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Drug Resistance in Infectious Agents – A Global Threat to Humanity

From the first antibiotic, penicillin introduced in 1940s, which came into wide scale use in the 1950s, anti-infective drugs to prevent mortality and morbidity arising from infections have unarguably been one of the most effective health interventions (besides chlorination of water and sanitation in general) in the history of modern medicine. Whether used to treat bacterial infections, or tuberculosis, malaria or HIV, these drugs have become a legacy arising from meticulous scientific and medical research over many decades that we all wish to pass on to future generations in as healthy a state as possible.

This aim is getting increasingly threatened by the growing problem of drug resistance in infectious disease agents and its spread globally. The pattern of emergence of drug resistance is almost uniform, independent of drug or infectious agent. It starts slowly, but then rises rapidly following a sigmoid shape of frequency change over time. The silent phase may be a decade or even longer, and its existence often lulls observers into a false sense of security post widespread use of a new drug. In recent decades, the rate of discovery of novel compounds, especially antibiotics, has slowed down considerably. From discovery to market it typically takes 10-15 years. The current need, therefore, is not only to extend the life of existing drugs but also to encourage discovery and development of new anti-infective drugs to combat the threat that drug resistance presents to human health.

The current situation is becoming serious with an increasing incidence of detection of resistance to all known drug treatments, especially amongst bacteria. Two examples are as follows. First, the incidence of Multi Drug Resistance (MDR) in *Mycobacterium tuberculosis*, which can result in untreatable tuberculosis infection, is rising steadily worldwide. According to a recent WHO report, an estimated 440,000 cases of MDR tuberculosis were notified worldwide in 2011¹. Furthermore, 84 countries have reported untreatable tubercular infection. The second example is that of common bacterial infections caused by Enterobacteria in hospital settings. Carbapenem-resistant Enterobacteriaceae (CRE) infections are on the rise, and have recently become resistant to 'last-resort antibiotics'. These bacteria are an increasing cause of mortality in many countries (CDC, 6th March 2013). According to a WHO report the "...world is heading towards a post-antibiotic era in which many common infections will no longer have a cure and

once again kill unabated”¹. A similar sentiment has been expressed by the Chief Medical Officer of UK who has described antibiotic resistance "as big a risk as terrorism"².

The resistant organisms are often very difficult to treat. They impose great health risks to individuals and significant costs to society. Since they are infectious agents they have the potential to spread to others, so that the problem which was initially encountered in hospital settings is now increasingly a community problem as well. More recently the World Economic Forum has included antibiotic resistance in its 2013 Global Risks report³.

Our aim in making these recommendations is threefold. First, we wish to draw increased attention of the world to this growing problem. Second, we hope to encourage the G20 countries to place the problem of combating the emergence and spread of drug resistant infectious agents high on their health agenda. We urge that the problem of resistance to anti-infective drugs be incorporated in the revised millennium developmental goals. And third, we would like the international community to find ways and means to encourage pharmaceutical companies to invest in the development of novel anti-infective drugs in general, but especially antibiotics.

The emergence of drug resistance is inherent to the basic biology and evolution of microorganisms. In any infection some organisms are likely to be resistant to the used antimicrobial agent as a result of existing spontaneous mutations and genetic exchanges. However, the frequency of such resistant organisms is quite low. The problem arises when the hardy variant gets selected and multiplies by the elimination of sensitive ones by the used antibiotic. The selection pressure exerted by the antibiotic gets intensified with the overuse, misuse or underuse of the antimicrobial agents. This is what happened with the emergence of Methicillin Resistant *Staphylococcus aureus* (MRSA), and now with vancomycin resistant enterococci. Another mechanism of drug resistance is acquisition of drug resistance mediated through plasmids or mobile genetic elements. Such resistance can be horizontally transferred from one organism to another organism, including from animal infectious agents to human pathogens. This is very common with enteric bacteria such as *Escherichia coli*, *Klebsiella*, *Acinetobacter*, *Pseudomonas*, *Enterobacter* and *Enterococcus*. It occurs not only in bacteria, but also in viruses, fungi and parasites that become resistant to various anti-infective agents.

Varied factors have been identified to be responsible for the emergence and spread of resistant microorganisms. These include:- 1) Irrational and self-use of antibiotics; 2) Lack of adherence to a prescribed regimen; and 3) Widespread non-human use of antibiotics and other anti-infective agents as growth promoters in livestock. Problems also arise due to lack of policy for rotation of antibiotics and infection-control in the hospital. Other factors that have aggravated the problem include increasing in use of antibiotics in patients with immune suppression (patients of cancer on chemo/radiotherapy, subjects receiving organ transplants, patients suffering with auto-immune disorders on immune suppressants and patients with HIV/AIDS). The problem is

further compounded by poor prescribing habits of doctors and lack of information about changing anti-biotic sensitivity patterns to guide antibiotic rotation. In some parts of the world poor quality of drugs can contribute to the emergence of drug resistance due to exposure to sub therapeutic levels of antibiotics in these preparations. In recent years the use of antibiotics in livestock farming has surpassed the use of these agents in humans. Besides their use for treatment of infections in animals, the agents are commonly used prophylactically to enhance growth rates that increase yields in livestock, poultry and fish farming. This has led to chronic sub-therapeutic consumption of antibiotics by man through eating of the meat from these animals, and also to the emergence of resistant micro-organisms in animals. In one study more than 50% of the bacteria in ground turkey were resistant to three or more classes of antibiotics, while a quarter were resistant to five classes⁴. It is known that resistant zoonotic bacteria may cause human diseases and also pass genetic material to bacteria that infect humans.

Effective surveillance systems have been put in place in some countries to track the emergence and spread of resistance to anti-infectives. Such surveillance has been able to bring about changes in national policies and practices. But there are wide variations between different countries and even within the same country. A country-based analysis is a logical initial step towards establishing a comprehensive open access global drug resistance database. Necessary expertise, information and resources would need to be shared for the purpose. The academies recommend the following actions to reduce the burden of drug resistance to improve global health and to enhance economic well-being.

1. **Promote integrated global surveillance systems.** Determined leadership, additional resource mobilization and strong commitment nationally and internationally is called for to promote co-operation between health agencies, clinicians, epidemiologists, microbiologists, animal husbandry experts, molecular biologists, information scientists and social scientists to prevent the spread of resistant microorganisms. The implementation of these goals would require strengthening of surveillance and laboratory capabilities worldwide.

This will require:

- Monitoring of antibiotic and anti-infective sensitivity patterns in human and zoonotic infections on a regular basis.
- Acquiring of knowledge through surveys of antimicrobial use and environmental impact of antibiotics in water and wildlife.
- Tracking of antimicrobial resistance in real time at the molecular level and creation of global data repository with open access.
- Monitoring of drug quality and detection of substandard anti-infective drugs.

2. **Promote Information and Education programs on the rational and responsible use of anti- infective drugs.** This should target medical doctors, patients and other members of society, particularly those involved in animal husbandry and industrial use of antibiotics.
3. **Set up a “drug policy” among member countries** with all necessary regulations for dispensation of vulnerable anti-infective drugs, standard guidelines for anti-infective drug prescriptions, limiting the use of these agents in animal husbandry and assuring availability of quality and appropriate anti-infective therapies.
4. **Enhance prevention and control policies.** This can be achieved by the prevention and control of infections through more systematic use of existing vaccines and in some cases development of new vaccines against problematic infections including bacterial infections acquired in hospital settings, and promotion of universal measures of hygiene and sanitation relevant to prevention of infection.
5. **Encourage pharmaceutical companies, in collaboration with public funded researchers, to develop new antimicrobials.** New scientific approaches using genomics, proteomics and bioinformatics can speed identification of new targets and development of new therapeutic molecules particularly against resistant microorganisms. The policies should include financial and regulatory measures to encourage pharmaceutical industry to develop novel antibiotics expeditiously. There is an urgent need to develop effective drugs against neglected tropical diseases. Development of new diagnostics tests and biomarkers for drug resistance are also important to fight the menace of antimicrobial drug resistance.
6. **Enhancement of R & D capability of developing countries to be a partner in the fight against emerging antimicrobial drug resistance.** The developing countries need to take a lead in all the above endeavours, more so than the developed countries, since the problem of antimicrobial drug resistance more acutely affects them. The co-operation, both amongst scientists and industry, between the North and South should be actively supported to achieve the desired end.

¹ www.who.int/pmnch/media/membernews/2011/20110407_who_whd/en/

² <http://www.bbc.co.uk/news/health-21737844>

³ www.weforum.org

⁴ <http://www.foodsafetynews.com/tag/narms/#.UVligxz-FSM>

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