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REVIEW

Advances in pharmacovigilance initiatives surrounding antimicrobial resistance-Indian perspective

Laxminarayana Kurady Bairy, Veena Nayak, Avinash A and Sushil Kiran Kunder

Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, India

ABSTRACT

Introduction: In recent years the development of antimicrobial resistance has been accelerating, the discovery of new antimicrobial agents has slowed substantially in past decades.

Area covered: This review mainly focuses on the problem of antimicrobial resistance(AMR); the various contributor mechanisms, consequences and future of AMR. The review also highlights the irrational use of antimicrobials, improving their usage and problems associated with pharmacovigilance of antimicrobial resistance.

Expert opinion: Pharmacovigilance in the form of surveillance of antibiotic use is being done in 90% of the countries worldwide through the WHONET program developed by WHO. However, the data comes from a limited area of the globe. Data from every part of the world is required, so that there is geographical representation of every region. A major hurdle in quantifying the extent of antimicrobial resistance is the fact that there are several known microbes, that may turn out to be resistant to one or more of the several known antimicrobial agents. The global action plan initiated by WHO, if implemented successfully will definitely reduce AMR and will help in evaluating treatment interventions.

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1. Introduction

Infectious diseases like malaria, diarrhea, pneumonia, etc. account for over 30% of deaths globally in children below five years.[1] These infections are the leading cause of deaths in low- and middle-income countries and also in India.[2] Though the mortality due to malnutrition is predictable in this age group, the contribution of antimicrobial resistance (AMR) to outcome of infectious diseases is difficult to predict.[2] The scenario is not different for adolescents as well as adults. The influence of AMR is maximum in developing countries, where the incidence of infectious diseases is higher and irrational use of antibiotic is unchecked. Even in developed countries where the development of new antimicrobials has slowed down substantially, increasing resistance among nosocomial pathogens has emerged. Constant attempts to overcome AMR are very crucial to treat such infections. 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.[3] Considering the magnitude of problem, a worldwide effort to combat AMR through network to associate and share the resources and efforts toward this common purpose could be successful.

2. Antimicrobial resistance: a worldwide problem

Antimicrobials at the time of discovery were magic bullets without a doubt. However, it was just a matter of time as the bacteria got used to these drugs. For example, Staphylococcal organisms developed resistance to the wonderdrug penicillin by producing beta lactamases and destroyed the beta lactam structure, rendering them ineffective. This problem was countered by the discovery of newer classes of drugs over a period of time, like aminoglycosides, glycopeptides, etc. However, the problem now is that the organisms have grown resistant to all these drugs, and newer drugs are just trickling down the pipeline.[4] The problem of antimicrobial resistance is now blown out of proportion so much so that pan-drug-resistant organisms have emerged, wherein all our drugs are ineffective.

2.1. What is our contribution to this growing problem?

Misuse of antimicrobials: Antimicrobial use is out of control, and that is the root of all the trouble. Prescribing drugs used in humans to animals, antibiotic application in the form of sprays in agriculture, using wrong antibiotics or right antibiotics at wrong doses for a wrong duration are some of the problems to list a few.[5]

Misuse of antibacterials: Increased use of goods like soaps, detergents, toys, mattress pads impregnated with antibacterials like triclosan, triclocarbon, etc. There is no definite evidence supporting this use, but it definitely raises some public health issues.[5]

Misuse of antimicrobials and antibacterials destroy the sensitive bugs. However, the resistant ones are unfazed. Moreover, there is no competition from the other microbes.[5]

CONTACT Laxminarayana Bairy Kurady kl.bairy@manipal.edu

Article highlights

- Various mechanism antimicrobial resistance and its consequences: bacteria may develop resistance due to efflux pump which pump the antibiotic out of bacteria, unable to bind to the target in bacteria as the target is modified, undergo degradation by certain enzymes elaborated by bacteria or by point mutation.
- Pharmacovigilance and antimicrobial resistance: This is essential because the data collected will guide the policy makers and government bodies to better their efforts, and target their strategies to prevent or overcome microbial resistance.
- Problems with pharmacovigilance of antimicrobial resistance: The lack of uniform definitions, lack of data from developing countries, inadequate laboratories facilities, insufficient budget, political constraints and lack of data on final clinical outcome.
- National surveillance system for antimicrobial resistance: National surveillance in the form of Sentinel surveillance have been found to be quite useful in place of comprehensive surveillance as the latter is not practicable and done through network of Antimicrobial Susceptibility Testing.

This box summarizes key points contained in the article.

2.2. What are the various mechanisms of resistance?

There are numerous mechanisms by which a microbe develops resistance to an antimicrobial drug, the details of which have been cited elsewhere.[6] However, few of the resistance mechanisms have been listed.

a. Chloramphenicol and tetracyclines either do not enter or are thrown out, due to the efflux pumps.[6]
b. Erythromycin, beta lactams, and lincomycin are unable to bind to the target as the target gets modified.[7]
c. Aminoglycosides, chloramphenicol, and beta lactams undergo modification or breakdown.[7]
d. The inhibited metabolic process is bypassed in case of cotrimoxazole.[7]
e. Point mutations are responsible for echinocandin resistance.[8]
f. Polyene resistance is due to reduced access to the targets.[8]

2.3. How do microbes acquire and spread the resistance?

a. Natural/innate resistance: This is in-built in the organisms. For instance, the bacteria do not possess a transporter required for an antibiotic. As a result of this, the drug is unable to enter the organism, *Pseudomonas* being a classical example.[9]
b. Acquired resistance: Here, the microbe acquires resistance to antibiotics. In vertical transfer, the progeny receives it after replication of genetic material. On the other hand, in case of horizontal transfer, the bacteria transfer the genetic material by conjugation, transduction, or transformation.[9]

2.4. What are superbugs? What is super resistance?

Superbugs are organisms that increase morbidity and mortality owing to the multiple resistances they possess to standard therapy. Some of the examples are multidrug-resistant tubercle bacilli, multidrug-resistant *Pseudomonas aeruginosa, Acinetobacter baumannii*, untreatable gonorrhea [10] and methicillin-resistant *Staphylococcus aureus*.[11] It is because of these resistant microbes that we are in the twilight of antibiotic era.

3. Consequences of antimicrobial resistance

Two major consequences of antimicrobial resistance are medical and economic consequences.

3.1. Medical consequences

The mere thought of how much impact antimicrobial resistance will have on human health is worrisome. In case the patient is infected with a resistant bug, the duration of hospital stay and therapy increases. In addition, the morbidity is higher and at times, fatal too. They remain infected for a longer duration, as a result of which the chances of transmission of the microbe rise. It also promotes the chance of colonization as well as spread of resistance, especially in a hospital setting. In addition, the need for emergency procedures and surgery goes up jeopardizing lives and increasing costs.[12] Surgical procedures depend on the use of antibiotics pre and post operatively. If the antibiotics are no longer effective, even the routine surgeries will be risky.[13]

3.2. Economic consequences

Coming to economic impact, it is an expensive affair. The cost includes the expenses of all the drugs that failed to counter the microbes plus the newer drugs. The longer the duration of disease, the longer will be the duration of hospital stay, which includes the more expensive Intensive Care Unit stay too. One more point to be noted here is the drugs that are used to treat these multiple drug-resistant strains are new and often quite expensive and beyond the reach of significant chunk of population, especially in a developing country like India. As we all know, assessment of cost of morbidity and mortality is quite difficult to evaluate on an economic platform.[12] In addition, with the increase in length of hospital stay, more number of diagnostic tests will be performed, which adds to the cost. From the perspective of drug industry, once the resistance sets to a particular drug, there are no more takers of that particular drug. The industry incurs heavy losses because of this simple fact.[14]

3.3. Impact on society

It can be simply called an indirect consequence of antimicrobial resistance. Similar to the principle of herd immunity, antimicrobial use by certain individuals in the community can make others susceptible to infections and colonization among individuals who have not got antimicrobials. By shifting the balance, in other words by killing the susceptible organisms, we are indirectly promoting the existence of resistant ones. The more the resistant microbes, the more is the transmission and chance of people getting infected by the organisms.[15]

3.4. Other consequences of misusing antimicrobials

Human and animal stools now contain microbes that are resistant to many drugs. Microbes come from the food we eat uncooked which has been sprayed with antimicrobials, therefore more common with vegetarians, as meat eaters cook the meat before eating it.[16]

4. Future of antimicrobial resistance

Antimicrobial resistance is one of the greatest threats to human health. The present times are such that we always lag behind the mutation rates of microbes. Despite our valiant efforts, the antimicrobial resistance increases, and the drug pipeline continues to deteriorate. Many research strategies have been proposed to combat antimicrobial resistance. The most important one would be to discover many more targets for antimicrobial action before the organisms could develop ways to overcome them. Development of newer vaccines to prevent diseases itself can limit the use of antibiotics. An innovative method suggested would be to target host responses to microbes rather than targeting microbes themselves.[17] The current concepts of health care have been built on the foundation that infectious diseases can be treated or prevented using antimicrobial agents. More and more of antimicrobial resistance is slowly pushing us toward the pre-antibiotic era and we are merely being over-optimistic. The fact of the matter is we are still unaware of the extent of trouble that is in store for us.[18] It is obvious that as long as we use classic antibiotics, the microbes will find a way to gain resistance to them. Investigators have pooled in their efforts of late to target genes relating to pathogenesis and virulence. What is appealing is the use of antisense nucleotides as novel antimicrobials. However, these are just concepts and we are far from implementing this in clinical practice.[19]

5. Post-antibiotic era

During the initial years following the discovery of antibiotics, researchers warned doctors regarding the concept of resistance development, which were then conveniently ignored by the physicians who put the health of the individual above the risk of resistance, which was nothing more than just a mere theory then. But following a few decades, this theoretical risk has been modified into an untreatable force.[20]

The term 'pan-drug-resistant microbes' is being used quite frequently. It simply means we have run out of drugs and ideas. The organisms simply will not respond. The latest addition to this list is pan-drug-resistant *Acinetobacter, Pseudomonas*, and *Klebsiella*. It has already been highlighted that we are on the verge of facing an antibiotic acocalypse wherein the bacteria will be totally resistant to treatment with no therapeutic options left.[20] Researchers have already started exploring new avenues like targeting the drug virulence.[21] Even older concepts like phage therapy are being reconsidered. Are antibiotics over? Or do we still have time? Only time will tell.[22]

6. Rational versus irrational use of antimicrobials

Irrational (or non-rational) use of antimicrobial drugs is the use of these drugs in patients, inappropriate to their needs, or in doses that are not appropriate, or for an inadequate period, or at an inappropriate cost to them. The World Health Organization (WHO) estimates that almost 50% of prescriptions worldwide are irrational at present. Similarly, 50% of medicines dispensed or sold are also irrational. Irrational use includes over-prescription, under-prescription, and prescription or dispensing of unnecessary antibiotic combinations.[23–25]

The most common examples of irrational drug intake include [23]:

a. Unnecessary polypharmacy (the usage of too many antimicrobials than required for the patient);
b. Inadequate dosage of the antimicrobials;
c. Non-compliance with existing and proven clinical or prescribing guidelines;
d. Irrational route of administration of antimicrobials;
e. Self-medication.

The WHO has brought out 12 core interventions to facilitate and promote rational drug usage.[23]

a. A mandated multi-disciplinary national body to coordinate medicine-use policies;
b. Clinical guidelines;
c. Essential medicines' list based on treatments of choice;
d. Drugs and therapeutics committees in districts and hospitals;
e. Problem-based pharmacotherapy training in undergraduate curricula;
f. Continuing in-service medical education as a licensure requirement;
g. Supervision, audit, and feedback;
h. Independent information on medicines;
i. Public education about medicines;
j. Avoidance of perverse financial incentives;
k. Appropriate and enforced regulation;
l. Sufficient government expenditure to ensure availability of medicines and staff.

7. Improving the usage of antimicrobials

Antimicrobial agents, which could be 'wonder drugs' if used in the right manner, are proving to be less effective in most of their primary or auxiliary indications, chiefly because of irrational use of the same. These drugs are misused mainly owing to their easy availability, easy affordability, and relative safety. The WHO recommends two steps to optimize antimicrobial use. These steps include: increasing appropriate use, and decreasing inappropriate use of these agents, i.e. ensure that infected patients who need antimicrobial therapy have access to quality medicines which conform with policy recommendations and standard treatment guidelines and discourage the indiscriminate use of antimicrobials in patients unlikely to derive any benefit.[24]

In addition, the non-human usage of antimicrobials should also be controlled, as a vast majority of the antimicrobial share goes to the animals like poultry, cattle, sheep, and fish. In addition, agricultural misuse and industrial misuse also account for the widespread antimicrobial resistance.[26,27]

'Antibiotic steward programmes' or 'Antibiotic stewardship' are a set of coordinated interventional procedures that aim at the appropriateness of the use of antimicrobials. Several such stewardships have been initiated, mainly in the developed and economically rich countries. This could prove to be an effective means of reducing and controlling the emergence and spread of antimicrobial resistance.[28]

8. Other measures to thwart antimicrobial resistance

These measures can be classified based on the population that has to act.[26,17]

a. People (general public and patients) can help by getting vaccinated according to the schedule, washing hands as and when required, using antimicrobials only when prescribed, and by completing the full-recommended course of antimicrobials.
b. Health professionals (doctors, nurses, pharmacists, etc.) can help by prescribing and dispensing the right amount of antimicrobials at the right time to the right person, and by improving the infection control status of the hospital or other health-care settings.
c. Scientists and researchers can help by discovering newer techniques and methods to minimize or fight antimicrobial resistance.
d. Governments and diplomats can help by proper regulation of the use of antimicrobial agents, forming and enforcing clear-cut policies, supporting the research and development happening in the field, and by bringing about good awareness among the general population regarding the impact of the current and future situations.

This awareness in the general population is being constantly updated in the Indian subcontinent, in the form of films, street plays, wall paintings, etc. However, Indian experts have maintained that although the general public corresponds with palpable enthusiasm, these efforts could not be continued owing to lack of financial resources.[29]

9. Gaps in research and development

At present, several gaps exist in the research and development wing of antimicrobial resistance. These gaps are more evident in low-economy and mid-economy countries. Most of the gaps correlate with the economic status of the nation. The biggest gap is the lack of adequate laboratory facilities and efficient manpower to analyze and report the presence of antimicrobial resistance patterns. Also, Government policies have to be changed in accordance with the existing and future status of the problem. Also, technical difficulties further complicate the gaps already present.[30]

10. Pharmacovigilance and antimicrobial resistance

Surveillance of antimicrobial resistance is essential because the data obtained from this surveillance will guide policy makers and health care providers to better their efforts, and moreover, target their strategies in a more focused manner. Various WHO regions have different surveillance programs, which are either functioning or in the early phases of formation. In South-East Asia, national and regional surveillance systems have been proposed since 2010.[30,31]

Pharmacovigilance is a broad area that comprises the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or other drug-related problems, as defined by the WHO. Under the pharmacovigilance program implemented by WHO, all member countries have regional monitoring centers and a national coordinating center. Finally, all national centers report to a central collaborating headquarters, located in Uppsala, Sweden (called as the Uppsala Monitoring Centre) [30]

The actual burden caused by antimicrobial resistance differs from region to region, which only adds to the difficulties faced in the actual assessment of the extent and rate of antimicrobial resistance. While USA, Canada, and a few European nations have systems in place to quantify the antimicrobial resistance, most other countries are still in the budding stage. This poses a major issue, as the maximal impact (both clinically and economically) will be in the developing and recently developed countries. Hence, pharmacovigilance could be one of the few solutions to obtain data on the actual scenario of antimicrobial resistance in individual patients.[32]

On behalf of the 7th Framework Programme of the European Commission, the Uppsala Monitoring Centre initiated a pilot study to analyze the feasibility of picking out treatment failure due to antimicrobial resistance. This was done by going through individual case safety reports, which were reported to the Monitoring Centre. According to this study, reaction terms related to lack of therapeutic efficacy were the ninth most commonly reported adverse effects, based on analysis of several individual case safety reports.[32]

A major hurdle in quantifying the extent of antimicrobial resistance is the fact that there are several known microbes, which may turn out to be resistant to one or more of the several known antimicrobial agents. To standardize this complex relationship, a 'Drug Resistance Index' has been recommended by the WHO. This new index provides us with aggregate information on resistance to various antimicrobials by the several microbes known to man.[32]

For the purpose of collaborative national and global surveillance of resistance, a software WHONET program has been developed for the management and analysis of microbial and clinical data with focus on antimicrobial susceptibility test results. This software puts each laboratory's data into a common code and file format to analyze. Hence, this program can help in formulating effective antibiotic policies at local, nodal, and national levels. This software can prove to be very effective provided, data from all over the world, from all laboratories is entered into it.[33]

11. Problems with pharmacovigilance relative to antimicrobial resistance

Although the field of pharmacovigilance has made significant progress in recent times in terms of monitoring and reporting of antimicrobial resistance, it is still a long path to establishing a global network of surveillance. The recent advances in the field have been made possible, chiefly because of the digital integration that has happened with the use of computerized technology. This has facilitated ease and comfort in collection of various events.[32]

A few of the challenges that exist at present include the following [32]:

a. Lack of uniformity in definitions: Very few diseases or conditions have proper definitions associated with their resistance (Tuberculosis, Malaria, etc.). This lack of uniformity in defining antimicrobial resistance makes it difficult to classify the lack of therapeutic response.
b. Lack of data reporting from developing nations: Several developing nations do not either have the laboratory facilities to check for antimicrobial resistance, or do not have facilities to report the diagnosed resistance patterns. Hence, whatever the WHO analyzes comes from a limited area of the globe. What we need is data from every part of the world, so that there is geographical representation of every region.
c. Need for more and better laboratory facilities: The laboratory facilities are either inadequate or not of good quality. Every attempt to increase the number facility as well as the standard of the facility should be made which will help to tackle the AMR.
d. Need for better budget allocation toward the field: As this is an important issue, the annual budget allocation for this purpose should not be compromised by any country.
e. Need for better informatics facilities to aid in proper network sustainability: Dissemination of data is utmost importance in tackling AMR; hence, every attempt has to be made for better networking for intra and inter-regional report.
f. Political constraints: As AMR is a global problem, every country should see that political influence will not affect it adversely.
g. Lack of linkage between data in humans and animals: Compartmentalization of data is not acceptable and attempts must be made to link humans' and animals' data and inference has to be drawn taking both in to consideration.
h. Lack of data on final clinical outcomes due to resistance: A National Coordination Center for each country has to analyze the data on AMR collected and this should reach the International Coordination Center for analysis and feedback has to be sent to each Regional Center in the form newsletter on a regular basis.

12. Indian scenario

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.

As a part of pharmacovigilance program of India, in an active surveillance study conducted at Kasturba Hospital, Manipal, where the author is also working, it has been observed that very expensive brands of drugs were mostly prescribed than their cheaper brands even though there is no proof that expensive brands are better in terms of pharmacokinetics or efficacy.[34] This practice of using expensive brands of antimicrobials which are *per se* costlier may result in poor patient compliance and thus may end up in increased antimicrobial resistance. Use of less expensive antimicrobials in the control of infectious disease management will make treatment affordable and in turn better compliance may help to prevent microbial resistance. Das S C et al. have reported that out of 7 drugs studied, costliest brands were sold more than cheapest brands in case of 5 drugs and this shows the tendency to prescribe costliest brands among the prescribers.[35]

There is clearly a need to educate the prescriber on the less expensive choices to bring some change in prescribing habit. Role of pharmaceutical companies with respect to use of costliest antimicrobial have to be assessed to understand this issue. In developing countries like India where the per capita income is less than 1000$, such high cost for controlling infection might put patients at financial trouble [36] as the patients are paying out of their pockets for their medical bills and are not covered by insurance schemes unlike developed countries.

There is an urgent need to form committees at hospital level to frame policies on these aspects. Also, a combined effort by regulatory authorities, clinicians, pharmacists, and community at large is required to address this issue of antibiotic cost variation. At the hospital level, authorities and concerned committees have to frame policies on these aspects. There is a need for concerted action from regulatory authorities, doctors, pharmacists, and general public at large to address this issue of antibiotic price variation.

12.1. Policies and perspectives on antimicrobial resistance for India

As antimicrobials are freely available in India without prescription, they are excessively used over the counter. Added to this, misuse of antimicrobials in veterinary practice and as growth-promoting agents in poultry leads to antimicrobial residues in the environment. In view of these practices, there is a real need for strict national policy for India to control this kind of antimicrobial use in the community in order to prevent the

AMR. In this direction in the year 2012, the Chennai Declaration: a road map by and for stakeholders to tackle the challenge of antimicrobial resistance was implemented.[37] The main theme of Chennai Declaration was: 'Practical, not perfect'. It recognizes the need that although a ban on sale of over-the-counter antibiotics without prescription will be the ideal step, it is not practical to implement at present. It recommends step-by-step regulation, beginning immediately with control on sales of third- and fourth-generation antibiotics and antitubercular agents and then gradually expanding the list. Additional recommendations encompass accreditation, hospital antibiotic usage policies, veterinary practices, strengthening diagnostic laboratories, education, training, and research. India needs 'An implementable antibiotic policy' and NOT 'A perfect policy'.[37] Further, Ministry of Health has come out with new policy measures. The idea is to create a national Surveillance system for antibiotic resistance and initiate studies documenting prescription patterns and to establish a monitoring system for the same. It also includes intervention measures for rational use of antibiotics in hospitals and develop and implement diagnostic methods pertaining to antimicrobial resistance monitoring.[38]

12.2. National surveillance system for antimicrobial resistance

Pathogens resistant to antibacterials causing important infectious diseases are a matter of great public health concern globally; India is not an exception. The main cause responsible for antimicrobial resistance is the widespread use and over-the-counter availability of antimicrobials for human as well as animal consumption. To develop antibiotic guidelines, the data on antimicrobial resistance for pathogens of public health importance are very much necessary. However, there is no reliable data of antimicrobial resistance of different pathogens except for those where there is a specific national health program.[38] Evidence from the experience of countries shows that a national plan on antimicrobial resistance monitoring has shown to impose restrictions on the injudicious use of antibiotics. It shall help to contain the problem of AMR in the country to a large extent.

12.2.1. Antimicrobial surveillance

As the data on antimicrobial resistance is not available, a national policy for containment of antimicrobial resistance was planned in the year 2011 by an expert committee.[38] It suggested three types of surveillance for antimicrobial resistance: comprehensive surveillance, sentinel surveillance, and point prevalence studies. Comprehensive AMR surveillance, though giving actual estimate of AMR burden, includes the study of the whole population at risk/under study and needs the involvement of a large number of laboratories which is not practical especially in India. Point prevalence studies are useful for validation of the representativeness of the surveillance data. Sentinel surveillance studies have been found to be quite useful in such situations. Though it provides only indicative data, the same can be extrapolated to the rest of the population. It is also a suitable mode of surveillance when prolonged and detailed data are needed. This seems to be the best approach for India. One or more central institutions under the Ministry of Health may be the coordinating center(s) at the national level depending on the size of the laboratory network.[38] The suggested design for identification of the pathogens/diseases is of public health importance for surveillance. The suggested bacterial species for monitoring are Salmonella, E.coli, Campylobacter, Enterococcus, Staphylococcus, Clostridium. Following bacterial pathogens isolated from different human infections/anatomical sites, e.g. blood stream infections, skin and soft tissue, and surgical site infections; respiratory infections, gastro intestinal tract infections, and urinary tract infections (UTI) may be included in a phased manner for the purpose of AMR surveillance.

The next step is to create a network of Antimicrobial Susceptibility Testing (AST) laboratories. Surveillance networks at different levels of health-care system should be set up with unified protocols and standard operating procedures (SOPs), at least up to district level. Later on, it may be expanded up to Peripheral Health Facility level also to obtain community-based data on AMR. It was felt that since at the moment the basic infrastructure for AMR surveillance does not exist at the district level in the country, it may not be feasible to carry out AMR surveillance at the district level to begin with. However, efforts should be made to develop the infrastructure at the district level in a phased manner.

The committee suggested identification of microbiology laboratories based in medical institutions or medical colleges across the country with an existing infrastructure for AST testing to generate data on the identified bacterial pathogens. The laboratory must have qualified microbiologists well versed with and carrying out antimicrobial susceptibility testing techniques for at least last 5 years. The laboratory must also be conversant with and following the quality control procedures for AST. Since at the moment very few laboratories in the country are National Accreditation Board for testing and calibration Laboratories (NABL) accredited, especially in the public sector, this need not be the criterion for selecting the Laboratories for the network at the moment and however, the network laboratories should be encouraged for NABL accreditation later on in a phased manner. Development of a system of regular and timely dissemination of AST data to the participating labs, clinicians, and policy makers is important. The AMR data generated by the respective network laboratories should be sent to the coordinating center, regularly on a quarterly (once in 3 months) basis. The data is to be sent electronically in a predefined template. The data shall be collated and analyzed by the coordinating institution and subsequently made available to the policy makers and other stake holders.[38]

12.2.2. Implementation of AMR surveillance plan

Training in the form of one-day sensitization workshop for the senior microbiologists of the network laboratories and 2–3 days training workshop for junior microbiologist/data reporting personnel on various aspects of AST, especially quality control and data analysis/transmission should be implemented.[38] This should be followed by regular monitoring and review meetings.

12.2.3. Establishment of national coordination center

There is need to initiate or strengthen the existing regulatory restrictions on the prescription and use of antimicrobials, surveillance activities, hand hygiene, and antimicrobial stewardship (AMS) programs, strict requirements to manage pathogen levels along the food production and processing chain, education for prescribers on the judicious use of antibiotics, and research into new products and approaches to prevent and respond to AMR. Where there is no national coordination on the above activities, it is prudent to have national coordination across all segments, better integrate efforts to address gaps, and ensure a more comprehensive response to AMR regionally and globally.

13. Conclusion

Antibiotic resistance imposes a substantial public health burden. Quantifying overall changes in resistance over time and across locations is difficult because resistance of pathogens to individual drugs must be aggregated to assess overall burden. Surveillance of AMR is essential and data obtained if pooled and analyzed may help in tackling AMR. WHO-initiated global action plan, if implemented all over the globe, will be helpful in controlling the spread of AMR and this will definitely prevent AMR infections that necessitate additional investigations, more complex and expensive treatments, longer hospital stays, and lead to greater mortality. Extended recovery time means that patients remain infectious for longer time, increasing the risk of resistant infections spreading to others. Treating resistant infections is also very costly, as more expensive medicines need to be used. Longer hospital stays result in increased health-care costs for patients and societies.

Implementing AMR-related initiatives all over the globe, such as Antibiotic Awareness Week and the Antimicrobial Stewardship Initiative, and education campaign targeting both consumers and health professionals, will help in controlling AMR. Finally, establishing national and international coordinating center to receive, analyze, and give feedback on all activities initiated toward AMR will help in developing national and international policy on antimicrobial usage.

13.1. Expert opinion

The AMR problem is now grown out of proportion so much so that many 'superbugs' have emerged. Misuse of antimicrobials is the root cause of this problem. Despite all efforts, the AMR increases and discovery of new antimicrobials is declining. To address the problem of AMR, several surveillance programs are either functioning or in early phase of formation. Only few nations (United States, Canada, and few European countries) have system in place to quantify AMR, while in most other countries it is still in budding stage. Hence, whatever the WHO analyzes comes from a limited area of the globe. What we need is data from every part of the world, so that there is geographical representation of every region. A major hurdle in quantifying the extent of antimicrobial resistance is the fact that there are several known microbes, which may turn out to be resistant to one or more of the several known antimicrobial agents. Pharmacovigilance can be one of the solutions to get data on AMR in individual patients. Pilot study done by Uppsala monitoring center to identify the therapeutic failure due to AMR showed that lack of efficacy was the ninth most commonly reported adverse effects based on analysis of several individual case safety report. If the surveillance program is implemented aggressively all over the globe, the data generated will definitely be useful in preventing the AMR. The ultimate goal of this type of program is to control the AMR and through this to prevent the medical, economic, and social consequences of AMR. To achieve this goal, pharmacovigilance program in terms of monitoring and reporting of AMR is a welcome move. The recent advances in this field have been made possible mainly because of digital integration.

A major hurdle in quantifying the extent of antimicrobial resistance is the fact that there are several known microbes, which may turn out to be resistant to one or more of the several known antimicrobial agents. To standardize this complex relationship, a 'Drug Resistance Index' has been recommended by the WHO. This new index provides us with aggregate information on resistance to various antimicrobials by the several microbes known to man.

The fact of the matter is we are still unaware of the extent of trouble that is in store for us. What is appealing is the use of antisense nucleotides as novel antimicrobials. However, these are just concepts and we are far from implementing this in clinical practice.

Declaration of interests

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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