*Journal of Advances in Science and Technology*

*Vol. V, Issue No. X, August-2013, ISSN 2230-9659*

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AN INTERNATIONALLY INDEXED PEER REVIEWED & REFEREED JOURNAL

www.ignited.in

*Journal of Advances in Science and Technology*
*Vol. V, Issue No. X, August-2013, ISSN 2230-9659*

# A Comparative Study on Challenges and Strategies of Antibiotic Resistance: The Requirement for World Wide Solutions

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***Abstract – The causes of antibiotic resistance are complex and include human behaviour at many levels of society; the consequences affect everybody in the world. Similarities with climate change are evident. Many efforts have been made to describe the many different facets of antibiotic resistance and the interventions needed to meet the challenge. However, coordinated action is largely absent, especially at the political level, both nationally and internationally. Antibiotics paved the way for unprecedented medical and societal developments, and are today indispensable in all health systems. Achievements in modern medicine, such as major surgery, organ transplantation, treatment of preterm babies, and cancer chemotherapy, which we today take for granted, would not be possible without access to effective treatment for bacterial infections. Within just a few years, we might be faced with dire setbacks, medically, socially, and economically, unless real and unprecedented global coordinated actions are immediately taken. Here, we describe the global situation of antibiotic resistance, its major causes and consequences, and identify key areas in which action is urgently needed.***

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## INTRODUCTION

Last year an event doctors had been fearing finally occurred. In three geographically separate patients, an often deadly bacterium, *Staphylococcus aureus,* responded poorly to a once reliable antidote—the antibiotic vancomycin. Fortunately, in those patients, the staph microbe remained susceptible to other drugs and was eradicated. But the appearance of *S. aureus* not readily cleared by vancomycin foreshadows trouble. Worldwide, many strains of *S. 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. *S.* acquired infections, has thus moved one step closer to becoming an unstoppable killer.

The looming threat of incurable *S.aureus* is just the latest twist in an international public health nightmare: increasing bacterial resistance to many antibiotics that once cured bacterial diseases readily. 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.

One component of the solution is recognizing that bacteria are a natural, and needed, part of life. Bacteria, which are microscopic, single-cell entities, abound on inanimate surfaces and on parts of the body that make contact with the outer world, including the skin, the mucous membranes and the lining of the intestinal tract. Most live blamelessly. In fact, they often protect us from disease, because they compete with, and thus limit the proliferation of, pathogenic bacteria—the minority of species that can multiply aggressively (into the millions) and damage tissues or otherwise cause illness. The benign competitors can be important allies in the fight against antibiotic-resistant pathogens.

Antibiotic resistance is a form of drug resistance whereby some (or, less commonly, all) sub-populations of a microorganism, usually a bacterial species, are able to survive exposure to one or more antibiotics. Accordingly, pathogenic species which have become resistant cause infections which cannot be treated with the usual, formerly efficacious antibiotic drugs and/or their usual, formerly efficacious, dosages and concentrations. Resistance may be intrinsic/primary (transmitted from another person) or acquired (where bacteria develop spontaneous mutations). Some clinically relevant pathogens have developed resistance to multiple antibiotics and are dubbed multidrug resistant (MDR pathogens). More recently, the colloquial term superbug has become widespread in both popular and technical accounts of the phenomenon with which it is synonymous.

## DESIGN FOR CREATION OF A NATIONAL SURVEILLANCE SYSTEM FOR ANTIMICROBIAL RESISTANCE

Antimicrobial resistance in pathogens causing important infectious diseases is a matter of great public health concern globally, as well as in India. A major factor responsible for this is the widespread use and availability of practically all antimicrobials over the counter for human as well as animal consumption.

Though, there are definite policies / standard treatment guidelines for appropriate use of antimicrobials in specific national health programmes e. g. RNTCP (Revised National Tuberculosis Control Programme), NACP (National AIDS Control Programme), NVBDCP (National Vector Borne Disease Control Programme), the same are not available for other diseases of public health importance like enteric fever, diarrhoea / dysentery, pneumonia, etc.

Three types of surveillance can be done for AMR - Comprehensive surveillance, sentinel surveillance and point prevalence studies. Comprehensive AMR surveillance though giving actual estimate of AMR burden, includes the study of the whole population at risk / under study and needs the involvement of a large number of laboratories which is not practical specially in our country. Point prevalence studies are useful for validation of the representativeness of the surveillance data. Sentinel surveillance studies have been found to be quite useful in such situations.

Following bacterial pathogens isolated from different human infections / anatomical sites e.g. Blood stream infections, Skin and Soft tissue and surgical site infections, Respiratory infections, Gastro intestinal tract infections and Urinary Tract Infections (UTI) may be included in a phased manner for the purpose of AMR surveillance.

**First phase (Non fastidious bacterial pathogens)**

1. Following Gram Negative Bacilli (should address Extended Spectrum β - lactamases [ESBLs] and Metallo β -lactamases [MBLs], including NDM-1) may be included.

- Pseudomonas aeruginosa
- Acinetobacter spps
- Klebsiella pneumoniae
- *Esch. coli*

2. Staphylococcus aureus (should address Methicillin Resistant *Staph aureus* - MRSA) Second phase in addition to the above the following organism surveillance will be added:

- Enterococci specially VRE (Vancomycin Resistant Enterococci)
- Salmonella , Shigella sp and *Vibrio cholerae*
- *Streptococcus pneumoniae*, and *H. influenza*

New and simple surveillance tools with the capability to detect AMR at the lowest capable health centre should be developed and its ability to track the infection should be established. All surveillance activities should be linked with epidemiological studies particularly surveillance around relevant vaccination programs. A National Health Policy Unit should be entrusted with analysis of the surveillance data and provide advisory for framing of policies for use of antibiotics according to region, nation or hotspots.

## ANTIBIOTIC USE IS OUT OF CONTROL

For those who understand that antibiotic delivery selects for resistance, it is not surprising that the international community currently faces a major public health crisis. Antibiotic use (and misuse) has soared since the first commercial versions were introduced and now includes many nonmedicinal applications. In 1954 two million pounds were produced in the U.S.; today the figure exceeds 50 million pounds.

Human treatment accounts for roughly half the antibiotics consumed every year in the U.S. Perhaps only half that use is appropriate, meant to cure bacterial infections and administered correctly— in ways that do not strongly encourage resistance. Notably, many physicians acquiesce to misguided patients who demand antibiotics to treat colds and other viral infections that cannot be cured by the drugs. 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. At a seminar I conducted, more than 80 percent of the physicians present admitted to having written antibiotic prescriptions on demand against their better judgment.

The same drugs prescribed for human therapy are widely exploited in animal husbandry and agriculture. More than 40 percent of the antibiotics manufactured in the U.S. are given to animals. Some of that amount goes to treating or preventing infection, but the lion's share is mixed into feed to promote growth. In this last application, amounts too small to combat infection are delivered for weeks or months at a time. No one is entirely sure how the drugs support growth. Clearly, though, this long-term exposure to low doses is the perfect formula for selecting increasing numbers of resistant bacteria in the treated animals— which may then pass the microbes to caretakers and, more broadly, to people who prepare and consume undercooked meat.

## ANTIBIOTIC RESISTANCE AND ITS IMPACT ON PERSON

For more than half a century, antibiotic drugs have ensured that potentially life-threatening bacterial infections are treatable. Today, however, more and more bacterial infections fail to respond to antibiotic treatment. A federal task force recently warned that antibiotic resistance is “a growing menace to all people” and concluded that if nothing is done, treatments for common infections will become “increasingly limited and expensive-and, in some cases, nonexistent.”

Antibiotic resistance poses a threat to everyone, but people with diabetes are at particular risk. Diabetes has become an epidemic illness in the United States affecting approximately 16 million people. It is now the seventh leading cause of mortality in this country, causing nearly 200,000 deaths annually. It is an illness that can be treated, but not cured.

Antibiotic resistance carries a significant economic toll as well as a medical one. The congressional Office of Technology Assessment calculated that resistance in just six types of bacteria increased hospital treatment costs by $1.3 billion as of 1995. Few new drugs are now in the pipeline, and any new antibiotics will be considerably more expensive than existing ones; research and development costs for a new drug may top $800 million, by some estimates, while prescription costs are likely to far exceed those for older, generic medicines.

The Centers for Disease Control and Prevention has observed that “decreasing inappropriate antibiotic use is the best way to control resistance.” Key steps in doing so include adoption of policies aimed at ending the inappropriate use of antibiotics in agriculture, as well as continued implementation of programs to educate patients, parents and physicians about the need to use antibiotics more sparingly.

## ESTABLISHED MECHANISMS OF ANTIBIOTIC RESISTANCE

For an antibiotic to be effective, it must reach the target site in an active form, bind to the target, and interfere with its function. Thus, bacterial resistance to an antimicrobial agent can occur due to three general mechanisms:

The drug does not reach its target - In Gram negative bacteria, many antibiotics enter the cell through protein channels called porins. Mutations or loss of these channels can prevent/slow the rate of antibiotic entry into a cell, effectively reducing drug concentration at the target site. If the drug target is intracellular and the drug requires active transport across the cell membrane, a mutation that interferes with the transport mechanism can confer resistance e.g. aminoglycosides. Bacteria can also transport antimicrobial drugs out of the cell through efflux pumps. Resistance to numerous drugs, including fluoroquinolones, macrolides, tetracyclines and beta lactam antibiotics, is mediated by this mechanism.

The drug is inactivated - Bacterial resistance to aminoglycosides can be due to a plasmid encoded aminoglycoside-modifying enzymes. Similarly, β-lactamase production is the most common mechanism of resistance to penicillins and other β-lactam drugs. Many hundreds of different β-lactamases have now been identified. A variation of this mechanism is failure of the bacterial cell to activate a prodrug e.g. loss of ability of M. tuberculosis to activate isoniazid (INH).

The target site is altered - This may be due to mutations in drug binding region of target enzyme e.g. fluoroquinolones, target modification e.g. ribosomal protection type of resistance to macrolides and acquirement of a resistant form of the susceptible target e.g., methicillin resistance in Staphylococcus Spp. due to production of a low-affinity penicillin-binding protein (PBP).

Strategies to prevent ABR in healthcare settings - Prudent antibiotic use: Antibiotics should be used only when they improve patient outcome. Not all infections need anti-biotic treatment e.g. in patients with sore throat, benefit from antimicrobial therapy is small and is counterbalanced by the risk of adverse events like rash. Narrow spectrum agents should be used whenever possible. Broad spectrum agents should not be used as a cover for lack of diagnostic precision. Antibiotics should be prescribed in optimal doses, regimens, and should be stopped when the infection is treated. Restrict the use of last line antibiotics for serious infections and only when simpler agents are likely to be ineffective. Whenever used for prophylaxis, antibiotics should be used for short courses and at appropriate times (e.g. during surgical prophylaxis, antibiotics should be given within an hour prior to incision).

Prevention of infection: Use of antimicrobials can also be reduced if infections are prevented in the first place. This can be achieved by improved use of vaccines and improved hygiene and infection control practices like compliance with hand washing protocols and aseptic techniques for catheterization. Catheters and drains should be removed when no longer needed.

## USES OF HUMAN AND AGRICULTURAL ANTIBIOTICS ARE INCREASING

Antibiotic use is a main driver of selection pressure that contributes to resistance, and because consumers do not understand this problem, the drugs are among the world's most commonly purchased. Most antibiotics are used unnecessarily, in commercially driven agriculture, and by physicians uncertain of a diagnosis or treating largely self-limiting bacterial or viral infections. In high-income countries, patients with resistant infections can turn to more expensive, newer-generation antibiotics, but in developing countries, where infectious diseases are common and the burden is high, patients might be unable to obtain or to afford second-line treatments.

Worldwide, antibiotic consumption is on the rise (figure 1). Although carbapenems are expensive, sales in Egypt, India, and Pakistan have increased with over-thecounter availability. Non-prescription antibiotic use is common in many LMICs, where ensuring that people who truly need antibiotics have access while discouraging unnecessary use is a challenge. Non-prescription use accounts for 19–100% of antibiotic use outside northern Europe and North America.61 Even when prescriptions are needed to obtain antibiotics, physicians might not adequately screen for appropriate use.

## CONCLUSIONS

It is imperative that all the clinicians understand the principles and standard methods of antibiotic susceptibility tests. They should also insist on the laboratory to follow these recommended procedures to generate antibiotic susceptibility test reports that are quality assured. Antimicrobial susceptibility data generated based on consistent reproducible and comparable data between different laboratories will produce better outcomes and help in developing region-wise antibiograms. All the tertiary care hospitals (public or private) need to develop their SOP's and guidelines as per the national guidelines and implement in their setting. The guidelines in the hospital to be reviewed every 6 months; national guidelines to be reviewed on yearly basis.

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