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Antibiotic Resistance In India: A Looming Health Catastrophe

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Abstract:

This review article traces the historical evolution of antibiotics, from Selman Waksman's coining of the term in 1942 to the ground- breaking discovery of penicillin by Dr. Alexander Fleming in 1928. The three phases of chemotherapy, including empirical use and Paul Ehrlich's "magic bullet" concept, are explored. The modern era of chemotherapy is highlighted, emphasizing the different classes of antibiotics available today. The focus then shifts to the concerning phenomenon of irrational antibiotic use, with a detailed examination of factors contributing to antibiotic resistance. Inappropriate prescription practices, self-medication, extensive agricultural use, inaccurate diagnosis, and the emergence of natural and acquired resistance mechanisms are scrutinized. The article underlines the global challenge of antimicrobial resistance, especially in developing countries, and emphasizes the pivotal role of awareness and education. The article sheds light on the current scenario of antibiotic resistance in India, addressing specific resistance patterns among different bacterial strains. In conclusion, the article stresses the imminent antibiotic resistance crisis in India due to irrational use. It calls for a multi-faceted approach, including awareness campaigns, stricter regulations, improved healthcare infrastructure, and rational prescribing practices. The urgency of these actions is underscored, emphasizing that without concerted efforts, the future of healthcare in India is at risk, with potentially devastating consequences for public health. The importance of global collaboration and research investments is emphasized as key components in safeguarding effective antimicrobial agents for future generations.

Keywords: antibiotic, chemotherapy, irrational antibiotic use, antimicrobial resistance, bacterial strains.

Introduction –

The term antibiotics was first coined in 1942 by microbiologist Selman Waksman who discovered streptomycin and known as father of antibiotics. The modern era of antibiotics started in 1928 when Dr Alexander Fleming discover penicillin from the culture filtrate of a fungus, penicillium notatum. After Fleming two scientist Howard Walter Florey and Ernst Boris chain, became interested in his work on penicillin and elucidated the structure of penicillin G which was the first penicillin to be used in the treatment of bacterial infection in 1939 and scale up the production of antibiotic during World War II. Antibiotics are one of the most successful forms of the chemotherapy in the history of medicine(1–3). the history of chemotherapy can be divided into three phases –

1) the period of empirical use of traditional Plasters of mouldy bread being used to treat open injuries in Serbia, China, Greece and Egypt further than 2000 times ago(4). From ancient time mercury use by Paracelsus for syphilis, chaulmoogra oil use by the Hindus in leprosy, cinchona bark use for fever(5).
2) Paul Ehrlich's (1854-1915) coined the term 'chemotherapy' because he used chemicals for treatment of diseases: Ehrlich's idea of "magic bullet" chemical compound (Salvarsan 606) that targets only disease-causing microbes and no harm caused to the host was based on an observation that aniline and other synthetic dyes, which first became available at that time, could stain specific microbes but not others. This idea led him to begin a large-scale and systematic screening program in 1904 to find a drug against a sexually transmitted disease syphilis that was endemic and caused by the spirochete Treponema pallidium. Together with chemist Alfred Bertheim and bacteriologist Sahachiro Hata, they synthesized hundred's of organoarsenic derivatives of a highly toxic drug Atoxyl And tested them in syphilis-infected rabbits. He found that the arsenicals atoxyl useful in case of sleeping sickness and developed arsphenamine and neoarsphenamine in 1906-1909 for syphilis(3).
3) The modern era of chemotherapy : in 1935,The systematic screening approach introduced by Paul Ehrlich became the cornerstone of drug search strategies in the pharmaceutical industry and resulted in thousands of drugs identified and translated into clinical practice, including, of course, a variety of antimicrobial drugs During the earlier days of antibiotics Research, this approach led in 1935 by Domagk who demonstrated the therapeutic effect of protonsil a sulfonamide dye use in pyogenic infection. It was soon found out that the active moiety was para-amino benzene sulphonamide(5).

In present scenario, there are different type of antibiotics are existed in the market and they are classified on the basis of their chemical structure, pharmacological action and spectrum of activity. Antibiotics act on bacterial physiology and biochemistry by causing microbial cell death or inhibit the growth of the microorganisms. A significant number of antibiotics inhibit the cell wall synthesis (e.g., β-lactam and glycopeptides like penicillin, cephalosporin and bacitracin etc.), while other act by inhibiting protein synthesis via interactions with ribosomal subunits and these include antibiotics such as tetracycline, chloramphenicol, cyclosporine, erythromycin, clindamycin, linezolid. Other Antibiotics groups include drugs which either inhibit DNA gyrase or interfere with DNA function/synthesis (e.g., fluoroquinolones, rifampin, acyclovir and zidovudin), while some other exerts their effect by interfere with intermediary metabolism include sulfonamides, sulfones, metronidazole, trimethoprim, PAS, pyrimethamine(1).

Irrational use of antibiotics:

Due to availability of different type of antibiotics, the inappropriate use of antibiotics also increases which include the steady rise in antibiotic resistance. Sometime the bacteria are intrinsically resistant to certain type of antibiotics but can also acquire resistance via chromosomal gene mutation and horizontal gene transfer(6–8).

Now day's antibiotics have allowed the development of several fields of medical practice like effective result of surgical operations and several immunosuppressive therapies that rely on antibiotic prophylaxis, and the potential to prevent infectious complications, antimicrobial resistance presents a significant challenge to all healthcare systems worldwide(2).

Antimicrobial resistance is one of the major public health problems especially in developing countries where higher incidence of inappropriate/ irrational use of Antibiotics are happen due to easy availability and higher consumption of medicine on daily routine and shows greater levels of resistance compared to developed countries(9).

Antibiotic resistance is caused by irrational use of Antibiotics which may occur in variety of ways:

Inappropriate prescription of antibiotics

When doctors are not sure about the infection is caused by bacteria or virus, they may prescribe antibiotic as prophylaxis treatment. The antibiotic does not act on viral infection and may develop resistance.

Self medication

In India, Antibiotics are widely used without physicians' prescription. These may lead to improper drug usage which results into adverse drug reactions and development of drug resistance.

Extensive use in agriculture

Antibiotics are also used as growth supplements and growth promoters for animals, these result into appearance of antibiotic resistant bacteria. This resistance may readily spread to humans by food chains.

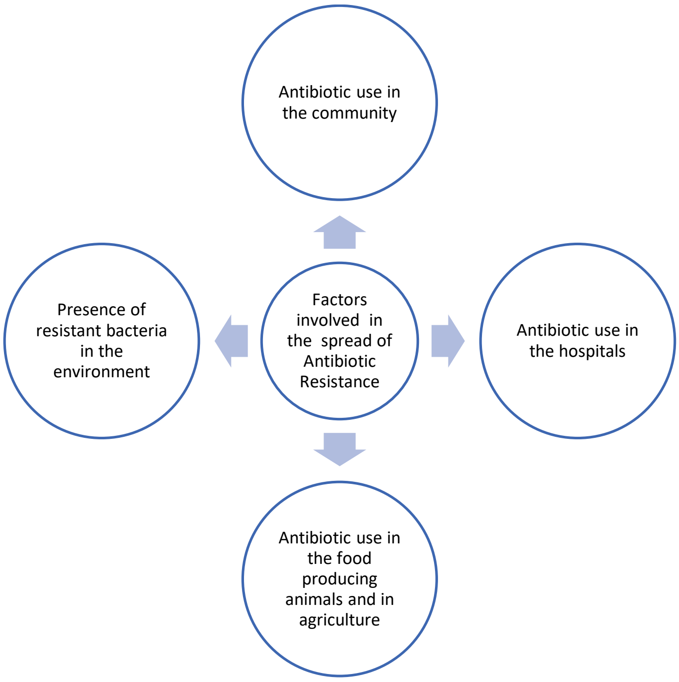
Inaccurate diagnosis

During diagnosis of an infection, the physician may rely on inaccurate knowledge and prescribe a broad-spectrum antibiotic when a particular narrow spectrum can be more appropriate and may led to development of resistance.

Antimicrobial agent act on particular target site or metabolic process, but in natural resistance the microbes lack the metabolic process or the target site which is affected by the drugs and shows resistance, e.g., Gram negative bacilli are normally resistant to penicillin G or Mycobacterium tuberculosis is not affected by tetracycline. Another type of resistance is acquired resistance, acquired resistance is the development of resistance by an organism (which was sensitive before) due to excessive use of an antimicrobial agent for a long time. Acquired resistance is major clinical problem in the world. Development of acquired resistance is dependent on the microorganisms and the drug. Some bacteria are well-known for rapid acquisition of resistance, E.g., Staphylococci, coliforms, tubercle bacilli(2).

Factors contributing to the emergence of antibiotic resistance:

Antimicrobial resistance refers to an unresponsiveness of a microorganism to an antimicrobial agent and show tolerance. India is among the countries having the highest burden of bacterial infections. Nowadays antimicrobial resistance become a major public health concern in India. There are many factors responsible for antibiotic resistance in which involves not only the overuse of Antibiotics but also the irrational uses like inadequate dosing, inappropriate choices, poor adherence to treatment guidelines. These are the contributing factors responsible for the increase of Antibiotics resistance(10,11).



The emergence of resistance is not only limited to the older people and more frequently used classes of drugs but there has also been a rapid increase in resistance to the newer and more expensive drugs, like carbapenems, which is worrisome. carbapenems are use when first- and second-line drugs options have failed and considered to be the last-resort antibiotics. The emergence of carbapenem resistance, particularly carbapenem resistant Enterobacteriaceae (CRE), has been a major concern in developed countries, especially in the hospital/health care setting. Although available data indicates only mild increase in carbapenem resistant isolates of E. coli from India (from 10% in 2008 to 13% in 2013), there has been a much larger increase in carbapenem resistant isolates of Klebsiella pneumoniae (from 29% in 2008 to 57% in 2014) and Acinetobacter baumanii(10).

There is rapidly increasing the proportion of isolates of Staphylococcus aureus bacteria that are resistant to methicillin. In 2008, the proportion of Methicillin-resistant staphylococcus aureus (MRSA) isolates was 29% and this had risen to 47% in 2014. The proportion of MRSA isolates has been decreasing in those countries who have established antimicrobial stewardship and infection prevention and control programmes 8. Neisseria gonorrhoeae isolates are resistant to ciprofloxacin. The emerging antibiotic resistance pattern in India is exemplified by the resistance profile of salmonella typhi isolates and resistance for fluoroquinolones has increased from 8% in 2008 to 28% in 2014. Compared to these antibiotics the resistance against older antibiotics is reducing (10).

In India extended spectrum beta-lactamase (ESBL) producing strains of Enteribacteriaceae have emerging as one of the most common resistances in hospitalised patients. In a multicentric study conducted in seven tertiary care hospitals in Indian cities, 61% of E. Coli were ESBL producers. In the same study, 31–51% Klebsiella species were carbapenem resistant, 65% Pseudomonas sp. were resistant to ceftazidime and 42% were resistant to imipenem. Acinetobacter species isolated from hospitalized patients in a tertiary care hospital in Delhi showed 57–80% resistance to imipenem/meropenem while 70% isolates were resistant to tigecycline(12,13).

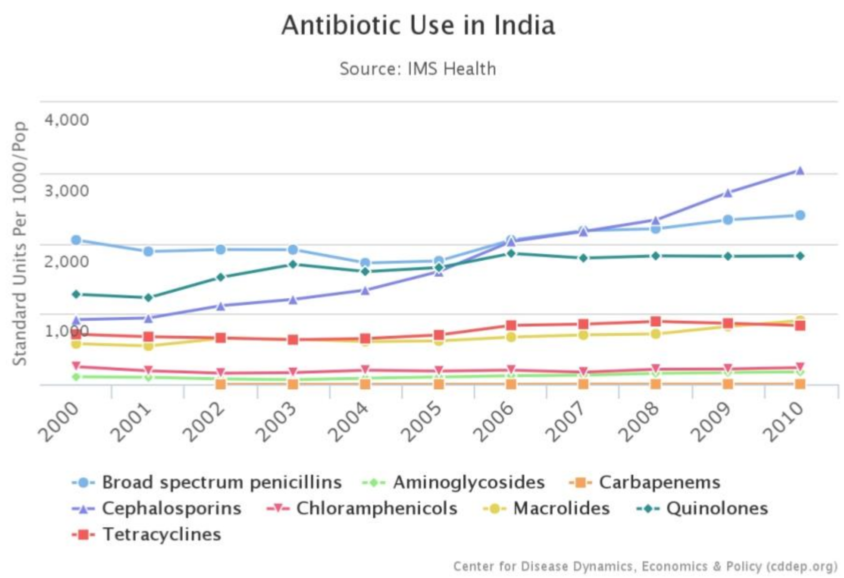
In a study conducted at 15 tertiary care centres on S. Aureus isolates, the Indian Network for Surveillance of Antimicrobial Resistance (INSAR) found MRSA prevalence rate of 41% which also showed a high rate of resistance to ciprofloxacin, gentamicin, cotrimoxazole, erythromycin, and clindamycin(13).

Another study showed prevalence of CA- MRSA at about 10 and reduced vulnerability to vancomycin in about 12 of the isolates of Enterococcus fecalis. Among blood culture isolates of Salmonella Typhi at a tertiary care sanitarium in Delhi, resistance was observed to nalidixic acid (96.7), ciprofloxacin (37.9) and azithromycin (7.3) and multi-drug resistance in 3.4 isolates. A report of Neisseria gonorrhoeae insulated from male and woman

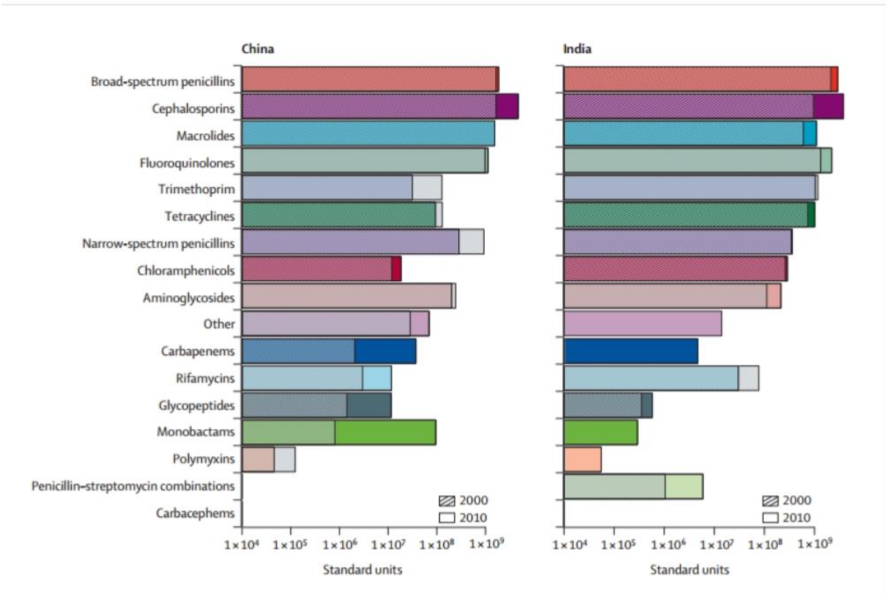
STD clinic at Delhi stressed intimidating increase in ciprofloxacin resistance (83.3), penicillinase- producing N. Gonorrhoeae (35.1), tetracycline resistance (19.3), ceftriaxone less-susceptible strains (5.5) and multi-drug resistant isolates (23.3) over 14 times from 1996 to 2008(14–16).

Use of antimicrobials in humans, animals and food:

Limited data is available in the public domain on antibiotic sales. Based on available data, Trends may be observed as shown in the figure below:



At 12.9 x10^9 units^2 of antibiotics consumed in 2010, India was the largest consumer of antibiotics for human health. Although the per capita consumption of antibiotics in India (10.7 units per capita) was lower than that seen in numerous other countries (e.g., 22 units per capita in USA), the overall population and infection cargo led to advanced total consumption. Nearly 23 of the increase in the retail antibiotics trade in the BRICS countries was attributable to India(17). From a study by van Boeckel et al, the consumption of antibiotics in India and China are compared, by class of medicines as follows:



With respect to consumption of antimicrobials in food creatures, the global consumption was estimated to be 63,151(± 1,560) units in 2010; India accounts for 3% of the global consumption and is the fourth loftiest in the world, behind China (23%), the United States (13%) and Brazil (9%). The consumption of antimicrobials in the food creatures' sector in India is anticipated to double by 2030. Ferocious parenting of food creatures has contributed to as important as 46% of the increase in the consumption of antimicrobials in Asia. In India, the loftiest situations of antimicrobial consumption are seen in the southern seacoast, Mumbai and Delhi. The total realty in which animal consumption of antimicrobials is veritably grandly (> 30 kg/sq. Km) in South Asia is anticipated to be driven by the growth of the poultry business in India. The expansion of realty with high animal consumption of antimicrobials is anticipated to increase by 312% in India by 2030, pushing the Asian swell in animal consumption of antimicrobials. An inpatient grounded study from New Delhi set up that 39% of the cases attending private retail pharmacies and public facilities and 43% of cases visiting private conventions were specified at least one antibiotic. The study further stressed the extremely high antibiotic consumption across public sector (43,390 DDDs/ 1000 cases for all antibiotics), private retail sector (125,544 DDDs/1000 patients for all antibiotics) and private clinics (81,467 DDDs/1000 patients for all antibiotics)(17–19).

Public awareness and education:

The GAP- AMR (Global Action Plan on Antimicrobial Resistance) states that the first strategic ideal in effectively containing AMR is to ameliorate mindfulness and understanding of AMR through effective communication, education and training. The strategy envisions that the mindfulness structure has to do on several fronts at the same time. On one hand it has to work public communication programmes to encourage behaviour change in target populations, most of the stakeholders in public health, animal health and husbandry; and on the other, there needs to be combined sweats to incorporate AMR as a core element in the professional education of medical and veterinary professionals. It's essential to identify stakeholders who can play a vital part in containing AMR in their professional capacity; this could include a wide spectrum of functionaries similar as, physicians, nurses, AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy) health care practitioners, pharmacists and druggists, veterinarians, para-veterinarians (including veterinary field sidekicks) and other health care support staff. Analogous views were expressed in the situation analysis on antibiotic use and resistance in India conducted by the Global Antibiotic Resistance Partnership (GARP) – India Working Group. The GARP had linked that of the three critical areas of intervention in India and countries with analogous resource limitations, a vital element is education and public mindfulness juggernauts to ameliorate the understanding of AMR in both providers as well as consumers. The need to focus on awareness building, both in consumers and providers, was highlighted by the results of the multi-country public awareness survey that was conducted by WHO(20–22).

Global collaboration:

India has some being transnational collaborations in the area of antimicrobial resistance. Sweden Collaboration between the NCDC and Central Drug Standard Control Organization (CDSCO) and the Public Health Agency of Sweden with a focus on surveillance, especially data analysis, lab strengthening, quality assurance, antimicrobial stewardship, mindfulness, infection control and regulations, was initiated in 2009.A collaboration exists between Australian pharmaceuticals, Public Health Foundation of India and Organisation of Pharmaceutical Producers of India (OPPI). Japan- there's collaboration between ICMR and National Institutes of Infectious Diseases (NIID) of Japan on development of integrated surveillance programme covering epidemiology and genomic data, initiated in April 2016 on the side- lines of the Asian Health Minister's meeting on AMR. Indo- Norwegian cooperation (Indo- Norwegian Research Effort – INNORES) on AMR between the Indian Council of Medical Research in collaboration and the Research Council of Norway was initiated in October 2014. The Indo- Norwegian Meeting on AMR concertedly organized by ICMR and Research Council of Norway was held in October 2016.

In September 2015, the NCDC and ICMR networks (through the All-India Institute of Medical sciences) each initiated AMR collaboration with the US Centers for Disease Control and Prevention (CDC) through the Global Health Security Agenda (GHSA) platform. These enterprise work the being AMR networks to further strengthen, regularize and expand capacity of the public health and health care systems in India to induce, apply and report accurate AMR data, apply applicable IPC procedures, enhance antimicrobial stewardship practices, and strengthen routine hospital based surveillance for HAIs(health care associated infection). The specific objects of the Goi/ CDC collaborations are

• Understand antimicrobial use practices and promote stewardship to ameliorate rational use

• Enhance laboratory surveillance of precedence AMR pathogens using externally quality- assured data

• Strengthen health care installation IPC programmes grounded on gaps linked through standardized assessments

• Ameliorate capacity to respond to outbreaks of AMR infections related to health care delivery

• apply standardized surveillance of HAIs caused by AMR pathogens

In addition, CDC also collaborates with the Government of Tamil Nadu on AMR, with a focus on quarter and sub-district position issues, realities and enterprises. The thing of this design is to make capacity of the public health system in Tamil Nadu to help and control HAIs and reduce the spread of AMR. The design conditioning concentrate on quarter and sub-district position health care facilities in three important districts in Tamil Nadu (Tirunelveli, Coimbatore, and Kancheepuram), with an end goal of scaling these conditioning to other sections and states in India(10).

Research and Development:

Research and development in the field of developing newer classes of antibiotics has been slow. There has been a definite retardation in the channel for product of effective new classes of antibiotics globally. It has been proposed that in order to develop truly new antimicrobial agents, medicines should be developed with three attributes(i) these medicines should be the one against which there's no provable resistance or cross-resistance with other classes of antimicrobials;(ii) they should have a narrow spectrum of activity to reduce the liability of rapid-fire development of resistance; and(iii) they should be developed against agents or conditions which have a direct public health implications. In 2004, in the 15 largest pharmaceutical companies, only 1.6 of the medicines in the development stages were antibiotics, and none of them were from new classes, nor were they targeted to treat multidrug- resistant agents. Despite the obvious need to develop newer classes of medicines to respond to the challenges of arising AMR, there are many late-stage campaigners in the process of development(10,23,24).

One of the first needs to have a strategic R&D docket for constraint of AMR is to establish a set of requirements and also prioritize them in order to understand the most critical gaps in our understanding of the AMR problem and how to contain it. Away from the need to develop newer classes of antibiotics, especially for Gram negative organisms, which regard for a major share of the mortality and morbidity performing from medicine resistant infections, there are three broad areas in which exploration and invention needs to be conducted surveillance, diagnostics and interventions(10).

Conclusion:

Irrational use of Antibiotics in India has set the stage for a looming antibiotic resistance crisis which has led to concerning about the issue developing resistance. This poses a serious threat to public health as common infections become harder to treat. To mitigate these crises, the situation demands multi-pronged approaches, awareness campaigns, Stricter regulation of antibiotic scales, improved healthcare infrastructure and an increased emphasis on rational prescribing practices by healthcare professionals. Without concerted efforts to curb this issue, the future of health care in India is at risk and it could have devastating consequences for India's health care system and its population. The effectiveness of antibiotics as a conerstone of modern medicine will be severely compromised. It is imperative that stakeholders at all levels come together to address this critical public health concern.

Poor public health Pointers, rising inflows, and the vacuity of affordable antibiotics over the counter without a tradition are clustering to produce the ideal conditions for a large- scale selection and dispersion of resistance genes in India. India isn't alone in this battle, and the gests of other countries in dealing with antimicrobial resistance are described in the most recent State of the World's Antibiotics Report (2015). On the positive side, sweats by groups like the Indian Association of Pediatrics, the Global Antibiotic Resistance Partnership, and the Chennai Declaration have helped make mindfulness about the problem among professional bodies, the media, policy makers, and the lay public(25–27).

As we navigate the complications of the antibiotic resistance extremity, it's imperative to emphasize the part of exploration in shaping substantiation- grounded programs. Investments in developing new antibiotics and exploring innovative remedial approaches are essential for securing our collaborative health. In conclusion, by fostering awareness, implementing stringent regulations, promoting responsible antibiotic use, and investing in research, we can collectively combat the irrational use of antibiotics and mitigate the looming threat of antibiotic resistance. Our commitment today will determine the efficacy of antibiotics for future generations, reinforcing the importance of a united global effort to safeguard the invaluable resource of effective antimicrobial agents.

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