THE NIGERIAN
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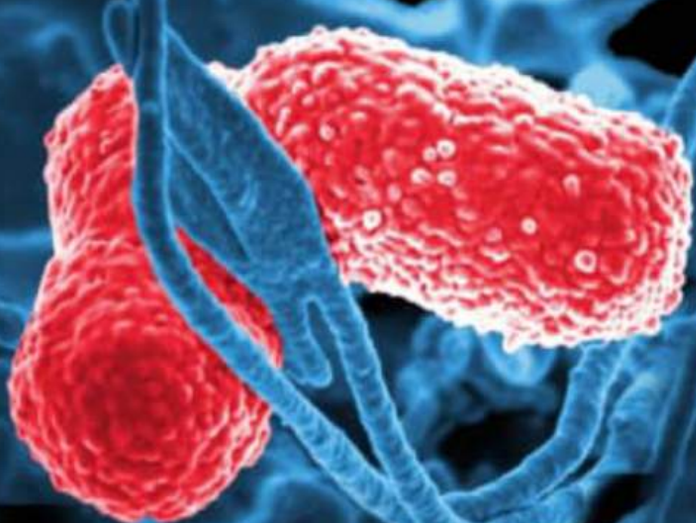
Public Lecture Series

ANTIBIOTIC RESISTANCE: A CONSEQUENCE OF DRUG MISUSE



by

Prof. Sunny E. Ohia, FAS

October 23rd, 2018

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Antibiotic Resistance: A Consequence of Drug Misuse

By

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Texas Southern University

Houston, Texas, USA

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Table of Contents

The Nigerian Academy of Science (NAS)

The Nigerian Academy of Science (NAS) is the foremost independent scientific body in Nigeria which was established in 1977, and incorporated in 1986. NAS is uniquely positioned to bring scientific knowledge to bear on the policies/strategic direction of the country, and is also dedicated to the development and advancement of science, technology, and innovation (STI) in Nigeria. The aims and objectives of the Academy are to promote the growth, acquisition, and dissemination of scientific knowledge, and to facilitate its use in solving problems of national interest. The Academy strives to do this by:

- Providing advice on specific problems of scientific or technological nature presented to it by the government and its agencies, as well as private organizations
- Bringing to the attention of the government and its agencies problems of national interest that science and technology can help solve
- Establishing and maintaining the highest standards of scientific endeavours and achievements in Nigeria, through the publication of journals, organization of conferences, seminars, workshops, and symposia, recognition of outstanding contributions to science in Nigeria, and the development of a working relationship with other national and international scientific bodies and academies

As with national academies in other countries, NAS is a not-for-profit organization with membership comprising 233 Fellows elected through a highly competitive process who have distinguished themselves in their fields both locally and internationally. Some of her members have served as vice-chancellors of universities, directors-general of government parastatals, and ministers in federal ministries. The Academy, given its clout, also has the ability to attract other experts from around the country and internationally when needed. NAS is Nigeria's national representative on such bodies as the International Council for Science (ISC), and the InterAcademy Partnership (IAP).

Speaker's Profile

SunnyE. Ohia, Ph.D., FARVO, FAS, is a Professor of Pharmacology in the College of Pharmacy and Health Sciences at Texas Southern University. Dr. Ohia served as the Provost and Vice President for Academic Affairs and Vice President for Research from September 2008 until June 2014. As provost, he implemented several new academic initiatives and programs including the Thomas F. Freeman Honors College. Prior to his appointment at Texas Southern University, Dr. Ohia was Dean of the College of Pharmacy at the University of Houston, Houston, TX for six years.

Prior to his tenure at the University of Houston, he served in a number of leadership positions at the Creighton University School of Pharmacy and Health Professions, Omaha, Nebraska, including department Chair and Associate Dean. He holds other academic appointments as adjunct professor of ophthalmology and visual sciences at the University of Nebraska Medical Center, Omaha and as an adjunct professor of integrative biology and pharmacology at the University of Texas Health Sciences Center in Houston.

Dr. Ohia is a member of several professional organizations, including the US Pharmacopeia Convention, the American Society for Pharmacology and Experimental Therapeutics, as well as the American Association of Colleges of Pharmacy. Internationally, he is a member of the Association for Research in Vision and Ophthalmology (was elected Fellow in 2007), the British Pharmacological Society and the International Society for Eye Research. Recently, Dr. Ohia was elected Fellow of the Nigerian Academy of Science (FAS).

Dr. Ohia received his Bachelor of Science degree in pharmacology and a Master of Science degree in pharmacology and therapeutics from the University of Ibadan, Nigeria. He received his Ph.D. in pharmacology from the University of Glasgow, in Scotland, United Kingdom. Dr. Ohia completed postdoctoral research training fellowships in neuroscience and in ophthalmology/visual sciences at Memorial University of Newfoundland, Canada and the University of Louisville, School of Medicine, Kentucky, respectively. Dr. Ohia is the principal investigator on a number of federal and corporate research grants and is the author of more than 250 original papers and abstracts and, holds three U.S. and five international patents for his scientific work.

Introduction

Bacteria

Bacteria are single cell microorganisms that represent the first forms of life on earth. They are simple organisms with cell walls, but lack organelles and an organized nucleus. They exist in soil, water and air, and also thrive in a symbiotic and parasitic relationship with plants and animals. They are approximately 0.5-5 micrometers long and have different shapes such as spherical, spirals or rods (Figures 1 and 2). A gram of soil contains about 40 million bacterial cells while a milliliter of fresh water contains about one million bacterial cells. The total biomass of bacteria exceeds that of all plants and animals on earth (Whitman et al., 1998).

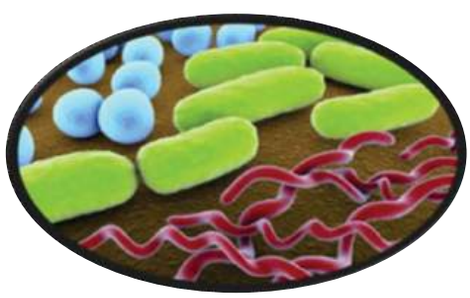


Figure 1: Different shapes of Bacteria (www.thoughtco.com)

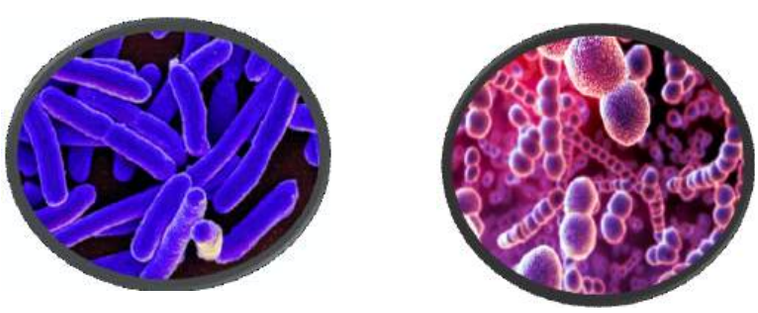


Figure 2: Examples of bacteria. Left Panel (*Escherichia coli* – www.health.hawaii.gov); Right Panel (*Streptococcus pneumoniae* – www.uk.pinterest.com)

Beneficial Roles of Bacteria

Bacteria have been shown to play an important role in several sectors of our food and chemical industries, and also in our day-to-day lives. In the food industry, bacteria are employed in the preparation of fermented foods such as cheese, pickles, soy sauce, sauerkraut, yoghurt, and wine (Johnson and Lucey, 2006). In the mining industry, these microorganisms are used for the recovery of gold, copper, and palladium. Bacteria are used in biotechnology industries for the manufacture of antibiotics and other chemicals (Ishige et al., 2005). In waste management, bacteria are important in sewage treatment and in the breakdown of oil spills (Cohen, 2002). Bacteria are used to treat infections in farm animals (which contributes to antibiotics resistance), and they can be used in the place of pesticides for pest control (Chattopadhyay et al.,2004). Bacteria are important for the nitrogen fixation process which is important for plant growth. Plants require nitrogen in the soil to live but are unable to acquire this gas on their own. Consequently, plant seeds store bacteria (containing nitrogen) which they use in the sprouting process. In the fields of molecular biology and genetics research, bacteria play an important role in the study of the function of genes and different metabolic pathways. Interestingly, the largest number of bacteria exists in our gut and skin where they aid in food digestion and the synthesis of vitamins B and K (Sears, 2005). The fact that the presence of useful bacteria in the gut inhibits the growth of their disease-causing counterparts has led to the development of probiotic dietary supplements (Salimen et al., 2005).

Harmful Roles of Bacteria

Bacteria are a major cause of diseases in animals and plants. In animals, these microorganisms are responsible for cholera, typhoid, pneumonia, tuberculosis, tetanus, food poisoning and other common human diseases. In plants, bacteria can cause bacterial wilt of tomato and brown rot of potato. Bacteria are also responsible for spoilage of unprotected food stuffs such as fruits and bread.

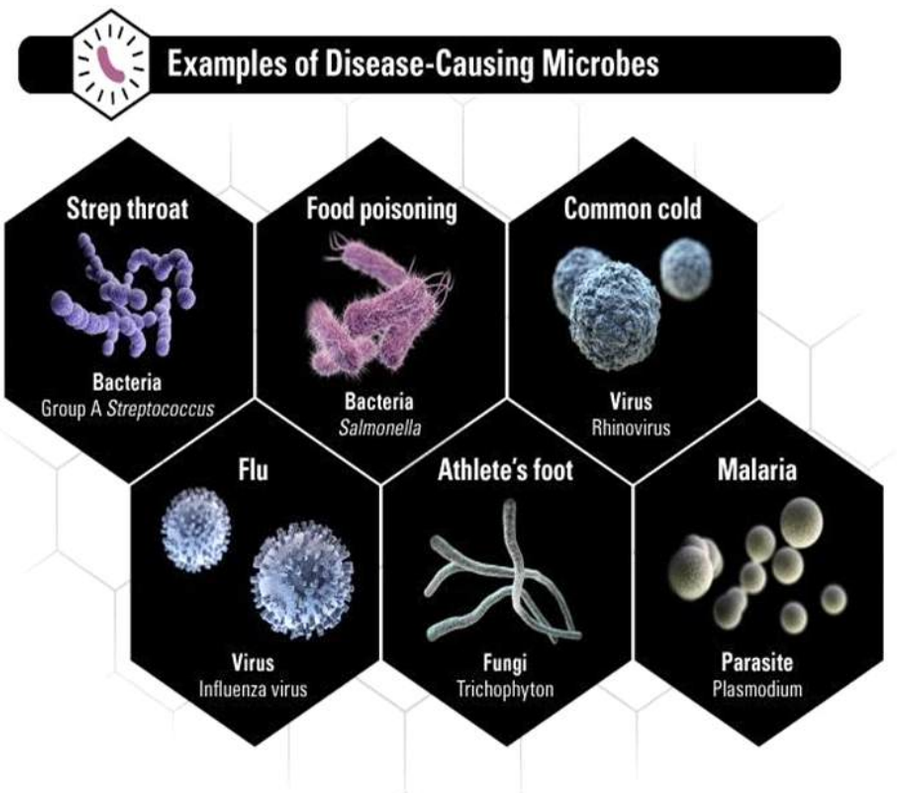


Figure 3: Examples of Disease-Causing Microbes (www.cdc.org).

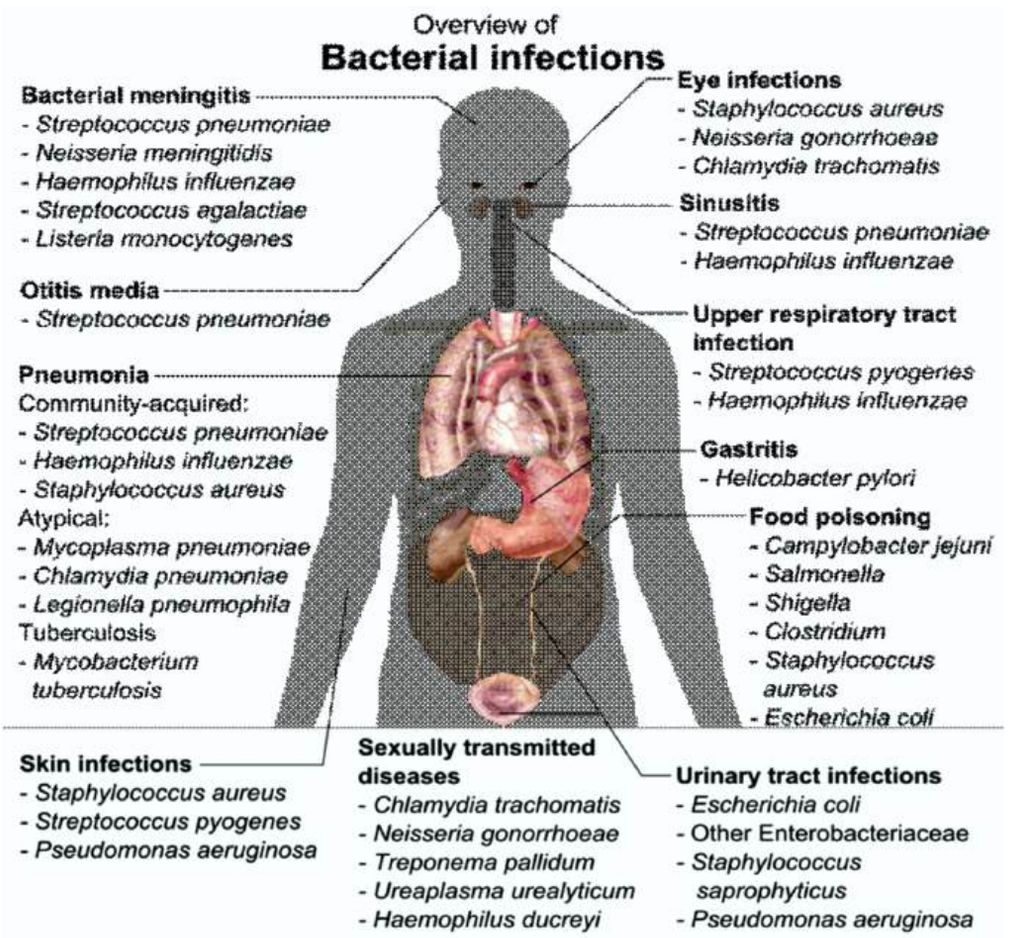


Figure 4:Overview of Bacterial Infections in Humans and the Main Species of Bacteria Involved [Fisher et al (2007) In Lipp. Illust. Rev. Microbiol. 367-392. ISBN 0781782155]

Antibiotics

Antibiotics are also known as "antibacterial agents." These drugs are used primarily in the prevention and treatment of infections caused by bacteria. Antibiotics are one of the most frequently prescribed classes of drugs in modern medicine. Antibiotics are chemicals produced naturally from living organisms such as fungi, mold and certain soil bacteria. Figure 5 illustrates the process for the manufacture of the antibiotic penicillin from the *Penicillium* mold.

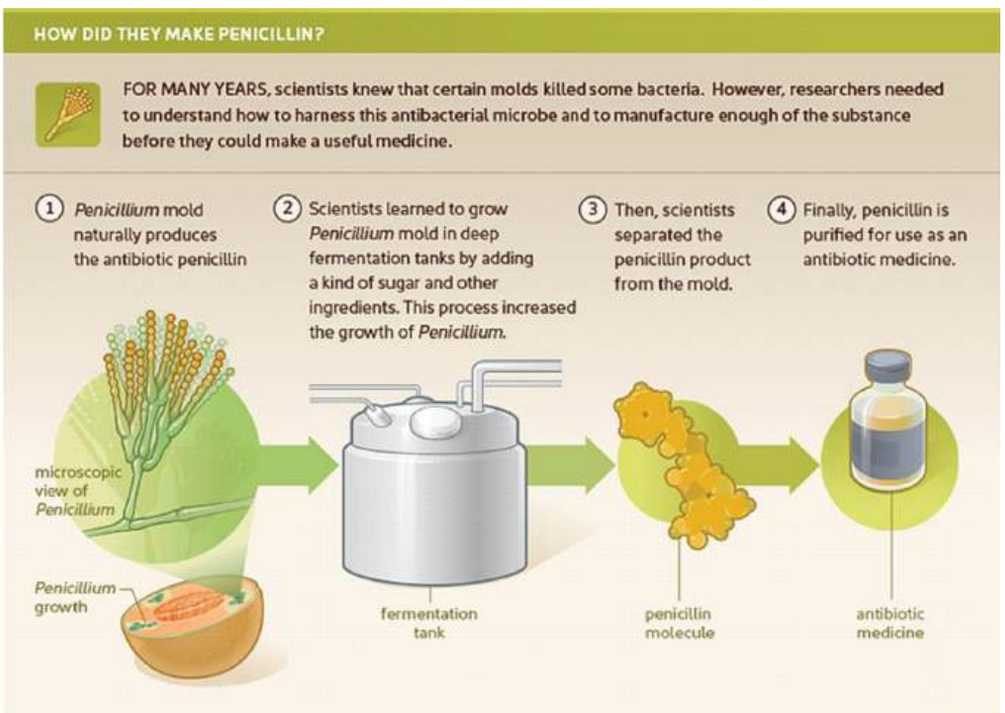


Figure 5:The industrial process used in the manufacture of the antibiotic, penicillin (www.nlm.nih.gov).

Antibiotics produce their pharmacological actions by utilizing the differences between host cells and bacterial cells in two ways: by preventing the bacterial cells from multiplying so that their population remains static enabling the host's defense mechanisms to fight the infection (bacteriostatic action), or by killing the bacteria (bactericidal action).

What do Antibiotics Treat?

Antibiotics are only needed to treat certain infections caused by bacteria such as pneumonia and sepsis. These drugs may not work on some common infections such as in most cases of bronchitis, many sinus infections and some ear infections. It is pertinent to note that antibiotics are not effective against viruses such as those that cause common colds and influenza.

Misuse/Overuse of Antibiotics

According to Marino (2007), “The first rule of antibiotics is try not to use them, and the second rule is try not to use too many of them.” There are several examples of how patients and healthcare professionals misuse or overuse antibiotics. In countries where there are no legal restrictions to the use of antibiotics and these drugs are available “over-the-counter” without prescriptions from a physician, the most common form of misuse is self-prescription. Another form of misuse by patients is the failure to take the entire prescribed dose of antibiotics especially when the symptoms associated with an infection resolves after a few doses. In some cases, a misuse may occur when patients use antibiotics as prophylactics forpossible infections associated with travel to infection-prone areas. Healthcare professionals also contribute to misuse or overuse of antibiotics by prescribing incorrect or suboptimal doses of these drugs for some bacterial infections. Furthermore, prescribing of antibiotics to treat symptoms or diseases that do not respond to these drugs (e.g. viral infections) could also contribute to the problem of misuse or overuse of these drugs. Tables 1 and 2 show summary of data that support the fact that misuse or overuse of antibiotics occurs in a US population.

Table 1:Data showing evidence of misuse/overuse of antibiotics in a US population (www.medscape.com)

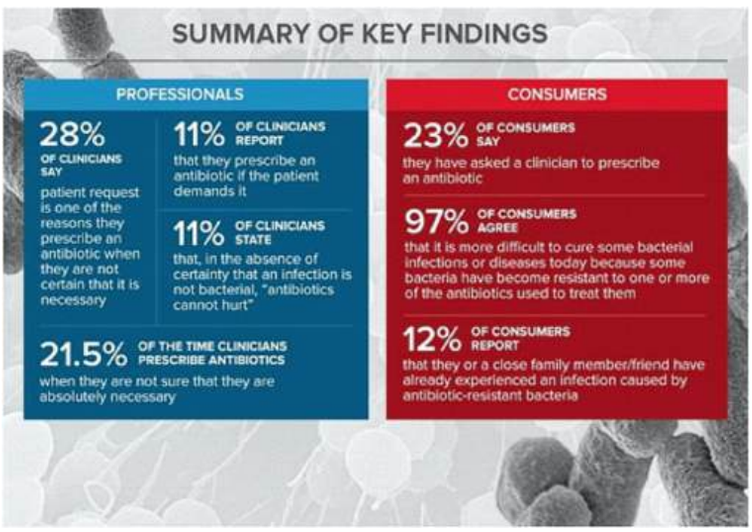
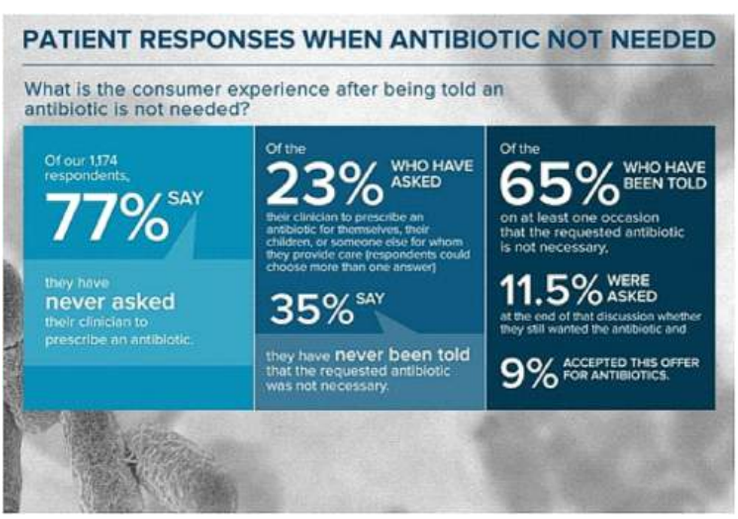


Table 2:Data showing responses of patients when informed that antibiotics are not needed for their disease (www.medscape.com)



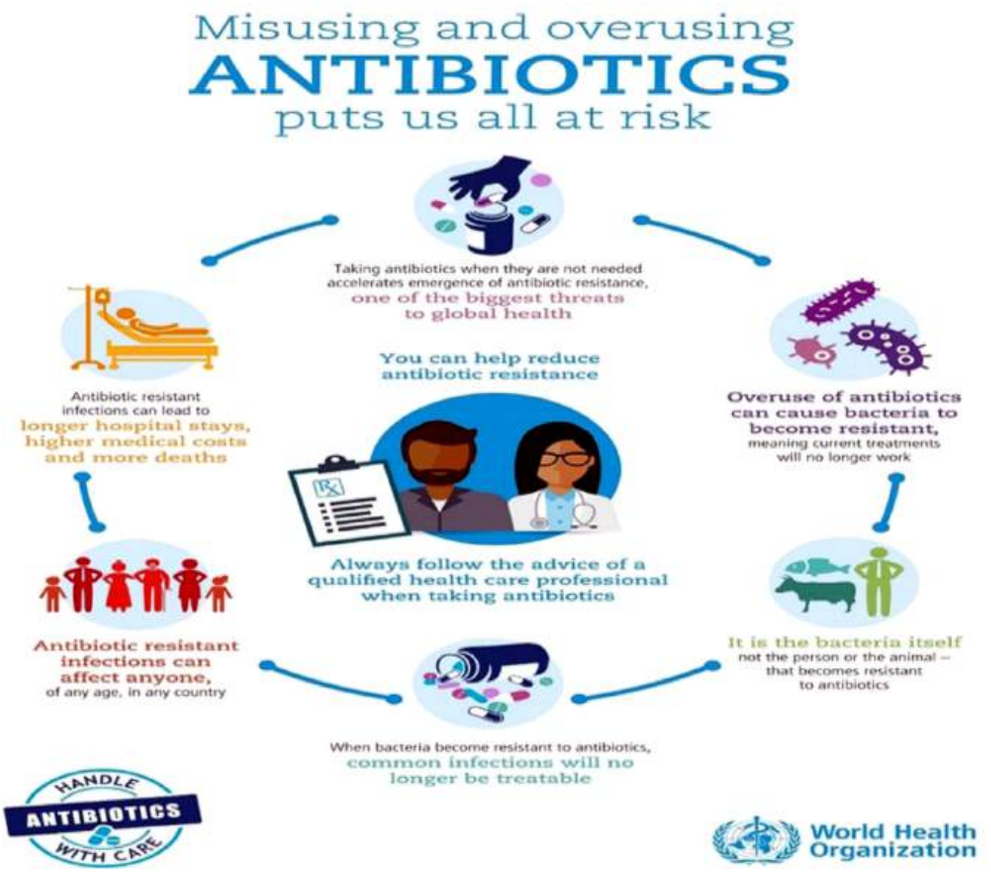


Figure 6:Effects of misusing and overusing of antibiotics endangers the society (source: WHO).

Antibiotic Resistance

What Is Antibiotic Resistance?

Antibiotic Resistance (AR) refers to the ability of the bacteria to resist the effects of drugs designed to kill or incapacitate them. Other microorganisms such as fungi, viruses and parasites also develop resistance to drugs designed to kill them (referred to as *Antimicrobial Resistance*). It is pertinent to note that it is bacteria, but not humans or animals that become resistant to antibiotics. Figure 7 shows typical responses of susceptible and resistant bacteria in culture to antibiotics.

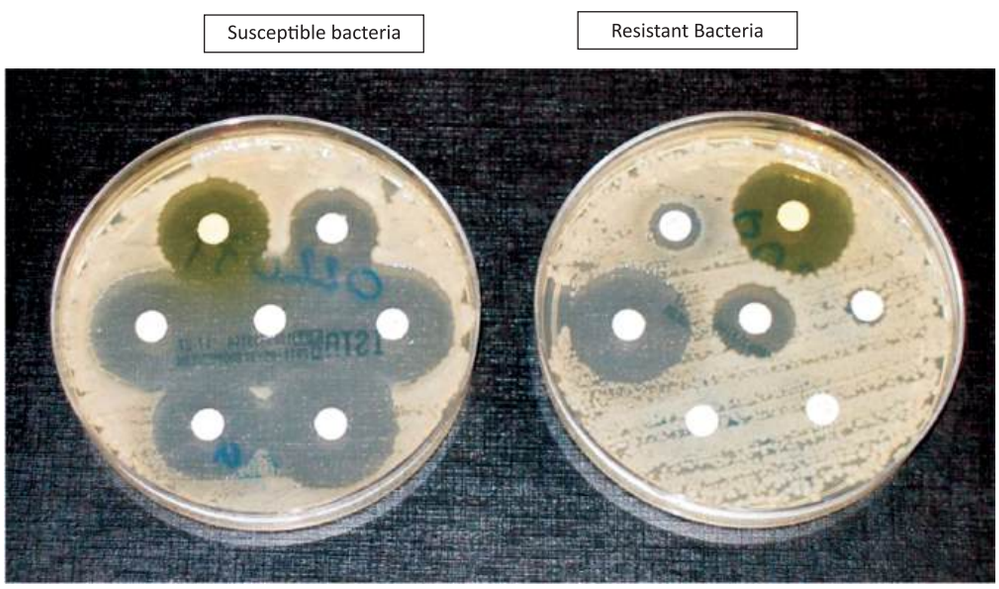


Figure 7:Antibiotic resistance tests; the bacteria in the culture on the left are sensitive to the antibiotics contained in the white paper discs. The bacteria on the right are resistant to most of the antibiotics (*Dr. Graham Beards @en.wikipedia*).

Why Does Antibiotic Resistance Occur?

The observation of resistance by bacteria to treatment with antibiotics reflects an evolutionary process that takes place during therapy. It appears that during treatment with antibiotics, the drug may preferentially select bacterial strains with physiologically or genetically enhanced capacity to survive high doses of these drugs. It is feasible that under certain conditions, there could be preferential growth of resistant bacteria while growth of susceptible bacteria is inhibited by the drug (Levy, 1994). Due to the development of resistance, antibiotics such aspenicillin and erythromycin which were highly efficacious against many bacterial species and strain are now less effective. Figure 8 illustrates the mechanism of development of resistance by bacteria.

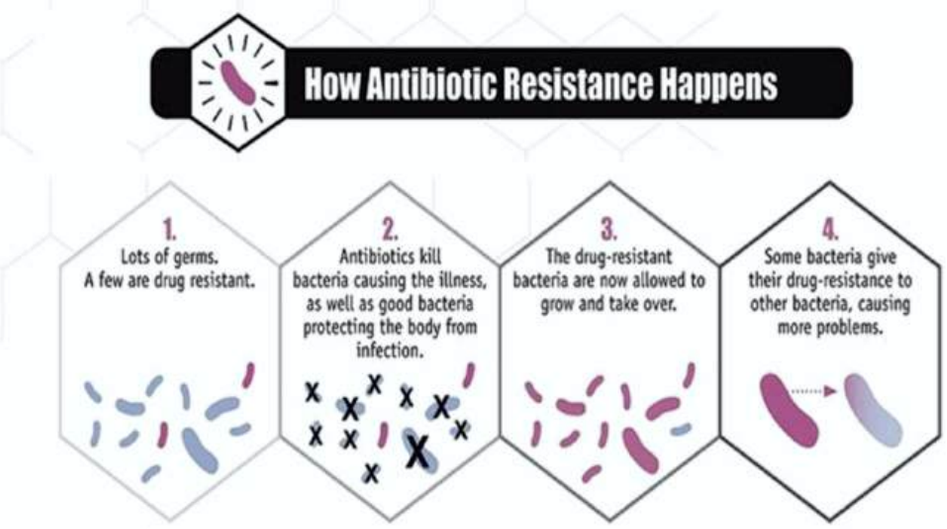


Figure 8:A possible mechanism of development of resistance by bacteria to antibiotics (www.cdc.org).

Common causes of resistance to antibiotics include: (a) over-prescribing of antibiotics by healthcare professionals, (b) patients not finishing their prescribed doses of antibiotics, (c) over- use of antibiotics in livestock and fish farming, (d) poor infection control in hospitals and clinics, (e) lack of hygiene and poor sanitation, and (f) lack of the development of new antibiotics by the pharmaceutical industry.

Mechanisms of Development of Resistance to Antibiotics in Bacteria

There are several possible ways that bacteria can develop resistance to antibiotics. There is evidence that intrinsic antibacterial resistance may be enshrined in the genes of these microorganisms (Pawlowski et al., 2016). Mechanisms of development of resistance by bacteria include: (a) inhibition of uptake of drugs into bacteria, (b) activation of efflux pumps to remove drugs from bacteria, (c) inactivation of drugs by bacterial enzymes, and (d) alteration of drug targets by the bacteria. Figure 9 shows the possible mechanisms by which bacteria can become resistant to an antibiotic agent.

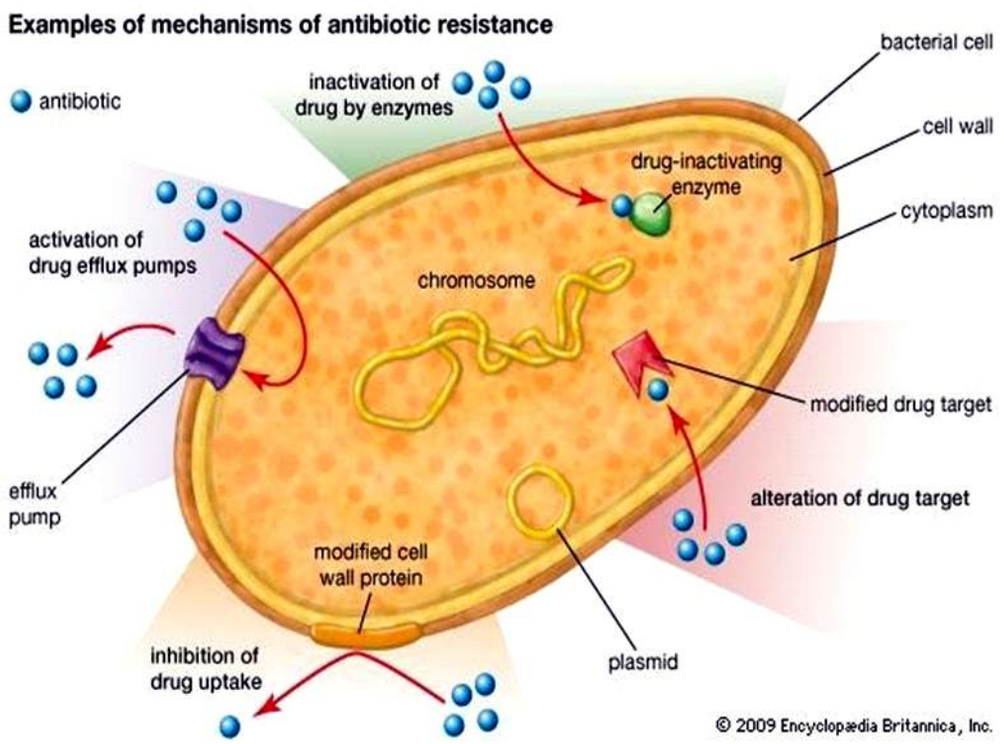


Figure 9:Possible mechanisms by which bacteria can develop resistance to antibiotics.

Consequences of Development of Antibiotic Resistance

According to the WHO, AR is one of the biggest threats to global health and food security that requires action across government sectors and the society. It is now well-known that the development of resistance to antibiotic therapy can affect anyone, of any age, in any country. Indeed, AR threatens the effective prevention and treatment of an increasing number of infections caused by bacteria (such as pneumonia, gonorrhea and tuberculosis). Without effective antibiotics, the success of major surgeries and cancer chemotherapy would be compromised with serious consequences for mankind. In economic terms, AR leads to longer hospital stays, higher medical costs and increased mortality. Even though AR occurs naturally, it is the misuse/overuse of antibiotics in humans and animals that is worsening the situation.

Antibiotic Use in Agriculture and the Spread of Antibiotic Resistance

In an era focused on increased use of scientific and technological methods in agriculture, there has been an increased use of antibiotics in preventing and treating diseases in food-producing animals and plants. Advantages of the use of antibiotics in food-producing animals include: (i) animals receiving antibiotics in their feed tend to gain more weight than their untreated counterparts, (ii) livestock treated with antibiotics tend to live longer than their untreated counterparts, and (iii) overall shell-life is increased for poultry, meat, eggs and dairy products when animals are treated with antibiotics. A disadvantage of the widespread use of antibiotics in food-producing animals is that it is now recognized as a major cause of the genesis of drug- resistant bacteria (Hao et al., 2014). According to the US FDA, in 2016, 70% of antibiotics used in the US were administered to animals (especially cows). Advantages of the use of antibiotics in food-producing plants include: (a) antibiotics are used for control of bacterial diseases of plants, (b) in the US, springtime antibiotic sprays suppress pathogen growth on flowers and leaf surfaces before infection, (c) antibiotics have been indispensable for crop protection in the US for more than 50 years without reports of adverse effects on human health, and (d) antibiotics are active on plants for less than a week and significant residues have not been found on harvested fruit (Stockwell and Duffy, 2012).

The seriousness of the lack of effective control of the use of antibiotics in food-producing animals is underscored by the recent publication of a study (October 17, 2018) by the US Public Interest Research Group which found that of the 25 Hamburger restaurant chains (including McDonald's), only two passed its test of using antibiotics-free beef on their menu. Clearly, the world still has a major problem with the use of antibiotics in food-producing animals if a developed country such as the US is contributing to the misuse of these important medicines.

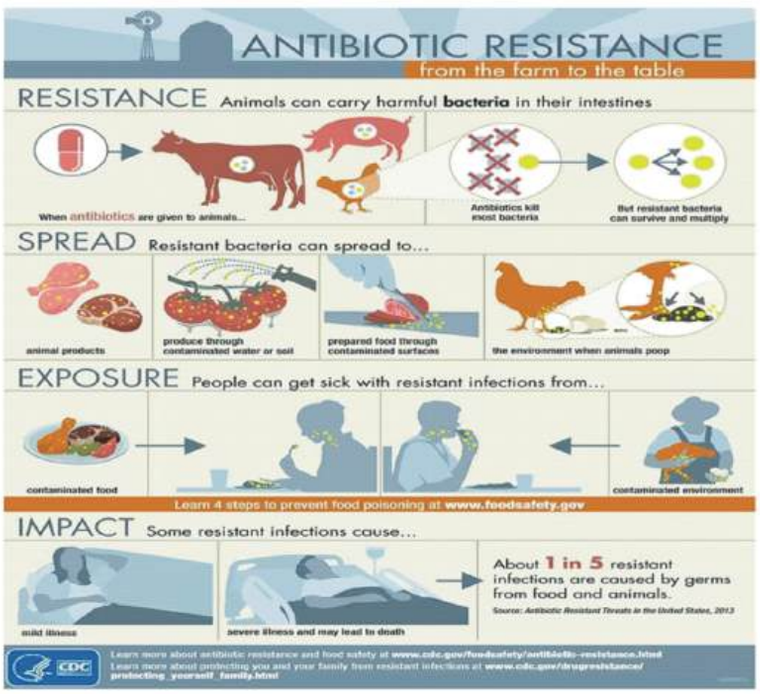


Figure 10:Possible pathways of development of antibiotics resistance from farm to table.

How Does Resistant Bacteria Spread?

The spread of resistance by bacteria to antibiotics can be facilitated by poor hygiene, poor sanitation and by poor infection control. The spread of antibiotics resistance can occur through person to person transmission and through animal to human transmission (and vice versa). Furthermore, it can occur through ingestion of contaminated food and water, and by traveling from bacteria- prone areas to uncontaminated ones. The spread of antibiotics resistance can also occur from contact with contaminated healthcare facilities, animal production facilities and the community. Figure 11 provides examples of how antibiotics resistance can spread in our community.

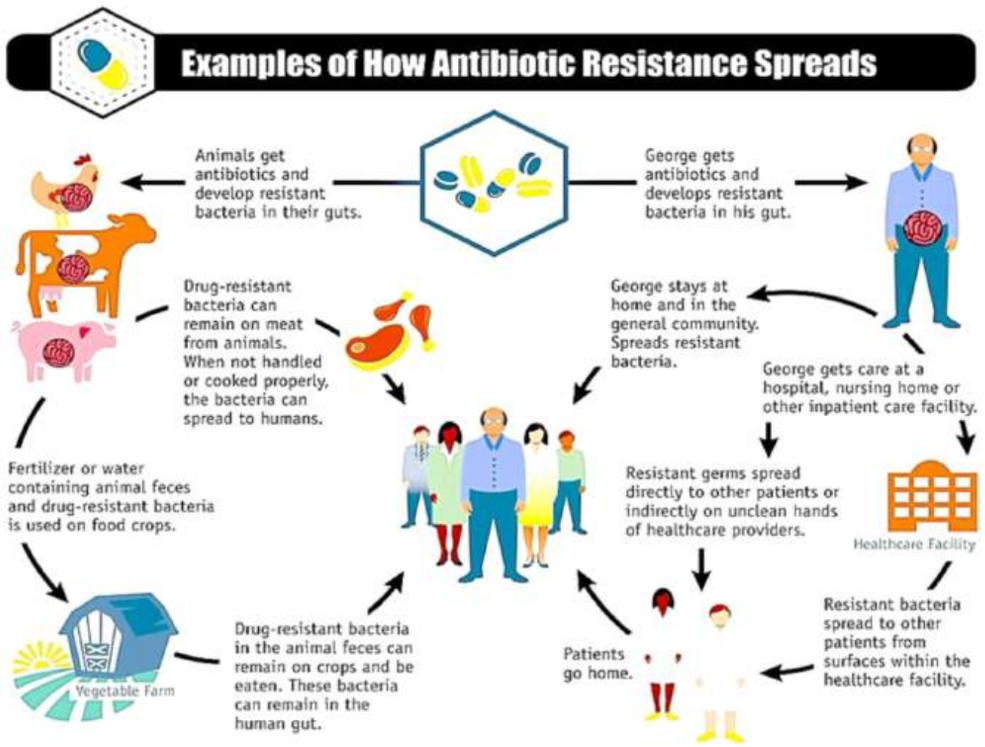


Figure 11:How antibiotics resistance can spread within our community (www.uws.edu).

WHO Guidelines on Use of Medically Important Antimicrobials in Food-Producing Animals (2017)

At the 68th World Health Assembly in May 2015, the importance of the public health problem posed by antimicrobial resistance led to the adoption of a global action plan which proposed interventions that included the reduction of unnecessary use of antimicrobial agents in humans and animals. In 2017, the following WHO recommendations and guidelines on the use of medically important antimicrobials in food-producing animals were published.

Recommendations:

- An overall reduction in use of all classes of medically important antimicrobials in food-producing animals.
- Complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion.
- Complete restriction of use of all classes of medically important antimicrobials in food-producing animals for prevention of infectious diseases that have not yet been clinically diagnosed.

- Antimicrobials classified as critically important for human medicine should not be used for control of the dissemination of a clinically-diagnosed infectious disease identified within a group of food-producing animals.

- Antimicrobials classified as highest priority/critically important for human medicine should not be used for treatment of food-producing animals with clinically-diagnosed infectious disease.

Best Practice Statements:

- Any new class of antimicrobials or new antimicrobial combination developed for use in humans will be considered critically important for human medicine unless categorized otherwise by the WHO.

- Medically-important antimicrobials that are not currently used in food production should not be used in the future in food production including in food-producing animals or plants.

Decline In the Development of New Antibiotics

Over the past 30 years, major pharmaceutical companies appear to have abandoned research into the discovery of new antibiotics. A major reason for this action is related to the fact that there is a decline in financial reward for these companies. Big pharmaceutical companies can make greater profits on drugs that can be used regularly without losing effectiveness (such as antidepressants andanti-inflammatory medications) than investing huge amounts of resources in the development of antibiotics that can be prone to resistance by bacteria. Another reason for the decline in the numbers of new antibiotics being produced is the fact that, due to economic risks, new pharmaceutical companies are unwilling to embark on the discovery of new antibiotics. As shown in Figure 12, there has been a steady decline in the number of new antibiotic agents approved in the US in the past 30 years. In 2002, no new antibiotic was approved out of the 89 new drugs for the treatment of several diseases. Indeed, there was a 90% decrease in the number of new antibiotics approved for use in the US in 2008-2012 when compared with 1983-1987. Incidentally as shown in Figure 13, there is an increasing incidence in the occurrence of antibacterial resistance. Data depicted in Table 3 shows that since 2013, only five new antibacterial agents were approved by the US Food and Drug Administration (FDA) with none approved in 2013. Incidentally, during the same period 11 new formulations of existing antibiotics were essentially repurposed for other indications.

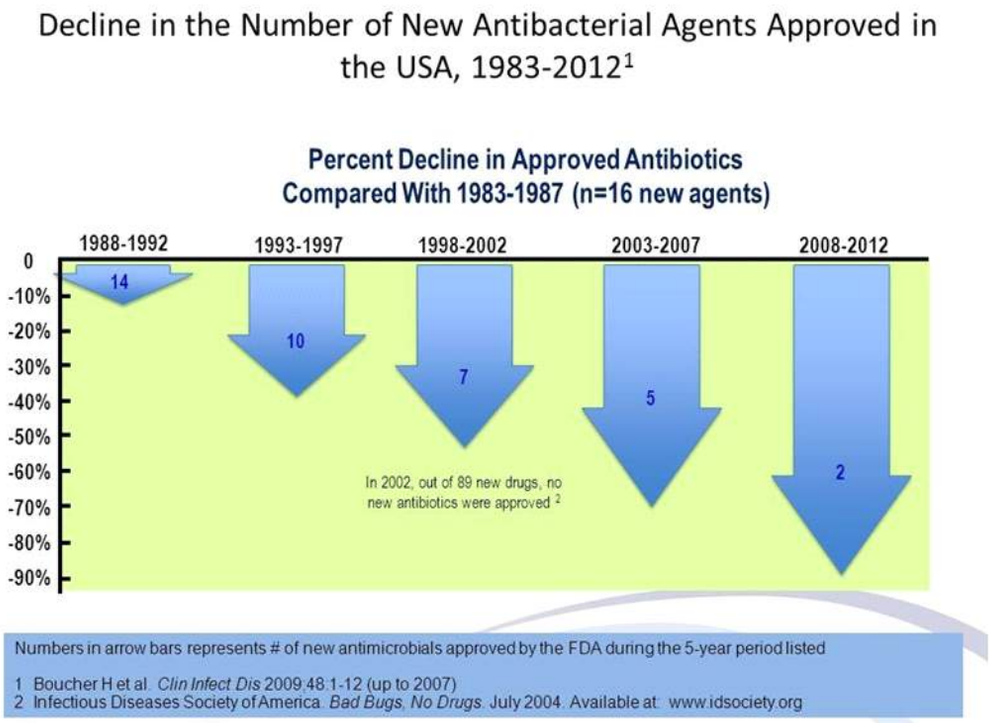


Figure 12:Decline in the number of antibiotics approved in the US during 1988-2012.

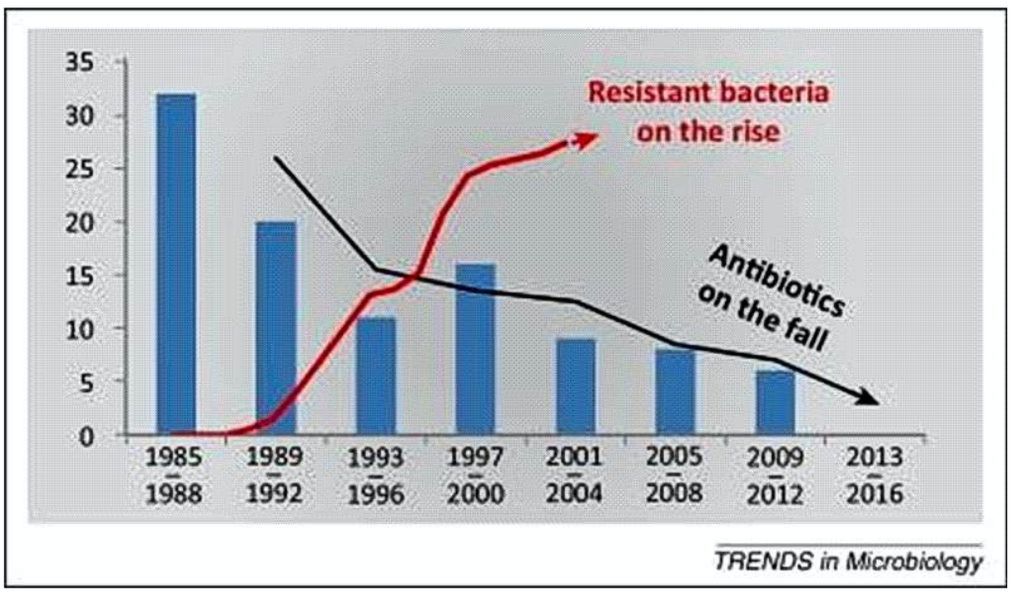


Figure 13:Decline in the number of antibiotics approved in the US when compared to the rising incidence of antibiotics resistance.

Table 3:Number of antibiotics approved by the US Food and Drug Administration during the period, 2013 till date (Ohia, 2018; unpublished data

YEAR	NUMBER OF ANTIBIOTICS APPROVED BY US FDA
2013	0
2014	1 NEW DRUG*; 4 new drug formulations
2015	4 new drug formulations
2016	1 NEW DRUG*
2017	2 NEW DRUGS*; 1 new formulation
2018 (up to Sept)	1 NEW DRUG*; 2 new formulations

Prevention and Control of Antibiotics Resistance

According to the WHO, antibiotics resistance is facilitated by: (a) misuse and overuse of antibiotics and, (b) poor infection prevention and control. Individuals, healthcare professionals (doctors, nurses, dentists, pharmacists), healthcare facilities (hospitals, clinics, rural health centers), the agriculture sector, policy makers, and governments have major roles to play in the prevention and control of antibiotics resistance.

Role of Individuals

- Only use antibiotics when prescribed by a certified/qualified health professional
- Never demand antibiotics if your health professional says you don't need them
- Always follow your health professional's advice when using antibiotics (never skip doses)
- Never share or use leftover antibiotics.
- Never take an antibiotic for a viral infection such as cold or flu.
- Prevent infections by:
    - Regularly washing hands
    - Preparing food hygienically
    - Avoiding contact with sick people
    - Utilizing methods for safe sex
    - Keeping vaccinations up to date

Utilizing WHO Recommendations for Safer Food:

- Keep food preparation environment clean
- Separate raw food from cooked
- Cook food thoroughly
- Store food at safe temperatures
- Use safe water
- Use safe raw materials for cooking
- Choose food that have been produced without the use of antibiotics for growth promotion or disease prevention in health animals

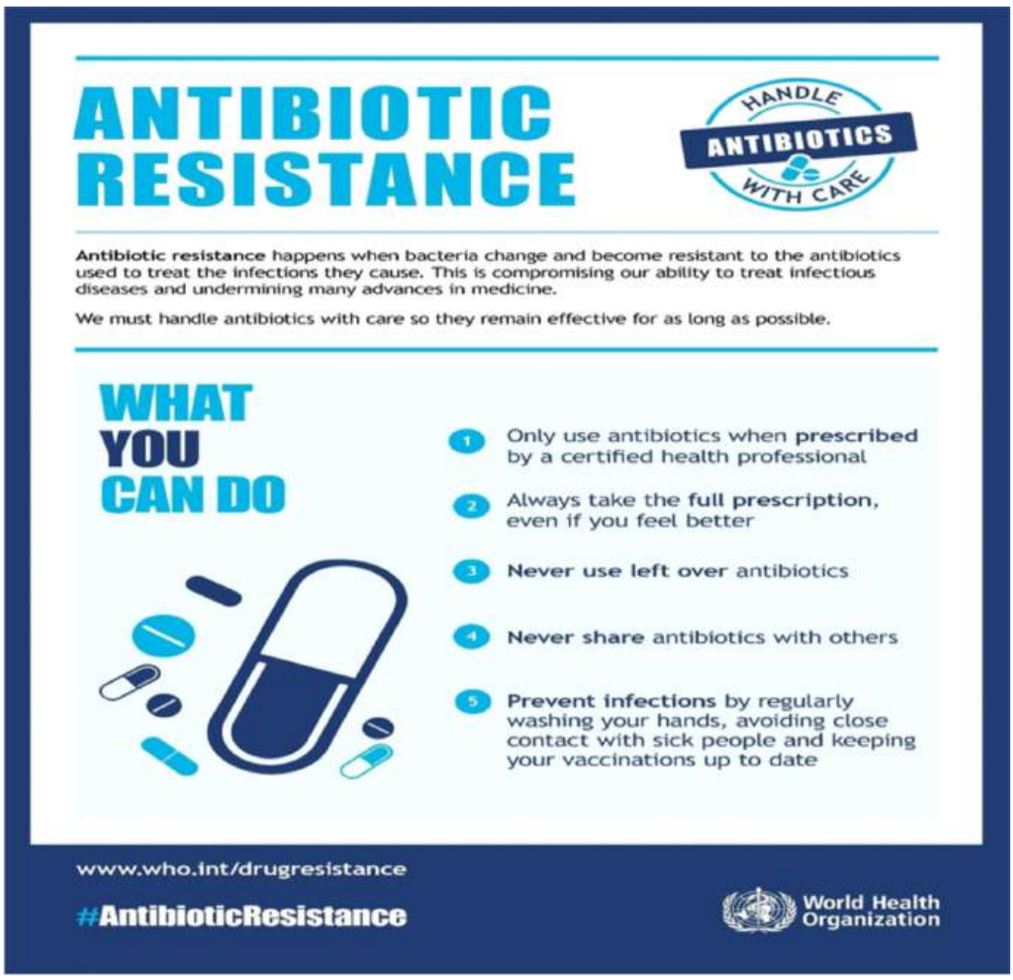


Figure 14:The role of individuals in the prevention and control of antibiotics resistance.

Role of Healthcare Professionals

To prevent and control the spread of Antibiotics Resistance, healthcare professionals can:

- Prevent infections by ensuring hands, instruments and practice environment are clean.
- Only prescribe and dispense antibiotics when they are needed using established guidelines.
- Report antibiotic-resistant infection to appropriate monitoring agencies.
- Talk to patients about how to take antibiotics correctly, antibiotic resistance and the dangers of misuse.

- Talk to patients about preventing infections (e.g., covering mouth and nose when sneezing, safe sex).

Role of Healthcare Facilities

To prevent and control the spread of Antibiotics Resistance, health care facilities (hospitals, clinics) can:

- Know what types of drug-resistant infections are present in the facility and patients
- Request immediate alert when the laboratory identifies drug-resistant infections in patients
- Alert receiving facility when transferring a patient with a drug-resistant infection
- Protect patients from drug-resistant infections
- Prescribe antibiotics wisely
- Remove temporary medical devices such as catheters and ventilators when no longer needed
- Follow relevant guidelines and precautions at every patient encounter

The role of hospitals and other healthcare settings in the spread of antibiotic-resistant infections is supported by a recent report by Brown (2018) which demonstrated that in the European
Union and European Economic Area (EEA),between2007-2015, more than 33,000 people died in hospitals and other healthcare settings. Clearly, the estimated burden of antibiotic-resistant infections doubled since 2007 and was similar to the combined burden of influenza, tuberculosis and the Human Immunodeficiency Virus (HIV).

Role of Agriculture Sector

To prevent and control the spread of Antibiotics Resistance, the agriculture sector can:

- Only give antibiotics to animals under veterinary supervision
- Not use antibiotics for growth promotion or to prevent diseases in health animals
- Vaccinate animals to reduce the need for antibiotics
- Promote and apply good practices at all steps of production and processing of foods from animal and plant sources
  Prevent infections through improved hygiene and animal welfare

Figure 15:The role of the agricultural sector in the prevention and control of antibiotics resistance.

Role of Policy Makers/Government

To prevent and control the spread of antibioticresistance, policy makers/government can:

- Ensure a robust national action plan to tackle antibiotic resistance
- Establish infrastructure to improve surveillance of antibiotic-resistant infections
- Strengthen policies, programs and implementation of infection prevention and control measures
- Make information available on the impact of antibiotic resistance through public health education
- Regulate and promote the appropriate use and safe disposal of medication

Figure 16: The role of policy makers/government in the prevention and control of antibiotics resistance.

Role of the WHO: Global Action Plan

As a body representing global health, the WHO has implemented the following actions:

- To improve awareness and understanding of antimicrobial resistance through effective communication, education and training.
- To strengthen knowledge and evidence base through surveillance and research.
- To reduce incidence of infection through effective sanitation, hygiene and infection prevention measures.
- To optimize the use of antimicrobial medicines in human and animal health.
- To ensure a sustainable economic investment in countering antimicrobial resistance by all countries.
- To increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Role of NAFDAC: Recommendations and Action Plan

As the main regulatory agency for food and drugs in Nigeria, the National Agency for Food Administration and Control(NAFDAC) has made the following recommendations and action plan:

Recommendations:

- Reduce availability and ease of access to antimicrobials from pharmacies and unauthorized sources with or without prescription (hawkers, vendor shops, buses)
- Stop the sale of antimicrobial prescription medicines as Over- the- Counter drugs in Nigeria and increase monitoring
- Use antimicrobials only as directed by the physician/veterinarian on humans and animals, respectively
- Always complete the dose of prescribed antimicrobial drugs
- Prescription should be based on appropriate diagnostic and sensitivity testing
- Buy antimicrobials only from registered pharmacies/veterinary outlets and insist on collecting a receipt
- Do not use antibiotics as feed additives except when prescribed by a veterinarian, because peopleingest antibiotics through meat, fish and poultry that they consume.
- Antibiotics sold in Nigeria must bear Mobile Authentication Scheme (MAS) hologram for tracking genuine product

Action Plan:

- Creation of awareness on the danger of antimicrobial resistance through:
  - Mass education on antimicrobial resistance
  - Public enlightenment by the use of jingles
  - Use of Information, Education and Communication (IEC) materials
- Securing our borders from influx of fake drugs
- Applying the full weight of the law by ensuring compliance with the MAS
- Educating farmers about the importance of biosecurity and good agricultural practice.
- NAFDAC is reviewing the technical requirements for the registration of antibiotics
- NAFDAC, in collaboration with the Ministry of Agriculture and Natural resources has prohibited the use of some antibiotics in food-producing animals
- NAFDAC seeks the cooperation of all health professionals, farmers and the general public to ensure that the menace of antimicrobial resistance is stopped

Summary and Conclusions

- While exposure to most bacteria can be harmful to human health, there are some bacteria that have beneficial effects to life

- If not properly prevented and controlled, the incidence of antibiotics/antimicrobial resistance will continue to be a major threat to our existence on earth

- Individuals, healthcare professionals, healthcare facilities, the agriculture sector, policy makers/government have a significant role to play in preventing and controlling the spread of antibiotic (antimicrobial) resistance

- Since antibiotic resistance has to be acknowledged as an integral part of our healthcare delivery process, the decline in research and discovery of new antibiotics by the pharmaceutical industry portends to be one of the greatest threats to the containment of bacterial infections in humans and animals

- ***Consequently, a future in which the treatment of common bacterial infections is not feasible due to the lack of active and potent antibiotics may, indeed, lead to the demise of man on earth!***

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Long live the Federal Republic of Nigeria!!!!

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