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Antibiotic resistance and the one health approach. The importance of teaching OMICS at Universities.

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In the past, much like today, the field of antibacterial drugs revolved around compounds featuring a crucial four-atom amide ring known as a β-lactam. These drugs occupied a prominent place in the world of antibacterial pharmacopeia. The most iconic among them was penicillin – to be precise, benzylpenicillin or penicillin G – accompanied by fellow penams like amoxicillin and ampicillin. Their shared structural feature set them apart: a β-lactam ring fused to a five-membered thiazolidine ring.

However, the remarkable feature of certain β-lactam antibiotics was their ability to combat the formidable Gram-negative bacteria. These types of bacteria have a characteristic double-layered cell wall, making it doubly challenging for drugs to penetrate compared to the single-layered cell walls of Gram-positive bacteria.

As Gram-negative bacteria became resistant to β-lactam antibiotics, by the 1980s, a new class of β-lactams, particularly cephalosporins like ceftriaxone and cefotaxime, emerged as front-runners in the battle against Gram-negative bacteria. These cephalosporins featured a non-β-lactam ring as a six-membered dihydrothiazine, enhancing their efficacy against these resilient microbes [1]. Additionally, non-β-lactam antibiotics, such as quinolones and fluoroquinolones like ciprofloxacin, demonstrated the capacity to breach the defences of Gram-negative bacteria, albeit through different mechanisms [2].

Later in the 1990s, a shift in the perception of antibiotics became evident as bacteria demonstrated their remarkable ability to adapt and develop resistance to these drugs rapidly. This shift was exemplified by the widespread emergence of methicillin-resistant Staphylococcus aureus (MRSA) and the production of β-lactamase enzymes by various bacteria, degrading β-lactam-based antibiotics. In response to the challenge posed by MRSA, researchers made noteworthy advancements in the field. They introduced the first oxazolidinone antibiotic, linezolid, as well as the lipopeptide antibiotic daptomycin. Concurrently, improved hospital practices played a pivotal role in preventing the transmission of resistant infections [3,4].

An ever-expanding global population, accompanied by a surge in international travel, has given rise to a pressing concern: the emergence of new resistance mechanisms against antibiotics. This alarming trend is exacerbated by the inadequate oversight of antibiotic usage in both human and animal populations. Thus, a paramount objective looms on the horizon: the discovery of an entirely novel structural class of antibiotics. The aim is to confound bacteria with substances they have never encountered, rendering them

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defenseless. Yet, this pursuit is riddled with challenges, from identifying such compounds to the arduous task of proving their effectiveness and safety to regulatory bodies. Consequently, many companies are actively exploring strategies to preserve the efficacy of older antibiotic classes while mitigating their inherent limitations [5].

Within the realm of pharmaceutical chemistry, the β-lactam structure stands as an enduring archetype. It bears a remarkable resemblance to a crucial element in the molecular dance of constructing bacterial cell walls. Specifically, the β-lactam structure mirrors a pair of alanine amino acids within peptidoglycan molecules, the favored targets of penicillin-binding proteins (PBPs)—essential components of bacterial cell walls. The β-lactam structure, inherently strained, is deftly harnessed in the meticulous design of antibiotic drugs. These drugs are engineered to divert electrons away from the β-lactam's carbonyl group, priming it for an irreversible interaction with PBPs. This artful maneuver effectively halts bacterial growth and culminates in cellular disintegration, liberating the cell's inner contents. Notably, β-lactam-containing drugs exhibit a remarkable degree of selectivity, as they discriminate between bacterial and human cell walls, ensuring precise targeting without harm to human cells.

Thus, currently, the following antibiotics can be found in the market: (i) Penicillins, including penicillin derivatives like amoxicillin and ampicillin, have long been cornerstones of antibiotic therapy. They primarily target Gram-positive bacteria by inhibiting bacterial cell wall synthesis. However, resistance to penicillins, often mediated by β-lactamase enzymes, is widespread. (ii) Cephalosporins, such as ceftriaxone and cefotaxime, are renowned for their broad-spectrum activity, effective against both Gram-negative and some Gram-positive bacteria. Yet, the emergence of extended-spectrum β-lactamases (ESBLs) has raised concerns about resistance. (iii) Fluoroquinolones like ciprofloxacin and levofloxacin are versatile antibiotics used to treat a range of infections. Resistance to fluoroquinolones can develop through chromosomal mutations in bacterial DNA gyrase and topoisomerase. (iv) Macrolide antibiotics, including erythromycin, clarithromycin, and azithromycin, find applications in respiratory and skin infections. Resistance mechanisms encompass efflux pumps and ribosomal modification. Finally (v) Tetracyclines like doxycycline and minocycline offer effectiveness against a broad spectrum of bacteria but face resistance challenges, primarily through efflux pumps and ribosomal protection proteins [6,7].

Furthermore, the Bacterial resistance mechanisms can be classified as follows. (i) Penicillins, including penicillin derivatives like amoxicillin and ampicillin, have long been cornerstones of antibiotic therapy. They primarily target Gram-positive bacteria by inhibiting bacterial cell wall synthesis. However, resistance to penicillins, often mediated by β-lactamase enzymes, is widespread. (ii) Cephalosporins, such as ceftriaxone and cefotaxime, are renowned for their broad-spectrum activity, effective against Gram-negative and some Gram-positive bacteria. Yet, the emergence of extended-spectrum β-lactamases (ESBLs) has raised concerns about resistance. (iii) Fluoroquinolones like ciprofloxacin and levofloxacin are versatile antibiotics used to treat various infections. Resistance to fluoroquinolones can develop through chromosomal mutations in bacterial DNA gyrase and topoisomerase. (iv) Macrolide antibiotics, including erythromycin, clarithromycin, and azithromycin, find applications in respiratory and skin infections. Resistance mechanisms encompass efflux pumps and ribosomal modification. (iv) Tetracyclines like doxycycline and minocycline offer effectiveness against a broad spectrum of bacteria but face resistance challenges, primarily through efflux pumps and ribosomal protection proteins [8].

Addressing antibiotic resistance demands a multifaceted approach. This includes the development of novel antibiotics, judicious antibiotic use to minimise selection pressure, and robust infection control measures in healthcare settings. In this sense, the one-health approach is an integrative and holistic framework that recognizes the interconnectedness of human health, animal health, and environmental health. It emphasizes the interdependence of these three domains and underscores the need for collaborative efforts to address global health challenges [9].

The One Health approach is characterized by several key principles. First, it promotes interdisciplinary collaboration among various disciplines, including medicine, veterinary science, environmental science, and public health. Experts from these fields work together to tackle complex health issues. Second, it acknowledges that human and animal health are intricately linked to the health of ecosystems. Environmental factors, such as climate change and habitat destruction, can influence disease transmission. Third, One Health emphasizes preventive measures to reduce the emergence and spread of diseases, including early detection, surveillance, and rapid response to outbreaks [3,5,9].

The One Health approach holds significant importance in addressing a range of global health challenges. Many emerging infectious diseases, including zoonotic diseases transmitted between animals and humans, have their origins in wildlife or domestic animals. One Health enhances our ability to detect and respond to these threats. Moreover, the misuse of antibiotics in both human healthcare and animal agriculture contributes to antimicrobial resistance. One Health addresses this issue by promoting responsible antimicrobial use in both sectors [10,11]. Additionally, protecting natural ecosystems is vital for maintaining biodiversity and preventing the spillover of diseases [12]. One Health advocates for sustainable practices that benefit

both health and the environment.

Practically, the One Health approach finds applications in various domains. It is crucial for controlling diseases like Ebola, HIV/AIDS, and COVID-19, which originated in animals and crossed into human populations. Ensuring the safety of the food supply chain requires collaboration between veterinarians, food scientists, and public health officials to prevent outbreaks of foodborne illnesses. Furthermore, One Health principles inform conservation efforts by considering the health of wildlife, domestic animals, and their habitats to prevent the emergence of diseases like West Nile virus and Lyme disease.

Implementing the One Health approach requires addressing several challenges. These include funding constraints, policy coordination, and institutional collaboration. Continued research is needed to better understand the complex interactions between humans, animals, and the environment. Advocacy and education are essential to raise awareness and build support for One Health initiatives at the global, national, and local levels [3,5,9].

As stated above, the emergence and spread of antibiotic resistance pose a grave threat to global health [11]. Addressing this challenge requires innovative approaches that transcend disciplinary boundaries. Omics technologies, which encompass genomics, metagenomics, transcriptomics, proteomics, and metabolomics, have emerged as powerful tools in the fight against antibiotic resistance [13,14]. These approaches contribute significantly to our understanding of resistance mechanisms and play a pivotal role in the One Health approach, which emphasises the interconnectedness of human, animal, and environmental health [15]. Thus, as a foundational omics discipline, genomics is instrumental in decoding the genetic basis of antibiotic resistance. Whole-genome sequencing enables the identification of resistance genes and mutations, providing clinicians with crucial information for treatment decisions [16,17]. Moreover, comparative genomics allows tracking of resistance-related genetic elements across diverse species and environments. Metagenomics, an extension of genomics, broadens our perspective by studying entire microbial communities. This approach is indispensable in assessing the resistome—the collective reservoir of resistance genes within microbial ecosystems. Researchers can identify potential reservoirs of resistance genes by characterising the resistome in various ecological niches and monitoring their dynamics over time. In addition, Transcriptomics delves into the realm of gene expression patterns under different conditions, shedding light on how bacteria respond to antibiotic exposure at the molecular level. This understanding aids in the development of diagnostic tools and predictive models for antibiotic resistance. Moreover, Proteomics complements genomics and transcriptomics by characterizing the proteins involved in antibiotic resistance mechanisms. It helps identify overexpressed or modified proteins, providing insights into resistance pathways and potential drug targets. Additionally, proteomic studies contribute to understanding the functional aspects of resistance genes [18]. Finally, Metabolomics focuses on the metabolic changes associated with antibiotic resistance, offering insights into altered metabolic pathways and potential vulnerabilities that can be exploited for therapeutic purposes.

The One Health approach recognises the intricate connections between human, animal, and environmental health to add another layer to the Omics importance. Omics technologies serve as vital instruments in translating this recognition into actionable strategies. Thus, Omics-based surveillance systems facilitate the early detection of emerging resistance threats in humans, animals, and environmental samples. Furthermore, monitoring the resistome in livestock, wildlife, and environmental reservoirs helps identify potential sources of resistant pathogens, enabling proactive interventions. Translational research guided by omics data aims to develop new antibiotics, antimicrobial therapies, and diagnostic tools. The insights gained from studying resistance mechanisms in diverse contexts inform the development of innovative solutions.

Omics data provide evidence-based support for policy decisions related to antimicrobial use in agriculture, healthcare, and the environment. This contribution promotes responsible antimicrobial stewardship and the implementation of effective regulatory measures.

Omics approaches are indispensable assets in the battle against antibiotic resistance, aligning seamlessly with the One Health approach's vision of holistic health solutions. These technologies empower us to unravel the intricate web of resistance mechanisms, track the dissemination of resistance genes, and inform evidence-based interventions. By harnessing the power of omics, we can more effectively safeguard the health of humans, animals, and the environment, mitigating the global threat posed by antibiotic resistance.

In the context of combatting antibiotic resistance and advancing the One Health approach, it is imperative that we equip the next generation of scientists and researchers with the knowledge and skills they need. This includes teaching omics technologies at universities—a crucial step in building a workforce capable of harnessing the potential of these powerful tools [9].

As omics technologies continue to evolve, students who are well-versed in these techniques will be at the forefront of cutting-edge research. They can contribute to innovative solutions and drive scientific progress in the fight against resistance.

Omics is inherently interdisciplinary, bridging gaps between

biology, chemistry, informatics, and more. Teaching omics encourages collaboration among students from diverse backgrounds, fostering a multidisciplinary approach to problem-solving.

In conclusion, the One Health approach is a vital framework for addressing the complex health challenges of our interconnected world. By recognizing the interdependence of human, animal, and environmental health and fostering collaboration across disciplines, we can better protect the health of all living beings and safeguard the planet for future generations.

To ensure that universities can effectively teach omics, providing them with the necessary resources and instrumentation is crucial. This support can come from various sources.

Governments should allocate funding specifically for acquiring omics equipment and developing omics-related programs at universities. Investing in education is an investment in the future of healthcare. Collaborations with biotechnology and pharmaceutical companies can help universities access cutting-edge omics technologies and offer students practical experience through internships and research projects. Finally, offering grants and scholarships to students pursuing omics-related studies can incentivise program enrolment. This financial support reduces barriers to entry and fosters talent development [9].

By teaching omics at universities and supporting them in acquiring the necessary instrumentation, we empower future generations to effectively tackle antibiotic resistance and other global health challenges. Through education and investment, we can bridge the gap between scientific knowledge and real-world solutions, ultimately safeguarding human, animal, and environmental health within the One Health framework.

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