagement of communities;
- Weak or absent surveillance and monitoring systems;
- Inadequate systems to ensure quality and uninterrupted supply of medicines
- Inappropriate and irrational use of medicines, including

in animal husbandry:
- Poor infection prevention and control practices;
- Depleted arsenals of diagnostics, medicines and vaccines as well as insufficient research and development on new products.

Consequences of Antimicrobial Resistance

The consequences of AMR are a cause for global concern. To begin with, failure of infections to respond to standard antimicrobial therapy leads to prolonged illness and increased case fatality and mortality rates. In extension, patients with such diseases remain infectious for a longer period, acting as a reservoir while transmitting resistant organisms, leading to spread in the community. This would make the control of infectious diseases more challenging. Uncontrollable infectious diseases arising from AMR would hamper the progress towards achieving the health related United Nations Millennium Development Goals (MDGs) set for 2015 especially MDG 4, MDG5 and MDG 6. This would threaten to throw us back to the "pre-antibiotic era". The cost of health care would also be greatly increased by AMR because of the need to use more expensive second or last line antibiotics in resistant infections; longer duration of illness and treatment compounds the financial burden on the families and societies. Expensive clinical trials are needed to assess new treatments when resistance emerges, health-care workers must be retrained and drug production processes changed. These increases in cost will affect the economy of a country. Risks associated with modern treatment such as organ transplantation, cancer chemotherapy and major surgery would increase; as these procedures may be complicated by drug resistant infections. AMR would negate these advances made in medicine. Globalization with associated international travel and trade promotes the spread of resistant microorganisms to distant countries. This would compromise health security and damage trade.[2,4]

These consequences would be acute in the developing countries who are still groping for solutions to current health and economic problems.[5]

Strategies for Decreasing Antimicrobial Resistance

Antimicrobial resistance develops as a natural response of microorganisms to the survival challenge posed by antimicrobials. Therefore an effective control strategy would focus on containment, and decreasing emergence and spread of resistance.[4] These can be achieved by following

- **Decrease in selective pressures**. This would decrease the emergence of new resistant microbes. Medicine contributes largely to the selective pressure on microbes due to misuse and overuse of antimicrobials. Therefore: rational drug use should be advocated, regulations that limit antibiotic choice put in place, antibiotic use audited, and development of prescription guidelines made. Continuing medical and public education should be emphasized. The public should be made aware of the dangers of poor drug compliance and poor drug quality. Poor quality antibiotics should also be eradicated from national circulation. Use of antimicrobials outside medicine, especially in food-producing animals should be curtailed.[4,5,8,22] Possible alternatives to antibiotics that will be effective against pathogenic microorganisms without any fear of development of resistance, have been proposed. Some of these alternatives include vaccines, phage therapy, probiotics, immune- boosting trace elements and some bioactive phytochemicals.[21]
- **Adoption of good infection control.** It is important to decrease the prevalence of infections by prevention, thereby decreasing the need for antibiotics and a consequent fall in emergence of AMR. Good infection control also limits the spread of resistant organisms. Hospital infection control programs should be enforced; simple infection control practices such as hand washing should be inculcated in health workers.[4,5,8,22]
- **Surveillance of antimicrobial resistance and use.** An efficient surveillance system should be set-up to detect, monitor and document AMR at local, national and international levels. The surveillance data generated should be serve as an "evidence for action" to combat AMR.[4,5,8]
- **Increase in research activities into generating newer drugs.** In spite of the advances in science and technology in current century, no new clinical structures of antimicrobials has been discovered since 1960s, most current drugs are modification of old antimicrobials which bacteria have "learned" to resist. Cross-resistance by microorganisms has made some antimicrobials ineffective. There is need to increase research efforts on developing new antimicrobials to reduce the pressure on existing ones.[4,8]

The WHO is engaged in guiding the response to AMR by providing policy guidance, support for surveillance, technical assistance, knowledge generation and partnerships, and through disease prevention and control programmes. It also assists in ensuring essential drugs quality, supply and rational use. It also promotes infection prevention and control, patient safety and laboratory quality assurance.[2]

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