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EDITORIAL COMMENTS – OPEN ACCESS

Antibiotic Resistance: A Global Concern; Current Situation and Action Plans

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Sir Alexander Fleming, after the discovery of the first antibiotic, penicillin, in 1928, alarmed against the overuse of antibiotics. Nowadays, after >70 years of the widespread use of antibiotics starting in 1943, severe bacterial infections resistant to available antibiotics are becoming a major health problem worldwide. They are more serious, requiring a much more expensive diagnosis cost and longer and more complex treatments. The "Post-Antibiotic Era" was first declared by the Centers for Disease Control and Prevention (CDC) in 2013 and then by the World Health Organization (WHO) in 2014. "The Review on Antimicrobial Resistance," chaired by Jim O'Neill, warned that by 2050, even mild infections could cause serious medical problems and that antimicrobial resistance attributable to mortality will prevail those with cancer (1, 2). There are already signs of this Post-Antibiotic Era in some parts of the world. In Nigeria, China, India, and Russia, >95% of individuals carry bacteria that are resistant to >90% of available antibiotics (3).

Recently, WHO declared the first list of bacteria that need urgent attention as the main threats to human health (4). The criteria for selecting pathogens on the list were the same as those previously announced by the CDC and included clinical impact, economic burden, incidence, a 10-year projection of incidence, transmissibility, availability of effective antibiotics, and barriers to prevention (5).

The WHO priority pathogens list the following:

Priority 1: Critical

- Acinetobacter baumannii, carbapenem-resistant
- Pseudomonas aeruginosa, carbapenem-resistant
- Enterobacteriaceae, carbapenem-resistant and extended spectrum beta-lactamase-producing

Priority 2: High

- Enterococcus faecium, vancomycin-resistant
- Staphylococcus aureus, methicillin-resistant and vancomycin-intermediate and -resistant
- Helicobacter pylori, clarithromycin-resistant
- Campylobacter spp., fluoroquinolone-resistant
- Salmonella, fluoroquinolone-resistant
- Neisseria gonorrhoeae, cephalosporin-resistant and fluoroquinolone-resistant

Priority 3: Medium

- Streptococcus pneumoniae, penicillin non-susceptible
- Haemophilus influenzae, ampicillin-resistant
- Shigella spp., fluoroquinolone-resistant (4).

The WHO list does not include *Clostridioides difficile* (*C. difficile*). However, the preceding CDC classification enumerates *C. difficile* as the most important urgent threat in antibiotic resistance (AR) list (5). WHO infers that *C. difficile* threat currently is not directly related to significant AR; however, the overuse of antibiotics made *C. difficile*

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an emerging cause of healthcare-related morbidity and mortality as referenced by the CDC (4, 5). In 2013, the CDC estimated the annual numbers of cases and deaths of *C. difficile* as at least 250,000 and 14,000, respectively, in the USA. The same values for other AR infections were 2,049,442 and 23,488, respectively (5). The estimated cost of *C. difficile* infections in the USA in 2015 is approximately US$4.8 billion/year for acute care facilities alone and comprises 10.6%–17% of the total yearly cost of healthcare-associated infections (HAIs), including 15,000 directly related deaths and 29,000 total deaths/year. One out of 5 patients experience recurrent infection, and 1 out of 11 patients age >65 years experiencing *C. difficile* infection will die in <30 days (6).

The clinical and economic burden of AR is closely related to HAI rates (7). The burden of HAIs in the USA is approximately 99,000 deaths/year. The economic cost for pneumonia and sepsis (the most common HAIs) calculated as US$8 billion in 2006 only for the USA. This cost is mostly due to AR (8).

The problem of AR in developing countries is more involute where the overuse and widespread illegal use of antibiotics in the outpatient setting are still very common. A considerable amount attributable to mortality due to AR in resource-limited countries results from poor regulation (3, 9). Some other causes might include loss of protective effects of antibiotics against foodborne diseases, poor sanitation, and poverty (8). In addition to self-prescription by the patient, studies showed that the indication for treatment, antibiotic choice, and duration of treatment might be far from minimal standards seen in developed countries (5, 10, 11). The widespread irregular consumption of antibiotics is considered to be the most important culprit; however, the extent of the effects of other factors is obscure, and it is not clear whether it results from the use of antibiotics for accelerating livestock growth, the release of antibiotics by drug producers into sewage, or the lack of sanitation (3, 5).

Knowledge of dynamic AR status is a precursor to infection control and is essential for public health policymakers to design effective control programs. The AR status changes over different periods in different geographic areas. These factors increase the importance of the establishment of an active timely updated surveillance system of AR from all hospitals. According to WHO, the member countries should track at least nine important bacteria. The greatest risks are about *S. aureus* and methicillin, *Escherichia coli* and cephalosporins, and *Klebsiella pneumoniae* and carbapenems (9). Currently, only 129 out of 194 countries provided national data on drug resistance; data were mostly from developed countries where national action plans are in place or developed (9). Only 22 out of 129 countries reported the situation with all nine bacteria (3).

The WHO and CDC have adopted several action plans to increase awareness and control the further emergence of resistant bacteria considering the high risk of AR on a global scale (1, 5, 12). Implementing antibiotic stewardship programs based on a well-defined surveillance system, promoting sensitive diagnostic indicators and prescription practices, and adopting strict preventive measures against infectious diseases are among the expected measures to limit the hazards of AR. AR surveillance should organize three levels including local, intermediate, and national according to the WHO guidelines. The Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (GLOBAL-PPS) developed at the University of Antwerp (www.global-PPS.com) provides a standardized and simple online tool for assessing antibiotic prescription and resistance from participating hospitals at all levels (10, 11, 13, 14). This tool developed following previous PPS conducted among children (9, 12, 13). The Global-PPS is instrumental in planning and supporting local and national stewardship interventions in a range of resource and geographical settings. Governments can use the Global-PPS tool to improve antimicrobial prescribing as part of their national action plan, which they are expected to draw up, with limited cost and investments in hospital staff.

AR is an inherent characteristic of bacteria, resisting against environmental pressures. In every colony of bacteria, there might be a population that is more resistant to environmental pressures, including antibiotics (5). Natural selection aids resistant bacteria to remain alive and become the dominant population (15). It is evident that the discovery of new antibiotics, with its many costs, cannot solve the problem alone (8). AR is a struggle between man and bacteria that continues forever. The illegal use of antibiotics will lead to a boost in this area and can lead to a rival of the arms race (16). Man cannot eradicate AR, but can only try to limit it.

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