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Animal-Food-Human Antimicrobial Resistance Fundamentals, Prevention Mechanisms and Global Surveillance Trends: A Terse Review

Charles Odilichukwu R. Okpala[1]*, Madubuike U. Anyanwu[2], Sebastian Łukańko[3], Obichukwu Chisom Nwobi[4], Małgorzata Korzeniowska[1], Ifeoma M. Ezeonu[5]

1. Faculty of Biotechnology and Food Science, Wroclaw University of Environmental and Life Sciences, 50-375 Wroclaw, Poland.
2. Department of Veterinary Pathology and Microbiology, University of Nigeria Nsukka, Enugu State, Nigeria.
3. Faculty of Biotechnology, University of Wroclaw, 50-383 Wroclaw, Poland.
4. Department of Veterinary Public Health and Preventive Medicine, University of Nigeria Nsukka, Enugu State, Nigeria.
5. Department of Microbiology, University of Nigeria Nsukka, Enugu State, Nigeria.

Abstract

Background and Objective: Food-producing animals can potentially transmit resistant bacterial pathogens to humans with various rates in various microbial species. Confronting the global antimicrobial resistance challenges needs collaboratively collective efforts by countries. Published literatures regarding antimicrobial resistance challenges and surveillance continually increase worldwide. Furthermore, understanding of antimicrobial resistance challenges and surveillance must be improved. Therefore, this brief review included antimicrobial resistance fundamentals and prevention mechanisms and its global surveillance trends specific to animal-food-human pathways.

Results and Conclusion: The capacity of antimicrobial resistance to include economic and health effects on various regions of the world must not be underestimated. The nature of antimicrobial resistance mechanisms contributes to its complicated spread mechanisms. Hence, there is the need for effective and efficient methods or strategies to challenge antimicrobial resistance. In addition to the concerns of antimicrobial agents with the developed understanding of the antimicrobial resistance prevention mechanisms, key facts of surveillance, specifically in microbiological contexts, are demonstrated in this review. In recent decades, global surveillance trends have been urged to overcome antimicrobial resistance problems. Due to its complexities, antimicrobial resistance remains a major public health concern with no single strategy to thoroughly prevent emergence or spread of infectious microorganisms.

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***Corresponding author:**
Charles Odilichukwu R. Okpala, Faculty of Biotechnology and Food Science, Wroclaw University of Environmental and Life Sciences, 50-375 Wroclaw, Poland.

Tel: +48501980949
E-mail: charlesokpala@gmail.com

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1. Introduction

The wide spectrum of microbial pathogens that contaminate animals and food products includes fundamental causes of foodborne diseases and producers of microbial toxins. To ensure safe food supplies worldwide, there are needs of surveillance programs on foodborne diseases, which data need effective interpretations [1,2]. Foodborne pathogens and their infections have dramatically changed over time as foodborne pathogens can be persistent. However, efforts must continue to either control or eliminate foodborne pathogens [2]. In recent years, excessive use of antimicrobials has increased [3]. In general, use of antimicrobials is still the key driver of resistance as well as their overuse (particularly for minor infections), misuse (due to lack of access to appropriate treatments) and underuse (due to lack of financial supports to ensure complete courses of treatments) [4]. Hence, emergence of antimicrobial resistant (AMR) bacteria is strengthened by this excessive use of antimicrobials. Used as growth

promoters in animal breeding, antimicrobials have contributed to decrease effects of infectious diseases [3]. Therefore, study of AMR in animals and humans is important because of following reasons: a) to understand changes in resistance to commonly used antimicrobials; b) to implement proactive measures that help control use of antimicrobials; and c) to stop the spread of multi-drug resistant bacterial strains [3].

In addition to foods and drinking waters that can be contaminated, animals continue to serve as potential microbial infection sources [5]. In general settings, use of antibiotics contributes to amplifying resistant and multi-resistant bacteria. Antibiotic-resistant bacteria have strong potentials to infect animals and humans. However, if the antibiotic fails to kill the bacteria (infection), minimal to life-threatening consequences can emerge [6]. Thus, understanding of the global spread of AMR microorganisms can specifically be useful, especially those which act through the animal-food-human routs. In addition, global AMR challenges need increased collaborative and collective efforts, especially for the involved professional bodies such as governments and academic/research institutions. To understand the basics of AMR especially from the global surveillance perspectives, investigation of mechanisms, by which AMR acts and available preventive approaches is particularly important. Recently, published literatures of AMR challenges and surveillance have significantly increased worldwide. Therefore, the aim of this study was to tersely review AMR fundamentals, prevention mechanisms and global surveillance trends, specific to animal-food-human routes. Specifically, the subsequent sections would be structured as follows: A) antimicrobial resistance and its development/transfer: basics; B) antimicrobial resistance mechanisms and spread; C) from antibiotics to antimicrobial agents; D) antimicrobial resistance prevention mechanisms; E) surveillance: key facts and methods/procedures; and F) major global antimicrobial resistance surveillance highlights in recent decades.

1.1. Antimicrobial resistance and its development /transfer: basics

Simply, AMR refers to the capacity of microorganisms to resist inhibitory or killing activities of antimicrobials. Additionally, resistance of bacteria to antibiotics used for the treatment of bacterial infections is termed antibiotic resistance [7-9]. Nowadays, AMR is a global threat to humanity with damaging economic and health effects, able to cause catastrophic situations comparable to those the climatic change does [10-12]. The extensive use of antimicrobial agents (e.g., in animals, crops and humans) has contributed to the emergence of AMR microorganisms in various environmental settings [13]. The AMR can develop naturally but is greatly enhanced by the practices such as misuse or overuse of antibiotics, poor infection controls, incorrect prescriptions and use of antimicrobials in food animal productions. As resistant strains spread between the animals, environments and humans, resistance to antibiotics rapidly develops [14]. For example, extensive use of antimicrobials in fresh and saltwater aquacultures reveals the rationale of why aquaculture-based foods are the major dissemination reservoirs/sources of AMR. Furthermore, if AMR is not challenged urgently from its sources, loss of 10 million human lives owed to AMR infections could be resulted by 2050 [15]. As reservoirs of various pathogens, food-producing animals can potentially transfer resistant pathogens to humans. Possibly, the magnitude of such transmission from animal reservoirs to humans varies within the various microbial species [16]. Raw foods of animal origins can become contaminated with such resistant enteric pathogens, including *Salmonella* spp., *Campylobacter jejuni* and *Campylobacter coli*, and/or resistant commensal bacteria, including *Escherichia coli* and *Enterococcus* spp. [17]. Healthy animals can be exposed to large quantities of antimicrobial agents used in food animal production, providing favorable conditions for the emergence, spread and persistence of AMR bacteria, which would result in infections in animals and humans [18,19]. Currently, there is increasing evidence that link AMR to animals and humans, particularly for common foodborne pathogens resistant to quinolones, including *Campylobacter* spp. and *Salmonella* spp. [8]. Additionally, microorganisms involved in such resistance include *Acinetobacter baumannii*, *E. coli*. *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, *Salmonella* spp., *Shigella* spp., *Staphylococcus aureus* and *Streptococcus pneumoniae* [20-21].

1.2. Antimicrobial resistance mechanisms and spread

Whether acquired (evolved through either acquisition of a specific gene via horizontal gene transfer or mutation in a microbial population) or intrinsic (inherent microbial resistance against specific antibiotics) [8], microbial resistance engages in various mechanisms, depending on specific inhibition mechanisms, to alternatively enable microbes to survive [8,22]. Specifically, there are four major AMR mechanisms; by which, microorganisms secure resistance to antibiotics (Fig. 1). These include: a) alternative activity escape mechanisms; b) antibiotic target modification; c) changes in permeability of the bacterial cell walls; and d) enzymatic degradation/modification of the antibiotics [8]. Briefly, an alternative escape mechanism is typically caused by the assembly of additional dihydrofolate, with R-plasmid-determined trimethoprim resistance, as cells resist the traditionally physiological pathway [8]. Antibiotic target modification is a mechanism; by which, resistance occurs because the target molecules of the antibiotics are modified. This causes the antibiotics to lose their binding activity and capability. Changes within the permeability of the bacterial cell walls involves a situation

where cell entry of antibiotics decreases or efflux of these chemicals increases, which regulates cell concen-tration of the antibiotics internally [8]. Enzymatic degradation/ modification of antibiotics usually occurs in Gram-negative bacteria. Examples include β-lactamase enzymes that hydr-olyze β-lactam rings within the antibiotics [8]. Mechanisms of horizontal gene transfer ARE highlighted by Verraes et al. [8], including conjugation, transformation and trans-duction processes. The AMR in foods can involve bacteria/genes contaminating the food matrices. Addit-ionally, AMR can be transferred through food processing facilities due to the effects of food preservation or processing techniques, biofilms, or cross-resistance to antibiotics and chemical biocides.

As AMR spreads from closed environments into open communities, new resistance mechanisms are able to spread horizontally between various bacterial species [23]. Additi-onally, mechanisms of horizontal gene transfer, involving conjugation (transfer of DNA between live bacterial cells that needs direct contacts between donor and recipient cells), transformation (transfer of naked DNA from the environments to bacterial cells) and transduction (bacterio-phage-mediated gene transfer), can occur in food products [8]. Understanding fundamentals of AMR mechanisms is essential using simpler and further effective methods. Moreover, AMR in foods can occur by a) food contami-nation with AMR bacteria and genes, and b) intentional addition of microorganisms (with AMR properties) to foods as auxiliary technical additives [8]. Furthermore, mechani-sms resulting in development of resistance in bacteria can include chromosomal mutations, plasmid-based mutations and acquisition of genes [23]. When AMR microorganisms affect food supplies of a country, it is possible for this phenomenon to become a potential problem for the neighboring countries [18]. Indeed, AMR populations are present in the bacterial communities and can expand through a variety of diverse/complex mechanisms such as those act via foods and waters [24].

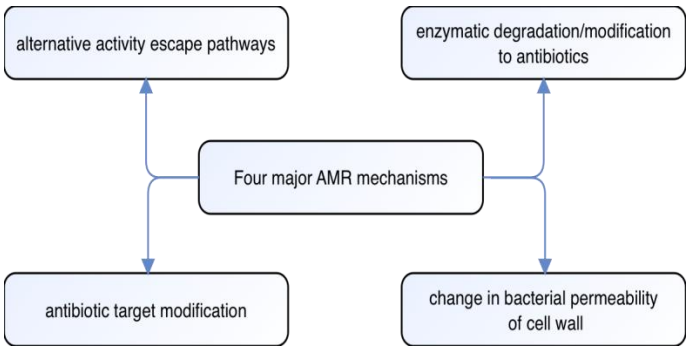

Figure 1. Four major antimicrobial resistance (AMR) mechanisms

1.3. From antibiotics to antimicrobial agents

Since antibiotics critically help decrease communicable diseases, AMR still threatens the effectiveness of successful infection treatments [25]. Regarding food processing domains, use of antibiotics can potentially cause bacterial resistance and once developed, the resistance is not limited to specific countries [23]. Nowadays, antibiotics are administered in large volumes to food-producing animals for growth promotion, prophylaxis and treatment purposes, wherein nearly 80% of such administration is considered unnecessary. Indeed, this largely affects human health due to the presence of drug residues in foods and hence selection of resistant bacteria in animals [26]. Undeniably, use of antibiotics in primary agricultural production contributes to AMR selection in bacteria. Transfer of AMR (in food processing environments) can occur due to the effects of food processing/preservation techniques and biofilms as well as cross-resistance to antibiotics and chemical biocides [8]. However antimicrobials have saved millions of human lives by killing the causative pathogens [27,28], microorganisms still survive from the effects of antimicrobial agents years after the use of the first antibiotics [22]. Limitation of the overused antimicrobials and unnecessary used antibiotics for animals/humans have become a vital global concern. Therefore, multinational global collaborations must be formed to improve antibiotic prescription [11,12]. Since decades ago, the use of antibiotics has played a vital role in animal feeds. However, such an antibiotic use can result in selection and transmission of antibiotic-resistant bacteria. Figure 2 shows how AMR bacteria are transferred from feces, manures and sewages through irrigation/water of crops to animal feeds. It is important to understand that when animal food products such as meat are consumed by humans, chances increase for the foodborne pathogens to spread within the community [29]. It is believed that the scale of agricultural use of antibiotics is massive. Quantitatively, antibiotic use in animals may be 100-1000 times greater than that in humans. Indeed, several antibiotics used in agriculture serve as growth promoters as well as prophylactic agents. Agro-practices are believed to affect the use of antibiotics and development of microbial resistance. For example, large operation farms are more likely to use antibiotics in feeds, compared to small farms [29].

Concerns of antimicrobial agents in developing world arise from certain practices such as unregulated sale or use of antibiotics, their over-prescription and releases into wastewaters and poor infection or sanitation control programs [30]. When administered to animals that are used as foods, antimicrobial agents can contribute to the emergence of resistant pathogenic bacteria. Continuous administration of antimicrobials at relatively low concentrations is believed to increase the likelihood of resistance development [29,31]. Examples of these antimicrobial agents include tetra-cyclines as well as other

antimicrobials in a chemical family such as tylosin and erythromycin [31,32]. Colistin and tigecycline are examples of last-line antibiotics, particularly recommended for treating a number of deadly infections. For several decades, however, these agents were largely used in several countries for food animal production, potentially resulting in the transmission of difficult-to-treat pathogens that carry mobile colistin and tigecycline resistance genes in animal-food-human ecosystems [33,34]. Routine prophylactic use of antimicrobial agents in preventing bacterial infections is a factor that facilitates the emergence of AMR [13]. As antimicrobial agents is a key player in driving emergence of AMR [35], regions with AMR peak levels need to act immediately to preserve antimicrobials [27-28]. Despite the fact that how bacterial resistance develops, it capably depends on the characteristics of the resistant genes as well as those of the exposed bacterial populations [17].

1.4. Antimicrobial resistance prevention mechanisms

Factors associated with the AMR can include a) availability of antimicrobial drugs for purchase with no prescriptions; b) inappropriate prescriptions; and c) inappropriate AMR prevention and control schemes [36]. There are needs of developing robust AMR infection controls and initiatives. This can involve coordination of long and short-term courses and programs as well as model-designed development of guidelines and networks. These should easily be available to health workers to proactively participate [36]. Essentially, use of antimicrobials is directly linked to the emergence of resistance. Therefore, containment and prevention action plans not only decrease AMR spread but also slow down healthcare associated infections and AMR emergence [4]. The AMR prevention plans have been described by various national and international healthcare authorities worldwide. Moreover, AMR prevention can involve adequate antibiotic treatment, diagnostic screening and infection control and diagnosis [37]. Prevention strategies need approaches that control and eradicate multi-drug resistant microorganisms, especially in healthcare settings. Examples can include administrative supports and accurate uses of antimicrobials as well as standard precaution, decolonization and surveillance schemes [36].

Several countries have initiated AMR containment and prevention programs, which focused on containing and preventing the (AMR) emergence and spread. An example is Thailand, where the 2012-2016 AMR containment and prevention program was carried out. This included a) estimating national AMR burden; b) establishing AMR chains/dynamics to understand AMR development and spread; c) developing nationwide AMR containment and prevention infrastructures; d) developing information technology and laboratory systems for AMR surveillance to monitor how antibiotics are used and how infections are acquired at hospitals; e) regulating antibiotic distribution and use in animal foods as well as humans; f) designing AMR containment and prevention campaigns; g) generating local evidence that promote responsible use of antibiotics; h) creating AMR containment and prevention packages; i) implementing AMR containment and prevention packages in pilot communities using selected fashion; and j) developing AMR diagnosis, prevention and therapy research [38].

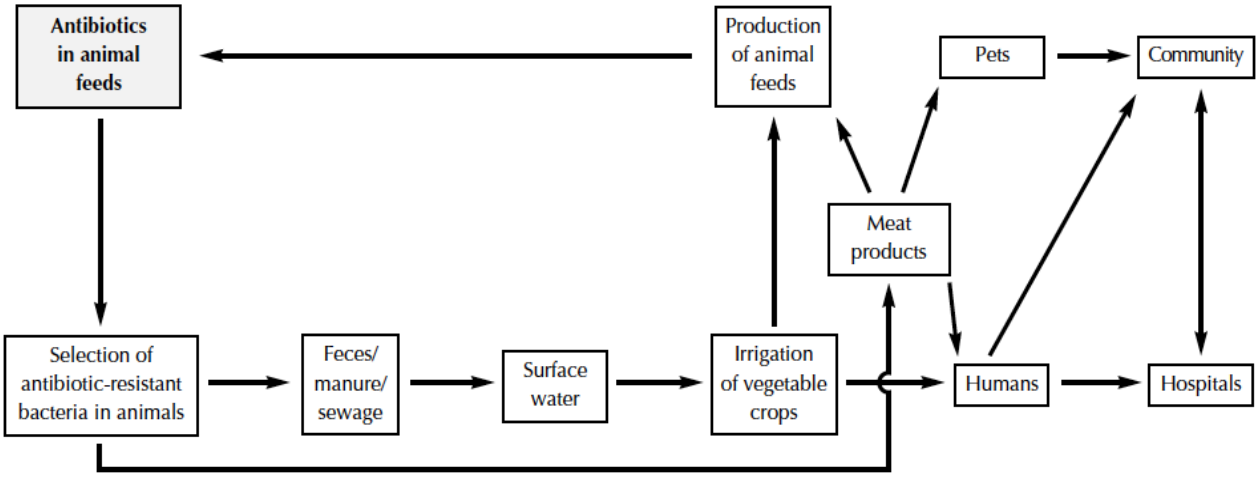

Figure 2. Antibiotic use in agricultures specific to animal feed and how it can result in transmission and selection of antibiotic-resistant bacteria (adopted from Khachatourians [29], courtesy of Canada Medical Association Journal)

The AMR prevention can occur through public, healthcare-related awareness strategies. For example, the European Antibiotics Awareness Day (2008-2010) included focus themes such as keeping antibiotics effective as a collective duty of the communities, communication with patients for primary-care center and hospital prescribers. Furthermore, AMR prevention can occur through infection control strategies, as launched by WHO Patient Safety Program (Fig. 3). Creating safer healthcare is directly connected to AMR-linked steps such as a) assessing and understanding AMR problem; b) developing and improving AMR knowledge access, standards and usage; c) promoting innovation and sustaining commitments; and d) strengthening problem-solving capacities. Figure 3 shows how the cycle revolves, from patient safety challenges, education and knowledge managements, solutions and technologies to classification and reporting of research. The patient safety and challenges associated with AMR are likely supported by improving access and knowledge as well as promoting innovation and sustaining commitments [4].

The AMR prevention can strengthen capacities of health systems through the harmonization of healthcare standards. Therefore, healthcare providers must comply with the recommended legislative policies [39]. The AMR prevention can be achieved through hand hygiene, which has been considered as an old but effective technique. For example, hand hygiene guidelines have been adapted and translated in several European languages in addition to dedicated campaigns and numerous healthcare facilities, all administering the "clean care" pledge [4]. The AMR containment not only improves access to appropriate antimicrobials and rationalizes antibiotic prescription and use, it enforces legislations and regulations and also strengthens health surveillance systems [4]. A typical example is STRAMA (Sweden Strategic Program against Antibiotic Resistance) with the overall aim of preserving effectiveness of antibiotics in animals and humans. It included a two-level (local and national) coordination strategy with news media. The outcome included substantial decreases in antibiotic use [4]. Another approach to prevent and control AMR includes implementation of evidence-based infection control interventions and measures, as well as decreasing excessive uses of broad-spectrum antimicrobials. Briefly, goals and strategies for AMR prevention and control can involve a) effective practices linked to antimicrobial use; and b) detection, prevention and report strategies regarding transmission of resistant microorganisms [40]. Despite AMR control and prevention activities worldwide, international spread of AMR microbes shows the global scale of the challenge, which needs both consensus and unified strategies [41].

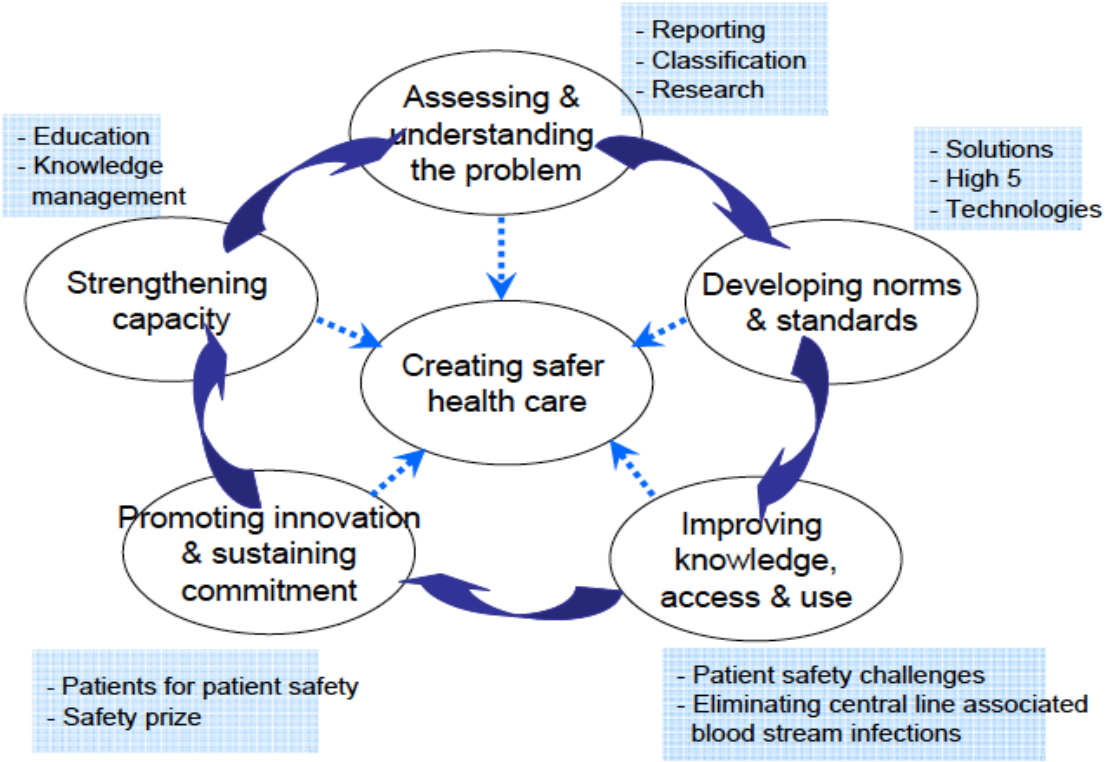

Figure 3. Antimicrobial resistance prevention through infection control as launched in WHO Patient Safety Program (source: Jakab [4])

1.5. Surveillance: key facts and methods/ procedures

According to World Organization for Animal Health (OIE), surveillance refers to the continuous investigation of a given population to detect occurrence of diseases for control purposes, which may involve partial testing of a population [17]. Antimicrobial concepts have been parts of the surveillance studies, typically associated with researchers and government officials. For example, knowledge of dosage, duration and reasons for antimicrobial use are the key determinants needed for the assessments of antibiotic exposures [42]. The AMR surveillance is a systematic, ongoing data collection, analysis and reporting process that quantitatively monitors temporal trends in distribution and occurrence of resistance and susceptibility to antimicrobial agents, providing useful information that guide disease control activities [43]. Surveillance, whether active (a program developed sampling schemes based on objectives of the program and actively collected isolates) or passive (samples submitted to laboratories for testing by sources outside the program), primarily involves a) risk analysis that calculates risks to human/animal health; b) emerging AMR detection; c) trend determination of the prevalence of decreased susceptibility to certain antimicrobials in specific populations; d) data generation to guide design of further studies; e) identification of regions that need potential interventions; f) providing of information for the prescription of protocols and use of recommendations; and g) providing of basis for the recommendation of health policies [17]. Furthermore, surveillance equally considers a) if human basic exposure mechanisms to food resistant bacteria do not necessarily differ within different countries; b) monitoring of bacteria (e.g., foodborne pathogens) from animal derived foods, which could be collected at any step of the food supply chains, including packaging, processing and retailing; and c) whether exposure of humans to resistant bacteria is direct (through exposure to zoonotic pathogens such as *Campylobacter* spp., and *Salmonella* spp.) or indirect (through exposure to resistant genes potentially transferable from commensal animal bacteria) [17].

There are major well-known analytical-based methods useful for the AMR surveillance (Fig. 4), which include a) confocal laser scanning microscopy (CLSM), b) culture-based techniques; c) major phenotypic techniques; d) multilocus sequence typing (MLST); e) pulse-field gel electrophoresis (PFGE); f) quantitative polymerase chain reaction (qPCR); g) whole/partial microbial genomic sequencing; and h) matrix-assisted laser desorption/ionization and time-of-flight mass spectrometry (MALDI-TOF MS). The CLSM basically includes resolution of images, advances in digital imaging methods and brighter and more photo-stable fluorescent probes with corresponding laser technology. In this optical imaging technique, there is an increasing optical visualization within living and fixed cells/tissues. Other advances include multiple label fluorescence, live-cell imaging and multi-dimensional microscopy [44]. However, the major disadvantage of CLSM includes co-localization of fluorophores. This occurs in confocal microscopy when two or more fluorescence emission signals overlap, often within its recorded digital images [45]. Culture-based techniques are largely used to identify microbial communities. Culture-dependent techniques, which involve foundational diagnostic techniques, are often standardized and customarily supplemented with molecular diagnostics. The latter reveals further microbial details, facilitates culture-dependent processes and improves identification of microorganisms. Therefore, antimicrobial treatments may be modified [46]. The other techniques, major phenotypic techniques, offer multiple advantages in comparison to genotypic techniques by identifying taxa of a wider range, detecting resistance as expresses and resisting genetic variability in resistance-associated detections [47].

The MLST technique involves molecular biology for the typing of multiple loci, while bacterial species are characterized via sequences of internal fragments, usually seven house-keeping genes. Various sequences assigned as distinct alleles are presented within a bacterial species, as per each house-keeping genes. Allelic profiles are defined by the alleles at each of the seven loci [48]. The PFGE, a technique used for the separation of large DNA molecules by producing DNA fingerprints for the bacterial isolates serving as members of the same bacterial group. The PFGE is not similar to conventional DNA electrophoresis. This is basically because PFGE can separate good quantities of DNA fragments to generate fingerprint profiles. This is carried out by constantly changing of the electric field direction [49].

The qPCR is a laboratory technique of molecular biology based on the PCR, which assess quantity of PCR products in real times. It does not rely on downstream analysis such as electrophoresis. Extremely versatile, it enables simultaneous assessments of multiple PCR targets. It can sometimes be a little complicate to set up, compared to routine PCR techniques [50]. An example is real-time PCR restriction fragment length polymorphism (RFLP). Simple for expert users to interpret its data, it remains a basic facility that is cheap and robust. The PCR RFLP data need evidence from previous studies to be well interpreted. Through the RFLP, AMR can be characterized by comparison of percentage results allocated to strains, identification of genotypic and phenotypic analysis [51]. Furthermore, PCR RFLP can help characterize class 1 and 2 integrons, specifically in the typing of each class. Antunes, Machado and Peixe [52] used PCR RFLP in characterizing AMR profiles of *Salmonella* isolates collected from several sources. To achieve AMR characterization through RFLP, the AMR patterns by RFLP need to be compared with those of the strains of assessed taxonomic statuses [53]. The RFLP

can help show the mutation profiles of AMR strains [54]. Another PCR technique includes single-strand conformation polymorphism (SSCP), which is capable to detect mutations, for example, single bases in short PCR-generated amplicons [55]. Through SSCP, strong and weak representations can be shown in distances and relative mobility of band patterns [56]. The PCR SSCP analysis can help establish variants within the microbial strains as well as differentiating two gene types within a single bacterial strain [57]. The SSCP can help investigate mutations of clinically diagnosed resistant bacteria [58]. Another PCR is amplified fragment length polymorphisms (AFLP), which uses DNA fingerprinting patterns to distinguish between the genomes of microorganisms. The AFLP PCR follows similar steps as RFLP but includes additional steps that allow for high-resolution interrogation of the entire genomes. The AFLP PCR produces highly specific and replicable genotypic data. However, AFLP PCR is useful with respect to dominant genetic markers, it does not rely on the previous information provided by the genome sequencing techniques [59]. In fact, AFLP can reveal the presence of a bacterial specific genotype through the characterization approaches. Using PCR AFLP, Pergola et al. [60] studied AMR in *Campylobacter* spp. from broiler chicken products in Italy.

Whole (partial) genome sequencing technique is an important tool for mapping genomes of novel microorganisms, able to compare genomes in various samples [61]. This technique is able to analyze complete DNA genome sequences, including various steps of library construction, random sequencing, closure and complete genome sequencing. The library construction step includes isolation, fragmentation and clone of DNA molecules and the closure step includes assembly of sequences and closing of gaps as well as editing and annotation of the molecules [62]. Indeed, GS is one of the novel surveillance methods, which has been described as a robust technique with benefits such as accuracy and precision, high resolution and rapid dissemination of results but with disadvantages such as high costs, complexity of bioinformatics processing and non-standard quality assurance [61]. Additionally, the omics-based approaches such as metatranscriptomics, proteomics and metabolomics are available with high potentials to progress next generation sequencing, facilitate monitoring of environmental hygiene particularly fresh food products and detect novel AMR microorganisms [63].

Matrix-assisted laser desorption/ionization and time-of-flight mass spectrometry (MALDI-TOF MS) contributes to advance microbiology by facilitating precision and rapid species identification [64] and revolutionizing pathogen identification. The MALDI-TOF technique includes four methodologies of a) detecting stable (non-radioactive) isotope-labeled amino acids; b) detecting differences in mass spectra of resistant/susceptible microbial isolates based on classical typing of the strains; c) analyzing bacterial growth with antibiotics absence/presence; and d) analyzing bacterial-induced hydrolysis of β-lactam antibiotics [65]. In whole-cell extracts, MALDI-TOF profiles bacterial proteins to achieve fingerprints, which discriminate various microbial isolates based on their genera and species [66]. Considered as a rapid reliable technique, MALDI-TOF is also a cost-effective approach to assess susceptibility of AMR isolates. Indeed, MALDI-TOF MS relies heavily on small specifications such as peak heights and areas under the peaks, both of which are empirically linked to the microbial species [64]. Detecting microbial AMR, Idelevich et al. [67] demonstrated the MALDI-TOF could be carried out within a few hours using direct-in-target micro-droplet growth assay. Specifically, the microbial isolates were incubated with/without micropenem in nutrient broth directly as droplets of MALDI-TOF MS. As a novel advanced replacement of biochemical identification methods, MALDI-TOF MS demonstrates strong accuracy and reliability in detecting virulence factors [68].

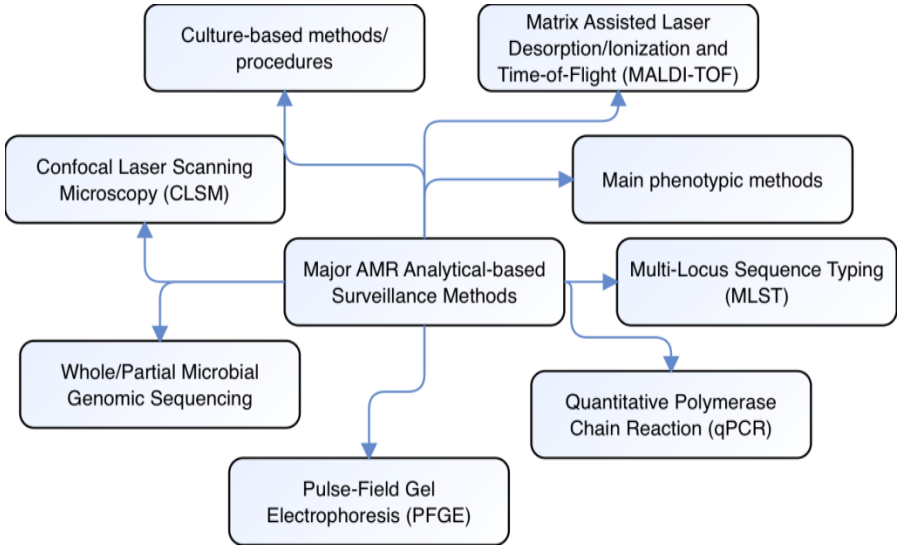

Figure 4. Major analytical-based methods used in antimicrobial resistance (AMR) surveillance

1.6. Major global antimicrobial resistance surveillance trends in recent decades

Including newly recognized untreatable infections in massive scales, the AMR is a complex global health challenge with no established schemes to successfully limit spread of infectious microorganisms, particularly those with resistance. Assessment of intervention results relies on the collection of accurate representative data, which determine degrees of the existing problems [7,16]. The AMR surveyllance systems are sources of multi-centric antimicrobial susceptibility data, especially when databases already exist with respect to clinical-based microbiology laboratories [41]. Therefore, the AMR surveillance systems play fundamental roles, which include investigation of resistance levels in specific geographical regions as well as monitoring changes in levels of the resistance [35]. When such a resistance develops within a population and subsequently spreads to other populations, it is critical in developing or monitoring intervention programs that help minimize the resistance spread [35]. The AMR surveillance at regular intervals and monitoring prevalence changes of resistance bacteria of food origin are critical strategies in limiting (AMR) spread [17].

Distinctive targets of AMR surveillance include a) how AMR trends generally evolve; b) how incidence of AMR infections evolves; c) how incidence of particular mechanisms of resistance evolve; and d) how incidence of particular resistant clones evolve [43]. Moreover, challenges of AMR surveillance can include a) absence of consensus on the minimum set of data to be collected; b) lack of standardization of methods and antimicrobials and variations in quality of susceptibility testing results; c) possible differences in frequency and distribution of sampling within countries and regions; d) presence of several measurement units that facilitates indication of specific AMR levels; and e) standardization of databases and stratification levels of reports [41]. The appropriateness of onsite food safety surveillance of AMR became the rationale for further studies such as that of catering services as reported by Garayoa et al. [69]. They established a way that included regular supervision of activities, continuous training of workers and checking of high-risk cross-contaminating surfaces (e.g., cutting boards and handles) by laboratory technicians and experimentation inspectors.

The fundamental global milestones of AMR surveillance associated with animals, foods and humans within the recent decades are shown in Fig. 5. Historically, interests on monitoring of AMR essentially began in the mid-1960s. By the late 1970s, new types of surveillance of resistant bacteria in human infections began in countries such as United States, United Kingdom, France, South Africa, Australia, Thailand and Venezuela [24]. During the 1990s, the World Health Organization (WHO) of the United Nations (UN) called concerned sectors to work together to eliminate the burden of AMR increasing from antimicrobial uses in food-producing animals [18]. By 1996, National Antimicrobial Resistance Monitoring System of the USA has been established on the basis that retail food sampling constituted a part of the integrated monitoring of AMR foodborne bacteria [24]. By 1998 in Geneva (Switzerland), WHA51.17 resolution on emerging and other commu-nicable diseases was adopted at the 51st World Health Assembly (WHA), formalizing concerns about the rapid emergence and spread of human pathogens resistant to available antibiotics, increased inefficacy of available antibiotics and high-costs of new-generation antimicrobials as well as extensive use of antibiotics in food productions that potentially accelerates resistance [70]. By 2000, WHO designated expert consultations under the following theme of Global principles for the containment of AMR in animals intended for foods. These expert consultations were carried out jointly with those of Food and Agriculture Organization (FAO) of the UN and World Organization for Animal Health (OIE). Through this platform, the AMR bacterial selection provided the necessary emphasis, especially with respect to use of antimicrobials in food animals [18].

From 2000 to recent years, increasing international efforts, particularly from the food safety and public health viewpoints, have been made to decrease AMR. By 2001, the OIE 69th General Session adopted the resolution no. XXV, which allowed OIE Specialist Commissions to develop international standards within the AMR framework. To establish objective and science-based limiting strategies of AMR, the member countries are continually encouraged to develop novel methodologies [23]. By 2008, the WHO Advising Group on Integrated Surveillance of Antimicrobial Resistance (WHO-AGISAR) was established to minimize the general public health effects of AMR, which were linked to antimicrobial agent use in food animals. Constituting over 20 internationally renowned experts in disciplines broadly relevant to AMR, WHO-AGISAR [18] has regularly convened to deliberate upon important global foodborne diseases or public health issues. The 1st meeting of 15-19 June, 2009, was held in Copenhagen, Denmark; the 2nd meeting of 5–7 June, 2010, was held in Guelph, Canada; the 3rd meeting of 14-17 June, 2011, was held in Oslo, Norway; the 4th meeting of 24-25 June, 2012, was held in Aix-en-Provence, France, the 5th meeting of 3-5 September, 2013, was held in Bogota, Columbia, the 6th meeting of 10-12 June, 2015, was held in Seoul, Republic of Korea; and the 7th meeting of 17-20 October, 2016, was held in Raleigh, USA [9].

From the global standpoint, regions should work together to consolidate committees and networks to strengthen capacities of limiting AMR threats [16]. In 2011, the WHO South-East Asia Region health ministers articulated their commitment to fight against AMR. Additi-onally, the WHO Western Pacific Region tries to step-up its commitments.

Similarly, ReLAVRA or the Latin American Antimicrobial Resistance Surveillance Network has shown significant efforts to extend its capacity to detect, monitor and manage antibacterial resistance data [16]. The Eastern Mediterranean Regional Committee adopted resolutions in 2013, targeting increased threats of AMR to public health. Another network is called Foodborne and Waterborne Diseases and Zoonoses Network (FWD-Net), which is coordinated by European Centre for Disease Prevention and Control (ECDC) and jointed by European Food Safety Authority (EFSA). The FWD-Net collects foodborne bacterial data, especially on how AMR and its zoonotic bacteria affects humans, animals and foods [16]. In addition to AMR foodborne surveillance and control schemes in Europe, there are increased emphases on decreasing use of antimicrobials [71]. Specific to the UK, a people-oriented surveillance measure (an AMR strategy) launched in 2013 that focuses on public-private sector volunteering [72,73], substantially decreased antimicrobial use in broilers and pigs by 21%, 2013-2016 [74].

By extending collaborations with the EU, the US has demonstrated importance of AMR to strategically control its spread from food products [75].

Particularly within the present decade, the WHO leads regional AMR surveillances. To improve AMR surveillance particularly at the country levels, the WHO Regional Office for Africa (AFRO) has published a 25-page guide that facilitates establishments of laboratory-based surveillances for priority bacterial diseases. The guide presents two broad sections of a) elements of a laboratory-based surveillance system for AMR; and b) steps for establishing laboratory-based surveillance for AMR [76].

It is noteworthy to reiterate that the highlighted global AMR surveillance advancements have largely evolved within the recent three to four decades. Indeed, calls have become stronger for the global and regional movements of food products that incorporate robust susceptibility testing and accurate monitoring systems for emerging AMR breakouts [77].

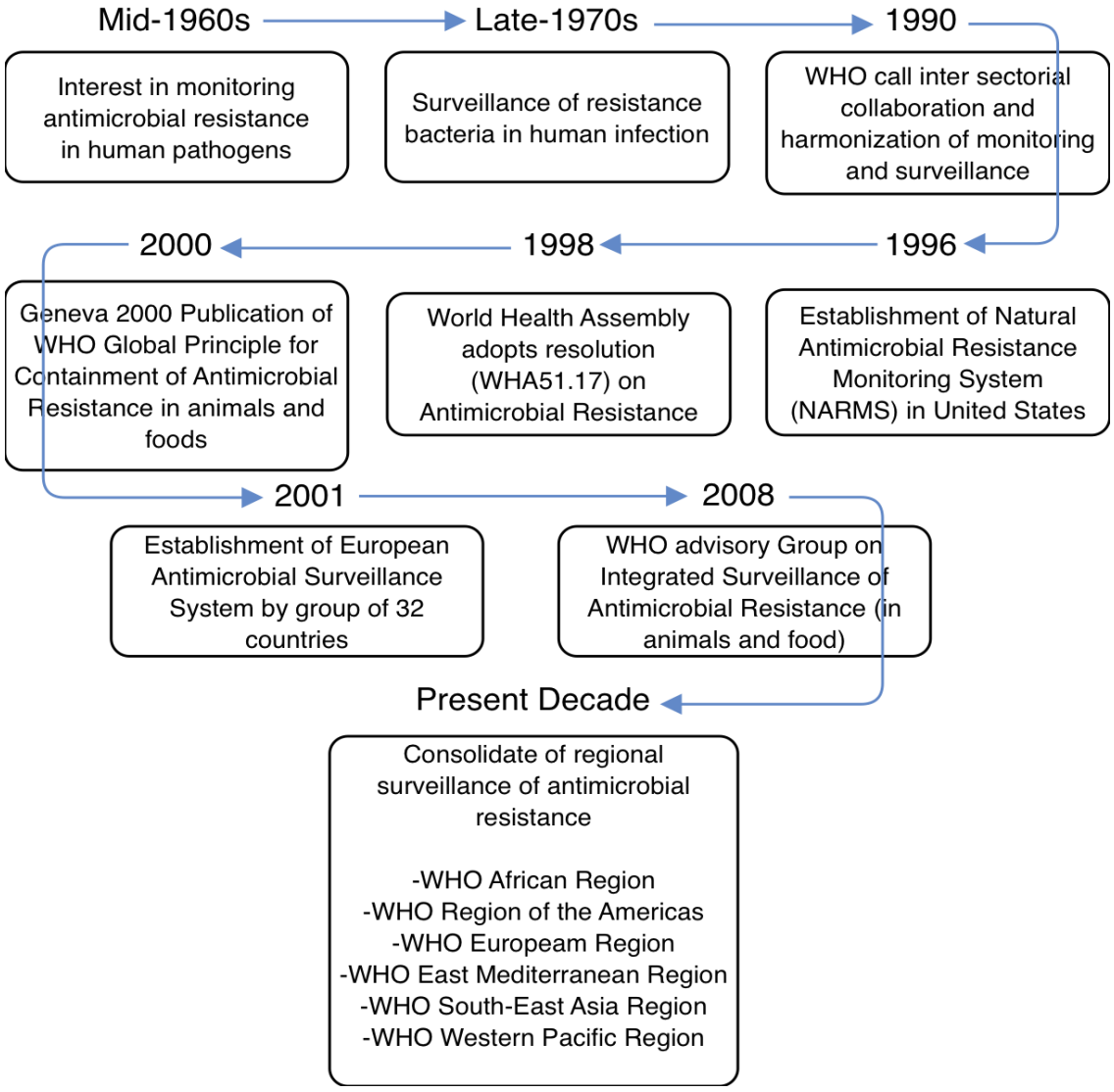

Figure 5. Fundamental global milestones of antimicrobial resistance surveillance associated with animals, foods and humans within the recent decades

Several developing countries face challenges in establishing practical projects with international collaborations to tackle the growing AMR problem [22,78,79]. The WHO Collaborating Center for Surveillance of AMR includes WHONET and its data capture module of BacLink, which is a free software that supports microbial laboratory data [80]. Since threats to effective treatments of the current infections are increasing; therefore, development of effective strategies to limit the emergence and spread of AMR is highly important [7,16].

2. Concluding remarks

Globally, AMR is still a big public health challenge due to its complexities with no strategies to thoroughly include emergence or spread of infectious microorganisms, especially those with broad resistance. Therefore, AMR involving animal-food-human routs needs significant interventions. In recent four decades, local, international, private and public sectors have tried to eradicate AMR through surveillance strategies. Laboratories, especially in developing countries, need supports for expensive AMR research facilities such as qPCR, genomic sequencing and MALDI-TOF MS. Such facilities can help, particularly in countries with emergent hotspots for AMR microorganisms. Foodborne AMR control/surveillance strategies help establish robust foundations to fight AMR emergence and spread.

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4. Conflict of Interest

The authors declare no conflict of interest.

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مبانی مقاومت ضدمیکروبی حیوان-غذا-انسان، سازوکارهای پیشگیری و روندهای نظارت جهانی: مروری کوتاه

چارلز اودیلیچیکوآ آر. اوکپالا[1*]، مادوبویک یو. آنایانو[2]، سباستین لوکانکو[3]، اوبیچوکو چیسوم نوبی[4]، مالگورزاتا کورزئینوسکا[1]، ایفئوما ام. ازئونو[5]

۱- دانشکده زیست فنوری و علوم غذایی، دانشگاه علوم زندگی و زیست محیطی روکلا، ۳۷۵-۵۰ روکلا، لهستان.
۲- گروه میکروب‌شناسی و آسیب شناسی دامی، دانشگاه نسوکا نیجریه، ایالت انوگو، نیجریه.
۳- دانشکده زیست فناوری، دانشگاه روکلا، ۸۳۸-۵۰ روکلا، لهستان.
۴- گروه بهداشت عمومی دامپزشکی و طب پیشگیری، دانشگاه نسوکا نیجریه، ایالت انوگو، نیجریه.
۵- گروه میکروب‌شناسی، دانشگاه نسوکا نیجریه، ایالت انوگو، نیجریه.

چکیده

سابقه و هدف: حیوانات تولید کننده مواد غذایی امکان انتقال میکروارگانیسم‌های دارای مقاومت باکتریایی به انسان، با سرعت‌های متفاوت در گونه‌های میکروبی گوناگون را می‌توانند داشته باشند. رویارویی با نظارت و چالش‌های جهانی مقاومت ضدمیکروبی نیازمند تلاش‌های مشترک جمعی کشورها می‌باشد. مقالات منتشر شده در زمینه مقاومت ضدمیکروبی به‌طور پیوسته در سطح جهان افزایش می‌یابد. بنابراین، این مقاله مروری کوتاه شامل مبانی مقاومت ضدمیکروبی و ساز و کار پیشگیری و روند نظارت جهانی به‌ویژه مسیرهای حیوان- غذا- انسان می‌باشد.

یافته‌ها و نتیجه‌گیری: ظرفیت مقاومت ضدمیکروبی شامل اثرات اقتصادی و سلامتی در مناطق گوناگون دنیا نباید کم اهمیت جلوه داده شود. ماهیت ساز و کارهای مقاومت ضدمیکروبی به ساز و کارهای پیچیده گسترش آن کمک می‌کند. از این رو، به روش‌های مناسب و کارآمد یا استراتژی‌هایی برای چالش مقاومت ضدمیکروبی نیاز است. علاوه بر نگرانی‌ها درباره عوامل ضدمیکروبی با توجه به اهمیت ساز و کارهای مقاومت ضدمیکروبی، حقایق کلیدی نظارت، به‌ویژه در زمینه‌های میکروب‌شناسی، در این مقاله مروری نشان داده شده است. در دهه‌های اخیر، به‌منظور غلبه بر مشکلات مقاومت ضدمیکروبی، روندهای نظارت جهانی تسریع شده‌اند. به‌علت پیچیدگی این مساله، مقاومت ضدمیکروبی همچنان یک نگرانیمهم سلامت عمومی به‌شمار می‌رود، بدون وجود هرگونه استراتژی کلی درباره پیشگیری کامل یا گسترش میکروارگانیسم‌های عفونت‌زا.

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- میکروارگانیسم‌ها
- مقاومت ضدمیکروبی
- نظارت جهانی
- عوامل ضدمیکروبی
- آنتی‌بیوتیک

***نویسنده مسئول**

چارلز اودیلیچیکوآ آر. اوکپالا
دانشکده زیست فنوری و علوم غذایی، دانشگاه علوم زندگی و زیست محیطی روکلا، ۳۷۵-۵۰ روکلا، لهستان.
تلفن: ۴۸۵۰۱۹۸۰۹۴۹+
پست الکترونیک:
charlesokpala@gmail.com