01 ANTIBIOTIC RESISTANCE

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ANTIBIOTIC RESISTANCE

Antibiotic resistance (ABR) refers to the resistance to antibiotics that occurs in bacteria that cause infections. The resistant bacteria can withstand the effect of the antibacterial drug (antibiotic) to make it ineffective. Antimicrobial resistance (AMR) on the other hand is a broader term, encompassing resistance to drugs to treat infections caused by other microbes as well, such as parasites, viruses and fungi.[1]

IMPACT OF ABR

Emergence and spread of ABR is a global concern. It is no longer a future prediction. Across the world, increasing number of bacteria are becoming resistant to growing number of antibiotics. Common infections such as of the urinary tract, respiratory tract and gut are becoming difficult or sometimes impossible to treat leading to prolonged recovery, increased length of hospital stay, more deaths, higher cost of treatment and greater spread of infection and resistance.[2,3]

Antibiotics that were originally effective against a particular bacteria are becoming ineffective. Drugs of choice are being replaced by second line of drugs which are expensive and have greater side effects. The situation is grave, as there are no new class of antibiotics developed since late 1980s. The antibacterial drug pipeline is near-empty, particularly for gram-negative bacteria such as *Escherichia coli* and *Klebsiella* that cause common infections such as respiratory and urinary tract infections and are becoming resistant.[4]

If existing antibiotics are not preserved and antibiotic discovery void continues, the achieved gains of modern medicine are at brink. Treatment options such as cancer chemotherapy and organ transplantation and post-surgery outcomes would fail or turn into high-risk procedures. As per the World Health Organization (WHO), a 'post-antibiotic era' — in which common infections and minor injuries can kill a person is a very real possibility for the 21st century.[5]

HEALTH AND ECONOMIC BURDEN OF ABR

There is a need to better understand the burden of ABR on health and economy. In the US, at least 2 million illnesses and 23,000 deaths per year are caused by antibiotic resistance.[6] Direct annual healthcare cost is estimated to be as high as USD 20 billion with additional productivity losses of up to USD 35 billion.[7] In the European Union (EU), resistant bacteria are estimated to result in about 25,000 deaths per year and EUR 1.5 billion of healthcare and productivity losses.[8]

In India, out of the two lakh children that die in the first four weeks of their lives, about 30 percent are attributable to Methicillin-resistant *Staphylococcus aureus* (MRSA) and bacteria which produce extended spectrum beta-lactamases (ESBL).[9] As per the 2013 Global Tuberculosis Report of WHO, about 15 percent of those undergoing retreatment for tuberculosis in India are resistant to multiple drugs.[10]

HOW ABR DEVELOPS

ABR is strongly linked with antibiotic use, misuse and overuse in humans and animals. Use of antibiotics puts selective pressure – a natural process – on bacteria, making them resistant against the antibiotic used. Overuse and misuse of antibiotics accelerates the emergence and spread of ABR. Resistance develops due to mutations in bacteria – that cause certain changes –and makes the

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antibiotic ineffective. Bacteria also acquire resistance from genes responsible for resistance in other bacteria but are transferred through genetic material such as plasmids.[11]

The structural and chemical changes leading to resistance to an antibiotic include decreased bacterial cell wall permeability to the drug; alteration of the drug binding site at cell wall; induced chemical modification of the drug and normal function of bacteria bypassing the drug effected enzyme or pathway.[12]

ANTIBIOTIC USE AND ABR IN FOOD-PRODUCING ANIMALS; TRANSMISSION OF ABR TO HUMANS

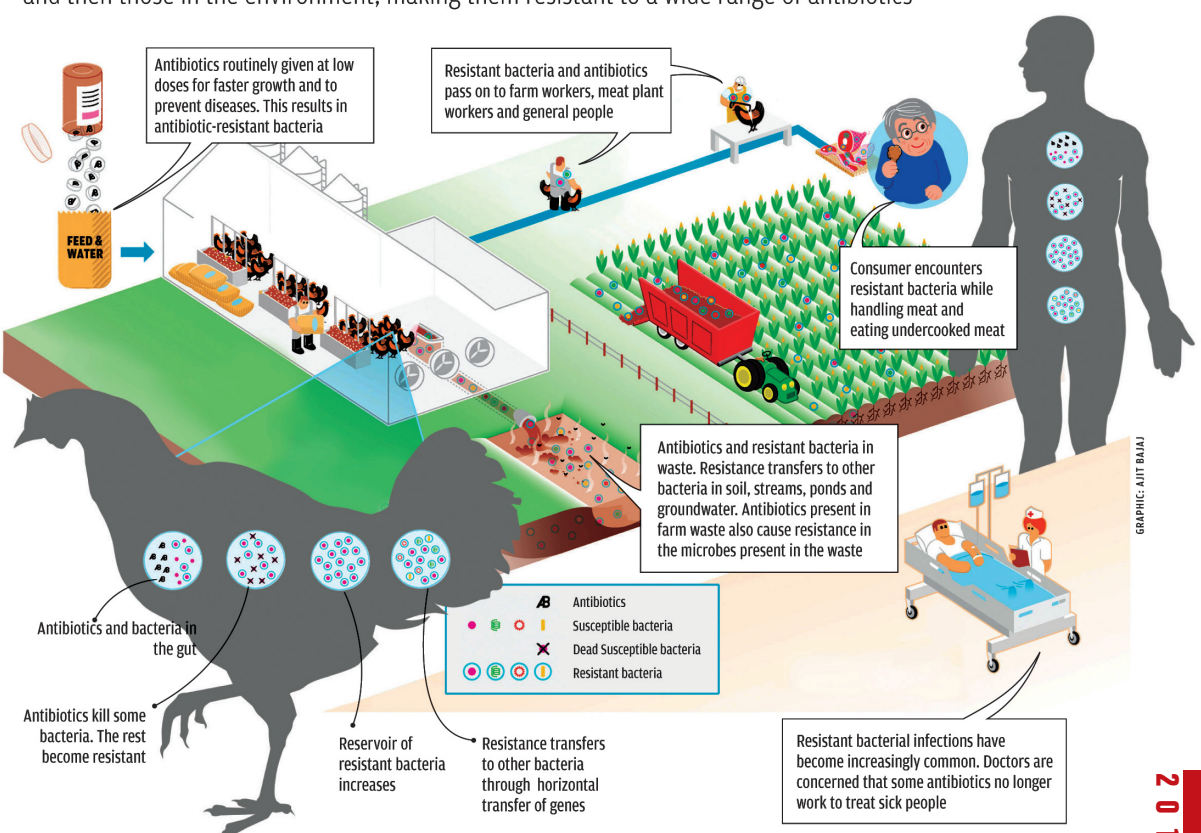
Low-doses of antibiotics used for longer duration in food-producing animals (such as meat or milk producing animals, poultry, fish or bees) favours emergence of resistant bacteria in animals.[13] Sub-optimum doses help step-wise selection of resistance. Such non-therapeutic use for reasons such as growth promotion is rampant across the world in intensive farming of food-producing animals such as poultry, pigs and fish.

Resistant bacteria proliferate and can make resistant other species of bacteria that are present in animals. Resistant bacteria can also be transfered to humans through several routes such as direct contact with live animals and carcass at poultry farms and slaughterhouses; human consumption of meat and food with resistant bacteria; and environmental contamination of soil, water and air through animal excreta (see Fig 1: *Smart moves of a deadly microbe*).

Antibiotic residues entering into humans through consumption of food with residues left may also be a cause for selective pressure in bacteria present in humans and lead to resistance generation.

Fig 1: Smart moves of a deadly microbe

As a microbe becomes resistant, it influences other microbes present in the gut of the chicken and then those in the environment, making them resistant to a wide range of antibiotics



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STRONG INTER-LINKAGES BETWEEN ABR IN ANIMALS AND IN HUMAN

Transmission of resistant bacteria from animals to humans is known as a key contributor to the increased ABR in humans.[14] There are several common classes of antibiotics that are used in animals and in humans such as fluoroquinolones, beta-lactams (such as penicillins and cephalosporins whose action can be prevented by an enzyme called beta-lactamase). At times even the antibiotics used are the same. This leads to an increased risk of emergence and spread of resistant bacteria, including those capable of causing infections in both animals and humans. Resistance against one antibiotic in animals can also cause onset of resistance against another but similar antibiotic of same class in humans. Bacteria such as *Salmonella, Campylobacter, Escherichia coli* and *Enterococci* are known to be commonly associated with resistance due to intensive use of antibiotics in animal farming.

GLOBAL PREVALENCE OF ABR

While the use of antibiotics is the single most important factor leading to ABR around the world, its spread is facilitated by global movement of people, animals, food and disease transmission. The WHO in its first such report, 'Antimicrobial Resistance, Global Report on Surveillance, 2014' observes very high rates of resistance in certain bacteria across the world (see Table 1).[15] These bacteria are causing some of the most common infections in the community, in hospitals or those transmitted through the food chain. The situation in India is similar or even worse in some cases.

In India, fluoroquinolones and cephalosporins are commonly used to treat highly prevalent infections of the urinary tract, blood stream, respiratory tract and other food borne infections. Resistance to these limits the treatment options and increases the cost of it. A large number of people are suffering from tuberculosis, a disease which has a potential to be resistant to multiple drugs.

Table 1: Antibiotic resistance in most common bacteria of concern

	Examples of typical Diseases	No. of WHO regions (out of six) with national reports of 50% resistance or more	India (% resistance/ non susceptibility)
Bacteria commonly causing infections in hospitals and in the community			
Escherichia coli: vs 3rd-generation cephalosporins	Urinary tract infections; Blood stream infections	Five	16–95
Escherichia coli: vs fluoroquinolones		Five	4–86.4
Klebsiella pneumoniae: vs 3rd-generation cephalosporins	Pneumonia; Urinary tract infections; Blood stream infections	Six	5–100
Klebsiella pneumoniae: vs carbapenems		Two	0–55
Bacteria commonly causing infections in the community			
S. aureus: vs methicillin 'MRSA'	Wound infections; Blood stream infections	Five	4.2–80.6
Streptococcus pneumoniae: vs penicillin (non-susceptibility or resistance)	Pneumonia; Meningitis; Otitis	Six	5.6 (one publication only)
Nontyphoidal Salmonella (NTS): vs fluorquinolones	Foodborne diarrhoea; Blood stream infections	Three	Not Available
Shigella: vs fluoroquinolones	Diarrhoea ("bacillary dysenteria")	Two	0–82
Neisseria gonorrhoeae: vs 3rd generation cephalosporins (decreased susceptibility)	Gonorrhoea	Three	3.9 (one publication only)

Source: *WHO, Antimicrobial resistance: global report on surveillance 2014*
Note: WHO regions: African Region, Region of the Americas, Eastern Mediterranean Region, European Region, South-East Asia Region, Western Pacific Region. No National data is available for India. Figures are based on short-listed publications by the WHO; Indian figures for *Streptococcus pneumoniae* and *Neisseria gonorrhoeae* are obtained from only one study. They may not reflect the extent of resistance. Figures for NTS are not available. 3rd generation cephalosporins include ceftazidim, cefotaxim and ceftriaxone. Fluoroquinolones include ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, refloxacin or sparfloxacin. Carbapenems include imipenem, meropenem, doripenem or ertapenem.

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Global spread of resistant bacteria. Hospitals not the only source; found in environmental samples also

New Delhi metallo-beta-lactamase (NDM-1), is a lactamase which renders ß-lactam antibiotics ineffective. In 2008, NDM-1positive Enterobacteriaceae was found in Sweden from an Indian patient hospitalized previously in New Delhi.[16] Since then, bacteria producing NDM-1 have been identified in several countries across the world. In 2010, NDM-1 was found prevalent in multidrug-resistant Enterobacteriaceae in India, Pakistan, and the UK. Few cases have also been reported from the United States and Canada. As per recent findings, the Balkan states and the Middle East may act as secondary reservoirs of NDM-1 producing bacteria. In 2011, NDM-1 producing bacteria was also found in environmental samples in New Delhi.[17] This suggests that hospitals as earlier believed are not the only source of NDM-1, they are also now spread across the environment and NDM-1 infections can be acquired in the community.

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