UNIVERSITY OF ILORIN

ONE HUNDRED AND FIFTY-FOURTH (154TH)
INAUGURAL LECTURE

"ANTIMICROBIALS AND SUPERBUGS: THE SURVIVAL GAME"

BY

PROFESSOR CHARLES NWABUISI

MB BS. (LAGOS), M. Sc. (LAGOS), FMC Path.
Department of Medical Microbiology and Parasitology, Faculty of Basic Medical Sciences
College of Health Sciences
University of Ilorin, Ilorin, Nigeria

27th NOVEMBER, 2014

This (154th) Inaugural Lecture was delivered under the Chairmanship of:

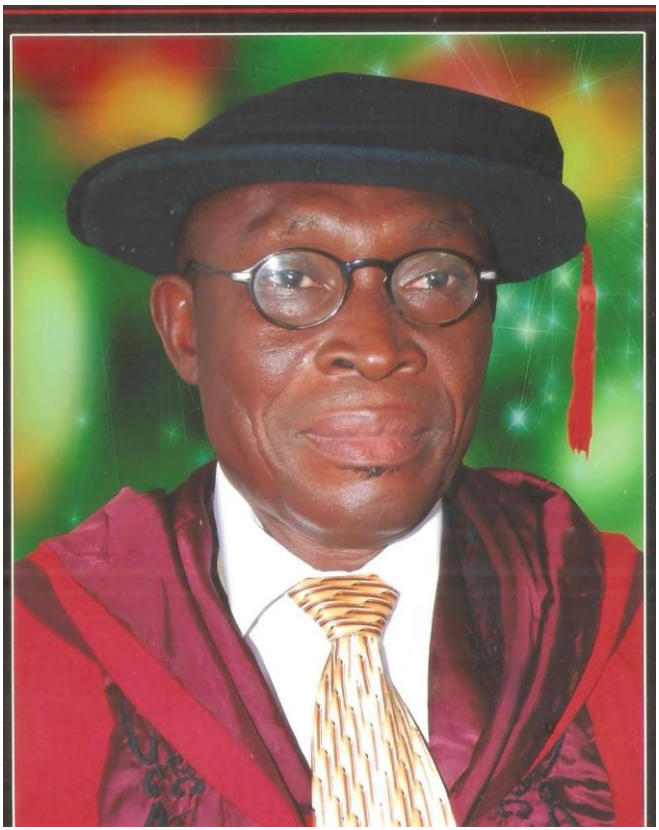
The Vice-Chancellor
Professor Abdul Ganiyu Ambali
DVM (Zaria); M.V.Sc., Ph.D. (Liverpool); MCVSN (Abuja)

November, 2014

ISBN: 978-987-53221-2-5

Published by
The Library and Publications Committee
University of Ilorin, Ilorin, Nigeria.

Printed by
Unilorin Press,
Ilorin, Nigeria.



PROFESSOR CHARLES NWABUISI
MB BS. (LAGOS), M. Sc. (LAGOS), FMC Path.
PROFESSOR OF MEDICAL MICROBIOLOGY AND PARASITOLOGY

BLANK

Protocol

The Vice-Chancellor
Deputy Vice-Chancellors (Academics, Management Services, and Research, Technology & Innovation)
The Registrar
The University Bursar
The University Librarian
Provost, College of Health Sciences
Deans of Faculties, Postgraduate School and Student Affairs
Professors and other Members of Senate
The Chief Medical Director, University of Ilorin Teaching Hospital (UITH)
Heads of Department and other Academic Colleagues
Members of Administrative and Technical Staff
My Lords Spiritual and Temporal
Members of my Family
Distinguished Invited Guests
Gentlemen of the Press
Security Operatives
Friends
Great Unilorin Students
Ladies and Gentlemen

Introduction

It is with great humility and glory to the Almighty God that I stand before you today to deliver the 154th Inaugural Lecture of this great University. This is the 3rd Inaugural Lecture from the Department of Medical Microbiology and Parasitology, Faculty of Basic Medical Sciences, College of Health Sciences. The first from the

Department which was delivered by Professor B. A. Onile on 13th December 1990 was titled "Morality and Microbes", while the second titled "The Crawling flyer— The flying Crawler, The Warring Worm and the Wormy World", was delivered by Professor L.D. Edungbola on 30th Nov.1995. The title of today's lecture is "**Antimicrobials and Superbugs: The Survival Game."**

This is the climax of a journey that started out of curiosity while a medical student at the College of Medicine, University of Lagos. We had just been introduced to Pathology posting in the fourth year of the course, where we were exposed to the use of the Microscope in identifying hitherto unseen living organisms (bacteria, fungi, viruses and parasites,) in Medical Microbiology and Parasitology. The early training in this field gave the impression that the various pathogenic micro organisms identified would be totally eliminated when treated with the antimicrobials to which they appear to be sensitive in-vitro. This optimism gave way to disillusionment and disappointment as it became clear with time that some of these microorganisms had devised some means of surviving in the face of every attempt to eliminate them. Thus, it became a challenge to me to study the mechanisms by which these organisms overcome the effects of antimicrobials, and this was possible through specialization and research in the field of Medical Microbiology and Parasitology or Infectious Diseases.

A Peep into the Title of the Inaugural Lecture

Mr. Vice-Chancellor sir, the problem of treatment failure of various infections prompted my interest in

Antimicrobial Chemotherapy which is a sub-unit of Medical Microbiology & Parasitology. This inaugural lecture titled **"Antimicrobials and Superbugs: The Survival Game"** will address issues related to human infections caused by bacterial and other pathogens with their associated contemporary challenges. I will, in the course of this inaugural lecture, therefore, shed light on the growing incidence of multidrug resistant (MDR) microorganisms.

Worldwide, infections with resistant organisms have resulted in prolonged hospital stay, and extra avoidable costs to the already overburdened healthcare system. Furthermore, in most cases, antibiotic-resistant infections require the use of more toxic and costlier drugs, necessitate additional doctor visits and healthcare use, and result in greater disability and death compared with infections that are easily treatable with antimicrobials (Shorr, Micekst, Welch, Doherty, Reichley & Kollef, 2005).

The World Health Organization (WHO), noted the increasing trend of infections due to multi-drug resistant organisms across the world and brought it into public attention by making it its theme for the year 2011 with the caption "**Antimicrobial resistance: No action today, No cure for tomorrow**". In Nigeria, like many other African nations, the magnitude of the morbidity, mortality and other associated challenges from infections caused by resistant microorganisms are not well defined due to either the absence of or poor surveillance systems (Jean, Ali, Abayneh, Georges, Bah, Assimawe & Wilfred, 2013). In the United States however, despite the strength of her

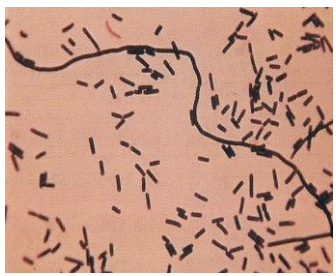
health system, relevant legislations and enforcement, at least 2 million people acquire serious infections with resistant microorganisms each year out of which about 23,000 (1.2%) die. Many more die from other conditions that were complicated by antimicrobial-resistant infections (CDC 2013). It is thus just rational, at this time, to get more serious about the plague called 'antimicrobial resistance' and this is why I have decided to address this issue in my inaugural lecture today.

Definition Of Terms

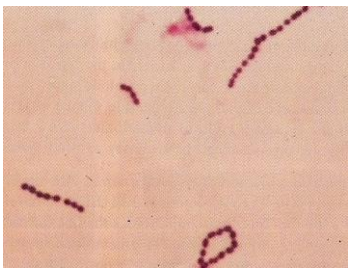
Before I proceed further, Mr. Vice-Chancellor sir, it will be desirable to define some of the terminologies that will feature during this lecture.

Microorganisms: These are living organisms so small that a microscope is required to see them. This term includes bacteria, fungi, parasites, and viruses.

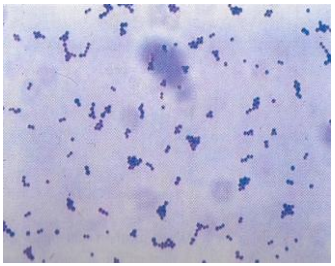
Bacteria: Single-celled organisms that live in and around us. Bacteria can be helpful, but in certain conditions can cause illnesses such as sore throat, ear infections, and bacterial pneumonia (figs. i-iv).



Clostridium perfringens X 1000 (fig. i)



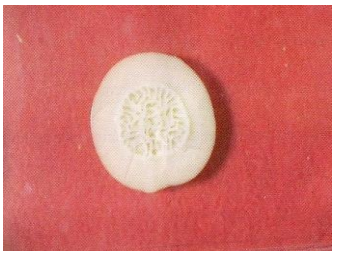
Streptococci X 1000 (fig. ii)



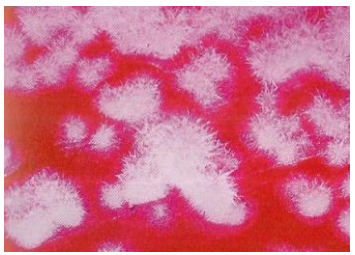
Staphylococcus aureus X 1000 (fig. iii)

Vibrio cholerae X 10,000 (fig. iv)

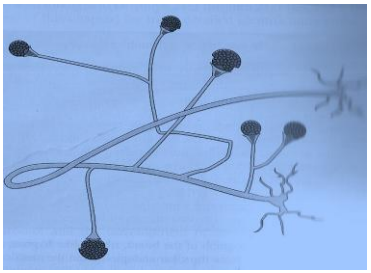
Fungus: A single-celled or multicellular filamentous organism. Fungi may or may not cause infections. Fungal infections are often opportunistic as they occur in people with compromised immune systems, such as cancer patients, transplant recipients, and people with HIV/AIDS or in healthy people. Fungi can be sources of antibiotics, antitoxins, and other drugs used to treat various diseases (figs. v-viii).



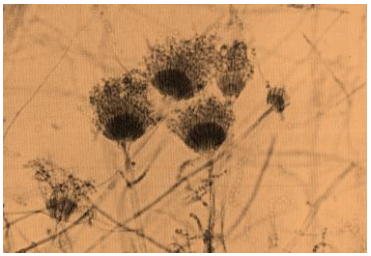
Candida albicans X 10,000 (fig. v)



Blastomyces dermatitidis X 10 (fig. vi)



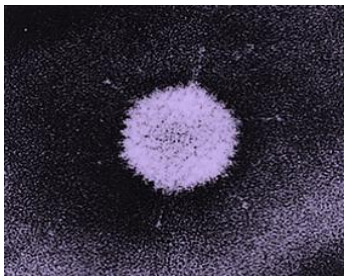
Absidia species X 400 (fig. vii)



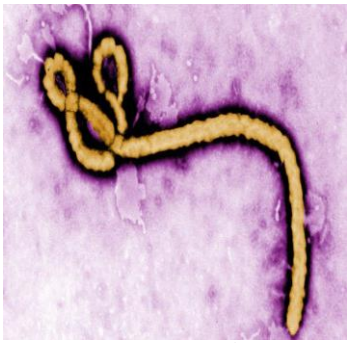
Aspergillus terreus X 400 (fig. viii)

Virus: A strand of DNA or RNA in a protein coat that must get inside a living cell to grow and reproduce. Examples are varicella virus: the cause of chickenpox, the human immunodeficiency virus (HIV), that causes acquired immune deficiency syndrome (AIDS), and Ebola virus that causes Ebola Virus Disease (EVD). (figs. ix-xii).

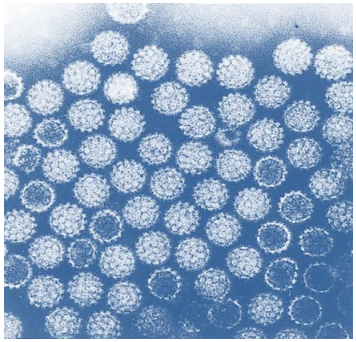
Bacteriophage T4 X 100,000 (fig. ix)



Adenovirus X 100,000 (fig. x)

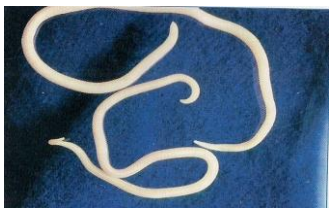


Ebola virus X 100,000 (fig .xi)

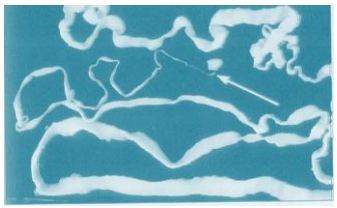


Simian virus X 100,000 (fig. xii)

Parasite: An organism, usually a lower invertebrate animal, that lives in or on another living organism, usually a higher invertebrate or vertebrate animal (its host) from where it derives all the necessities of life to the detriment of the host that gives everything but gains nothing (figs. xiii-xvi).

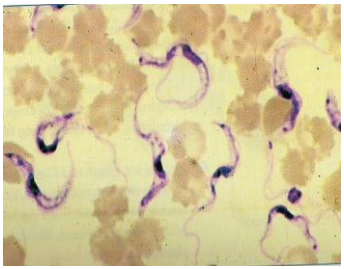


Male & Female *Ascaris lumbricoides* X1 (fig.xiii) (Round worm)



Taenia saginata X1 (fig. xiv) (Tape worm)

Male & Female *Schistosoma* X10, 000 (fig. xv)



Trypanosomes X1000 (fig. xvi)
(Sleeping sickness)

Antimicrobial agents: A general term for the drugs, chemicals, or other substances that either kill or slow the growth of microorganisms. Among the antimicrobial agents in use today are antibacterial drugs (which kill bacteria), antiviral agents (which kill viruses), antifungal agents (which kill fungi), and anti-parasitic drugs (which kill parasites).

Chemotherapeutic agent: A chemical of natural or synthetic origin used for its specific action against diseases. A chemotherapeutic agent is all encompassing and includes antimicrobials, anti-neoplastic drugs, and drugs used to treat endocrine and neurodegenerative disorders and other disease conditions.

Antimicrobial resistance: The result of microorganisms changing in ways that reduce or eliminate the effectiveness of drugs, chemicals, or other agents used to cure or prevent infections. This occurs when an antimicrobial agent becomes ineffective in killing or inhibiting the growth of the targeted microbes at concentrations of the drug achievable in the body after normal dosage.

Bugs/ Pathogens: Disease causing microorganisms.

Superbug: A microorganism e.g. a strain of a bacterium that is resistant to one or more antibiotic(s) that would normally treat the disease caused by the microorganism. Superbugs can be dangerous because of the limited number of treatment options available against them. Examples are Methicillin Resistant *Staphylococcus aureus* (MRSA), Multi-drug or extensively drug resistant tuberculosis (MDR-TB and XDR-TB), and multi-drug resistant malaria.

Short History of Antimicrobial Agents

The first antimicrobial agent the world over was salvarsan, a drug used for syphilis treatment that was synthesized by Ehrlich in 1911. (Zaffiri, Gardner, & Tolledo-Pereyra, 2012). In 1935, sulphonamides were developed by Domagk and other researchers. (Domagk, 1935) These drugs were synthetic compounds and had limitations in terms of safety and efficacy. Penicillin, the 'magical bullet' was discovered by Alexander Fleming in 1928, when he noticed that the growth of *Staphylococcus aureus* was inhibited in a zone surrounding a contaminant (a fungus *Penicillium notatum*) in culture plate, leading to the finding that a microorganism could produce substances that may inhibit the growth of other microorganisms (Fleming, 1929). Thus, Penicillin was introduced into clinical use in the 1940s and as a wonder drug in terms of safety and efficacy, ushered in the era of antimicrobial chemotherapy by saving the lives of many wounded soldiers during the World War II. By this breakthrough, it appeared, though momentarily, that mankind was winning in the survival game.

In 1944, streptomycin, an aminoglycoside antibiotic, was obtained from the soil bacterium *Streptomyces griseus* by Schatz and Waksman (Schatz & Waksman, 1944). It was very effective in the treatment of tuberculosis, thereby halting the menace of the white plague or consumption as TB was then known. Thereafter, many other antibiotics like chloramphenicol, tetracycline, macrolides, and glycopeptides (e.g., Vancomycin) were discovered from soil bacteria and they played significant roles in curtailing various infections (Table1).

Table 1: Evolution of antimicrobial agents

ANTIBIOTIC	YEAR OF DISCOVERY	BACTERIUM / FUNGUS (SOURCE)
Sulphonamides	1935	Synthetic
Penicillin	1941	*Penicillium notatum*
Streptomycin	1944	*Streptomyces griseus*
Chloramphenicol	1947	*Streptomyces venezuelae*
Tetracycline	1948	*Streptomyces aureofaciens*
Macrolides	1952	Synthetic
Vancomycin	1956	*Streptomyces orientalis*
Quiniolones	1962	Synthetic
Trimethoprim	1968	Synthetic
Oxazolidindione	2000	Synthetic
Lipopeptide	2003	Synthetic

Several years after the introduction of penicillin as a therapeutic agent, a bacterial penicillinase (a beta-lactamase enzyme capable of inactivating penicillin) was identified as the bugs fought back to alter the balance of the survival equation hitherto favouring humans (Abraham and Chain, 1940). This soon posed a great challenge as resistant bacterial strains capable of inactivating penicillin became prevalent, and efforts were undertaken to synthetically modify penicillin chemical structure to prevent its cleavage by penicillinases.

During the subsequent two decades, new classes of antimicrobial agents were developed, leading to a golden age of antimicrobial chemotherapy. Improvements in each class of antimicrobial agents continued to achieve a broader antimicrobial spectrum, higher antimicrobial activity and in some cases improved pharmacodynamics and safety.

Classification of Antibacterials

Nowadays different classes of antibacterials are known. The various ways of classifying antibacterials are based on: their mechanisms of action; whether they are bactericidal or bacteriostatic; range of activity and the origin (design).

Classification based on the mechanisms of action:

Antimicrobials act on the principles of selective toxicity, whereby several potential antibacterial targets within the bacterial cell, but not present in the human cell, are selectively destroyed. The structures or pathways most frequently targeted include cell wall, cell membrane,

protein, and RNA and DNA synthesis (Forbes, Sahm & Weissfield, 2007).

Those that inhibit the synthesis of, or damage the bacterial cell wall include β-lactams and glycopeptides. The β-Lactams contain a beta-lactam ring at the core of their structure. They comprise the largest group of antibacterials available for clinical use, due to their bactericidal action and relative lack of toxicity. In addition, their molecular structure can be manipulated to achieve greater activity. The β-lactams can be further classified into penicillins; cephems; penems (e.g. imipenem, meropenem) and monobactams (e.g. Aztreonam).

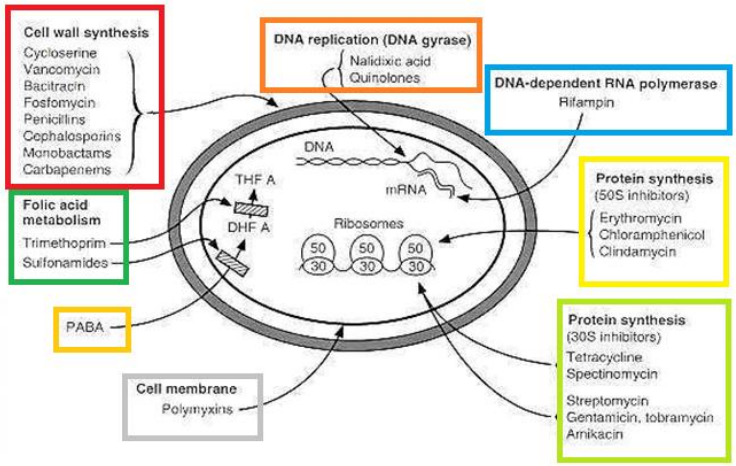


Figure 1: Classification of antibacterials based on their mechanisms of action (Forbes, Sahm & Weissfield, 2007).

Inhibitors of ribosomal functions: Those inhibiting protein synthesis include aminoglycosides, chloramphenicol, macrolides, and tetracycline.
Those that interfere with the synthesis of DNA and RNA include quinolone and rifampin. Other groups **modify the energy metabolism** of a microbial cell, for instance inhibition of folate metabolism by sulphonamide and trimethoprim.

Classification based on whether they are bactericidal or bacteriostatic
Bacteriostatic agents: inhibit growth of the microorganism at normal concentrations. The duration of therapy must be sufficient to allow cellular and humoral defense mechanisms to eradicate the bacteria. Final elimination is dependent on host immune system. Examples of bacteriostatic agents include tetracycline, erythromycin, sulphonamides, and chloramphenicol.
Bactericidal agents kill the microorganism. They are used in most infections where the host defenses are relatively ineffective and dangers imposed by such infections require prompt eradication of the organisms. Examples include; aminoglycosides, fluoroquinolones, penicillins, cephalosporins.
Based on range of activity, antibacterials are classified as narrow or broad spectrum. **Narrow-spectrum antibacterials** - are effective against only specific families of bacteria. Examples of narrow-spectrum antibiotics are the older penicillins e.g. (penicillin G), and Vancomycin.
Broad-spectrum antibacterials: These are active against a wider number of bacterial types including ***Gram-positive***

and Gram-negative bacteria. Examples are the aminoglycosides, the 2nd and 3rd generation cephalosporins, the quinolones and some synthetic penicillins.

Based on origin or design, antibiotics are classified as **natural** – products of fungi and bacteria that kill or inhibit the growth of other microorganisms (e.g. aminoglycosides); **Semisynthetic**: This result from modification of natural products: e.g., the beta lactams. T**otally synthetic:** Represented by the quinolones which were referred to in the past as '*chemotherapeutic agents.'*

Challenges and Types of Antimicrobial Resistance

Microorganisms are an essential component of the earth and have a great impact on the maintenance and sustainability of ecosystems. They have existed on the earth for more than 3.8 billion years and exhibit the greatest genetic and metabolic diversity (Sosa, Byarugaba, Amabile, Hsueh, Kariuki, & Okeke, 2000). Majority of microorganisms are beneficial to man and are of use in industries. The few however that cause diseases are of special interest to our discipline (Medical Microbiology) and have been our subject of study. In the bid to live a healthy life, man needs to find a solution to the deleterious effects of pathogenic microorganisms in the name of antimicrobials among other infection prevention strategies. This is the reason for various modifications of antimicrobials available to provide vast armamentaria for the prosecution of the war of survival on the human side. These microorganisms on the other hand appear well

prepared through resistance mechanisms as a survival game strategy against antimicrobials and humanity.

To survive, microbes have evolved mechanisms that enable them to respond to selective pressure exerted by various environments and competitive challenges. Thus, antimicrobial resistance mechanisms have always been part of evolution of bacteria as a means of survival among antibiotic-producing counterparts. However, with the introduction of antimicrobial agents into clinical practice to treat infectious diseases, a survival of the fittest strategy was adopted by bacteria to adapt to the pressure of antimicrobial attacks used for man's survival from these infections.

The World Health Organization estimated that infectious diseases accounted for 45% of deaths in Africa (Okeke & Sosa, 2014). Bacteria cause a significant proportion of these infectious diseases. Unfortunately, the hope that infectious disease will cease to be an important cause of morbidity and mortality is being undermined by resistance to antimicrobial agents. Globally, antimicrobial resistance among bacteria and other disease-causing microorganisms is a serious threat to management of infectious diseases, both in hospital and community settings. As antimicrobial resistant pathogens know no boundary, many forms of resistance spread with remarkable speed such that world health leaders have even described antibiotic-resistant microorganisms as "nightmare bacteria" that "pose a catastrophic threat" to people in every country in the world (CDC, 2013).

Antimicrobials and the “Superbugs”

“Superbugs” are microbes with enhanced morbidity and mortality capabilities due to multiple mutations endowing high levels of resistance to the antibiotic classes specifically recommended for their treatment. Both gram-positive and gram-negative bacteria are affected by the emergence and rise of antimicrobial resistance. Examples of some clinically important superbugs are shown in table 2 below:

Table 2: Some clinically important superbugs

GRAM POSITIVE BACTERIA	GRAM NEGATIVE BACTERIA	OTHERS
Methicillin-resistant *Staphylococcus aureus (MRSA)*	Extended-spectrum β-lactamases (ESBL) producing *E. coli and K. Pneumonia*	Multi-drug resistant *M. tuberculosis* (MDR-TB)
Vancomycin-intermediate and Vancomycin-resistant *S. aureus* (VISA/VRSA)	Carbapenem-resistant *Pseudomonas aeruginosa*	Extensively drug-resistant *M. tuberculosis*(XDR-TB)
Vancomycin-resistant *Enterococcus faecium*	Carbapenem-resistant K. *Pneumonia*	Extremely resistant *M. tuberculosis* (XXDR-TB)
Penicillin-resistant *Streptococcus pneumonia*		

Based on their level of concern, the Centre for Disease Control (CDC) has categorised superbugs into three groups as urgent, serious, and concerned, (table 3).

Table 3: CDC grouping of superbugs based on level of concern

URGENT	SERIOUS	CONCERNED
Clostridium difficile	**Extended-spectrum β-lactamases (ESBL) producing *E. coli and K. Pneumonia***	**Vancomycin-intermediate and vancomycin-resistant *S. aureus* (VISA/VRSA)**
Carbapenem-resistant Enterobacteriaceae (CRE)	**Multidrug-resistant *Pseudomonas aeruginosa***	**Erythromycin-resistant Group A *Streptococcus***
Drug-resistant *Neisseria gonorrhoeae*	**Drug-resistant Salmonella and Shigella**	**Clindamycin-resistant Group B *Streptococcus***
	Methicillin-resistant *Staphylococcus aureus (MRSA)*	
	Vancomycin-resistant *Enterococcus faecium (*VRE*)*	
	Drug-resistant *Streptococcus pneumonia*	
	Drug resistant T*uberculosis*	

The Burden of Antimicrobial Resistance

There is growing prevalence and incidence of multidrug resistant (MDR) microorganisms globally. Health care associated infections dominate cases where MDR pathogens are implicated, although MDR infections are also becoming more common in the community (Enright, Robinson, Randle, Feil, Grundmann, & Spratt, 2002). Unfortunately, some of these hyper resistant strains have acquired increased virulence and enhanced transmissibility.

In our environment, some relevant antimicrobial-resistant organisms with potential impact on public health care system are methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Staphylococcus aureus* (VRSE), vancomycin-resistant Enterococci (VRE), multidrug-resistant *Neisseria gonorrhoeae,* multidrug-resistant *Streptococcus pneumoniae,* penicillin-resistant *Streptococcus pneumoniae* (PRSP), multidrug-resistant tuberculosis (MDR-TB) and the extended spectrum beta-lactamase (ESBL) producing gram negative bacteria, classified as multi-drug resistant organisms (MDROS), (Siegel, Rhinehart, Jackson and Chiarellon, 2006). These are the leading superbugs with which medical science is engaged in the ‘’Survival Game’’

Methicillin resistant S*taphylococcus aureus* (MRSA), Vancomycin resistant *Staphylococcus aureus* (VRSA) and Vancomycin resistant enterococcus (VRE):

Staphylococcus aureus, a gram positive bacterium, is the most familiar resistant bacterium in clinical settings. It is currently one of the most notorious sources of superbugs.

Staphylococcus aureus has a close relationship with humans. It is carried as a nasal commensal in 30% of the population, and can cause various kinds of infections ranging from common skin infections such as boils to serious and invasive diseases such as septicaemia, endocarditis, pneumonia and toxic shock syndrome (Holmes *et al*., 2005).

My Contributions towards Reducing the Burden of Antimicrobial Resistance

Mr. Vice Chancellor sir, in our study on bacterial agents of septicaemia in childhood, *S. aureus* was found to be the most common agent of septicaemia, accounting for 30.3% of all bacterial pathogens and exhibiting multi-drug resistance **(Nwabuisi** & Nwofor, 2000). In a similar study involving patients of all age groups in our centre, we found that *S. aureus* with MDR characteristics was also the single predominant cause of septicaemia (Samuel *et al*., 2006). This super bug *S. aureus* was reported as a leading agent of infection in our patients with chronic otitis media (26.0%), where it was also multi-drug resistant (**Nwabuisi** & Ologe, 2002). That this organism is involved in many infections in our environment is attested to by its recovery from male patients with STDs and infertility in a high proportion of 18.0% **(Nwabuisi** & Onile, 2001). It has been reported as a contaminant of soft drinks consumed in various centres in Nigeria (**Nwabuisi** & Awogun, 2003), has been found as a major contributor to chronic sinusitis (Ologe & **Nwabuisi**, 2003), played a leading role as an agent of Premature Rupture of Membranes in pregnant women (Aboyeji, Abdul, Ijaya, **Nwabuisi**, & Ologe, 2005), contributed

significantly in nosocomial infections in the University of Ilorin Teaching Hospital (Odimayo, **Nwabuisi** & Adegboro, 2008), and as an important agent in the Urinary tract infections of pregnant women in Ilorin (Ajayi, **Nwabuisi**, Aboyeji, Fowotade & Fakeye, 2012).

Penicillin was initially effective for the treatment of *S. aureus* infections, but resistant strains that produce penicillinase, increased in the 1950s. Staphylococci are the gram positive bacteria that most commonly produce beta-lactamase; approximately 90% or more of clinical isolates are producers of this enzyme. Therefore, penicillinase-stable methicillin was developed in 1960, as mentioned previously. However, later that same year methicillin-resistant *S. aureus* (MRSA) was isolated (Jevons, Coe & Parker, 1963), and since 1990, nosocomial or hospital acquired infections with MRSA (HA-MRSA) became a public health problem.

Mr. Vice chancellor sir, distinguished ladies and gentlemen, in one of the studies at the University of Ilorin Teaching Hospital (UITH), it was reported that 34.7% of all staphylococci infecting our patients were MRSA with approximately 13.7% of those infected under intensive care (Taiwo, Onile & Akanbi 11, 2004). Because there are human carriers of MRSA who might serve as transmitters, we screened healthcare workers in the critical care units of our hospital for MRSA and found 52.2% carriage rate with doctors and nurses being predominant carriers (Fadeyi, Bolaji, Oyedepo, Adesiyun, Adeboye, Olanrewaju, Aderibigbe, Salami, Desalu, Fowotade, **Nwabuisi,** Akanbi II, Raheem, & Olalere, 2010). The result of this study made us recommend to the hospital authorities robust infection

control practices whose implementation is contributing to saving the lives of Nigerians.

Multi-drug resistant *Streptococcus pneumonia*

Similar to *S. aureus,* S. *pneumoniae,* another gram positive bacterium, was originally susceptible to penicillin, until penicillin-intermediate *S. pneumoniae* (PISP) strains emerged in the latter half of the 1960s, and penicillin-resistant *S. pneumoniae* (PRSP) strains were seen in the 1970s (Saga & Yamaguchi, 2009). In one of our investigations of chronic sinusitis patients, we reported that half (50%) of the *S. pneumonia* isolates were resistant to penicillin (Ologe & **Nwabuisi,** 2003) and therefore recommended against the use of this drug in our patients with ear disease.

Extended spectrum beta-lactamase (ESBL) and carbapenemase producing gram negative bacilli

Among the superbugs are the most prevalent gram-negative pathogens, such as *Escherichia coli* and *Klebsiella pneumonia*. These bacteria cause different kinds of infectious diseases in humans and animals, and a strong correlation between antibiotic use in the treatment of these diseases and antibiotic resistance development has been observed over the past half-century. This is especially apparent with the beta-lactam class of antibiotics and their related inactivating enzymes, the beta-lactamases.

Mr. Vice Chancellor sir, our research in the area of gram-negative bacteria revealed that ESBL-producing organisms are entrenched in our environment as the leading contenders (*E. coli and Klebsiella pneumonia*) were

isolated from patients with chronic otitis media (**Nwabuisi** & Ologe, 2002). They were equally encountered as contaminants of beverages and soft drinks consumed in Nigeria **(Nwabuisi** & Awogun, 2003), as significant agents of chronic sinusitis (Ologe & **Nwabuisi**, 2003), and as agents of nosocomial infections (Odimayo, **Nwabuisi** & Adegboro, 2008). As single agents of infection, *K. pneumoniae* was involved in premature rupture of membranes in pregnant women (Aboyeji, Abdul, Ijaya, **Nwabuisi** & Ologe, 2005), while *E. coli* was implicated in asymptomatic bacteriuria in pregnancy (Ajayi, **Nwabuisi**, Aboyeji, Fowotade & Fakeye, 2012).

Furthermore, among other common gram negative bacteria, *Pseudomonas aeruginosa* is notoriously multi-drug resistant. Although *P. aeruginosa* is intrinsically resistant to many antimicrobial agents, the emergence of *P. aeruginosa* strains resistant to all of three classes of antimicrobials, i.e., carbapenems, quinolones, and aminoglycosides is a recent concern. Again in our study conducted in 2003, *P. Aeruginosa* strains obtained from infected persons in our hospital were resistant to cephalosporins (ceftazidime) and aminoglycosides (gentamicin) in a proportion higher than previously documented (Fadeyi, Akanbi11, **Nwabuisi** & Onile, 2005). The multidrug resistant *P. aeruginosa* (MDRP) sometimes causes infection outbreaks and has complex mechanisms of drug resistance, including reduced membrane permeability due to decreased outer membrane protein (D2 porin), over expression of efflux pump, mutation of the quinolone target (DNA gyrase), production of aminoglycoside modification enzyme, and production of

metallo-beta- lactamase, (Saga & Yamaguchi, 2009). This difficult to treat organism was reported in our studies on chronic otitis media (**Nwabuisi** & Ologe, 2002; Afolabi, Salaudeen, Ologe, **Nwabuisi** & Nwawolo, 2014; Adebola, Ologe, Alabi, **Nwabuisi** & Fowotade, 2014), and as an important nosocomial infection agent (Odimayo, **Nwabuisi** & Adegboro, 2008).

Neisseria gonorrhoeae is another gram negative bacterium with multi-drug resistant properties. This important cause of human infections is still present in our environment although with reduced prevalence as reported in our studies on STD in pregnant women (Aboyeji & **Nwabuisi,** 2003). *Neisseria gonorrhoeae* still retains its high multi-drug resistant capacity; hence guideline for successful treatment of this infection has been published (Yoneda, Fujimoto & Uno, 2004).

Other superbugs encountered in the course of our studies in various strata of infectious diseases include coagulase negative staphylococci, *S.faecalis* and coliform bacteria, all implicated in male infertility and were multi-drug resistant (**Nwabuisi** & Onile, 2001), Proteus spp., and Serratia spp. with mult- drug resistant features isolated from chronic otitis media patients **(Nwabuisi** & Ologe, 2002), Bacillus spp., contaminating soft drinks and beverages **(Nwabuisi** & Awogun, 2003), *Gardnerella vaginalis* and syphilis infecting pregnant women (Aboyeji & **Nwabuisi,** 2003), syphilis infecting patients with mental illness (Issa et al., 2013), anaerobic organisms, associated with middle ear infections (Adebola, Ologe, Alabi, **Nwabuisi** & Fowotade, 2014) and MDR-TB, among our patients (Nwofor et al., in press.)

My Further Contributions to Knowledge

Mr. Vice-Chancellor sir, my further contributions to knowledge on the Human side of this survival game include the detection of another superbug in Ilorin and its environs for the first time in 1998, called ***Cryptosporidium.*** This is a protozoan parasite which causes diarrhoea in children and immunodificient adults especially those infected with Human Immunodeficiency Virus (HIV). *Cryptosporidium* is resistant to all known chemotherapeutic agents employed in its treatment as at now. It is spread through the faecal-oral route and through contaminated source of water and in swimming pools. To prevent infection, provision of portable water and improved personal hygiene are necessary **(Nwabuisi,** 1998, **Nwabuisi,** 2001). Other protozoae that we have encountered in the course of our research include Microsporidium spp. and *Cyclospora caytanensis.* These are also refractile to commonly available antimicrobials (Amase et al., 2013; Babatunde et al., 2013). In another study on the resistance of malaria parasite to conventional chemotherapeutic agents, a locally available decoction '*Agbo Iba*' which is popularly used in treating human malaria was investigated to substantiate the claim of its efficacy in mouse model, as the first step towards documenting its scientific usefulness. The preliminary result showed that this preparation has high therapeutic effect in mouse model and further research involving human beings would establish its efficacy in the treatment of human malaria.. (**Nwabuisi,** 2002).

The superbugs among fungi in our environment that cause ear infections and are difficult to treat as reported by

Nwabuisi & Ologe (2001), Ologe & **Nwabuisi** (2002), include *Candida albicans, Candida tropicalis, Candida pseudotropicalis, Aspergilus fumigatus, Aspergilus niger* and *Mucor*. **Nwabuisi,** Abdullahi, Salami & Agbede, (2003), for the first time in Ilorin, documented the presence of an uncommon fungal agent known as Scopulariopsis spp. which was associated with meningitis in an AIDS patient. This organism did not respond to any known chemotherapeutic agent as the 38 year old patient died. In another study on meningitis, *Cryptococcus neoformans* was isolated in an AIDS patient thus confirming the presence of fungal superbugs in our centre (Salami, Ogunmodede, Fowotade, **Nwabuisi,** Wahab, Desalu & Fadeyi (2009). Furthermore, in an effort to provide effective treatment for fungi in our environment, we tested the susceptibility of dermatophytes to *Aloe vera* juices and found them to be very active. This result if widely applied would provide an alternative source for treating these organisms (Oladejo, Raheem-Ademola, Banjo, Makanjuola, **Nwabuisi** & Oluwadun, 2013).

Other studies that reveal the presence of viral superbugs in our midst are captured in the work of **Nwabuisi** & Olatunji (1999), where the prevalence of Hepatitis B virus among health care workers of UITH was reported as 7.7%. The publication advised on the action to embark to stem the tide of Hepatitis B transmission in the work place being a nosocomial infection, which UITH management implemented by providing vaccination cover to all staff. In another study, the emerging pandemic on Swine Influenza was reviewed and useful advice offered to the scientific world and the general public (Fowotade,

Nwabuisi, Fadeyi & Agbede (2009). In a recent study, the Sero-prevalence of hepatitis B surface antigen was investigated among blood donors in UITH where a high prevalence rate of 10.9% was recorded (Shittu, Olawumi, Issa, **Nwabuisi,** Durotoye, Yussuf, Ajiboye, Adegunloye, Sulyman & Salami, 2014). In all these studies where superbugs were encountered, preventive measures were advised in an attempt to reduce their deleterious effects on health, as the option of developing new antimicrobials is at the infantile stage in our environment at present. And where these recommendations have been implemented, there has been noticeable improvement in patient care.

Factors Contributing to the Emergence and Spread of Antimicrobial Resistance in Nigeria

At this juncture, it is desirable to mention some factors contributing to the emergence of anti microbial resistance in Nigeria.

1. Knowledge & Attitude: One of the most important factors contributing to the emergence and spread of antimicrobial resistance is poor knowledge. There are significant gaps in the knowledge about antimicrobial resistance in our environment. Most health care workers are not even aware of the superbugs, not to talk of the general populace. My Vice-Chancellor sir, in a multi-centre study we carried out to determine the level of Nigerian healthcare givers' awareness, knowledge and disposition to screening for MRSA, 52.0% of the respondents were aware of this notorious pathogen, while about 61% of the participants considered MRSA as of any threat in the hospital. Predictably, these HCW lack the ability to assess the risk

and predict the future impacts of resistance on public health using MRSA as a model (Fadeyi *et al*., 2010).

2. Surveillance systems: Active surveillance programme on antimicrobial use and antimicrobial resistance are lacking in our country. There are no States or national data on the types of multidrug resistant organisms in the country as well as, the burden of such pathogens to various sectors of the nation. This affects our understanding of the magnitude of the risks posed by the emergence and spread of antimicrobial-resistant organisms to our health as a nation.

3. Laboratory Infrastructure: Mr. Chairman sir, laboratory infrastructure in Nigeria is obviously sub-optimal and little has been done to address this challenge which is hampering international collaboration. It is disheartening that many African countries that gained independence after Nigeria, and which are less populous and naturally endowed are even better- off in this area. Most antimicrobial agents prescribed in clinical settings are not laboratory-individualized or even laboratory-extrapolated. Unconfirmed infectious conditions are treated without laboratory investigations or consideration. The concept of immediate empiric therapy for life-threatening infections is wrongly explored and, thus, predisposing to resistance that is only detected by therapeutic failure.

4. Availability & Quality of Antimicrobial drugs: Antimicrobial resistance is closely linked to availability of good quality drugs. Poor quality drugs may be consequent upon deliberate manufacturing of drugs with low or no active content (counterfeits) or degradation of active ingredients under poor storage and transport conditions

(heat or humidity). In spite of the establishment and efforts of National Agency for Food and Drugs Administration and Control (NAFDAC), fake antimicrobials are on sale in Nigeria. The prohibitive costs of newer potent antimicrobials, when available, put them out of reach of the common man. Alternative antimicrobials used in these instances add to morbidity and mortality from antimicrobial resistance while giving room for the spread of resistant pathogens.

5. Uncoordinated use & sale of Antimicrobials: There are no measures in place to regulate antimicrobial use and misuse in our environs such as antibiotics prescription policy. When these antibacterials are imprudently employed, in treating infections caused by parasites, or viruses, they provide no benefit to the patient, while enhancing selective pressure with the possibility of resistance developing. The use of sub-optimal doses of antibiotics can also create a situation where highly resistant strains are selected sequentially and this is a condition that prevails when antibiotics are used without proper prescription, or there is in- patient non-compliance and when poor quality drugs are used.

6. Infection Control: The lack of proper infection control practices in many health care facilities also constitutes another major challenge. Unclean environments are not only conducive for the spread of pathogenic microorganisms, but they also encourage the spread of resistant organisms that may not be pathogenic. These organisms often carry resistance genes that can be spread to pathogens and therefore constitute a hidden reservoir of antimicrobial resistance.

7. Advanced Molecular Detection (AMD) Technologies: The limited capacity to detect and respond to antimicrobial resistance threat at both local and national levels is another problem. Today, the international identification of antibiotic resistance threats occurs through domestic importation of novel antibiotic resistant strains or through identification of overseas outbreaks. There is the general lack of advanced technologies such as advanced molecular detection (AMD) technologies, which can identify threats much faster than current practice in many countries, including Nigeria.

The Survival Game against Antimicrobial Resistance; Any End in Sight?

Given our experience and pattern of responses by pathogenic microorganisms, to chemotherapeutic agents, an end to antimicrobial resistance appears not very promising. It is believed that the development of antimicrobial resistance is a natural phenomenon and can only be slowed by a few changes in our actions and attitudes. As such, four core action interventions have been developed by the CDC for the prevention of antibiotic resistance (CDC, 2013). These interventions include:

i) Preventing infections and preventing the spread of resistance;
ii) Tracking resistance;
iii) Improving antimicrobial prescribing/ stewardship; and
iv) Developing new drugs and diagnostic tests.

Preventing infections, and preventing the spread of resistance

By preventing infections from occurring in the first place, the amount of antimicrobials used will be reduced and this reduces the likelihood that resistance will develop during therapy. It should be remembered that antimicrobial use is the single most important factor responsible for increased antimicrobial resistance. Infection prevention will inhibit the spread of drug-resistant pathogens and it is achievable through immunization, safe food preparation, good hand hygiene, and use of antibiotics as directed and only when necessary.

Mr. Chairman sir, proper hand hygiene has been identified as a single most important means of reducing the spread of infections. Unfortunately, only 6.1% of health care workers (HCW) in a study identified hand washing as an important simple MRSA control measure (Fadeyi et al. 2010).

Tracking

Instituting and maintaining good surveillance programmes is essential to determine the trend of events in order to prevent these resistant microorganisms from spreading. Data accumulating from such surveillance are the necessary tools for making policies.

Improving antimicrobial prescribing/stewardship

Perhaps the single most important action needed to greatly slow down the development and spread of antimicrobial-resistant infections is to regulate and enforce the way antimicrobials are used in our country. A high

proportion of antimicrobials use in humans and animals is unnecessary and inappropriate. Stopping the abuse and unnecessary use of antibiotics would help greatly in slowing down the spread of resistant microorganisms. This commitment to always use antimicrobials appropriately and safely is known as antimicrobial stewardship. (CDC, 2013)

Developing new drugs and diagnostic tests

In view of the fact that the evolution of antimicrobial resistance is a natural process, it can only be controlled but not stopped. Therefore, there will always be the need for new antimicrobials to tackle new resistant microorganisms as well as new diagnostic tests to help monitor the trends of antimicrobial resistance development.

Conclusion and Recommendations

My Vice Chancellor sir, ladies and gentlemen, from the foregoing, it is very clear that the survival game between humans and the superbugs is a game of wits. While humans are doing all in their power to prevail, the superbugs are not resting on their oars. The situation is so dicey that there is now re-emergence of almost conquered infections like tuberculosis and if urgent and proper action is not taken, the human race may be at the verge of extermination. It is therefore important that all hands must be on deck so that, collectively, we shall overcome, as everybody has a role to play in this game of survival against resistant bacteria and other pathogens.

Therefore, the following recommendations if seriously implemented will go a long way in helping mankind win the battle against antimicrobial resistance.

1. As **patients** or a **patient's relative**: You should give proper medical history when seeking medical attention in relation to infections. Tell your doctor if you have been hospitalized in another facility or country, take antibiotics or other antimicrobials only when and as prescribed. Also, insist that those attending to you wash their hands before touching you. This also means that portable water must be available at required locations in the clinic or hospital.
2. As **Health Care Providers:** Take proper history**.** Ask if your patients have received medical care elsewhere, including another country. Always follow infection control recommendations while handling all patients, using contact standard precautions. Prescribe antibiotics wisely, and use culture results to modify prescriptions if needed. Also, remove temporary medical devices as soon as possible.
3. As Health **Managers or Government Officials**: Ensure that clinical laboratories are well equipped to accurately identify the superbugs. Alert clinical and infection prevention staff when these superbugs are identified. Coordinate regional antimicrobial resistance surveillance programmes, and help medical facilities improve antibiotic prescribing practices.
4. Health Education: Continuous and massive public enlightenment on antibiotic/antimicrobial resistance should be mounted on TV, radio and other means of mass communication.
5. Proper antibiotic stewardship: Health Care Workers must be trained and re-trained, and compelled to abide with the principle of proper antibiotic stewardship.
6. Control of on the counter sale and counterfeit antimicrobials: Necessary regulations must be evolved

and enforced to control the un-regulated on the counter sale and counterfeit antimicrobials with expired dates and little or no active ingredients.

7. Active surveillance: Active monitoring of resistance patterns are necessary for control of resistant pathogens. This must be instituted by appropriate authorities and made to work.

8. Standard infection control practices: This must be put in place in all health care facilities and compliance enforced.

9. Well-equipped laboratory: Standard molecular laboratories are needed for detection and effective monitoring of resistant organisms. Efforts should be made to locate them regionally in the country.

10. Training: There is need for intensified training and retraining of infectious diseases physicians and scientists who will be able to assist in the tracking and control of resistant pathogens. This could be effected by external collaboration for short or long periods of attachment abroad depending on need.

Acknowledgements

To the Sovereign Almighty God, I owe all gratitude for what He has made out of me from a humble beginning. I am also grateful to my parents late Mr. Matthew and Mrs. Mary Nwabuisi for all their care and sacrifice in giving me a good start in life that laid the foundation of what is happening today.

I am greatly indebted to my teachers in primary, secondary and tertiary institutions who for one second never doubted the potentials God deposited in me to the

extent that Mr. Mackey Maduagwu the principal of my secondary school often visited my father at home to encourage him not to relent in supporting my education no matter the cost. How I wish you are alive today to witness the climax of your effort!

To my academic colleagues, who are too numerous to be mentioned one by one, spanning various Universities, I salute you. My day has been made today by your presence and I pray that all of you will have the same opportunity to show case your worth in the academic arena some day.

To my indefatigable research team comprising Dr. Abayomi Fadeyi, Dr. Halimat Ekundayo, Dr. Sherifat Suleiman, Dr. Nyamngee Amase, Mrs. Lateefat Saadu, Mr. Razak Adewole, Mr. Adebola Oshodi, who provided logistic and secretarial assistance during the preparation of this presentation, and all the staff of the Department of Medical Microbiology of both the University of Ilorin and the University of Ilorin Teaching Hospital, I say a big thank you for your support and encouragement.

I must appreciate my mentors, Prof. L.D. Edungbola, Prof. Bayo Parakoyi, Prof. I. A. Awogun and my loving wife Dr. (Mrs.) Grace Nwabuisi who offered invaluable contributions through suggestions and finding time to proof read this presentation. I shall for ever be grateful.

In the same vein, I must recognise the Medical and non-medical students, postgraduate students, and resident doctors who have had course to interact with me in teaching and research thereby providing the experience I gathered over the years. Without you, today would not have been possible, thank you indeed.

Finally, to members of my Church, UMCATC Chapel, Ilorin, Gideons International and their Auxiliary members here present, my family members, my sister Mrs. Chikerenma Nelson, my Children, Charles Nwabuisi Jr., and Victor Gbenga Nwabuisi, especially my better half with great understanding, my in-laws, my bosom friends from far and near, including Rev (Prof.) S. P. Ango, Mr. Chidiebere Ogazi, Barr. Emmanuel Uche, Prof. Chika Ogbonna, and all those I may not have mentioned who by way of prayers, advice, physical and financial support contributed in one way or the other to the success of this day, may the Almighty God reward you abundantly.

Thank you for your esteemed attention and time.

References

Abraham EP & Chain E. (1940). An enzyme from bacteria able to destroy penicillin. Rev. Infect. Dis. 10**:**677–678.

Adebola SO, Ologe EF, Alabi BS, **Nwabuisi C** & Fowotade A. (2014). Profile of anaerobic bacteriology of middle ear aspirates in a developing country: Does immunocompromise play a role? Anaerobe. 31-35.

Afolabi AO, Salaudeen AG, Ologe FE, **Nwabuisi C,** & Nwawolo CC (2012). Pattern of bacterial isolates in the middle ear discharge of patients with chronic suppurative otitis media in a tertiary hospital in North central Nigeria. African Health Sciences. 12 (3): 362-368.

Amase N, Edungbola LD, Agbede OO, Salami AK, **Nwabuisi C,** Akanbi 11 AA, Ibrahim OK, Talahun M & Moser DB (2013). Prevalence, intensity and complication of Microsporidium spores amongst HIV-positive hospital patients in Ilorin, Nigeria. Afri. J. Lab. Med. 2 (1), Art. #66, 6 pages.

Babatunde SK, Fadeyi A, Akanbi 11 AA, **Nwabuisi C,** & Abdulraheem JY (2013). Cyclosporiasis and other intestinal parasitoses in association with diarrhoea in Ilorin, Nigeria. African Journal of Microbiology Research. 7(21):2613-2617.

CDC (2013). Antibiotic resistance threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf

Domagk GJ. (1935). Ein beitrag zur chemotherapie der bakteriellen infektionen. Dtsch. Med. Wochen-schr. 61: 250–253.

Enright MC, D. A. Robinson, G. Randle, E. J. Feil, H. Grundmann, & B. G. Spratt. (2002). The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA). Proc. Natl. Acad. Sci. U. S. A. 99:7687–7692.

Fadeyi A, Bolaji BO, Oyedepo OO, Adesiyun OO, Adeboye MAN, Olanrewaju TO, Aderibigbe A, Salami AK, Desalu OO, Fowotade A, **Nwabuisi C,** Akanbi II AA, Raheem RA & Olalere A. (2010). Methicillin-resistant *Staphylococcus aureus* carriage among healthcare workers of the critical care unit in a Nigerian hospital. Am. J. Inf. Dis. 6(1): 18-23

Fadeyi A, Adeboye MAN, Fowotade A, **Nwabuisi C,** Bolaji BO, Oyedepo OO, Adesiyun OO, Olanrewaju TO, Aderibigbe A, Salami AK, Desalu OO, Akanbi II AA, Raheem RA & Olalere A. (2011). Methicillin-resistant *Staphylococcus aureus:* Awareness, Knowledge and Disposition to screening among healthcare workers of the critical care unit in a Nigerian hospital. West Afr. J. Med. 30(4): 282-287.

Fadeyi A, Akanbi II AA, **Nwabuisi C** & Onile BA. Antibiotics disc sensitivity pattern of *P. aeruginosa* isolates obtained from clinical specimens in Ilorin, Nigeria.(2005). Afr. J. Med. Sci. 34: 303-306.

Fleming A.(1929). Classics in infectious diseases: on the antibacterial action of cultures of a penicillium, with

special reference to their use in the isolation of *B. influenzae.* Brit.J. Exp.Pathol. 10: 226–236.

Forbes BA, Sahm DF, & Weissfeld AS. (2007). Bailey & Scott's Diagnostic Microbiology 12th edition. USA: Mosby Elsevier.

Holmes A, Ganner M, McGuane S, Pitt TL, Cookson BD, & Kearns AM. (2005). *Staphylococcus aureus* isolates carrying Panton-Valentine leucocidin genes in England and Wales: frequency, characterization and association with clinical diseases. J. Clin. Microbiol. 43: 2384-2390.

Issa BA, Fadeyi A, Durotoye IA, Yussuf AD, Salami AK, Shittu OA, Ajiboye PO, Olawumi HO, Adegunloye OA, Nwabuisi & Sulyman D. (2013). Sero-Pervalence of Syphilis among Patients with Mental Illness: Comparisn with Blood Donors. WAJM. 32(2): 210-215.

Jean, B. N., Ali, A. Y., Abyneh, T. D., Georges, K. Z., Emil, A.O., Bah, K.A., Assimawe, P. P & Wilfred, N. (2013). Antimicrobial resistance in the African Region: issues, challenges and actions proposed. Key Determinants for the African Region.16:27-30. http//www.aho.afro.who.ins/sites/defult/files/ahm/reports/576/ahm1607.pdf

Jevons MP, Coe AW, & Parker MT. (1963). Methicillin resistance in staphylococci. Lancet 281: 904–907.

Nwabuisi C. (1998). Cryptosporidiosis among diarrhoea patients in Ilorin, Kwara State, Nigeria. Nigerian Journal of Medical Research 2 (1 & 2): 21-23.

Nwabuisi C. (2001). Childhood Cryptosporidiosis and Intestinal Parasitosis in Association with Diarrhoea

in Kwara State. West African Journal of Medicine. 20 (2); *165-168.*

Nwabuisi C. (2002). Prophylactic Effect of Multi-Herbal Extract "Agbo-Iba" on Malaria induced in Mice. East African Medical Journal. 79 (7); 343-6.

Nwabuisi C. Aderinola C. & Ibegbulam O.G. (2005). The Sero-Prevalence of Syphilis in Unscreened and Unstored Blood Transfused in Ilorin, Nigeria. Medipharm Medical Journal. 2 (3); 109-113.

Nwabuisi C. & Awogun I.A. (2003). Microbial Contaminants of some industrially manufactured soft drinks in Nigeria. Tropical Journal of Health Sciences. 10 (1); 12-14.

Nwabuisi C. & Nwofor A.C. (2000). Bacterial Agents of Septicaemia in Childhood in Ilorin. Nigerian Journal of Medicine. 9 (3); 86-88.

Nwabuisi C. & Ologe F.E. (2001). Fungal Profile of Otomycosis Patients in Ilorin, Nigeria. Nigerian Journal of Medicine**.** 10 (3); 124-126.

Nwabuisi C. & Ologe F.E. (2002). The Pathogenic Agents of CSOM in Ilorin, Nigeria. East African Medical Journal. *79 (4)* 21 (1); *202-205.*

Nwabuisi C, & Onile B A, (2001). Male Infertility Among Sexually Transmitted Disease Clinic Attendees in Ilorin, Nigeria. Nigerian Journal of Medicine. 10 (2); 68-71.

Nwabuisi C, & PO Olatunji (1999). Prevalence of Hepatitis B. Surface Antigen Among Tertiary Health Workers in Ilorin. Nigerian Quarterly Journal of Hospital Medicine. 9 (2): 95-97.

Nwabuisi C, Abdullahi NA, Salami AK, & Agbede OO, (2003). Scopulariopsis Associated Meningitis in Adult Nigerian AIDS Patient. (A Case Report). West African Journal of Medicine. 22 (4); 364-365.9.

Nwofor AC, Nyamngee A, **Nwabuisi C,** Iwakun M, Gidado M, Dakum P, Agbede OO, Ndembi N, Abimiku A & Blattner W. Performance of Genotype MTBDR plus in Detection of Resistance of Rifampicin and Isoniazid among Mycobacterium Isolates in Ilorin, Current HIV Journal. Nigeria. In press.

Oladejo JM, Raheem-Ademola RR, Banjo TA, Makanjuola SO, **Nwabuisi C** & Oluwadun A. (2013). Susceptibility of dermatophytes to Aloe vera juices using agar diffusion and broth dilution techniques. American Journal of Research Communication. 1(8): 53-62.

Ologe F.E. and **Nwabuisi C.** (2002). Treatment Outcome of Otomycosis Patients in Ilorin, Nigeria. ***West African Journal of Medicine.*** 34-36 ;(Publication of the West African Medical College, http.//www.wacs//_coac.org).

Ologe FE & **Nwabuisi C**. (2003). Bacteriology of chronic sinusitis in Ilorin, Nigeria. Afr. J. Clin. Exp. Microbiol. (4)2: 91-96.

Okeke IN & Sosa A. Antibiotic Resistance in Africa-Discerning the enemy and plotting a defence. www.fufts.edu/med/apua/about_issue/africahealth.pdf.accessed September, 2014.

Saga T, & Yamaguchi K. (2009). History of antimicrobial agents and resistant bacteria. Japan Medical Association Journal. 52(2): 103–108,

Samuel SO, Akanbi II AA, Ameen NB, **Nwabuisi C** & Onile BA. (2006). Bacterial isolates of blood cultures in patients with suspected septicaemia in Ilorin, Nigeria. Afr. J. Med. Sci. 35: 137-141

Schatz A & Waksman SA. (1944). Effect of streptomycin and other antibiotic substances upon *Mycobacterium* tuberculosis and related organisms. Proc. Soc. Exp. Biol. Med. 57:244–248.

Shorr, A. F., Micek, S. T., Welch, E. C., Doherty, J. A., Reichley, R. M & Kollef MH (2011). Inappropriate antibiotic therapy in Gram-negative sepsis increases hospital length of stay. Crit Care Med 39: 46-51.10.1097/CCM.0b013e3181fa41a7 PubMed: 20890186 {PubMed]

Shittu AO, Olawumi HO, Issa BA, **Nwabuisi C,** Durotoye IA, Yussuf AD, Ajiboye PO, Adegunloye OA, Sulyman D & Salami AK. (2014). Risk factors and Sero-Prevalence of Hepatitis B surface antigen among Blood Donors in Lagos University Teaching Hospital, Ilorin, Nigeria. East African Medical Journal. 91(3): 1-5.

Siegel JD, Rhinehart E, Jackson M & Chiarellon L. (2006). Healthcare infection control practices advisory committee. Atlanta (GA): Centres for Disease Control and Prevention; Management of Multidrug resistance organisms in healthcare settings. http://www.cdc.gov.ncidod/dhqp/pdf/ar/mdrguideline2006.pdf

Sosa A, Byarugaba D, Amabile C, Hsueh S, Kariuki S, & Okeke IN (2000). Antimicrobial Resistance in developing countries. Doi 10.1007/987-0-387-89370-9_2 (C) springer science + Business media LLC, 2010.

Taiwo SS, Onile BA, & Akanbi 11, AA, (2004). Methicillin-resistant *Staphylococcus aureus* (MRSA) isolates in Ilorin, Nigeria. Afr. J. Clin. Exper. Microbiol. 5 (2): 189-197.

Yoneda N, Fujimoto Y, Uno M, (2004) Annual changes in drug sensitivity of gonococci derived from urethritis in men. Jpn J Chemother. 52(1):31–34

Zaffiri L, Gardner J, & Tolledo-Pereyra LH. (2012) History of antibiotics. From salvarsan to cephalosporins. *J. Inv. Surg*. 25(2): 67-77