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WHO AWaRe strategy and antimicrobial stewardship to combat antimicrobial resistance: An Indian perspective

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REVIEW ARTICLE

WHO AWaRe Strategy and Antimicrobial Stewardship to Combat Antimicrobial Resistance: An Indian Perspective

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Abstract

Antimicrobial resistance is a serious problem to solve especially in developing countries like India. Antibiotic use in India increased several times since 2005. Many studies in India have reported inappropriate and overuse of antibiotics which could be one of the possible reasons for increased antibiotic resistance in the country. This is an important and urgent issue that mandates strict regulations regarding the rational use of antibiotics. World Health Organization (WHO) has done a major revision to the essential medicines list which classifies antibiotics into three categories (access, watch, and reserve) to ensure the availability and correct use of antibiotics. Several countries started antimicrobial stewardship programs to promote e appropriate use of antibiotics, reduce antibiotic resistance as well a financial burden. Indian government started a national action plan on antibiotic resistance in 2017 to promote the rational use of antibiotics but it is still in its formative stage as all stewardship components are yet to be implemented. This review emphasizes the importance and the need for implementing WHO's AWaRe strategy and antimicrobial stewardship to promote rational antibiotic use in the country.

Keywords: Antibiotic consumption, Antibiotic resistance, National action plan on antimicrobial resistance, AWaRe classification, Antimicrobial stewardship

Key messages

Antimicrobial resistance is a serious problem to solve for the public health authorities specially in developing countries like India. Conducting interventional studies to implement the WHO AWaRe strategy and antimicrobial stewardship program could be beneficial in promoting the rational use of antibiotics in India.

1. Introduction

The development of antimicrobial resistance has become a matter of great public health concern [1]. Antimicrobial resistance is a serious problem and worldwide deaths directly attributable to antimicrobial resistance are 700,000 per year which is further projected to increase to 10 million by the year 2050 if current trends continue. The estimated cumulative loss of economic output from antimicrobial resistance by 2050 would amount to 20 to 35 trillion US dollars [2]. Antimicrobial resistance

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is a serious problem to solve for the public health authorities at the global level, particularly in developing countries like India. Data on studies conducted in hospitals and communities in India reveal an increased burden of antimicrobial resistance [3]. As per the report of the center for disease control, in India there is an increase in the risk of antibiotic resistance for commonly seen diseases of public health concern (Table 1). Recently, NDM-1-positive bacteria have also been reported resistant [1]. The clinical impact of antibiotic resistance is huge, with increased morbidity and mortality, extended hospital stays, and increased costs of health care [4,5].

2. Inappropriate use of antibiotics: a major concern

One of the possible reasons for antibiotic resistance could be the inappropriate or overuse of antibiotics [6]. In 2015, an analysis of antibiotic use in 76 countries, reported that total worldwide antibiotic consumption was 35 billion DDDs, which was an increase of 65% from 2000 [7]. India is one of the world's largest antibiotics consumers [8]. Antibiotic use in India became doubled between 2000 (3.2 Billion defined daily doses) and 2015 (6.5 billion defined daily doses) [7]. Evidence suggested that there is a high proportion of antibiotic use in the private sector also. Studies from India reported that in the private sector, expensive newer class antibiotic use was more as compared to older ones [9]. The relationship between antibiotic exposure and antibiotic resistance is unclear on the population and individual level [10,11]. WHO headquarters developed a database for developing countries that include quantitative information on antibiotic use in primary care, which has been systematically collected data from studies published between 1990 and 2007. Toof tal 679 studies from 97 countries were identified of which 151 studies came from the SEA (South East Asia) region. It was found that 50% of viral upper respiratory tract infections are treated unnecessarily with antibiotics, even though only 53% of pneumonia cases receive an appropriate antibiotic; about 54% of acute diarrhea cases are treated unnecessarily with antibiotics, while only 55% receive oral rehydration solution as suggested in the treatment guidelines; and 40% of prescribed antibiotics are under-dose [12]. Published community studies have reported that for diseases like diarrhea and fever, which are primarily viral, approximately 70% of patients in the healthcare facilities are given antibiotics [13]. In many countries of the SEA Region, antibiotics are freely available over the counter without prescription which is against regulations [14]. Another study was done in three Indian cities, and reported that the most commonly prescribed antibiotic class in the community was fluoroquinolones, often for coughs and colds, which is entirely inappropriate [15]. The 2015 WHO multi-country survey revealed widespread public misunderstanding about antibiotic usage and resistance. The survey highlights for India are of concern: Three quarters (75%) of respondents thought incorrectly, that colds and flu can be treated with antibiotics; and only 58% knew that they should stop the antibiotics only when the course is completed as directed. More than three-quarters (76%) of respondents reported taking antibiotics within the past 6 months; 90% said they were prescribed or provided by a doctor or nurse [16]. Studies support that restricting misuse of antibiotics reduces resistance [17]. An issue that needs to be addressed in India is the regulation of the medical sector, particularly in the prescription of medicines [16].

3. India's National Action Plan on Antimicrobial Resistance (NAP-AMR)

India needs to take active steps to overcome antimicrobial resistance. All stakeholders within a country and an area must take collective action to achieve this goal [18]. The Indian government as well as all healthcare stakeholders in India accepted AMR (Antimicrobial Resistance) as a major issue to be solved. India is coming forward to resolve this

Table 1. Drug resistance in common diseases of public health importance in India.

Disease	Resistant antibiotic	Percentage resistance
Cholera	Furazolindone	60–80%
	Cotrimoxazole	60–80%
	Nalidixic acid	80–90%
Enteric fever	Chloramphenicol, Ampicillin, and Cotrimoxazole	30–50%
	Fluroquinolones	Up to 30%
Meningococcal infection	Cotrimoxazole, Ciprofloxacin, and Tetracyclin	50–100%
Gonococcal infection	Penicillin	50–80%
	Ciprofloxacin	20–80%

problem by implementing National Action Plan on antimicrobial resistance and improving the use of antibiotics by doctors, consumers, and health institutions [19]. Indian government implemented National Action Plan on antimicrobial resistance (NAP-AMR) in 2017 [20]. NAP-AMR emphasizes the need for improving the knowledge of rational use of antibiotics among various healthcare stakeholders through monitoring and research activities [21]. The plan set out five objectives i.e. to improve awareness and understanding of antimicrobial resistance; to strengthen surveillance and research; to reduce the incidence of infection; to optimize the use of antimicrobials, and to ensure sustainable investment in countering antimicrobial resistance [18]. Indian Medical Association (IMA) also has launched four campaigns for health care professionals to tackle this public health hazard − 'Jarrurat Bhi hai kya', '3A" means Avoid Antibiotic Abuse', 'use wisely not widely' and 'Think before ink". Indian Council of Medical Research (ICMR) has also promoted this plan by implementing an anti-microbial stewardship program at 20 private and public hospitals in country [22].

4. WHO AWaRe strategy against antimicrobial resistance

The WHO's essential drug list includes a list of the minimum medicines required for a basic health care system. This list contains only those medicines which are most effective, safe, and cost-effective for the major priority of the public [23]. In 2017, WHO experts have done major revision in the antibiotic section of EML which is categorized antibiotics into three categories i.e. Access, Watch, and Reserve. It provides advice on which antibiotics to use to treat common bacterial infections and which antibiotics to save for severe diseases. It recognizes the importance of optimizing antibiotic use and reducing antibiotic resistance without access restriction. The purpose of this modification is to ensure that antibiotic is available when needed and the correct antibiotic is prescribed for an appropriate infection. It should increase treatment effectiveness, minimize drug resistance development, and should preserve the effectiveness of "last resort" antibiotics. These changes support the WHO's Global Action, which aims to overcome the development of drug resistance by ensuring the rational use of antibiotics [23]. The three categories of antibiotics are as follows [24,25].

Access: This class of antibiotics includes those which have very low potency to develop resistance. These antibiotics are to be used as a first or second choice for empiric treatment of most common infections and thus should be available at all times at appropriate quality, dose, formulation, and price.

Watch: This class of antibiotics includes antibiotics that were considered in general to have higher toxicity concerns and resistance potential. This group contains antibiotics which are advised to be used as a first or second choice for a small number of infections. The use of these antibiotics has been reduced adequately to avoid further development of resistance.

Reserve: This category contains antibiotics that are considered the "last resort" option and are only used in the most severe infections when all other options fail such as multidrug-resistant bacterial infections. These antibiotics are the main goals of high-intensity national and international level programs involving central monitoring and reporting to preserve their effectiveness. A complete list of Access, Watch, and Reserve antibiotics is given in Table 2.

WHO suggested that the Access group of antibiotics should be available widely at all healthcare institutions and at an affordable cost to control the use of the other two groups of antibiotics. A recent report on antibiotic sales data in India between 2007 and 2012 showed that the consumption of the Watch group and Reserve group antibiotics is increasing rapidly compared to the Access group [26]. The first global collaborative study based on the WHO AWaRe approach was conducted on hospitalized children. The study reported variation between countries in the use of Access, Watch, and Reserve antibiotics in children and neonates. In children, Acto cess antibiotic use ranged from 7.8% in China to 61.2% in The Gambia, and Watch antibiotic use ranged from 23.0% in Finland to 77.3% in Iran [27].

In India, total systemic antibiotic sales increased by 26% from 2056 million Units in 2007−08, to 2583 million in 2011−12. The increase was due to the growth in sales of FDCs, which rose by 38%, whereas sales of SDFs increased by 20%. By 2011−12, FDCs comprised 34% (872 million units), and SDFs 66% (1711 million units), of total sales in India [28]. As per WHO AWARe categories, FDC antibiotics sales in India in 2011−12 include: 499 million units of access antibiotics, 367 million units of watch group antibiotics, 3 million units of reserve antibiotics, and 3 million units were included in uncategorized antibiotics. Compared to 2007−08, Key Access antibiotic sales had increased by 20%; However, FDC sales with watch group or reserve group antibiotics increased by 73% and 174% respectively [29]. Indian healthcare authorities should consider modifying the national EML based on WHO EML in three categories (AWaRe) for

Table 2. 2019 WHO AWaRe classification of antibiotics.

Class	Antibiotics
ACCESS	Amikacin, Amoxicillin, Amoxicillin/clavulanic Acid, Ampicillin, Ampicillin/sulbactam, Bacampicillin, Benzathine benzylpenicillin, Benzylpenicillin, Cefacetrile, Cefadroxil, Cefalexin, Cefalotin, Cefapirin, Cefatrizine, Cefazedone, Cefazolin, Cefradine, Cefroxadine, Ceftezole, Chloramphenicol, Clindamycin, Clometocillin, Cloxacillin, Dicloxacillin, Doxycycline, Flucloxacillin, Gentamicin, Mecillinam, Metronidazole (IV), Metronidazole (oral), Nafcillin, Nitrofurantoin, Oxacillin, Penamecillin, Phenoxymethylpenicillin, Pivampicillin, Pivmecillinam, Procaine benzylpenicillin, Spectinomycin, Sulfadiazine/trimethoprim, Sulfamethizole/trimethoprim, Sulfamethoxazole/trimethoprim, Sulfametrole/trimethoprim, Sulfamoxole/trimethoprim, Sultamicillin, Tetracycline, Thiamphenicol, Trimethoprim
WATCH	Arbekacin, Azithromycin, Azlocillin, Biapenem, Carbenicillin, Cefaclor, Cefamandole, Cefbuperazone, Cefcapene pivoxil, Cefdinir, Cefditoren pivoxil, Cefepime, Cefetamet pivoxil, Cefixime, Cefmenoxime, Cefmetazole, Cefminox, Cefodizime, Cefonicid, Cefoperazone, Ceforanide, Cefoselis, Cefotaxime, Cefotetan, Cefotiam, Cefotiam hexetil, Cefoxitin, Cefozopran, Cefpiramide, Cefpirome, Cefpodoxime proxetil, Cefprozil, Ceftazidime, Cefteram pivoxil, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefuroxime, Chlortetracycline, Ciprofloxacin, Clarithromycin, Clofoctol, Delafloxacin, Dibekacin, Dirithromycin, Doripenem, Enoxacin, Ertapenem, Erythromycin, Fleroxacin, Flomoxef, Flumequine, Fosfomycin (oral), Fusidic Acid, Garenoxacin, Gatifloxacin, Gemifloxacin, Imipenem/cilastatin, Isepamicin, Josamycin, Kanamycin, Latamoxef, Levofloxacin, Lincomycin, Lomefloxacin, Lymecycline, Meropenem, Metacycline, Mezlocillin, Micronomicin, Midecamycin, Minocycline (oral), Moxifloxacin, Neomycin, Netilmicin, Norfloxacin, Ofloxacin, Oleandomycin, Oxytetracycline, Panipenem, Pazufloxacin, Pefloxacin, Pheneticillin, Piperacillin, Piperacillin/tazobactam, Pristinamycin, Prulifloxacin, Ribostamycin, Rifabutin, Rifampicin, Rifamycin, Rifaximin, Roxithromycin, Rufloxacin, Sisomicin, Sitafloxacin, Sparfloxacin, Spiramycin, Spiramycin/metronidazole, Streptomycin, Sulbenicillin, Tebipenem, Teicoplanin, Telithromycin, Temocillin, Ticarcillin, Tobramycin, Tosufloxacin, Vancomycin (IV), Vancomycin (oral)
RESERVE	Aztreonam, Ceftaroline fosamil, Ceftazidime-avibactam, Ceftobiprole medocaril, Ceftolozane-tazobactam, Colistin, Dalbavancin, Dalfopristin-quinupristin, Daptomycin, Eravacycline, Faropenem, Fosfomycin (IV), Linezolid, Meropenem-vaborbactam, Minocycline (IV), Omadacycline, Oritavancin, Plazomicin, Polymyxin B, Tedizolid, Telavancin, Tigecycline

This list was adapted from World Health Organization.

antibiotics. Actions should be taken by regulators and policymakers to improve the availability and use of access antibiotic groups, as well as a reduction and rational use of watch and reserve antibiotics in both the public and private sectors.

5. Antimicrobial stewardship

AMS (Antimicrobial Stewardship) refers to "coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration'' [30]. These programs are beneficial in reducing treatment failures, reducing hospital-acquired infections and reducing antibiotic resistance while being financially beneficial for hospital [31]. There are "4 Ds" required for optimal antimicrobial prescribing: drug, dose, duration, and de-escalation. Ideally, the prescriber selects the right drug (e.g. most narrow spectrum), at the right dose (e.g. adjusted for patient renal function), for the right duration (e.g. shortest to successfully treat infection), and considers de-escalation whenever possible (e.g. narrow-spectrum based on culture results). A fifth "D" of stewardship, which is perhaps most critical in the context of emergency care, is diagnosis. Prescribing of antibiotics for inappropriate diagnoses (i.e. non-responsive conditions) is prevalent in the emergency department for all common infection types. This includes upper respiratory tract infections (e.g. bronchitis, sinusitis), urinary tract infections (e.g. asymptomatic bacteriuria), and skin and soft tissue infections (e.g. "pseudocellulitis") [32]. In general, AMS teams should monitor antibiotic use in the hospital to find out the most common misused antibiotics and multidrug-resistance organisms and should decide on appropriate interventions to improve this problem [33].

6. Importance of antimicrobial stewardship program

The Antimicrobial Stewardship Program (AMSP) has shown obvious benefits in reducing the rate of improper use of antibiotics [34–36]. There is enough evidence to prove that AMSP is useful to promote rational antibiotic use and reduce the cost of therapy. Various countries have implemented AMSP and reported a reduction in antimicrobial use associated with significant cost savings. Evidence suggested that implementing AMSP resulted in reducing the cost of antibiotics expenditure by 3$ million over 3 years [37]. A systematic review and meta-analysis of 26 studies to determine the efficacy of hospital-based antimicrobial stewardship showed significant improvement in clinical and economic

outcomes and significant reductions in antimicrobial consumption as well as cost in the critical care setting [38]. Surveys conducted in different hospitals in Australia to monitor the effectiveness of AMSP found that comprehensive AMS programs resulted in an overall reduction in antimicrobial use by 22–36% and substantial pharmacy cost savings. Successful implementation of AMS programs has been shown to improve the appropriateness of antimicrobial use and thereby reduce institutional resistance rates, morbidity, mortality, and healthcare costs [39]. Implementing AMSP has proven to be effective in reducing *C. Difficile* in hospitals [40]. Studies suggested that AMSP was found to be effective in rationalizing the use of antibiotics used in surgical prophylaxis and also helped clinicians in optimizing the dose in patients with impaired renal functions [41]. One study reported that implementing AMS resulted in a 70% increase in infections cure and an 80% decrease in treatment failure [42].

A questionnaire-based survey was conducted by United States Centres for Disease Control and Prevention 'Core Elements of Hospital Antibiotic Stewardship Programs' to monitor the status and possible problems in implementing antimicrobial stewardship (AMS) in 116 Grade-A tertiary hospitals in China. Reported significant improvement in AMS, mainly including the antibiotic consumption index [43]. A systematic review was conducted to assess the effectiveness of antibiotic stewardship interventions in hospitals in low-middle-income countries. This included 27 studies from 11 middle-income and two low-income countries that reported positive effects of hospital antibiotic stewardship interventions in many countries [44].

7. Antimicrobial stewardship program: Indian scenario

Implementation of AMSP in India is still in its formative stage as all the stewardship components are yet to be fully implemented in the country. A survey conducted in India to monitor the implementation of all components of the AMSP showed that only 35% (6 studies) of the 17 studies involved were based on the entire AMSP implementation, while other studies included at least one of the AMSP Implementation components [45]. Another survey carried out about AMSP components implementation and outcome by ICMR in 2013 among 20 tertiary Health care institutions reported that only 40 percent of institutions had AMSP written documents, 65 percent had AMAs prescription guidelines and 75 percent had HIS (Healthcare Infection Society) guidelines [46]. AMSP program is not fully implemented in India, especially at the primary care level. There is a need of conducting an educational program for various health care professionals regarding AMS and also a need to promote research to implement AMS in both public as well as private health facilities.

8. Barriers to implementing AMS and WHO AWaRe strategy

Many factors can act as a barrier to the successful implementation of AMSP and the WHO Aware Strategy. One of the important factors is the limited availability of antimicrobials. Various surveys conducted in different parts of India reported a lack of access to essential medicines including antimicrobials, especially in the public health sector [47]. Lack of access to antimicrobials has been reported in other LMICs as well [48]. A recent report analyzed antibiotic sales data in India between 2007 and 2012 which showed that the consumption of Watch group and Reserve group antibiotics is increasing rapidly when compared to the Access group of antibiotics [49]. Therefore ensuring the availability of quality antimicrobials is important for the successful implementation of AMSP and AWaRe strategy. Indian authorities should consider revising the National EML and adopting the WHO EML for antibiotics in three categories (AWaRe) to optimize the use of antimicrobials. Another important factor is limited diagnostic facilities. The lack of diagnostic facilities has been attributed to the overuse of antibiotics [50]. Improved laboratory capacity and structured surveillance techniques to create an antibiogram are required in India. Resistance to changing current practices can also play role in the failure of AMSP. As resistance rates differ in different countries, this could lead to inappropriate use of antimicrobials in different clinical situations. The lack of updated guidelines regarding antimicrobial prescribing may lead to failure of AMSP. Therefore Infectious Disease Society of America (IDSA) is recommended to create guidelines based on local resistance patterns for successful utilization of antimicrobials [51]. A study conducted in Kerala, India to examine key barriers and facilitators of implementing ASP in a tertiary hospital using the SEIPS (System Engineering Initiative for Patient Safety) model found that inadequate physical visibility of stewardship activities, limited access to clinical pharmacists, high physician workload and high antibiotic use in the community were major barriers to effective ASP implementation [52].

India needs trained pharmacists and microbiologists to meet the need for antibiotic stewardship and

infection control across different institutions and hospitals throughout the country. This is essential to improve the implementation activities by building and strengthening components such as the use of information technology in monitoring and surveillance, use of antibiotic cycling, sensitizing staff, and broadening the role of different staff members to develop an effective program in the nation that meets the goals of NAP-AMR. Health care professionals, healthcare authorities, and other stakeholders should move forward for a common goal of antimicrobial stewardship and should work to assess ground realities in antibiotic use and hospital infections, as well as a collaborative approach, should be developed to reduce the infection as well as antimicrobial resistance.

9. Conclusion

Studies reported that the implementation of an antimicrobial stewardship program is beneficial in promoting the rational use of antibiotics. India needs to implement a stewardship program and use antibiotics according to the AWaRe (Access, Watch, and Reserve) classification in both public and private health facilities. A collaborative approach by all health care providers and government towards stewardship programs is necessary to make India's National Action Plan on Antimicrobial Resistance (NAP-AMR) successful. Conducting interventional studies on antibiotic use in health facilities and creating awareness in public about the harmful effect of self-medication could help to save antibiotics for present and future generations.

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