Editorial Commentary

Combat drug resistance: no action today means no cure tomorrow. World health day 2011: a microbiologist's perspective

It is no exaggeration to say that antibiotics make modern medicine possible. Complex medical interventions like organ transplants, hip replacements and even chemotherapy are all made possible or better by the use of antibiotics. And rightly so, major diseases like syphilis, gonorrhoea, leprosy, and tuberculosis, have lost much of their sting. But antibiotics lose their effectiveness over time as bacteria naturally evolve and mutate and so become resistant. The world is on the brink of losing these miracle cures. Even World Health Organisation (WHO) has selected "combating antimicrobial resistance" as the theme for World Health Day 2011.

We seem to have come a full circle from the pre-antibiotic phase through a successful phase of infection control to a seemingly frightening post-antibiotic era of multidrug resistant bacteria desperate for the elusive magic bullet.

Resistance in microorganisms is defined as their unresponsiveness to the standard doses of drugs. The development of resistance is a natural biological process that will occur, sooner or later, with every drug. However, irrational use of antimicrobial agents, faulty practices and flawed assumptions has clearly made the inevitable development of drug resistance happen much sooner, rather than later.

Resistance is not a new phenomenon; it was recognised early as a scientific curiosity and then as a threat to effective treatment outcome. Antimicrobial resistance is one of the biggest challenges to face global public health at the beginning of the third millennium. Ever since antibiotics became widely available in the 1940s, they have been hailed as miracle drugs- magic bullets able to eliminate bacteria without doing much harm to the cells of treated individuals. Yet with each passing decade, bacteria that defy not only single but multiple antibiotics, and therefore are extremely difficult to control, have become increasingly common. After more than 50 years, however, widespread use of antibiotics is thought to have spurred evolutionary adaptations that enable bacteria to survive these powerful drugs. Antimicrobial resistance provides a survival benefit to microbes and makes it harder to eliminate infections from the body. Antibiotic resistance has become a serious public health concern with economic and social implications throughout the world, be it community acquired infections like streptococcal infections, pneumonia, typhoid fever, etc., or hospital acquired infections due to methicillin resistant *Staphylococcus aureus* (MRSA),vancomycin resistant enterococci (VRE), vancomycin intermediate *S. aureus* (VISA) or extended spectrum beta-lactamase (ESBL) enzyme producing Gram negative bacteria. However, developing countries are hit hard with increasing reports of development of resistance to drugs commonly used to treat most of the communicable diseases. The emerging threat of resistance in malaria, tuberculosis (TB) and human immunodeficiency virus (HIV) infection is a huge impediment in achieving the Millennium Development Goals (MDGs) by 2015. Infections caused by resistant microorganisms often fail to respond to conventional treatment, resulting in prolonged illness and greater risk of death. Antibiotic-resistant pathogens are not more virulent than susceptible ones: the same numbers of resistant and susceptible bacterial cells are required to produce disease. The looming threat of incurable *Staphylococcus aureus* is just the latest

twist in an international public health nightmare: Worldwide, many strains of *Staphylococcus aureus* are already resistant to all antibiotics except vancomycin. Emergence of forms lacking sensitivity to vancomycin signifies that variants untreatable by every known antibiotic are on their way. Resistance to first-line anti-TB drugs has become a concern for national TB control programmes. It is estimated that around 180,000 cases of MDR-TB reside/occur annually in the south east Asian region with more than 80 per cent of these being in Bangladesh, India, Indonesia, Myanmar and Thailand. Although the generic antiretroviral (ART) drugs available in this region are contributing greatly towards improving the survival rate of patients worldwide and in rendering HIV as a chronic but a manageable condition, there are reports of the emergence of resistance that is a serious cause of concern. There has been a substantial change in the antimicrobial susceptibility of *Neisseria gonorrhoeae*. Resistant malaria has already become a major issue for a population of 400 million living in areas that expose them to a high risk of contracting it. Multidrug resistant *Klebsiella*, *Pseudomonas* and *Acinetobacter* species have given new dimensions to the problem of hospital-associated infections [1].

How did we end up in this worrisome, and worsening, situation?

Several interacting processes are at fault. One component of the solution is recognising that bacteria are a natural, and needed, part of life. People should realise that although antibiotics are needed to control bacterial infections, they can have broad, undesirable effects on microbial ecology not only in the treated individual but also in the environment and society at large. Although many factors can influence whether bacteria in a person or in a community will become insensitive to an antibiotic, the two main forces are the prevalence of resistance genes (which give rise to proteins that shield bacteria from an antibiotic's effects) and the extent of antibiotic use. And frequently, bacteria will gain a defense against an antibiotic by taking up resistance genes from other bacterial cells in the vicinity. Indeed, the exchange of genes is so pervasive that the entire bacterial world can be thought of as one huge multicellular organism in which the cells interchange their genes with ease. In a regrettable twist of fate for human beings, many bacteria play host to specialised transposons, termed integrons that are like flypaper in their propensity for capturing new genes. These integrons can consist of several different resistance genes, which are passed to other bacteria as whole regiments of antibiotic-defying guerrillas.

How antibiotics promote resistance?

The selection process is fairly straightforward. When an antibiotic attacks a group of bacteria, cells that are highly susceptible to the medicine will die. But cells that have some resistance from the start, or that acquire it later (through mutation or gene exchange), may survive, especially if too little drug is given to overwhelm the cells that are present. Those cells, facing reduced competition from susceptible bacteria, will then go on to proliferate. When confronted with an antibiotic, the most resistant cells in a group will inevitably outcompete all others. Promoting resistance in known pathogens is not the only self-defeating activity of antibiotics. When the medicines attack disease-causing bacteria, they also affect benign bacteria--innocent bystanders-in their path. They eliminate drug-susceptible bystanders that could otherwise limit the expansion of pathogens, and they simultaneously encourage the growth of resistant bystanders. Propagation of these resistant, nonpathogenic bacteria increases the reservoir of resistance traits in the bacterial population as a whole and raises the odds that such traits will spread to pathogens. In addition, sometimes the growing populations of bystanders themselves become agents of disease. Widespread use of cephalosporin antibiotics, for example, has promoted the proliferation of the once benign intestinal bacterium *Enterococcus faecalis*, which is naturally resistant to those drugs. The ever increasing volume of international travel has hastened transfer of antibiotic resistance, that emerges in one place can often spread far and wide [2]. Researchers at the Centers for Disease Control and Prevention have estimated that some 50 million of the 150 million outpatient prescriptions for antibiotics every year are unneeded. In the developing world, antibiotic use is even less controlled. Many of the same drugs marketed in the industrial nations are available over the counter. Unfortunately, when resistance

becomes a clinical problem, those countries, which often do not have access to expensive drugs, may have no substitutes available.

The growing challenge of antimicrobial resistance - need to comtemplate!

It is clear that bacteria will continue to develop resistance to currently available antibacterial drugs by either new mutations or the exchange of genetic information. Absence of appropriate legislation or its enforcement may result in the proliferation where untrained or poorly trained persons dispense antimicrobials, leading to overuse and inappropriate use. Using the appropriate drug at the appropriate dosage and for the appropriate duration is one important means of reducing the selective pressure that helps resistant organisms emerge. If an infection is addressed in a comprehensive and timely manner, resistance can be contained. Optimal use of existing antimicrobial agents, using alternative treatment options (where possible), reducing the need for antimicrobials by increasing immunity, reducing the use of antimicrobials without providing an alternative form of treatment through education of health professionals and patients, antibiotic policies implementation of infection control measures (e.g., hand washing, screening and isolation) are the strategies aimed at prevention of emergence and spread of antibiotic resistance. Advertising and promotion can also be used to improve the appropriate use of antibiotics. Microbiologic culture-based or targeted antibiotic therapy is an important factor in decreasing inappropriate antibiotic usage. Using the most cost-effective antibiotic with the least resistance-inducing capacity, combination therapies and vaccination are of critical importance.

Historically, several approaches to antibiotic prescribing have been employed to address antimicrobial resistance. One approach is to use a newer more potent antimicrobial in settings where resistance has emerged to an older agent. Another approach to combating resistance is to continue using older agents as first line choices, in preference to newer, more potent drugs, in an effort to preserve the activity of the new drugs. Efforts to overcome bacterial resistance range from judicious and rationale use of antibiotics, effective hospital infection control programme and research in the field related to development of newer antibiotics. The use of antibiotics in the community can be restricted by implementing laws to stop over the counter sale of antibiotics. Another approach is to use a combination therapy.

On World Health Day 2011, WHO is urging intensified global commitment to safeguard antibiotics for preventing and controlling infectious diseases as well as for future generations. Growing resistance in microbes to antibiotics threatens the continued effectiveness of many medicines. WHO has therefore made antimicrobial resistance the theme of this year's World Health Day. The WHO defines appropriate use of antibiotics as "the cost-effective use of antibiotics, which maximises clinical therapeutic effect while minimising both drug-related toxicity and the development of antibiotic resistance" [3]. "No action today means no cure tomorrow". At a time of multiple calamities in the world, we cannot allow the loss of essential medicines – essential cures for many millions of people – to become the next global crisis.

On this World Health Day, WHO is issuing a policy package to get everyone, especially governments and their drug regulatory systems, on the right track, with the right measures, quickly-

1. Promote national coordination.
2. Strengthen the surveillance of antibiotic resistance.
3. Promote the rational use of antibiotics, including surveillance of antibiotic consumption.
4. Improve infection control and the stewardship of antibiotic use in health care settings.
5. Promote the surveillance, prevention and control of antibiotic resistance in the food chain.
6. Promote research and innovation on new antibiotics.
7. Improve awareness on antibiotic use and the risk of increasing resistance.

How healthcare providers can help?

Healthcare providers can address antimicrobial resistance and have a tremendous impact on protecting patients. There are several steps healthcare providers can take to prevent drug-resistant germs from infecting their patients or

being spread in their healthcare facilities.

- Ensure prompt diagnosis of antimicrobial-resistant infections.
- Provide appropriate and early treatment.
  - Be a good steward of antimicrobials.
  - Make sure all orders have a dose, duration, and indication.
  - Include laboratory cultures when placing an order.
- Take an "antimicrobial time out", reassessing therapy after 48-72 hours.
- Prevention is the key.

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