MODERN APPROACHES TO ANTIBIOTIC RESISTANCE

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Abstract: Antibiotic resistance (insensitivity or resistance of infectious disease pathogens to antibiotics prescribed to combat them) is a topic that concerns all of humanity today. Medical professionals, scientists, pharmaceutical industry representatives, politicians, and even ordinary people are well aware that each year, we have increasingly limited means to wage an unequal battle not only with the microbes around us but also with those inhabiting our bodies.

Keywords: infection, antibiotics, anti-bacterial agents, antibiotic resistance, children.

In May 2015, the World Health Assembly adopted the Global Action Plan to combat antimicrobial resistance (including antibiotic resistance). This plan focuses on ensuring the prevention (primarily through vaccination) and treatment of infectious diseases using safe and effective medicines. It includes five strategic objectives:

- ✓ Raising public awareness and understanding of antimicrobial resistance.
- ✓ Strengthening epidemiological surveillance and supporting research in this field.
- ✓ Reducing the incidence of infections, primarily by expanding immunization programs.
- ✓ Optimizing the use of antimicrobial medicines, including antibiotics.
- ✓ Securing sustainable investments to counter microbial resistance.

In September 2016, during a session of the UN General Assembly, world leaders committed to launching a broad and coordinated response to antibiotic resistance. They reaffirmed their determination to develop national action plans to address antimicrobial resistance. Notably, the WHO's earlier initiative, "Antibiotic Awareness Week" was launched as part of efforts to fulfill the first objective.

According to the Global Action Plan on Antimicrobial Resistance (2016, as in 2001), measures must be taken at all levels of society:

At the Policy-Making Level

- ✓ Develop and adopt a National Action Plan to combat antimicrobial resistance.
- ✓ Enhance surveillance of antibiotic-resistant bacteria.
- ✓ Strengthen infection prevention and control measures (e.g., optimize national immunization schedules).
- ✓ Regulate and promote the proper use of antibiotics.
- ✓ Provide national data on antibiotic resistance.

In the Agricultural Sector

➢ Administer antibiotics to animals only under veterinary supervision and strictly for treatment, not for disease prevention or growth promotion.

➢ Vaccinate animals to prevent infections and use alternatives to antibiotics where possible.

➢ Promote and apply good practices at all stages of food production and processing.

➢ Improve farm biosecurity, including better hygiene for animals and infection prevention.

In Healthcare Systems

➢ Invest in research and development of new antibiotics, vaccines, diagnostic tools, and other effective instruments.

For Healthcare Professionals

➢ Promote infection prevention (e.g., adherence to aseptic and antiseptic protocols).

➢ Prescribe antibiotics only for bacterial infections, following modern treatment protocols.

➢ Report detected cases of antibiotic resistance to surveillance authorities.

➢ Educate patients on antibiotic resistance and the proper use of antibiotics.

➢ Teach patients about infection prevention (e.g., the importance of vaccination, handwashing, and other hygiene practices).

At the Individual Level

✓ Take antibiotics only as prescribed by a doctor.

✓ Never demand antibiotics if not recommended by a doctor, and avoid self-purchasing them.

✓ Always follow medical advice on antibiotic use.

✓ Never share antibiotics with others or use leftover antibiotics.

✓ Prevent infections through timely vaccination, proper handwashing, practicing safe sex, and following food safety practices.

At the end of February 2017, the World Health Organization (WHO) published a list of 12 antibiotic-resistant "priority pathogens" divided into three groups (critical, high, and medium priority) based on the urgent need to develop new antibiotics against them. This list is intended to guide countries in conducting scientific research and development. In spring 2017, health experts from the G20 met in Berlin to discuss and support this initiative. Germany's Minister of Health, Hermann Gröhe, commented on the agenda:

"The healthcare systems of our countries need new, effective antibiotics. We must take new joint actions today to ensure a healthier tomorrow!" Later, WHO's new Director-General, Tedros Adhanom Ghebreyesus, warned that "humanity could be left unprotected due to antibiotic resistance" and emphasized that "antimicrobial resistance is an urgent global health challenge that threatens progress in modern medicine."

The May 2017 WHO report highlighted that most currently available medicines are merely "modifications of existing classes of antibiotics" which serve as only a short-term solution. This underscores the pressing need for coordinated global action.

These warnings from the WHO Director-General echo earlier concerns voiced by Vytenis Andriukaitis, European Commissioner for Health and Food Safety:

"Antibiotic resistance is one of the most pressing public health issues of our time. If left unaddressed, we could return to an era when even the simplest medical procedures were impossible—let alone organ transplants, cancer chemotherapy, or intensive care."

But perhaps things aren't as bad as they seem? Could this be just another conspiracy by global imperialism, the WHO, and some mythical representatives of "big pharma"? Maybe the reality is much better? Or, to frame the question differently: are there scientific data proving that the WHO's concerns are well-founded, that antibiotics are far from safe for humans and their descendants, and that antibiotic resistance indeed plays a dramatic role in the lives of Earth's inhabitants? Is there undeniable evidence of its relentless growth, making it imperative for everyone to recognize this threat and confront it at their own level?

The answer is undoubtedly yes. Moreover, in the past few years, this trend has become alarmingly active. For example, according to the European Centre for Disease Prevention and Control (ECDC, 2016), resistance of Klebsiella pneumoniae—a pathogen responsible for severe bacterial lung infections in humans—rose from 6.2% to 8.1% between 2012 and 2015. This resistance spans multiple antibiotic groups, including carbapenems and colistin, a highly concerning sign indicating that doctors are nearly out of options to save patients. Additionally, the unpleasant trend extends to antibiotic resistance in Escherichia coli, another frequent cause of various infectious complications.

Yet, humanity, with its characteristic stubbornness often misplaced, continues to live with its "head buried in the sand" regarding antibiotic resistance. This is evidenced by public opinion surveys conducted in 12 countries (Barbados, Vietnam, Egypt, India, Indonesia, China, Mexico, Nigeria, the Russian Federation, Serbia, Sudan, and South Africa) and published on the WHO's website. These surveys, involving around 10,000 participants, aimed to assess people's knowledge of antibiotic therapy, antibiotic resistance, and their potential consequences. The results were surprising: two-thirds of respondents were generally aware of antibiotic resistance, but 76% believed it develops as an individual's "adaptation" to specific antibiotics. Furthermore, 66% thought that following a doctor's instructions made one immune to resistant microbes, and 44% associated antibiotic resistance only with patients who regularly take antimicrobial drugs.

The survey results for Russians (over 1,000 participants in the WHO's online test) reveal a similar lack of awareness. For instance, 56% reported using antibiotics in the past six months, primarily prescribed by doctors. However, two-thirds (67%) admitted to using antibiotics for acute respiratory viral infections (ARVIs) and influenza, where they are entirely ineffective. Moreover, one-fourth of Russians believe that antibiotics can be stopped as soon as they feel better, disregarding the prescribed course—an approach that directly contributes to growing antibiotic resistance.

Clearly, these findings highlight the urgent need for public education on proper antibiotic use and combating antibiotic resistance.

Incidentally, infectious disease rates in Russia continue to rise for many illnesses. According to Rospotrebnadzor, in 2016, the incidence of rubella increased by 2.8 times compared to the previous year, epidemic parotitis by 1.9 times, pertussis by 1.9 times, and Q fever by 4 times. Salmonellosis cases rose by 14.7%, unspecified intestinal infections by 5%, Siberian tick-borne typhus by 4.7%, and trichinosis by 6 times. Fifty new cases of malaria and 79 cases of dengue fever were also reported. Most of these diseases require antibiotic treatment, but their effectiveness is declining in Russia and globally.

A recent study published in the Journal of Pediatric Infectious Diseases Society analyzed medical data from 94,000 children under 18 hospitalized in 48 U.S. states with enterobacterial infections. It found a staggering 700-fold increase in infections caused by antibiotic-resistant strains between 2007 and 2015, rising from 0.2% to 1.5%. Notably, over 75% of these resistant microbes were present at admission, indicating the infections were not hospital-acquired. Patients with resistant infections had 20% longer hospital stays.

Similarly, antibiotics are now ineffective against approximately one-fourth of adult pneumonia cases, based on an analysis of data from 252,000 patients treated for community-acquired pneumonia in the U.S. between 2011 and 2015.

In children, problems with irrational antibiotic use are also evident. Many pediatricians prescribe antibiotics not recommended by clinical guidelines. For example, in a study of over 10,000 children treated in Pennsylvania and New Jersey outpatient clinics, only 40.7% received the recommended amoxicillin, while macrolides were prescribed in 42.5% of cases, and broad-spectrum antibiotics in 16.8%.

This underscores the critical importance of promoting rational antibiotic use worldwide.

By the way, clinical guidelines do influence physicians' decisions [12]. For instance, before the introduction of joint clinical guidelines by the Society of Infectious Diseases and the Pediatric Infectious Diseases Society of America in pediatric practice in 2011, less than 10% of children hospitalized with pneumonia were treated with penicillin-based antibiotics (2009–2011). After their adoption (2012–2015), this figure increased to 27.6%. Moreover, in hospitals where doctors received educational training, correct prescriptions occurred in 29.5% of cases, compared to only 20.1% in facilities without such programs. A similar study was conducted in the Russian Federation, which demonstrated an even greater impact of medical education on rational antibiotic therapy. According to Russian researchers, incorrect antibiotic prescriptions occurred in 78–90% of clinical situations before educational programs, but this number dropped to 20–30% after training for doctors and nurses [13]. Interestingly, in the U.S., antibiotics are prescribed for viral infections in 30% of cases, while in Russia and other post-Soviet countries, this rate reaches up to 90% [14].

It is particularly troubling that children often receive antibiotics at an early age. A study conducted in eight countries examined the use of antibiotics in children under two years old. Over five years (2009–2014), researchers observed 2,134 children in Bangladesh, Brazil, India, Nepal, Pakistan, Peru, Tanzania, and South Africa. On average, each child was prescribed 4.9 antibiotic courses per year, with the highest frequency in South Asian countries. Antibiotics were often prescribed for viral infections, such as 44.2% of viral gastroenteritis cases and 39.5% of upper respiratory tract infections, which is inconsistent with treatment protocols [15].

Irrational antibiotic use invariably increases antibiotic resistance. The connection between antibiotic prescriptions and subsequent resistance has been well-documented by Israeli scientists . Monitoring two communities of Jewish and Arab Israelis for five years, they recorded seasonal fluctuations in antibiotic prescriptions and the resulting antibiotic resistance, which lagged by about three months. Using this data, they developed a mathematical model capable of predicting future resistance to various antibiotic classes.

An intriguing but less widely known scientific fact is that resistant bacteria are spread globally by travelers. Swedish students who studied abroad in India and Central Africa returned home with a more resistant gut microbiome, despite not being ill or taking antibiotics during their trips. Metagenomic analysis of the students' fecal samples showed a 2.6-fold increase in genes resistant to sulfonamides and beta-lactams and a 7.7-fold increase in trimethoprim resistance compared to pre-trip levels. Beta-lactamase genes, present in only one student before travel, were found in 12 after returning. This phenomenon likely results from exposure to resistant bacteria through food or water.

This helps explain the differences in gut microbiome resistance genes across global regions, as described in a study by Indian researchers . Analyzing gut microbiome characteristics and resistance genes for 240 antibacterial drugs in 275 individuals from the Americas (U.S.), Europe (Denmark, Spain, Italy, France), and Asia (China, Japan), they identified four clusters (termed resistotypes) specific to various regions. For example, resistotype 1a was mainly found in Europeans and Japanese, resistotype 1b was common in Americans and Europeans, resistotype 1c was predominantly American, and resistotype 2 was unique to

Chinese populations. Each resistotype exhibited distinct patterns of resistance, providing a foundation for developing national strategies to combat antibiotic resistance.

The gut microbiota and its impact on human health are currently a hot topic. Notably, Harvard scientists, decoding the genome of gut microbes, discovered thousands of previously unknown bacteria. The microbiome changes with age, birth method (natural or cesarean), feeding type (breastmilk or formula), and early antibiotic exposure. Microbiome alterations are now linked not only to somatic diseases but also to many mental health issues.

For example, Finnish scientists concluded that early-life changes in gut microbiota could predispose preschool children to excess weight, increasing their risk of obesity. Observing two cohorts of healthy Finnish and Dutch children born via natural delivery, they analyzed the relationship between gut microbiota at three months and body mass index (BMI) at ages 5–6. They found a direct connection between gut bacteria composition changes due to antibiotics and preschoolers' BMI. Bifidobacteria and streptococci positively and negatively influenced weight, respectively, serving as early predictors of future problems. Thus, antibiotics given in the first months of life can dramatically alter a child's developmental trajectory, often leading to excess weight, obesity, diabetes, early hypertension, and other modern health issues. Preventing early antibiotic use can therefore safeguard a child's health for years.

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