

SEMINAR ON THE GLOBAL THREAT OF ANTIBIOTIC RESISTANCE:

Exploring Roads towards Concerted Action

The Dag Hammarskjöld Foundation in collaboration with Swedish Strategic Programme for The Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA) and Division of International Health (IHCAR) at the Karolinska Institutet.

THE MISUSE OF THE MIRACLE

Among several alarming global public health problems with the potential to rapidly reach disastrous levels, resistance to antibiotics seems to be one of the most serious. Figures from urban areas of China and some countries in Latin America, where overuse has placed ‘a ticking bomb’, are alarming. At the same time, the lack of essential drugs in rural areas creates different but equally serious problems. The situation in industrialised countries is as complex with escalating resistance and a shrinking interest in investing resources in new antibiotics.

This paradox – the worldwide increase of resistant biologically fit bacteria and, simultaneously, the downward trend in developing new drugs – has fatal implications. Incentives for the pharmaceutical industry to invest are declining along with the disturbing fact that multiresistant bacteria consistently find ways to disarm any new antibiotic agent. Increased public awareness of the need for appropriate use and the higher costs associated with accelerating demands of regulatory bodies are driving the industry into other pharmaceutical areas where the returns on investment are safer.

There is an evident need for a wider, international response to overcome the inertia that surrounds the issue of antibiotic resistance. Strategies for containment of antimicrobial resistance are there, but the translation into concrete policy action is missing.

“I did glimpse the disappearance of the chambers of horrors which seems to be the best way to describe those old septic wards and could see that we should never again have to fear the streptococcus and the more deadly staphylococcus”

(C Fletcher. 1984. First clinical use of penicillin, British Medical Journal 289: 1721-1723)

Alexander Fleming’s accidental discovery of penicillin in 1928 was a sensation and became one of the major therapeutical advances in the history of medicine. When the availability of penicillin increased after World War II, one could rapidly see the enormous benefits in the management of critical medical conditions that earlier were considered as untreatable.

A new world opened. Researchers started to screen biological compounds for antibiotic activity and came up with new substances. Drugs with different modes of antibacterial action were developed and led to new and wider indications in clinical practice. The use of antibiotics increased explosively and the economic benefits were obvious when many infections could be treated with pills distributed in outpatient clinics instead of long hospital stays with often serious outcomes. In the late 1970s the development of new classes of antibiotics diminished and, instead, the focus of research moved to the refining of already existing products. A universal optimism prevailed and some scientists solemnly declared that the war against bacteria was over.

“We may look back at the antibiotic era as just a passing phase in the history of medicine, an era when a great natural resource was squandered, and the bugs proved smarter than the scientists”

(G Cannon. 1995. Superbug. Nature's Revenge. London: Virgin Publishing.)

Nothing lasts forever. Fleming himself had observed that some strains of *Staphylococcus aureus* were unresponsive to penicillin and statistics from British hospitals in the late 1940s indicated that the prevalence of resistant *Staphylococcus aureus* was around 50 percent after less than a decade in practice. A superb example of biological evolution had begun. Bacterial strains with natural and acquired resistance were selected through the use of antibiotics. Besides this, it was discovered that mechanisms of resistance could be spread horizontally between different strains and different organisms and, consequently, clones with multiresistant qualities could develop. This sophisticated way of spreading DNA between microbes has shaped multiresistant bacteria with successful properties for transmission into the community.

The subsequent production of new antibiotics to meet the escalating demands of multiresistant bacteria has, in a sense, only increased the problem, and the continuing accumulation of resistance mechanisms appears hard to reverse. Recent findings indicate an increasing level of biologically fit resistant bacteria in the community with no decrease in vitality compared to non-resistant strains. Thus, even in environments where antibiotic pressure is absent, these bacteria will be difficult to remove.

The global ecological consequences of large-scale consumption of antibiotics are basically still unknown. The use of antibacterial drugs, in human- and veterinary medicine, live-stock production and agriculture is altering the balance where microorganisms have coexisted for millions of years. Antibiotic compounds can currently be detected in liquid waste at animal feedlots as well as in ground water supplies and, accordingly, ecological niches outside the health care sector are affected and changing as bacteria, susceptible to antibiotics, are replaced by non-susceptible.

All major antibiotics have been confronted with the evolution of resistance within a certain time after being put on

the market and the short life expectancy of antibacterial drugs is one of the reasons why the development of new products is decelerating. The flat global market is another one. Antibiotics are given as short courses of treatment and the current emphasis is on less use. Other areas have bigger markets and the industry's investment is shifting from therapy for acute conditions towards long-term treatment of chronic diseases. There are also the high demands from regulatory bodies, which increase the development cost of new products.

Today, the introduction of new antibiotics is lagging behind the emergence of resistance, which increases the risk of serious health implications. In some cases there are practically no alternatives when it comes to treatment of severe infections caused by certain strains of multiresistant bacteria. Older antibiotics with severe toxic side effects, that earlier were rejected for clinical purposes, are now reintroduced to treat these infections.

Many of the developments in modern medicine have been achieved under the umbrella of antibiotic efficacy. With high-risk patients – such as those having cytostatic therapy for cancer, transplantation surgery, or implantation of prostheses – treatment to prevent infections and to deal with complications is essential. Other susceptible groups who depend on effective antibiotics are neonatal babies with undeveloped immune defence and immuno-compromised patients, such as those with HIV/AIDS. The emergence of antibiotic resistance is thus threatening our chances of successfully treating these particularly vulnerable groups.

HOW DID WE END UP HERE?

The global trend shows increasing mortality in infectious diseases, which accounts for around 20 percent of the total deaths. According to the World Health Report 2003, respiratory infections are the leading cause in this group, with nearly four million deaths annually followed by HIV/AIDS and diarrhoeal diseases. These cases occur mainly in the developing world and are traditionally regarded as deaths that could be prevented with access to health care and drugs. But are these deaths still preventable? Has the one-sided use of antibiotics led to resistant bacteria that already affect mortality globally?

“...whenever I get these symptoms and go to a doctor, he gives me the same medicine and charges me 10 rupees. So why not just buy the medicine?”

(Dua V. et al. 1994. The use of antimicrobial drugs in Nagpur, India: A window on medical care in a developing country. *Social science and Medicine*, 38, 5, 717-724)

The factors affecting the overuse of antibiotics are many and complex. Individual advantages that health care personnel, drug distributors and patients obtain from excessive use of antibiotics have to be confronted and considered in a public perspective. Obviously, this is an intricate task in a society that is becoming increasingly individualistic. To demand that people should restrict their use of antibiotics in favour of the public good is difficult, perhaps even unrealistic. Around 80 percent of antibiotic prescription is taking place in the community and it is estimated that at least half of this is based on incorrect indications, i.e. viral infections. Cultural aspects, the level of knowledge, and perceived patient demands are some of the determinants affecting the prescriber's decision. Economic incentives may promote irrational prescribing. Among them are the dual roles of the physician, as doctor and pharmacist; the fear of losing customers if a fast cure is not delivered; and promotion by the industry.

Consumer behaviour has a major impact on irrational use. Self-medication with antibiotics is common in most parts of the world. A person's decision to self-medicate can be influenced by various factors including poverty and restricted access to health care. Often people consult the doctor only after several treatments advised by community members or pharmacists have failed. The quality of the drugs and how they are distributed, legislative measures to deal with pharmaceuticals and the influence of the industry at all levels are other fundamental factors that need to be considered.

THE SILENT EPIDEMIC –WHAT CAN BE DONE?

Multiresistant bacteria are accumulating all over the world, affecting the severity of infections and resulting in longer hospital stays and higher mortality. The problem is not limited to hospital wards, where the antibiotic pressure is higher. Bacterial strains are also emerging in the community and the rapid patient flux creates a two-way transmission process, spreading new mechanisms of resistance in the

society. Neither is resistance an isolated Western phenomenon although it is easier to detect in the developed world because of the greater access to surveillance facilities. Resistance that develops in one region may easily spread nationwide. Increased migration widens the range for infectious diseases. Pathogens are spreading across international, cultural and ethnic boundaries, creating a 'global genome'.

The global consequences of bacterial resistance are there, just around the corner. The deceitful invisibility of the problem makes it difficult to attack and to place on the global agenda. Is it necessary to depict scenarios of international catastrophe such as HIV/AIDS and epidemics such as SARS to provoke decision-makers to act? Is there a need for a prophecy of doom to break down this state of complacency? An immediate call for short- and long-term strategies is required to contain the development of antibiotic resistance and to prevent a gap where no effective antibiotics are available for treatment. Rational use may prolong the 'expiry date' of already existing drugs and slows down the transmission and emergence of resistance. Re-evaluation of older products could possibly contribute to temporary solutions in clinical practice. However, to meet the urgent demands, concrete incentives for the development of new antibacterial drugs with novel mechanisms of action are essential. These mentioned strategies may seem incompatible since private interests, in many respects, diverge from the public ones.

Who are interested in a change? Who are willing to lead the way through system failures of politics, regulatory obstacles and market interest? And finally, can we do anything about it? Efforts on the part of all stakeholders are required so as to break the current paralysis and look into the matter in a broader societal context. Questions of social responsibility must be raised. We have to think in unconventional ways and create alliances between public and private stakeholders who can cross system boundaries. We have to move forward to find a global solution to the silent epidemic!

Fleming kept his discovery of penicillin in a drawer for many years before it was further developed for therapeutical purposes by Florey and Chain. Was the miracle meant to be kept there?