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Inadvertent Use of Antibiotics in India

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Abstract: ***India is considered as an antibiotic capital of the world. Unnecessary use of antibiotics is a well-known driver of antibiotic resistance. It is a well-known fact that microorganisms are developing resistance to antimicrobial drugs which are present in the market that is known as antimicrobial resistance (AMR). This resistance in microbes is a matter of concern among the scientific fraternity. The decentralized model of the Indian health system and the shortage of allopathic doctors in rural areas has been seen where a wide variety of healthcare providers cater to the needs of patients in urban and rural settings. Antibiotic resistance is a global concern which is particularly pressing in developing nations, including India, where the burden of infectious disease is high and healthcare spending is very low. Measures have been discussed to reduce the spread of antibiotic resistance, improve public health directly and reduce pressure on the healthcare system. Further, increasing the types and coverage of childhood vaccines which are offered by the government would reduce the disease burden enormously and spare antibiotics. This paper focuses on inadvertent use of antibiotics, antibiotic resistance and their respective resistant microbes, factors that cause resistance among microbes, and consequences of AMR at Indian scenario. It would be a very helpful resource in nutshell for making the ground for discovery of new antibiotics that will be more effective towards microbes.***

Keywords: Antibiotics, Antibiotic resistance, patient's perception, inadvertent, government, infection

Introduction

The first antibiotic was accidentally discovered by Alexander Fleming[1] in 1928 revolutionized the therapy of infection, and saved millions of lives especially during the two World Wars. The dramatic impact leads to the scarcity of antibiotics with a high cost which necessitated extraordinary prudence in their use.

Then a time came when, with progressively falling costs and increasing availability of antibiotics, prescribing became less judicious. The global pharmaceutical industry was very quick to take advantage of the declining costs of production, expanding world markets especially in the developing countries. Every week a new antibiotic started to be pumped into the market which leaves no time for doctors to fully get acquainted with new products while, at the same time, it provides ample chances to microorganisms to develop different means of resistance to guarantee their survival.

We know day by day the medicines are becoming less effective because of the ability of microorganisms to resist the effects of the medications that were once used to kill them. This ability of the microorganisms is known as antimicrobial resistance (AMR). Because of which, the medications have become ineffective and the microorganisms persist for a longer time in the body and the risk of the spread of the infections and diseases increases and also threatens our ability to cure even the most common infections. This may result in prolonged illness, disability, and even the death. And without effective antimicrobials, medical procedures and major surgeries also become risky. In addition, AMR increases the cost of healthcare as it stay in the hospitals and will be longer where more intensive care will be required.

Current Scenario

The bacterial disease burden in India is among the highest in the world where antibiotics will play a critical role in limiting morbidity and mortality in the country. Antibiotics are used in situations where antibiotics cannot be expected to improve the patient's condition, particularly as treatment for the common cold and uncomplicated cases of diarrhea or other.

'Drug selection pressure' is the most important factor in the evolution of drug resistance in bacteria. The reasons for drug pressure are involved in both human and animal use. Although drug resistance is primarily a medical problem and the factors that influence the spread of resistance are ecological, cultural, social, and economic.

Every time an antibiotic is used whether appropriately or not in human beings or in animals whosoever the probability of the development and spread of antibiotic-resistant bacteria is most likely increased. The responsibility is to maintain antibiotic effectiveness as long as possible while allowing the maximum possible health benefits to accrue to the world's population. The actions needed to achieve this goal cannot be decided globally solely. Each nation must adopt strategies and tailored to its own conditions.

Antimicrobial Resistance

Resistance to an antibiotic occurs when a microorganism is able to grow or survive in the presence of a concentration of antibiotic that is usually sufficient to inhibit or kill organisms of the same species. The terms 'susceptible' and 'resistant' relating to antibiotics are usually used in clinical practice to infer the likely success or failure of treatment. Resistance is more likely when the concentration which is required to inhibit or kill microorganisms exceeds that achievable in a patient.

Microorganisms can be either intrinsically resistant to an antibiotic or develop resistance by following the exposure to that antibiotic (acquired resistance). Resistance can develop as a result of mutation or direct transfer of genes and encodes a resistance mechanism. Transfer of resistance genes can occur by a variety of mechanisms including conjugation, transformation or transduction. Genetic

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4520913/

material, including antibiotic resistance genes, can spread effectively between bacteria, even those of many unrelated species.

Factors that Causes AMR

- Increase in AMR is linked with the amount of the antibiotic prescribed, missed number of doses, and inappropriate and unnecessary prescribing of antibiotics which happen maybe because sometimes patients insist physicians for antibiotics and the physicians prescribe them as they do not have enough time to explain why they are not needed.[2]
- Lower antibiotic concentrations and longer duration of treatment contribute to the increase of AMR.
- Underlying diseases in the healthcare setup such as mechanical ventilation and poor hygiene by hospital staff.
- AMR raise the crescendo when counterfeit medications with subtherapeutic concentrations of antibiotics are mainly used.
- Some of the pharmaceutical companies release large amounts of antibiotics in the form of waste due to inappropriate wastewater treatment which eventually increases AMR.
- Antibacterial components and antiseptics may also be contributing to AMR.
- Inappropriate use of antibiotics in animal husbandries is also found to be an underlying contributor to the emergence and spread of antibiotic-resistant microbes.
- Resistance toward antibiotics sometimes is natural. These genes that gain resistance are called as environmental resistomes. These genes may be transferrable from non-pathogenic to pathogenic microbomes which may lead to antibiotic microbial resistance.
- It has been found that heavy metals and other pollutants may also contribute toward this global public health hazard.

Resistance to Antibiotics

Antibiotic resistance has been a low-priority area in the most developing and many developed countries. Compared with the immediate challenges of HIV/AIDS, tuberculosis, malaria and many other infectious diseases, the loss of antibiotics at some future time does not capture the same attention.

Resistance against certain antibiotics is already at high levels in certain places in India (and around the world), but the problem has remained unknown because relatively few studies were published and nationwide surveillance was not being carried out. But the issue came to the fore in India when New Delhi metallo-ί-lactamase-1 (NDM-1) was first reported in 2009 and made the front-page news in 2010.

A World Health Organization (WHO)[3] study in which *E. coli* was used as an indicator organism at all four sites found high levels of resistance, especially in pathogenic isolates. The study measured both antibiotic resistance and antibiotic use over the course of at least one year. Resistance rates were highest to those antibiotics in use the longest. However, resistance rates to the newer antibiotics, such as fluoroquinolones, were particularly high in India.[4]

Antibiotic resistance surveillance has been limited to small-scale efforts by the Indian Council of Medical Research (ICMR)[5].The Invasive Bacterial Infection Surveillance (IBIS) project produced valuable information on pneumonia in India, though it was unable to meet its goal of establishing a permanent surveillance system for antibiotic resistance.[6]

Infections Acquired in Hospital

Hospital-acquired infections (HAIs) are a particular concern and indicate the level of infection control in a hospital, since many HAIs can be prevented through better maintenance and hygiene. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are among the most common causes of HAIs. Recent findings on the levels of HAIs and the causative organisms in India are similar to those in other parts of the world and include:

- A prospective study of 71 burn patients at Post Graduate Institute of Medical Education and Research (PGIMER) in Chandigarh found that up to 59 patients (83%) had hospital-acquired infections.[7]
- A six-month study conducted in the intensive-care units in the All India Institute of Medical Sciences (AIIMS), New Delhi, found that 140 of 1,253 patients (11%) had 152 hospital-acquired infections.[8]

Patterns of Antibiotic Overuse

A few hospital- and city-based studies of antibiotic use suggest that antibiotics are often prescribed in irrational or inappropriate ways in India; that is, the drugs are prescribed at an incorrect dose, frequency, or duration, are redundant, or have the potential for adverse interactions with other drugs. Some studies on antibiotic use have employed indicators, such as the average number of drugs prescribed per encounter and the frequency with which fixed-dose combinations are prescribed.

[2]Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database Syst Rev. 2005 doi: 101002/14651858CD003539pub2. [PMC free article] [PubMed] [Google Scholar]

[3] https://www.who.int/about

[4]Holloway K, Mathai E, S8
orensen TL, Gray A. (US Agency for International Development). Community-Based Surveillance of Antimicrobial Use and Resistance in Resource-Constrained Settings. Report on five pilot projects. Geneva: World Health Organization; 2009.

[5] https://www.icmr.gov.in/aboutus.html

[6]*http://www.inclentrust.org/resources/iphid/iidi/Annex 1-IBISI 2final.pdf* .

[7]Taneja N, Emmanuel R, Chari PS, Sharma M. A prospective study of hospital-acquired infections in burn patients at a tertiary care referral centre in North India. *Burns* 2004; *30* : 665-9.

[8]Mathur P, Kapil A, Das B. Nosocomial bacteraemia in intensive care unit patients of a tertiary care centre. *Indian J Med Res* 2005; *122* : 305-8.

Other studies have detailed the reasons for prescribing (or purchasing) antibiotics in particular, for upper respiratory tract infections, an inappropriate indication. Unnecessary prescribing and overuse are seen in all settings: public and private hospitals, clinics and pharmacies.[9] For example, depending on where they live and the type of practitioner they visit, 45 to 80 per cent of patients with symptoms of acute respiratory infections and diarrhea are likely to receive an antibiotic, even if it will not be effective.

Antibiotic use in Animals

Antibiotics are not only used to treat human illness but have also been used in livestock and poultry for more than half a century to control and treat diseases and, in low doses in animal feed, to promote growth and improve production of animal products.[10]

There is no regulation in India of the use of antibiotics in food animals such as poultry, dairy cows, and buffaloes raised for the domestic consumption.

The precise effect of agricultural antibiotic use on resistance levels in the general population is not known. In 2003, an expert committee convened by WHO, the UN Food and Agriculture Organization, and the World Organization for Animal Health concluded, 'there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials leads to AMR.

These consequences include infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases leas to death), and increased severity of infections. Cattle farming is a common livelihood in many parts of India, and a large proportion of the population is in close contact with livestock, which puts people at risk of acquiring resistant infections from their animals.

A few studies on antibiotic residues in animal products have been conducted in India, but one on honey was publicized.[11]This study, conducted by the Centre for Science and Environment, New Delhi, found that 11 out of 12 samples of honey taken from the domestic market and were not compliant with standards for export.

It concluded that the level of antibiotic residues found was not high enough to trigger an adverse effect in consumers, but it called for regulation and monitoring of antibiotic residues in honey as continuous long-term exposure to low levels of antibiotics could in due course of time lead to antibiotic resistance in pathogenic bacteria making their treatment difficult.[12]

Patients Perceptions and Expectations from Healthcare Providers

Patients usually named environmental factors being a cause of illness. In general, patients had no idea of what constituted an antibiotic. Patients appeared to draw distinctions between (light or lower-power) medicines and more powerful medicines, and some even associated the name “antibiotic” with a faster cure, but there was no knowledge of functions and uses. Patients switched health providers frequently if the treatment was perceived as being too slow or ineffective.

In addition, patients did not hesitate to approach a combination of Ayurvedic, homeopathic and allopathic doctors; the underlying motivation was the best cure in the fastest amount of time. Some patients used Ayurvedic products such as “Chawanprash” but preferred allopathic medicines over homeopathic treatments, as they were perceived to cure the disease more quickly. If the prescribed treatment was not working however, patients did not hesitate to switch providers.

Measures Taken to Overcome AMR

Some of the approaches for combating AMR are:

- Educating people about AMR.
- Educating people about the rational use of antimicrobials.
- Control of substandard and counterfeit antimicrobials.
- Inducements such as developing new vaccines, drugs, etc.
- Usage of alcohol-based hand cleansers for hands.
- 72 h after the symptoms resolve, antibiotics can be safely stopped.
- Usage of antibiotics with short course along with regular reevaluation with the doctor is very necessary. The course must be stopped if no signs of clinical infection are seen as most of the time individuals do not complete the full course which can be serious.
- Increasing awareness among the nurses and other health care providers is necessary as they are in direct contact with the patients and automatically being responsible for infection spread or control of AMR.[13]
- The standards of drug advertising and promotions should be followed by pharmaceutical companies. Moreover, action toward pharmaceutical companies that encourage inappropriate use of antimicrobials should be taken.[14]

[9]Kotwani A, Holloway K. Trends in antibiotic use among outpatients in New Delhi, India. *BMC Infect Dis* 2011

[10]Manna SK, Brahmane MP, Manna C, Batabyal K, Das R. Occurrence, virulence characteristics and antimicrobial resistance of *Escherichia coli* O157 in slaughtered cattle and diarrhoeic calves in West Bengal, India. *Lett ApplMicrobiol* 2006

[11]*http://www.deccanherald.com/content/96888/honey-popular-brands-contaminated-antibiotics.html*

[12]Johnson S, Jadon N, Mathur HB, Agarwal HC. *Antibiotic residues in honey*. New Delhi: Centre for Science and Environment; 2010.

[13]Moongtui W, Picheansathian W, Senaratana W. Role of nurses in prevention of antimicrobial resistance. Regional Health Forum. 2011

[14]WHO Global Strategy for Containment of Antimicrobial Resistance. World Health Organization. 2001. [Last accessed on 2019 Apr 12]. Available from: https://wwwwhoint/drugresistance/WHO_Global_Strategy_Englishpdf

- Minimized antimicrobial usage in animals, improved sanitization along with the regulated provision of probiotics or supplements in vaccination and feed to control common animal diseases need to be administered.
- National and international academic networks are necessary to identify new categories of antibiotics along with diagnostic technologies.
- Providing incentives for the development of new antimicrobials to pharmaceutical companies and others.

The objective will be successful if a common infection like a cold is precisely diagnosed and treated with the right antibiotic for the shortest time to ensure eradication of the bacterial infection. We have a long way to go before we achieve this seemingly simple objective even in industrialized affluent countries. And it is very important to have this.
In India, as in other developing countries, we have not taken the initial steps. Antimicrobial resistance is a major emerging infection and needs to be tackled as much as possible.

Government Policy Towards Antibiotic Use and Resistance

Regardless of whether NDM-1 turns out to threaten patient's health in India, the attention directed to this pathogen has spurred the Government to action on antibiotic resistance. As a result, a Ministry of Health and Family Welfare task force announced a new national anti-microbial policy The National Policy for Containment of Antimicrobial Resistance. India covers a range of topics, including curbing antibiotic use in animals, particularly those raised for human consumption; conducting infection surveillance in hospitals; improving hospital surveillance for monitoring antibiotic resistance; promoting rational drug use through education, monitoring, and supervision; researching various new drugs; and developing and implementing a proper standard and more restrictive antibiotic policy. Under the new Schedule H1 (now called HX), which will regulate antibiotic use selling antibiotics over the counter will be banned. Certain antibiotics will be available at only tertiary hospitals.

National Antimicrobial Resistance Policy in India

In 2011, national policy on AMR has been introduced. The objective of this policy is to increase awareness in the emergence of AMR, measures to be taken and the factors influencing it. In addition, to establish programs such as antimicrobial rationalized usage and to provide incentives to develop new effective antimicrobial drugs, this policy came into an act. This policy concentrates on three categories such as sentinel surveillance, point prevalence, and comprehensive surveillance. Some of the action plans which are included in the policy are as follows:[15]

- To establish surveillance system of AMR.
- Prevention of infections along with respective control measures.
- To increase awareness of rational antimicrobial use in all stakeholders.

National Action Plan on AMR

The objective of NAP-AMR is to combat AMR and contribute to tackle this enormous global health threat. This policy will help establishing and strengthen governance mechanisms and volume of stakeholders to decrease the aftermath of AMR in India. The extent of NAP-AMR primarily emphasizes on resistance in bacteria.

The objectives of the NAP-AMR are:

1) To define the strategic priorities, outputs, responsibilities, and indicative timeline and budget to slow the emergence of AMR in India and to strengthen the organizational and management structures to ensure intra-sectoral as well as inter-sectoral coordination with a One Health approach;
2) To combat AMR in India through better understanding and awareness of AMR, strengthened surveillance, prevention of emergence and spread of resistant bacteria through infection prevention and control, optimized use of antibiotics in all the sectors and enhanced investments for AMR activities, research, and innovations; and
3) To enable monitoring and evaluation (M and E) of the NAP-AMR implementation based on the M and E framework.

The NAP-AMR has outlined six strategic priorities to tackle this public health challenge and these are to be implemented over 2017–2021. The first 5 strategic priorities of NAP-AMR are aligned with the Global Action Plan on AMR and the sixth strategic priority highlights India's role in the containment of AMR at international level and at subnational/state level to ensure action at the ground level. The focus areas of the six strategic priorities of NAP-AMR are as follows:

1) Improve awareness and understanding of AMR through effective communication and IEC resources to raise awareness among all stakeholders, including policymakers, general public, and farmers, and education and training to improve the knowledge and behavior of the professionals.
2) Strengthen knowledge and evidence through surveillance by strengthening laboratories for evidence-informed policy-making in human, animal, food, and environment sectors. And by surveillance of AMR for evidence-informed policy-making in human, animal/food, and environment sectors.
3) Reduce the incidence of infection through effective infection prevention and control in-
   - Healthcare to reduce the burden of infection
   - Animal health/food to reduce the spread of AMR through animals and food
   - Community and community environment to reduce the spread of AMR and antimicrobials in the community and in the environment.
4) Optimize the use of antimicrobial agents in health, animals, and food with the help of

[15]https://mohfw.gov.in/sites/default/files/3203490350abpolicy%20%281%29.pdf

- Regulations, access, and surveillance of antimicrobial use to ensure rational use without affecting access to antimicrobials
- Antimicrobial stewardship in healthcare sector to optimize the use of antimicrobials in humans
- Animal health and agriculture to optimize the use of antimicrobials in animal and food sectors.

5) Promote investments for AMR activities, research, and innovations by
   - New medicines and diagnostics to ensure availability of effective diagnostics and drugs to treat infections against AMR.
   - Innovations to develop alternative approaches to manage infectious disease which may cause death.
   - Financing to ensure sustainable resources for containment of AMR.
6) Strengthen India's leadership on AMR with
   - International collaborations to ensure India's contributions toward global efforts to contain AMR.
   - National collaborations to facilitate collaborations among vertical disease control programs.
   - State level collaborations to ensure action at the ground level against AMR.

Legal Framework

Laws, regulations, rules, policies and strategies on the quality of care of the patients exist in the country. However they are fragmented. Let's discuss some of them:

- Consumer Protection Act: It deals with the medical negligence and deficiency of the services but has failed to define the rights of the patients.
- Legal rights of the patients are set out in the Clinical Establishment Act (CEA), but this Act is not being implemented across India.
- National Pharmaceutical Pricing Authority (NPPA) and Drugs Controller General of India (DCGI) have mechanisms which look after the patients' rights in terms of medication (be used in prescribed manner)and they are not overcharged anytime.
- National Health System Resource Centre (NHSRC) has been designated as nodal agency at National level for implementing the Quality Assurance program in public health facilities. National Quality Assurance Standards have been developed by NHSRC for specific quality and patient safety needs of public health institutions. By this public can be more secure and safe.
- The Right to Information Act: All public facilities must report all the information available at Institutional level. By doing so, it is assumed that the quality of care is perceived as inadequate in quality, the facility might face the risk of media scrutiny and trials in case of honest reporting. But this is for the public welfare and for the proper knowledge and awareness.
- Selected Private sector chain hospitals and individual institutions have implemented substantial measures to implement the patient safety. As these hospitals constitute very small proportion of overall care providers these measures remain isolated and has limited in effect. And they all have their own terms and conditions.
- Public reporting on quality of care to some extent exists in the country, but needs adjustment and improvement. By spreading awareness and taking steps further
- National Accreditation Board for Hospitals and Healthcare Providers (NABH) is pertinent and provides Enough flexibility. Insurance Regulatory Development Authority (IRDA) has issued a notification for the health entities to consider NABH Entry level accreditation for availing reimbursement Benefits from the insurance providers. Public can avail for reimbursement benefits from insurance providers.

Conclusion

One of the most important statistics in the public health sector is AMR. The relentless rise in antibiotic resistance is a major and gross public health concern which will need to be acted upon now. We might not be able to stop antibiotic resistance or, in many cases reverse the trend to ever-increasing resistance but we can certainly need to contain or limit the speed to which this is happening. Not even a single action or initiative by a single country would be able to achieve this. It requires participation and support from all levels; political, medical, veterinary, agricultural, environmental, academic, industry and the general public. Different policies give different and broad guidelines on how to combat the microbes from developing resistance. It is time that a National effort should be initiated to tackle these problem of antimicrobial resistance which can have disastrous effects on our population.