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Controlling Antimicrobial Resistance: Lessons from Scotland for India

Suchita Bhattacharyya [1] , *Kanchan Mukherjee* [*2] , *Alan Haycox* [3]

ABSTRACT

Introduction

In India, antimicrobial resistance (AMR) is a serious public health problem. While some official policies have been formulated, they are not comprehensive and their enforcement is not monitored or regulated. This paper discusses the success achieved by the Scottish Antimicrobial Prescribing Group (SAPG) and derives lessons relevant for AMR policies in India.

Methods

This study involved secondary data review and discussions with SAPG representatives.

Results

India is the largest consumer of antibiotics for human health (10.7 units/person) and this consumption is steadily increasing. Irrational use, fixed-dose combinations and growing antibiotic use in livestock have resulted in newer drug-resistant pathogens. In 2008, the Scottish government initiated the SAPG that has achieved nationwide success in AMR control. The enormous success achieved by SAPG has demonstrated that this delivery model is effective in addressing AMR and can also be used in India, with country-specific modifications.

Conclusions

In India, strong political and stakeholder support is required for a pragmatic one-health approach to antimicrobial governance that would involve the interplay between agriculture, livestock and pharmaceutical industries. Project management, quality improvement, information management and performance assessment through accountability measures are essential. These can be coordinated nationally and implemented locally through existing structures and institutes. This needs to be supported by a powerful clinical network and underpinned by robust educational support that is dynamic to meet the needs of local healthcare professionals and general population.

Keywords: Antibiotics, Resistance, Stewardship

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[1]Visiting Fellow, University of Liverpool, UK

[2]Professor, Tata Institute of Social Sciences, Mumbai

[3]Reader, Management School, University of Liverpool, UK

***Corresponding Author**
Kanchan Mukherjee
Centre for Health Policy, Planning and Management, School of Health System Studies, Tata Institute of Social Sciences (TISS)
V. N. Purav Marg, Deonar, Mumbai – 400088, India
kanch@tiss.edu
Telephone No. 91-22-25525533

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INTRODUCTION

Antibiotics are lifesaving, with penicillin being a critical discovery for protecting human health. Therefore, a major public health failure and challenge is the downward spiral from the discovery of penicillin to the development of antimicrobial resistance (AMR) and emergence of deadly multi-drug resistant (MDR) pathogens. Antibiotics are known to destroy normal bacterial flora in the body, which are an important defense against infections.[1]

Moreover, overuse or improper use of antibiotics causes AMR in some deadly bacteria such as Mycobacterium tuberculosis, Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli (E. coli), Pseudomonas aeruginosa and Clostridium difficile (C. difficile), which is a major public health concern worldwide. AMR is currently estimated to cause more than 700,000 annual deaths worldwide, with an estimated 10 million annual deaths by 2050. The economic and public health consequences of AMR are enormous. A continued rise in AMR would lead to a global reduction of 2-3.5% in Gross Domestic Product (GDP) by 2050 and the world is estimated to lose USD 100 trillion worth of economic output by 2030.[2] The emergence of carbapenemase producing bacteria, especially New Delhi metallo-β-lactamase (NDM-1) and its variants, worldwide, is a major public health concern. Asia serves as the major reservoir of NDM producers, with around 58.15% abundance of NDM-1 variant distributed mostly in China and India.[3] Antibiotic abuse is a major driver of AMR. This abuse involvevs a combination of poor patient awareness as well as irrational prescription practices by healthcare providers. The Scottish government attempted to tackle this challenge by creating the Scottish Antimicrobial Prescribing Group (SAPG), which has made a significant contribution in controlling AMR.[4] In this context, this study reviews the success of SAPG in controlling AMR in Scotland and suggests recommendations to control AMR, in India.

OBJECTIVES

1) To understand the drivers of AMR worldwide as well as in India
2) To derive lessons from SAPG for creating and enforcing effective policies on AMR in India

MATERIAL AND METHODS

The study involved discussions with SAPG representatives in November 2016 as well as extensive secondary data review. The discussions with SAPG representatives were aimed at understanding the context, development and current status of the SAPG programme. Secondary data included relevant documents, publications and SAPG annual reports on AMR. Reports, publications and policy documents related to AMR in India were also reviewed.

RESULTS AND DISCUSSIONS

There are three key drivers for AMR. First is antibiotic use in humans. Second is antibiotic use in environment and third is antibiotic use in the livestock sector (poultry).

Antibiotic Use and Abuse in Humans

In 2010, India was the world's largest consumer of antibiotics for human health (10.7 units per person), followed by China and USA. The BRICS countries, i.e., Brazil, Russia, India, China, and South Africa contributed to 7% of the overall increase in global antibiotic consumption between 2000 and 2010, of which 23% of the increase in the retail antibiotic sales volume was attributable to India. Outside BRICS, Australia (248%) and New Zealand (169%) had the highest increase in consumption of antibiotics.[5] The massive increase in antibiotic use in India is attributed to rapid economic growth and rising incomes, with no major improvements in water, sanitation, and public health. [6] Antibiotics continue to be widely prescribed or sold for diarrheal diseases and upper respiratory infections, with limited or no effects,[7,8] which could be efficiently prevented by improving water and sanitation. Hence, one of the major contributors to AMR in India is the lack of basic public health measures. In addition, there are misconceptions among the population regarding conditions treatable by antibiotics. A multi-country WHO study, which included India, found 64% of respondents incorrectly claiming that colds and flu could be treated by antibiotics.[9]

Doctors in India routinely receive compensation/gifts from pharmaceutical companies and pharmacists in exchange for antibiotic prescriptions.[10] Also, infection control in hospitals is poorly monitored as indicated by a study in a large tertiary care hospital in India, which found an overall healthcare-associated infection prevalence of 7%, with a third of these being surgical site infections.[11] Half of the patients were receiving antimicrobials. Over-the-counter access to antibiotics is also a major contributor to AMR. AMR is exacerbated by a wide range of fixed-dose combinations available in the market, often

without scientific/medical merit or evaluation. A recent study reported 48 fixed-dose combinations and 22 antimicrobials for tuberculosis.[12] Another factor is poor clinician awareness of the rationality and dosing of fixed-dose combinations.[13] A recent paper in the British Medical Journal suggested that completion of a prescribed antibiotic course may be unnecessary, and may in fact contribute to AMR due to overuse. Patients are at unnecessary risk of antibiotic resistance when treatment duration is longer than necessary, since studies to identify minimum effective treatment duration have not been performed for most diseases.[14] However, doctors in India caution against patients stopping antibiotics on their own stating that the clinician's assessment is critical.[15]

Antibiotics in the Environment

Environmental antibiotic pollution facilitates the transfer of resistance genes to human commensal and pathogenic bacteria.[16] Notably, waste water treatment plants serving antibiotic manufacturing facilities have been implicated in the transfer of resistance genes into human microbiota, and pose a serious threat to antibiotic effectiveness given the size of India's pharmaceutical sector.[17] India has no regulations governing the discharge of antimicrobial waste into the environment, which needs immediate attention.

Antibiotic Use in Animal Sector

Growing antibiotic use in the animal sector is resulting in a greater selection of pathogens and is being driven by the increased demand for meat and poultry. The extreme growth in consumption of chickens worldwide is primarily due to the expansion of this sector in India alone, where areas of high consumption (30 kg/km^2) are expected to grow by 312% by 2030.[18] A recent Organisation for Economic Co-operation and Development (OECD) report indicated that the costs of withdrawing antimicrobial growth promoters in India would be roughly USD 1.1 billion.[19] A recent study on poultry chickens in India conducted in 18 poultry farms in Punjab, has demonstrated a very high prevalence of MDR E. coli due to unregulated use of antimicrobials such as ampicillin, nalidixic acid, etc., and has emphasised the need to curb the use of such antimicrobials in poultry/livestock.[20] NDM-producing E. coli has also been identified in piglets in farms of India.[21]

Drivers of Antibiotic Resistance in India

India tops the list as the largest consumer of antibiotics for human health.[22] The crude infectious disease mortality rate in India is 416.75 per 100,000 persons, [23] which is twice that in the United States when antibiotics were introduced (roughly 200 per 100,000 persons).[24] Factors such as poor public health infrastructure, nosocomial infections, rising incomes, a high burden of disease, and relatively low cost and unregulated sales of antibiotics have greatly facilitated the rapid rise in resistant pathogens in India.[22, 25] Although an accurate estimate of the overall burden of AMR in India is unavailable, about 57,000 annual neonatal deaths are attributable to sepsis caused by drug-resistance to first-line antibiotics.[25]

In the case of tuberculosis, WHO estimates that 61,000 people are living with MDR-TB in India, the highest in the world, with only half the number of cases being identified. The actual incidence and prevalence rates of XDR-TB in India are unknown, although some scattered data is available. A study in Delhi among 611 TB patients found that 483 patients were infected with MDR-M. tuberculosis (MTB) strains. Eighteen MDR-TB isolates (3.7%) were XDR-MTB strains. Family history of TB, socioeconomic status, concomitant illness and previous intake of second line injectable drugs were significantly associated with the occurrence of XDR-TB.[26] Studies in India have shown poor compliance to surgical antibiotic prophylaxis in urban[27, 28, 29] and rural hospitals.[30] In India, studies have recorded Carbapenem-Resistant Enterobacteriaceae (CRE) prevalence rates of 12–50%.[31] A study found 26.3% of CRE having multiple co-carriage genes in India with nosocomial origin as major source.[32] Hence, hospital infection control is critical.

Widespread AMR may have more severe consequences for India than other countries because of India's high bacterial disease burden. Currently, India does not have any regulations for the use of antimicrobials in cattle, chickens and pigs raised for domestic consumption. Recent studies in India have

discovered antimicrobial residues and MDR bacteria in food animal products (such as chicken meat and milk),[20, 33] indicating rampant and unregulated antibiotic use in livestock production. There are no standards in India for tolerance of antibiotic residues in poultry.[34]

In addition to E. coli, C. difficile is an emerging concern. Major epidemics of C. difficile infection (CDI) have occurred in North America and Europe over the recent decade, but awareness and surveillance of CDI in Asia have remained poor. Limited studies performed throughout Asia indicated that CDI is also a significant nosocomial pathogen in this region, but its true prevalence remains unknown.[35] C. difficile has also been identified as a neglected but emerging pathogen in India.[36] While initially thought to be a nosocomial infection only,[37] recent studies have shown that community-acquired CDI is increasing.[38]

Steps Taken to Address Antibiotic Resistance in India

The challenges associated with antibiotic resistance in India are multifaceted and multidimensional. At the laboratory level, molecular-based detection of antibiotic resistance is a challenge, as is monitoring their circulation in hospitals and community. Prescription monitoring is another major issue. To tackle the problem of AMR, the Central Government created a committee, which formulated the national policy for containment of AMR in 2011. The antimicrobial guidelines (AMGL) developed by the Indian Council of Medical Research (ICMR) advises the clinician managing an infection to customize these guidelines in accordance with the local AMR data.[39] However, local AMR data is frequently unavailable.

A more complex problem involves regulating the sales of substandard and illegal antimicrobials, the extent of which is poorly quantified.[40] To prevent over-the-counter (OTC) sales of important antibiotics, the Central Drugs Standard Control Organization (CDSCO) implemented packaging, reporting and prescription norms in 2014 for 24 antibiotics that should be followed by pharmacists. However, its enforcement remains limited.[23, 41]

Steps Taken to Address Antibiotic Resistance in Scotland

The emergence of the CDI epidemic in Scottish healthcare facilities suggested a link between inappropriate prescribing practice and CDI. The CDI outbreak in the Vale of Leven Hospital, NHS Greater Glasgow and Clyde, with a high number of deaths, brought major attention to this problem among the public, politicians and national media.[42] The need to implement a national antimicrobial stewardship programme in all healthcare settings to support existing infection control and environmental decontamination measures was considered a priority to contain and reduce CDI. In 2008, The Scottish Management of Antimicrobial Resistance Action Plan (ScotMARAP) was published by the Scottish Government.[43] One of the key actions was initiation of the SAPG in March 2008, hosted by the Scottish Medicines Consortium (SMC), to ensure national implementation of the key recommendations of this action plan. The primary objective of SAPG is to coordinate and deliver a national antimicrobial stewardship programme. The key successes of SAPG include providing local clinical prescribing leadership through Antimicrobial Management Teams (AMT) and organisational accountability through agreed national targets for prescribing. The work of SAPG is supported by a national framework for education, timely sharing of data using the Institute for Healthcare Improvement, extranet and several local improvement strategies in collaboration with local infection prevention and quality improvement teams. Aligning antimicrobial stewardship with patient safety and quality improvement, which are key elements of the National Quality Strategy, has also been particularly helpful.[44] SAPG works to reduce unnecessary antibiotic use through promoting the use of narrow-spectrum agents and reducing the use of broad-spectrum antibiotics; drive improvement in the quality of antibiotic use to improve clinical outcomes; and minimise harm from antibiotics (mortality, CDI, resistance, adverse reactions).

Impact of SAPG

Using the transfer function statistical model, 59% of CDI reduction in medicine and 42% of CDI reduction in surgery was explained by changes in antibiotic

use.[45] A comparison between Scottish and European data showed Scotland performing better in some key parameters related to AMR such as reason for use recorded in notes, compliance with local guidelines and surgical prophylaxis for ≤24 hours. The national prevalence of antimicrobial use was 27.8%. The results demonstrated a lower use of antimicrobials in Scotland as compared to participating European hospitals.[46] Between 2006 and 2011, the CDI incidence rates in patients ≥65 years significantly decreased in Scotland from 1/1000 bed days to 0.3/1000 bed days.[40]

CONCLUSION

Non-compliance with antibiotic full course, irrational prescription, high cost of antibiotics, self-medication by patients without consulting doctors, illiteracy, etc., are some of the key factors that contribute to AMR worldwide. To compound the problem, pharmaceutical companies are increasingly withdrawing from antibiotics research and very few new antibiotics were approved in recent decades. Between 1990 and 2010, the number of companies conducting antibiotics research decreased from 18 to four.[47] In the last 25 years, virtually no new antibiotics have been developed.[2] The antimicrobial stewardship programme in Scotland, led by the SAPG, is delivered by NHS National Services Scotland (Health Protection Scotland and Information Services Division), NHS Quality Improvement Scotland, and NHS National Education Scotland as well as NHS board Antimicrobial Management Teams. SAPG has achieved numerous successes:

1) Through measures to optimise prescriptions in hospital and primary care, combined with infection prevention measures, SAPG has significantly contributed to reducing CDI rates in Scotland
2) All key stakeholders at local and national levels have been engaged to ensure an integrated approach to antimicrobial stewardship within the wider healthcare-associated infection agenda
3) Development and implementation of data management systems to support quality improvement
4) Creation of training materials on antimicrobial stewardship for healthcare professionals
5) Improving clinical management of infections (e.g. community-acquired pneumonia) through quality improvement methodology

The tremendous success achieved by SAPG has demonstrated that this delivery model is effective, and provides the leadership and focus required to implement antimicrobial stewardship to improve antimicrobial prescribing and infection management.

Lessons for India

From the discovery of lifesaving penicillin to the emergence of lethal MDR bacteria, antibiotic usage has been marred by controversies. In India, the problem is manifold due to excessive and improper use of antibiotics (for viral infections, etc.) by patients, as well as indiscriminate prescriptions by doctors. Better water quality and sanitation can lower antibiotic consumption. Hence, improving basic public health facilities will be a cost-effective and long-term strategy to address AMR in India. The Central Government's Swachh Bharat (Clean India) initiative is a step in the right direction and if properly implemented, it can lower the AMR levels in India. The SAPG experience demonstrates that building a strong and effective antibiotic awareness campaign with strong political and stakeholder support is essential. A pragmatic 'real-world' approach to antimicrobial stewardship is required in India that would combine project management, quality improvement, information management and performance assessment through accountability measures. These can be coordinated nationally but implemented locally by pre-existing structures and institutes. These teams need to be supported by a powerful clinical network (e.g., association of doctors, hospitals, etc.) and a robust educational programme (e.g., Continuous Medical Education) that is dynamic to meet the needs of local/regional healthcare professionals.

The Scottish Intercollegiate Guidelines Network (SIGN) provides evidence-based regulations, which can be used to establish local therapeutic guidelines and implemented for antibiotic prophylaxis

administration in patients undergoing surgery. In addition, a strong public awareness programme using media and internet should be initiated in India to spread awareness about AMR. The principles of antimicrobial stewardship and appropriate use can be incorporated into undergraduate and postgraduate medical education courses in India.

Antibiotic use among poultry, cattle and pigs is common in India, but no guidelines or policies exist regarding their use. The British Poultry Council (BPC) regulates the use of antibiotics in the poultry sector in Scotland. India also needs a governing body for regulating the use of antibiotics in poultry. In Scotland, good cooperation and a systematic process of building the antibiotic awareness campaign, strong political and stakeholder support, and the development of campaign materials based on scientific evidence were key elements that contributed to successfully lowering AMR. Based on the experiences of SAPG, we recommend the STEP approach for addressing AMR in India. STEP stands for:

S: Stewardship, surveillance and strict regulations for antibiotic use by healthcare providers, pharmacists, etc.

T: Translational research focusing on development of new and safe antibiotics

E: Environmental improvement through better water and sanitation facilities, which would decrease the need for antibiotics

P: Poultry and livestock interventions through policies restricting the misuse of antibiotics in animals

STEP is a multi-sectoral integrated approach with involvement of key stakeholders across different sectors like healthcare, pharmaceutical, environment, basic sciences and veterinary sciences. Unless, such a comprehensive approach is implemented, it would be impossible to control AMR in India.

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