

Antimicrobial resistance in India: A review

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Abstract

Antimicrobial resistance is an important concern for the public health authorities at global level. However, in developing countries like India, recent hospital and some community based data showed increase in burden of antimicrobial resistance. Research related to antimicrobial use, determinants and development of antimicrobial resistance, regional variation and interventional strategies according to the existing health care situation in each country is a big challenge. This paper discusses the situational analysis of antimicrobial resistance with respect to its problem, determinants and challenges ahead with strategies required in future to reduce the burden in India. Recent data from Google search, Medline and other sources were collected which was reviewed and analyzed by the authors. Hospital based studies showed higher and varied spectrum of resistance in different regions while there are limited number of community based studies at country level. There exists lacunae in the structure and functioning of public health care delivery system with regard to quantification of the problem and various determining factors related to antimicrobial resistance. There is an urgent need to develop and strengthen antimicrobial policy, standard treatment guidelines, national plan for containment of AMR and research related to public health aspects of AMR at community and hospital level in India.

Key words: Antimicrobial resistance, challenges, determinants, India, problem burden, strategies

INTRODUCTION

Antimicrobial resistance is one of the major public health problems especially in developing countries where relatively easy availability and higher consumption of medicines have lead to disproportionately higher incidence of inappropriate use of antibiotics and greater levels of resistance compared to developed countries.^[1] In India the infectious disease burden is among the highest in the world and recent report showed the inappropriate and irrational use of antimicrobial agents against these diseases, which led to increase in development of antimicrobial resistance.^[2] Besides, it has shown that health sector in India suffers from gross inadequacy of public finance which will result in the conditions favorable for development of drug

resistance.^[3] A recent study highlighted the importance of rationalizing antibiotic use to limit antibiotic resistance in India.^[4] Antimicrobial resistance will result in difficulty in controlling the diseases in the community and ineffective delivery of the health care services.

Little is known regarding the epidemiological aspects of antimicrobial resistance in most of South East Asian countries.^[5] Although many International agencies like World Health Organization, European Centre for Disease Control and World Health Assembly resolutions highlighted the antimicrobial resistance as a major public health issue, it will be a big challenge to tackle the problem for the policy makers and health care providers. World Health Organization has proposed regional strategy on antimicrobial resistance with the goal to minimize the morbidity and mortality due to antimicrobial resistant infection to preserve the effectiveness of antimicrobial agents in the treatment and prevention of microbial infections.^[2] In the public health point of view, it is important to look for the existing situational analysis in Indian context, so that appropriate interventions can be initiated at community level to tackle the problem. With this background, the study analyzed the situation

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of problem burden and various factors with recent developments, challenges and strategies required to tackle the Antimicrobial Resistance.

MATERIALS AND METHODS

The review was conducted during January 2011 to April 2011. Data were collected by Google search engine, Medline and others. The key words used for the search included: Antimicrobial resistance, problem burden, determinants, challenges, strategies, India. Primarily the search was conducted for the relevant information in Indian context since the year 2006 till date which yielded 41 references out of which 29 references were included for analysis. A total of 12 articles including animal studies and letters were excluded after thoroughly reviewing and cleaning the search results which are not found to be relevant to the article. Also, four older articles were included after expert opinion, thus 33 articles were selected for final analysis. The articles were analyzed for discrepancies and the information was presented in the form of description and a table.

Problem burden

Antimicrobial resistance is a major public health problem in South East Asian countries.^[6] It is known that the infectious disease burden in India is among the highest in the world and burden of poor sanitation and malnutrition exacerbates these conditions.^[7] Presently under various national health program there are definite policies or guidelines for appropriate use of antimicrobials like Integrated Management of Neonatal and Childhood Illness (IMNCI) in diarrheal diseases and respiratory infections, but these are not available for other diseases of public health importance like enteric fever and others. During the recent H1N1 pandemic, national guidelines were framed and implemented regarding restricted sale and use of oseltamivir in the country. Another major issue is that there is no national data based on antimicrobial resistance in different pathogens except for those where there is a specific national health program. Networking of laboratories in the Revised National Tuberculosis Control Program in the country generated some useful data on drug resistance in tuberculosis and recently a laboratory network has also been established for antimicrobial testing of HIV under National AIDS Control organization.^[5]

The resistance spectrum of pathogens varies in different regions. Therefore local resistance patterns have to be known for appropriate antimicrobial use.^[8] There are some hospital based data which showed that antibiotic resistance is increasing and will be a greater problem if not tackled properly according to present needs as in other developed countries.^[9] Meta analyses of the drug

susceptibility results of various laboratories in India reveal an increasing trend of development of resistance to commonly used antimicrobials in pathogens like *Salmonella*, *Shigella*, *Vibrio cholerae*, *Staphylococcus aureus*, *Neisseria gonorrhoeae*, *N. meningitidis*, *Klebsiella*, *Mycobacterium tuberculosis*, HIV, plasmodium and others.^[5] Resistance is an emerging concern for treatment of HIV infection, following the rapid expansion in access to antiretroviral medicines in recent years and national surveys are underway to detect and monitor resistance. New resistance mechanisms, such as the metallo-beta-lactamase NDM-1, have emerged among several gram-negative bacilli. This can render powerful antibiotics ineffective, which are often used as last line of defense against multi-resistant strains of bacteria^[5].

Table 1 shows the various studies on antimicrobial resistance in India.^[9-20] Multi-resistant enterobacteriaceae due to the production of extended spectrum β -lactamases (ESBL) have become very common in India.^[11,12] In addition, various studies in South India highlighted the drug resistance pattern like multidrug resistant Extended-Spectrum β -Lactamase Producing *Klebsiella pneumoniae*, Ciprofloxacin resistant *Salmonella enteric serovar Typhi*, emergence of *vancomycin-intermediate staphylococci*, fluoroquinolone resistance among *Salmonella enteric serovar Paratyphi A*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* resistant to ceftazidime, cefepime and ciprofloxacin.^[14,16,21-23] Metallo- β - lactamases (MBL) are the enzymes that mediate resistance to carbapenems. MBL producing *P. aeruginosa* are emerging as important causes of nosocomial infection. Prevalence of MBL producing organisms ranges from 7-65% in India. A recent study in Sikkim, India found that MRSA was seen in 111 out of 291 clinical specimens (38.14%) of *S. aureus* and 41 out of 196 carrier screening nasal samples (20.92%) of *S. aureus* and overall a total of 152 isolates of *S. aureus* from 487 specimens (31.21%) were found to be methicillin resistant.^[20] Result of 88 references showed a steady increase in the number of vancomycin-intermediate and vancomycin-resistant *S. aureus* in hospitalized patients with highlighting the spread of MRSA from the hospital to the community.^[24] Another study showed increased rate of inducible clindamycin resistance among CA-MRSA.^[17] Methicillin Resistant Staphylococci constituted 4.16% of the *S. aureus* strains in a study conducted among children in an urban community in Nagpur, India.^[14] A recent study discussed the importance of MRSA related to its epidemiological aspects, clinical presentations, diagnostic modalities, therapeutic options, contributing factors, growing cost and other pertinent elements.^[25] Community acquired- MRSA (CA- MRSA) is known to cause skin and soft tissue infections among young and healthy individuals in the community. It is also known to cause severe infections like septic shock and necrotizing pneumonia.^[26] Studies

Table 1: Antibiotic resistance rates of various organisms in India

Location (year published)	Isolates	Organism	Resistance rate (%)	Reference number
MVIDH, Delhi (2007)	9858 stool samples	<i>V. cholera 01</i>	96 to furazolidone, Cotrimoxazole and nalidixic acid.	[10]
Kolkata (2007)	284 clinical isolates	<i>metallo-beta-lactamase (MBL) producing bacteria</i>	43.3 were resistant to at least seven antibiotics (ampicillin, amoxicillin, cephalixin, ciprofloxacin, cotrimaxazole, erythromycin, gentamycin)	[11]
Lucknow (2007)	2995 blood samples	<i>Klebsiellasp.</i>	ESBL producing <i>Klebsiellasp.</i> were 98.28 resistant to ampicillin, ticarcillin and piperacillin. Monobactam and cephalosporin resistance was also higher (>60%).	[12]
Puducherry (2008)	261 clinical isolates	<i>Staphylococcus isolates</i>	72.34 of <i>staphylococcus aureus</i> resistant to oxacillin	[13]
Nagpur (2009)	1300 nasopharyngeal swabs from school children	MRSA	4.16	[14]
CMC Vellore, Various centres across India (2010)	176 clinical specimens	<i>P. aeruginosa</i>	Among the 61 <i>P. aeruginosa</i> isolates, resistance to carbapenem was 42.6.	[15]
Puducherry (2010)	31 clinical samples	<i>K. Pneumoniae</i>	93.55 multiple drug resistant and ESBL producer	[16]
Mangalore (2010)	83 CA-MRSA clinical isolates	Community-associated methicillin resistant <i>Staphylococcus aureus</i> (CA-MRSA) strains	92.8% were resistant to penicillin, 31.32 to erythromycin.	[17]
LokNayak Hospital, New Delhi (2010)	83 isolates from OPD cases of pyoderma	CA-MRSA	9.6	[18]
Mangalore (2010)	180 clinical samples	Enterococcal strains	16.67 to 42.86 to aminoglycosides	[19]
Sikkim (2011)	291 clinical specimens 196 carrier screening nasal samples	MRSA	38.14 in clinical specimens 20.92 in nasal samples	[20]
Tertiary trauma center of AIIMS, New Delhi (2011)	3,984 clinical specimens	<i>Gram Negative Pseudomonas Acinetobactor Klebsiella E. coli Enterobactor spp. Gram positive S.aureus Coagulase negative staphylococci</i>	Overall resistance of gram negative organisms were 50 against carbapenems, 66 aminoglycosides, 76 Fluoroquinolones, 88 third generation cephalosporins, 66 beta lactam-betalactamase inhibitor combinations 58 methicillin resistant 85 methicillin resistant	[9]

in India have shown that the incidence of CA-MRSA is about 10%. These isolates of CA-MRSA are not multidrug resistant unlike the hospital acquired MRSA, in that way being a boon to the clinician as it keeps the treatment options wide.^[18] There is not much data on high incidence of vancomycin resistant enterococci (VRE) in India. However, reduced susceptibility to vancomycin was observed in a study in about 12% of the isolates of *Enterococcus faecalis*.^[19]

Though there is no national database on surveillance of use of antimicrobials in the community, there are a few studies in India in this regard. Studies carried out in Delhi and Vellore, with support from World Health Organization during 2003-2005 suggested a very high use of fluoroquinolones in the community as compared to

other antimicrobials. Presently there is no national program for prevention of drug resistance and there is inadequacy of quality assured laboratories, insufficient data analysis and dissemination, absence of national guidelines on antimicrobial usage, no control on sale of these drugs for public consumption.^[5]

Determinants

Although antimicrobial resistance is a multifaceted problem, it is related to existing health care delivery system of the country. In India, around 5% of GDP is spent on health out of which public health sector contributes to 0.9% and a major portion of the remaining is by the private health sector. Again around 80% share of private health sector contribution comes from out of pocket expenditure mostly for medicines.^[7] In private sector, many

of the doctors are poorly trained or unlicensed. Provision of essential medicines by the public sector is one of the measures to prevent antimicrobial resistance. But the non availability of some medicines because of irregular supply and problems related to monitoring the external and internal drug quality will further increase the problem. Inappropriate and irrational use of medicines provides favorable conditions for resistant microorganisms to emerge and spread.^[2,4,7] Administration of broad spectrum antibiotics as an empirical therapy to the outpatients is another factor that leads to emergence of resistant strains. Prescription of antibiotics by the doctors according to patient needs without any indications and involvement of pharmacists in direct sale of drugs to patients increase the problem of antimicrobial resistance. Compounding this problem, consumers and public have lack of knowledge regarding appropriate use of antibiotics. Self medication and poor compliance are the other factors responsible for antimicrobial resistance among consumers. So, behavioral pattern of the health care providers and consumers is of paramount importance in the emergence of antimicrobial resistance.

Inadequate national commitment to a comprehensive and coordinated response and ill-defined accountability with respect to antimicrobial use and resistance is an issue to be considered. Weak surveillance and regulatory system is also an important determinant of antimicrobial resistance. Samples are generally tested only when patients fail to respond to common treatments. Antimicrobial resistance is the best example for ice berg phenomenon of disease with superbugs the visible manifestations of our prolonged failure to preserve antibiotics.^[2] Although antimicrobial resistance to some extent is inevitable because of continuous natural evolution of resistance in microorganisms, major proportion can be prevented further through the appropriate interventional measures in the existing health care delivery system. Poor infection prevention and control practices in hospitals will lead to transmission of resistant strains to vulnerable people. Paucity of data at national level makes it difficult to understand the magnitude of the problem and various factors responsible for emergence of antimicrobial resistance.

AMR results in many consequences. The patient remains sick for a longer period thus requiring prolonged treatment usually with expensive and at times toxic drugs which results in increased morbidity and mortality. The burden on health system also increases.^[15] Hospital acquired infection in vulnerable patients with resistant strains is another major threat in the Indian context. The success of treatments such as organ transplantation, cancer chemotherapy and major surgery would be compromised without effective

antimicrobials for care and prevention of infections. There will be longer period of reservoir of infection which leads to transmission of infections to others in the hospitals and community. All these have substantial effect on economy at individual level and society level. Many infectious diseases risk becoming uncontrollable and could derail the progress made towards reaching the targets of the health-related United Nations Millennium Development Goals set for 2015. Recently the growth of global trade and travel has allowed resistant microorganisms to be spread rapidly to distant countries and continents.

Recent developments

In the last decade, a large number of new initiatives have been launched by various agencies to contain this problem. These include India Clen (Indian Clinical Epidemiology Network) which has generated some quality data on AMR in pathogens like pneumococcus, *H.influenzae* across the country; IIMAR (Indian Initiative for Management of Antibiotic Resistance) launched in March 2008, with WHO support, by a consortium of NGOs to promote prudent use of antimicrobials, INSAR (Indian Network for Surveillance of Antimicrobial Resistance) a network of 20 laboratories in the private as well as public sector across the country to generate quality data on AMR, organization by the ICMR of an expert group meeting in December 2009 and an Indo-Swedish workshop held at New Delhi on 2 February 2010 to discuss a joint strategy for containment of AMR.^[5]

WHO has supported a few community-based surveillance studies to determine the antimicrobial resistance as well as use of antimicrobial agents and generated some baseline data on Antimicrobial use and resistance in five pilot sites in India (Delhi, Mumbai, Vellore) and South Africa (Durban, Brits) showed very high AMR rates to cotrimoxazole and amoxicillin (>70% for *H.influenzae*). Higher resistance was seen in pathogens compared to commensals. It was also observed that inexpensive older antibiotics (cotrimoxazole and tetracycline) were used more in public facilities and expensive newer ones (fluoroquinolones, cephalosporins) were used in private facilities.^[9]

In India, several initiatives are under way to address the problem. A national antibiotic policy is being prepared which highlights about the hospitals incorporating into their guidelines. The government is urging hospitals to get accredited with the National Accreditation Board for Hospitals and Health Care Providers which will result in practices relating to judicious use of antibiotics.^[27] Though there are many interventional studies in developing countries,^[28] very few studies have been conducted to improve the use of antimicrobials and evaluate the evidence of their effectiveness in India.^[29-31] Before recommending

a series of interventions, it will be necessary to investigate the relative effectiveness of different strategies in the Indian context.^[6] Implementation and follow up of intervention research should be strengthened by health care planners, managers and practitioners to identify the most appropriate strategies to improve drug use and prevent the emergence of drug resistance.

Challenges

- Strengthening of Surveillance Data
- Standard Operating Guidelines
- Improvement in antibiotic prescription practices
- Over the counter sale of antibiotics
- Poor sanitation, endemic infections, malnutrition
- Limited public awareness and government commitment
- Lack of coordination and fragmentation of effort
- Perverse incentives.

A critical issue at the regional level is the need for and difficulty in taking effective measures as the responsibility for health remains essentially a national problem.^[32] National policy for containment of antimicrobial resistance 2011 is the recent development and welcome step by Ministry of Health and Family Welfare, Government of India which address the intervention strategies required and the steps for formulation and implementation of a standard antibiotic policy.^[33] Government health policies and the health care systems in which they are implemented play a crucial role in determining the efficacy of interventions to contain antimicrobial resistance. In the present context, national commitment to understand and address the problem and the designation of authority and responsibility are the major prerequisites. Effective action requires the introduction and enforcement of appropriate regulations and allocation of appropriate resources for education and surveillance.

Strategies

Establish a national alliance against antimicrobial resistance with all key stakeholders as its members. There should be an integrated approach between provider and consumer sides to effectively prevent the antimicrobial resistance. From the provider side policy makers, planners, practitioners and prescribers, pharmacists and dispensers, institution managers, diagnostic and pharmaceutical industries, department of animal husbandry and from the consumer side patients and community is important in this regard. The implementation of national efforts to prevent and contain antimicrobial resistance should be through a multi-sectorial national steering committee headed by the senior-most health executive and facilitated through advisory or expert groups.

Implement appropriate surveillance mechanisms in the health and veterinary sectors to generate reliable

epidemiological information, baseline data, trends on antimicrobial resistance, utilization of antimicrobial agents and impact on the economy and health through designated national and regional reference centre's. Discourage non-therapeutic use of antimicrobial agents in veterinary, agriculture and fishery practices as growth-promoting agents.

Develop national standard treatment and infection control guidelines and ensure their application at all levels of health care and veterinary services through training, continuous educational activities, establishment of functional drugs and therapeutic committees and hospital infection control committees in health facilities with the focus on proven cost-effective interventions such as isolation, hand washing.

To regulate and promote rational use of medicines and ensure proper patient care at all levels, there is a need to take necessary steps to stop across the counter sale of antibiotics without physicians prescription and ensure uninterrupted access to essential medicines of assured quality at hospital and community. Also, vaccination strategies should be improved to further reduce the burden of infections.

Conduct of operational research for better understanding of the technical and behavioral aspects of prevention and control of antimicrobial resistance. Utilize the outcomes of these research studies or interventions in policy and program development improvement in the national context.

Constructive interactions with the pharmaceutical industry for ensuring appropriate licensure, promotion and marketing of existing antimicrobials and for encouraging the development of new drugs and vaccines.

Educational and awareness program for communities and different categories of health care professionals.

Strengthen communicable diseases control program to reduce disease burden and accord priority to the discipline of infectious diseases in medical education and health services.

CONCLUSION

Hospital based studies showed higher and varied spectrum of resistance in different regions, while there are limited number of community based studies at country level. There exists lacunae in the structure and functioning of public health care delivery system with regard to quantification of the problem and various determining factors related to antimicrobial resistance. There is an urgent need to develop

and strengthen antimicrobial policy, standard treatment guidelines and national plan for containment of AMR in India. There should be more focus on research related to public health aspects of AMR at community and hospital level. Information Education Communication activities with monitoring and evaluation of the existing health care delivery system for both health care providers and consumers to improve drug use, should be undertaken simultaneously.

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