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Epidemiology of antimicrobial resistance and its clinical, economic and humanistic outcomes in developing countries

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Abstract

The important therapeutic role played by antimicrobial agents is seriously being threatened by the continually increasing antibacterial resistance (AMR) across the globe. Efforts at stemming the increment is grossly sub-optimal in most developing countries. Epidemiology of the commonly encountered bacterial isolates and their respective susceptivity/resistance patterns is highly essential in supply chain decision making, patient management and in policy formulation. The most prevalent resistant bacterial isolates in Nigeria include Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Klebsiella pneumoniae among others. For instance, the incidence of methicillin resistant S. aureus is skyrocketing. It has increased from less than 2.0% in 2005 to more than 40.0% in 2020 across the country. In addition, resistance to affordable antimicrobial agents is gradually overwhelming the fragile health care system mostly being financed from out-of-pocket expenses. Treatment costs of resistant isolates is huge and not sustainable, apart from its impacts on disease complications, morbidity, mortality and human capital development. Overall, it grossly reduces health related quality of life. In consonant with the global pledge of the World Health Assembly, improved awareness and an understanding of its implications should be a priority. Strengthening diagnosis and surveillance activities as related to AMR is imperative. The primary health care (PHC) basic roles, which include provision of portable water, sanitation, immunization, and nutrition need to be strengthened as long advocated. Research into new antimicrobial agents as well as evidence-based re-purposing/rational usage of the existing ones should also be topical at all levels. Standard Treatment Guidelines and drug formularies equally need to be reviewed at regular intervals to include updated resistant/susceptibility patterns. Formulating adequate legal frame work and policy to facilitate implementation of strategies are of utmost important as well. And lastly, there should be relevant incentives to encourage implementation of AMR related stewardship activities and its sustainability.

Key words: Antibacterial agents, Outcomes of Therapy, Resistant Isolates, Patterns of Resistance, Nigeria

Épidémiologie de la résistance aux antimicrobiens et ses conséquences cliniques, économiques et humaines dans les pays en développement

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Résumé

L'important rôle thérapeutique joué par les agents antimicrobiens est sérieusement menacé par l'augmentation continue de la résistance antibactérienne (RAM) dans le monde. Les efforts déployés pour enrayer cette progression sont nettement insuffisants dans la plupart des pays en développement. L'épidémiologie des isolats bactériens les plus courants et leurs profils respectifs de sensibilité/résistance sont essentiels pour la prise de décision dans la chaîne d'approvisionnement, la gestion des patients et la formulation des politiques. Les isolats bactériens résistants les plus répandus au Nigeria sont, entre autres, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa et Klebsiella pneumoniae. Par exemple, l'incidence du S. aureus résistant à la méthicilline monte en flèche. Elle est passée de moins de 2,0 % en 2005 à plus de 40,0 % en 2020 dans tout le pays. En outre, la résistance aux agents antimicrobiens abordables submerge progressivement le fragile système de soins de santé, financé principalement par les dépenses personnelles. Les coûts de traitement des isolats résistants sont énormes et non durables, sans compter leurs impacts sur les complications de la maladie, la morbidité, la mortalité et le développement du capital humain. Dans l'ensemble, cela réduit considérablement la qualité de vie liée à la santé. Conformément à l'engagement mondial de l'Assemblée mondiale de la santé, l'amélioration de la sensibilisation et la compréhension de ses implications devraient être une priorité, et le renforcement des activités de diagnostic et de surveillance liées à la RAM est impératif. Les rôles fondamentaux des soins de santé primaires (SSP), qui comprennent la fourniture d'eau potable, l'assainissement, la vaccination et la nutrition, doivent être renforcés, comme on le préconise depuis longtemps. La recherche de nouveaux agents antimicrobiens ainsi que la réorientation et l'utilisation rationnelle des agents existants, fondées sur des données probantes, devraient également être d'actualité à tous les niveaux. Les directives de traitement standard et les listes de médicaments doivent également être révisées à intervalles réguliers afin d'y inclure les nouveaux schémas de résistance/susceptibilité mis à jour. La formulation d'un cadre juridique et d'une politique adéquats pour faciliter la mise en œuvre des stratégies est également de la plus haute importance. Enfin, il faudrait prévoir des mesures incitatives pertinentes pour encourager la mise en œuvre d'activités d'intendance liées à la RAM et leur durabilité.

Mots clés : Agents antibactériens, résultats de la thérapie, isolats résistants, modèles de résistance, Nigeria.

Introduction

Antimicrobial resistance is gradually overwhelming the health care systems of many nations and is of grave concern across the globe. Antimicrobials are medicines used in the prevention and treatment of infecting microbes in humans among other living organisms. They include drugs used to treat viruses, fungi, parasites and bacteria. Antimicrobial Resistance (AMR) occurs "when microbes including bacteria, viruses, fungi and parasites change over time and no longer respond to medicines, making infections harder to treat and increasing the risk of disease spread, severity of illness and even death"[1,2] Antimicrobial resistance has become a pandemic issue with varying epidemiology and is of huge cost to the health care system and the society. It is a major threat to public health interventions on infectious diseases and capable of impacting negatively on sustainable human capital development[3] and is regarded as one of the top ten threats of the century to public health.[3] The world is heading towards a situation similar to the pre- antibiotic era due to the fact that some of the commonly encountered infections have become terribly difficult to treat.[3] Presently, the goals on health, food security and environmental related components of the global Sustainable Development Goals (SDGs) are seriously being threatened with increasing prevalence of AMR.[4]

Epidemiology of Antimicrobial Resistance

Epidemiology is concerned with the occurrence, distribution and control of epidemic diseases or health related events in large populations.[5] Databases of susceptibility/resistance profile of commonly encountered pathogens need to be developed and regularly updated and are of immense importance for decision in selecting agents for empiric treatment. Such epidemiological data are veritable tools for effective antimicrobial stewardship programmes in the communities and hospitals.[6] The acronyms 'ESKAPE' and 'ESCAPE' were proposed to represent the most commonly encountered resistant bacterial pathogens responsible for most nosocomial infections[7,8] Antimicrobial-resistant 'ESKAPE' comprising *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species) pathogens have been regarded as global threats due to their increasing virulence and resistance development. In 'ESCAPE' considered to be a more appropriate, acronym, "C" stands for Clostridium difficile, while "E" refers to Enterobacteriaceae family covering all Gram-negative enteric bacteria including E. coli, *K. Pneumoniae*, *Proteus* spp and *Enterobacter* spp.[8] The various organisms acquired resistance genes thereby becoming difficult to eradicate with resultant increment in disease burden and higher death rates.[9] Continuous surveillance of antimicrobial usage/resistance is imperative, especially for the most commonly encountered pathogens in each locality.

Of all the resistant microbes in ESCAPE, methicillin resistant *S. aureus* (MRSA) is the most virulent gram-positive bacterial isolate of immense clinical significance and is widely studied. The prevalence of MRSA

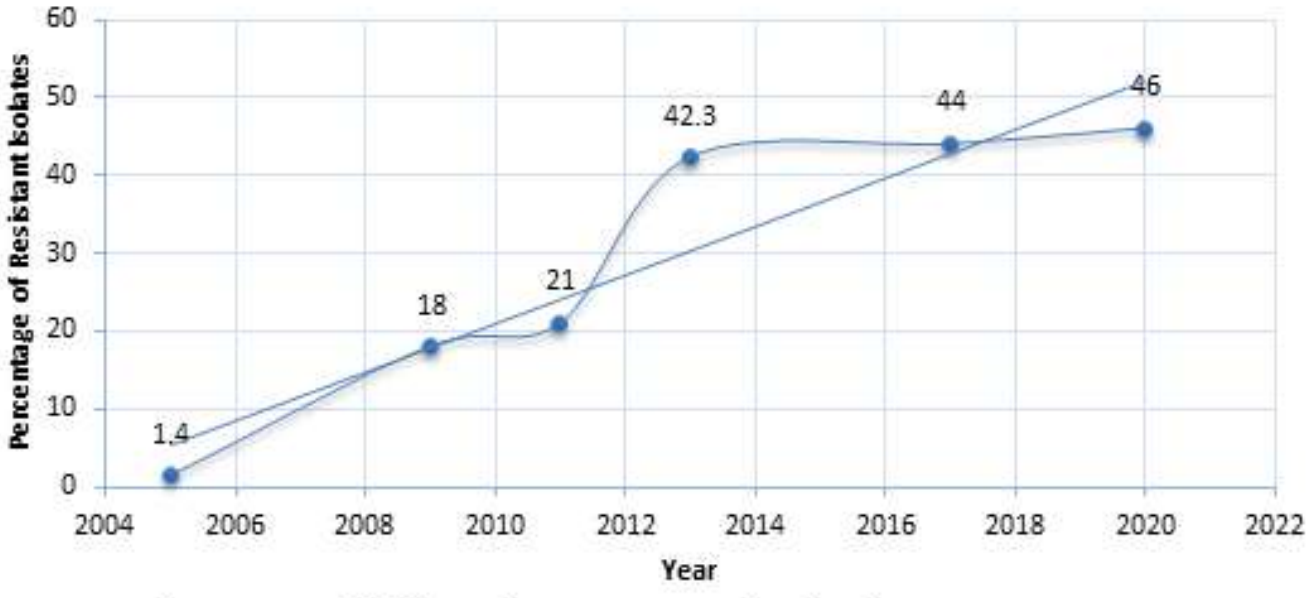

Figure 1: Methicilin Resistant *S. aureus* in Nigeria

was low previously in Nigeria but is rapidly increasing. Adesida *et al*[10] (2005) as cited by Suleiman *et al* (2012)[11] reported 1.4% after resistance profiling of 276 clinical isolates of *S. aureus* from 10 different hospitals in Lagos and Ibadan, southwest Nigeria. Few years later, specifically in 2009, and 2011, proportion of MRSA reported were as high as 20 -21%.[12,13] In a similar review of published works in Nigeria in 2009 and 2013; 18.3 and 42.3% MRSA were reported. This indicates an overall increase in MRSA within the years under review.[14] Highest proportion of MRSA were recorded in specimens from wound, blood and urine isolates and 85% of the strains were resistant to tetracycline and cotrimoxazole.[14] In 2017, a prevalence of 44% MRSA was also reported in Benin city, South-South, Nigeria.[15] More recently, In North West Nigeria, a 46% prevalence of MRSA was published.[16] In Jos, North Central Nigeria 97.3% MRSA, which was made up of seventy one out of seventy-three *S. aureus isolates*, was reported[17] all indicating increasing resistant isolates. A graphical sketch of the picture of MRSA in Nigeria outlined is as depicted in Figure 1. *S. aureus isolates* in meat shops in Pakistan had MRSA proportion of 79% and a complete resistance to ciprofloxacin, methicillin, neomycin and tetracycline was as well recorded.[18]

At the same time, E. coli is the most frequent of all Gram-negative bacteria and has consistently demonstrated high level of resistance to most antibacterial agents as far back as 2007.[19,20] Other Gram-negative organisms that are also highly resistant are Klebsiella and Pseudomonas aeruginosa.[21] High degree of susceptibility of E coli isolates was exhibited in the past to ciprofloxacin and ceftriaxone; 77.0% and 78.2% respectively. However, the isolates were highly resistant to amoxicillin (86.6%), tetracycline (91.0%), and cotrimoxazole (82.2%) [21]. This was similar to an Ethiopian Study (2011) in which high resistance was demonstrated by E. coli to erythromycin (89.4%), amoxicillin (86.0%), tetracycline (72.6%) but with high susceptibility to Nitrofurantoin (96.4%), norfloxacin (90.6%), gentamicin (79.6%), and ciprofloxacin 74.7%).[22] In another study, resistance of E coli was reported to be high for every agent tested, ranging from 51.1% to 94.3% except Nitrofurantoin which was 7.3%.[23] It was 94.2% for amoxicillin, 96.4% for tetracycline, 83.3% for co-amoxiclav, 86.6% for norfloxacin, 65.7% for ciprofloxacin and 51.1% for ofloxacin.[23] The degrees of resistance were generally higher than previous values as earlier mentioned.[24]

More recently, in Northwest Nigeria, Olowo-okere, *et al*., (2020) reported that 397 (54.0%) of 735 bacteria isolates that were isolated are Gram-negative with E coli being the most frequent (104; 26.2%) followed by *Klebsiella* spp (58; 14.6%). The isolates exhibited high degree of resistance to most of the agents tested. More than three-quarter (88.9%) of isolates were also multidrug resistant, with 86.6% resistance to amoxicillin, 76% to cephalothin, 77.2% to co-amoxiclav, while ceftriaxone and cefepime were 46.2% and 44.4% respectively. The least resistance was observed for piperacillin-tazobactam and amikacin at a rate of 22.5% and 5.5% respectively.[20] Also, in Abeokuta, Southwestern Nigeria, it was reported that abattoir effluent and its receiving water showed heavy contamination and pollution with highly resistant Gram-negative organisms.[19] The 54 isolates that were obtained from 30 samples showed E coli as the most frequent isolates (15) followed by *Pseudomonas* spp (12). Others were *Salmonella* spp, (9), *Klebisiella* spp (7) as well as *Enterobacter* spp (6). Sixty Six percent of *Pseudomonas isolates* and thirty one percent of Enterobacteriaceae demonstrated high resistance to all antibacterial agents except ertapenem with a 98% susceptibility rate. All these indicate sky-rocketing prevalence of resistant strains to commonly encountered pathogenic organisms.

Causes and Mechanism of Microbial Adaptation

Resistance to antimicrobial agents is said to occur when pathogenic microorganisms suddenly develop the ability to withstand their destructive capacity. They rapidly alter their attributes and become more adaptable to the selective pressure of the hostile antimicrobial environment.

AMR is partly an inevitable adaptive evolutionary necessity for microbial survival. However, poor compliance to principles of infection control contribute tremendously to its propagation.[25] Causes of AMR could be natural (biological) due to inherent property or mutation, among others. Selective pressure of antimicrobial usage followed by survival of resistant strains, which eventually replicate and become dominant type within the microbial population is very common. Mutation also occurs among microbes due to rapid multiplication, leading to production of mutant strains that can adapt/withstand adverse conditions, including antimicrobial agents.

Normal bacteria flora, which are usually non-resistant in nature can receive the genetic particle from resistant pathogens and become extremely resistant to drugs. These later multiply to become dominant species. Inappropriate usage of the antimicrobial agents in agriculture and treatment of human diseases, poor

adherence to therapy and inadequate diagnostics for specific infecting organisms to be identified are contributing factors to occurrence of resistance.[26,27,28]

Majority of bacterial isolates have varieties of mechanisms of resistance to any antimicrobial agent, once becoming resistant, within a short time, a large population of resistant progeny is produced. As known from time immemorial, the varying sustainable survival and reproductive ability of individuals resulting from phenotypic differences referred to as natural selection[29] favours the most efficient propagation mechanism. This implied the least fitness cost and least burdened[30,31]. The simplest and most natural constitutive/intrinsic resistance can be exemplified by some anaerobic bacteria such as resistance of Enterococcus species to gentamicin, Pseudomonas species to penicillin (except ureidopenicillin) and tetracycline, among others. Acquired resistance traits could be developed through mutagenic changes or transfer of genetic particles through the process of conjugation, transformation or transduction.[32] There are varieties of targets for mutation occurrence, which include gene encoding target protein, drug activation/promoter protein or transport protein, among others.

Normal commensal flora often serves as reservoirs of AMR transposons, plasmids and genes. This can be exemplified by E coli and enterococci of the gut which may facilitate spread of several resistance genes.[33]

Enzymatic inactivation is also a very common mechanism of resistance. For example, beta-lactam agents are inactivated by beta-lactamase enzymes and as much as 200 types of variants of the enzyme are available.[34] Efflux mechanism, which is energy dependent, is a prime defense for bacteria against tetracycline, quinolones and macrolides.

The wide but sometimes inevitable applications of these agents in agriculture have overwhelming and grave consequences on human health. A number of enteric organisms, including Salmonella and E, coli was originally propagated among animals, which subsequently infected people.[35] Animal handlers of the food chain channels are the routes by which those resistant organisms get to infect humans, and if they are multi drug resistant, it has serious consequences. The effects of animal contribution to the resistance problems in humans are particularly significant when enteric organisms are involved.[36] The reasons for AMR are numerous and some of the most important include the following:[30, 36, 37]

a. inappropriate use of antibacterial for prophylaxis and chemotherapeutic treatment of infections
b. Nonconformity with approved infection-control practices and principles
c. Prolonged hospitalizations
d. increased number and duration of stay in intensive care-unit
e. multifarious co-morbidities that may exist in hospitalized patients
f. growing usage of invasive devices and catheters
g. movement of colonized patients within the same hospital/ward and in some cases transferring to another hospital.
h. clustering of colonized patients in long-term-care facilities
i. Antibacterial utilization in agriculture and household burden
j. growing national and international travels.

Clinical, Economic and Humanistic Outcomes

Public health has been heavily impacted due to gradually increasing incidence of resistance across the globe. The overall direct, indirect and intangible costs of AMR are very significant.[38] Without AMR, treatment cost of infections is already enormous.[39,40] The cost implications are further compounded with increasing resistant proportion.[38] Resistance to hitherto sensitive microbes normally lead to prolonged illness, extended stay in hospital, higher incidence of morbidity, disability and death. It also necessitates the use of more expensive drugs which may not be easily affordable.[1]

According to the Centers for Disease Control (CDC), annual illness in United States due to antibiotic resistance occurs in over two million people with a resultant mortality of about 23,000.[41] Diseases from drug-resistant organisms is responsible for about 700,000 deaths annually worldwide.[42,43] This implies a massive depletion of human capital. An estimated population of 10 million people may die globally by 2050 if urgent measures are not taken against AMR.[44]

The immune system of the body is weakened by AMR which makes it difficult to effectively fight infections, in addition to the fact that a great deal of complications is developed, particularly among the vulnerable ones, such as those undergoing chemotherapy, surgical procedures, dialysis and joint replacement.[45]

AMR leads to a higher rate of patient's morbidity and mortality,[46,47] and doubles the probability of having severe illnesses while tripling the likelihood of death.[48]

Evidences showed that nosocomial infections by Gram-negative bacteria have higher chances to be resistant compared to community-acquired infections.[33,38] Worldwide, infections from MRSA have been linked with high rate of morbidity and mortality.[46] Serious complications of MRSA bacteremia, such as infective endocarditis, osteomyelitis and sepsis are extremely hard to treat. Multiple resistance to gonorrhoea, typhoid fever and tuberculosis are continually on the increase yearly, thereby contributing to the higher cost to the individual, healthcare systems and the society, a worrisome situation in developing countries due to low per capital income.[49] The growing number of Carbapenem-resistant *K. pneumonia* infections is alarming and is a serious threat across the globe with high incidence of morbidity and mortality.[50]

Antibacterial Resistance impact has negative effect on the humanistic outcomes of therapy. This ranges from patient dissatisfaction to poor health-related quality of life. The need for combination therapy to combat AMR also leads to numerous side effects, which in turn affects patient psychosocial outcomes. Constant usage of antibacterial agents reduces the life span of these agents; hence instituting antibacterial stewardship programme is of immense importance.[51]

An estimate of $20 billion in direct healthcare costs and higher magnitude of indirect cost of US$35 billion due to lost productivity has been calculated as the cost of antimicrobial resistance in the United States due to infections resulting from more than 2 million antibacterial resistant microbes and 23,000 deaths.[41,45] As high as 10 million deaths annually and cost implication in the range of $100 trillion loss to global economy resulting from AMR have been predicted by 2050.[42,43] According to research by the World Bank (2015), the already high rate of poverty would increase in low-income countries due to the negative impact of AMR. The resultant GDP loss in these nations may be in the range of 5-7% by 2050. In Nigeria with a perpetually low standard of living, where majority of the populace are living under $3.10 per day, poverty is definitely a significant contributor to worsening health status. Health care funding is very poor and Out-Of-Pocket (OOP) expenses remain the sole financial source for health care. Hence, health financing initiatives need to be introduced for improved health status among the populace.[52, 53]

MRSA infections have been reported to prolong hospital stay by 2 to 10 days with a direct cost of about 1.5 to 3 times higher than the cost with no infection.[54] The fluoroquinolones which have been demonstrated to be one of the most cost-effective in treating *S. aureus* infections in Lagos, South western region[11] are becoming increasingly ineffective on daily basis. Amoxicillin and co-amoxiclav which were previously published to be the most widely used in Ear Nose and Throat infections[55], and ciprofloxacin in STI treatment[39,40] are gradually becoming outdated due to AMR. A multivariate analysis of matched case group of 233 vancomycin-resistant enterococci (VRE) infected hospitalized patients with 647 hospitalized control patients revealed that VRE was linked with higher mortality rate, increased surgical procedures, and admissions to the intensive care unit and treatment cost in excess of US$12,000.00 per case.[56] In another report, resistant isolates of Pseudomonas were shown to be extremely expensive to treat relative to sensitive ones.[57] Ciprofloxacin tablet which was dominantly more cost effective than gentamicin and ceftazidime injections for sensitive isolates of Pseudomonas aeruginosa in Lagos Metropolis with the least cost effectiveness ratio of NGN4,241.82 (USD28.28) from societal perspective, was by far cheaper as compared to amikacin, the most cost effective among the drugs evaluated for resistant isolates with a cost effectiveness ratio of NGN50,118.85 (USD334.13). Incremental cost analysis showed that additional benefit gained using the more expensive ceftazidime with higher probability of cure over gentamicin will cost NGN157, 340.43 (USD1, 048.94) per treatment success.[57]

Used rationally, antibacterial agents are of great benefit to patients by improving their health status through timely clearance of infections. In addition, they reduce episodes of infection due to minimized spread referred to as positive externalities across the populations. They also increase the life expectancy, promote productivity and enhance overall health related quality of life.

Strategies towards reduction in Antimicrobial Resistance

There is an urgent need for new agents to be developed as only few drug candidates are in the pipeline and they resemble the existing ones.[4] Harmonization and immediate action on a global scale to stem the rate is of absolute necessity. In May 2015, The World Health Assembly (WHA) adopted a global action plan on AMR.[58]

The objectives of the plan were to;

1. improve awareness, understanding and implications of AMR through training and effective information, education and communication.

2. strengthen evidence-based practice through surveillance and research,
3. to reduce infection incidence through sanitation, hygiene and infection preventive measures
4. to effectively optimize antimicrobial usage in human and agricultural practices and lastly,
5. to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

In Nigeria, awareness and understanding of AMR is still poor and reported knowledge was also low.[27] In Ethiopia, physicians and nurses had information gap on AMR as well as poor awareness. Majority desired training in antimicrobial stewardship.[59] Sixty five percent of physicians and 98% of nurses desired training in stewardship programme on antimicrobial agents.

Monitoring of antimicrobial agents' prescriptions is of essence for comparison to resistance patterns. However, this has been shown to be poor in developing countries, including Nigeria.[52] Robust surveillance systems need to be put in place in every country. This implies "the ongoing systematic collection, and analysis of information related to public health (animal and human), and the timely dissemination of information so that action can be taken". This may include prevention and/or control of an infectious disease.[60]

Less than 50 countries of the world have a comprehensive record of details of antibacterial usage, which implies inadequate data for planning and taking proactive decisions on appropriate strategies.[61] It is important for countries to have comprehensive records of antimicrobial usage as well as resistance patterns in animal and human health for optimal fight against AMR, particularly in areas of empiric therapy and surveillance.

Policy Implications and Recommendations

There are different policy implications of AMR to the various stakeholders. As mentioned in the global action plan,[58] improved awareness at all levels, including the communities, is imperative. The government agencies at national and international levels, institutions of health sciences, professional bodies, health care workers, non-governmental organizations (NGOs) should take proactive steps at stemming the skyrocketing trends of AMR. Formal and informal channels need to be adopted to educate and communicate the implications of unchecked AMR in sustaining health and human capital development.

Quality and updated diagnostic and monitoring tools are very necessary to ensure satisfactory and conclusive identification of any infecting organisms. Without adequate facilities, surveillance data to take individual patients decisions, monitor the epidemiological patterns and propagate appropriate policies, finding a solution to AMR would be elusive. Research into patterns of AMR and relevant sentinel programmes need to be developed and properly implemented on a regular basis. Standard Treatment Guidelines should also be reviewed at regular intervals to reflect the current realities of resistance patterns. New drugs should be introduced into the formulary by relevant institutions and extravagant prescriptions should be prohibited. Most of the drugs for resistant organisms are still scarce in many hospitals. Drugs such as cefepime, ertapenem and extended-spectrum beta-lactamase inhibitor penicillins (piperacillin/tazobactam, ticarcillin/clavulanate) imipenem/cilastatin, meropenem are few examples. Recommendations similar to this is cautiously being advocated in many countries.[62] Many of them are very expensive and require to be aided financially if it becomes the only option of choice. Regular economic evaluation along epidemiological studies is needed to get the best value for limited resources. Generic products, higher strength, solid dosage forms and oral formulations are more cost effective than branded agents, lower strength, liquid formulations and injections of the same drug entity respectively.[61]

The PHC centers and private practitioners including hospitals, nursing homes and community pharmacies need to be carried along in policy development and in implementation strategies. Optimal knowledge of pharmacokinetics is important in rational antimicrobial therapy. Most health professionals have inadequate knowledge in this regard.

The Primary Health Care level of health should be strengthened for improved sanitation activities. Adequate water provision is key to infection control and provision of effective waste disposal system. The communities need to be sensitized and encouraged to take responsibility for their environment by maintaining good sanitation. Involvement and coordination in conjunction with traditional rulers may facilitate such efforts. Nutritional education is also vital at micro level to ensure that the immune system is boosted, thereby enhancing herd immunity. Strengthening the routine

immunization programme is equally imperative.

With the array of relevant professionals in Africa coupled with the abundance of herbal/natural resources, searching for new drugs need to be intensified. Provision of standard facilities and effective collaboration should ease the task. Collection, validation, and clinical trials of available crude formulations need to be encouraged by the Ministry of Health and other relevant agencies.

Research into repurposing appropriate combinations of existing agents may also help in minimizing the complications of AMR. Examples are the combination of fluoroquinolones and the penicillins, ureidopenicillins and fluoroquinolones, among others. Government should take decisions and make deliberate efforts by ensuring development of qualitative database of susceptibility/resistance patterns at state, regional and national levels.

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