NATIONAL POLICY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE

INDIA

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Directorate General of Health Services
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EXECUTIVE SUMMARY

Antimicrobial Resistance Monitoring

Antimicrobial resistance in pathogens causing important communicable diseases has become a matter of great public health concern globally including our country. Resistance has emerged even to newer, more potent antimicrobial agents like carbapenems. The factors responsible for this are widespread use and availability of practically all the antimicrobials across the counter meant for human, animal and industrial consumption. There are definite policies / guidelines for appropriate use of antimicrobials at national level in specific national health programmes being run in the country e.g. RNTCP, National AIDS control programme, etc. For other diseases of public health importance like enteric fever, diarrhoeal disease, respiratory infections, etc the individual hospitals are following their own antimicrobial policies and hospital infection control guidelines. To monitor antimicrobial resistance it is necessary to have regulations for use and misuse of antibiotics in the country, creation of national surveillance system for antibiotic resistance, mechanism of monitoring prescription audits, regulatory provision for monitoring use of antibiotics in human, veterinary & industrial sectors and identification of specific intervention measures for rational use of antibiotics.

In this regard a task force has been constituted with following terms of reference:

1. To review the current situation regarding manufacture, use and misuse of antibiotics in the country.
2. To recommend the design for creation of a national Surveillance System for Antibiotic Resistance
3. To initiate studies documenting prescriptions patterns & establish a Monitoring system for the same.
4. To enforce and enhance regulatory provisions for use of antibiotics in human & veterinary and industrial use.

5. To recommend specific intervention measures such as rational use of antibiotics and antibiotic policies in hospitals

6. Diagnostic Methods pertaining to antimicrobial Resistance Monitoring

The official from Animal husbandry Department was co-opted for providing inputs on use of antimicrobials in veterinary sector. The members of the task force worked on various ToRs and made a work plan for monitoring of antimicrobial resistance in the country. Briefly the action plan of various ToRs is as follows:

- **For monitoring use and misuse of antibiotics**: **Schedule H** of the drug and cosmetics act contains a list of **536 drugs** which are required to be dispensed on the prescriptions of a registered medical practitioner. In order to have separate regulation to check unauthorized sale of antibiotics, a separate schedule as **Schedule H1** may be introduced under the Drugs and Cosmetics Rules to regulate sale of antibiotics exclusively. Corresponding provisions under the Rules could be framed for their implementation. *A system of colour coding of **third generation antibiotics and all newer molecules like Carbapenems (Ertapenem, Imipenem, Meropenem), Tigecycline, Daptomycin** may be put in place restricting their access to only tertiary hospitals. Appropriate steps should be taken to curtail the availability of fixed dose combination of antibiotics in the market*
- **Hospital based sentinel Surveillance System for monitoring antibiotic resistance** will be set up with the identification of one of more Central Institutions under the ministry of health as coordinating centres at the National Level. The design for AMR surveillance consists of

    - Identification of pathogens/diseases of public health importance
    - Creation of network of Antibiotic Susceptibility Testing (AST)
    - Standardizing methodology for microbial identification and AST

- The laboratories will perform AST using standardized methods and carbapenem resistant isolates will be stocked and sent to designated central laboratory for further analysis, like identification of NDM-1 isolates.
- Strengthen Quality Systems in the network laboratories

- *We may also identify a central reference centre for Characterization and epidemiological study of resistance factors in microbial pathogens.*
- **For documenting prescription patterns and establishing a monitoring system** for the same following would be done
  - To study the consumption of various antibiotics in tertiary care public hospitals in Delhi under central government
  - To study the trends in antibiotic use in these hospitals of Delhi
  - Data generated will be used for intervention studies for rational use of antibiotics.

- **For enforcement and enhancement of regulatory provisions for use of antibiotics in human, veterinary and industrial use**.
  - In India, the antibiotics are used widely in food animals as growth promoters and to prevent and treat infection. Non-therapeutic usage of antibiotics has been especially common in poultry production. However, there is no regulatory provision regarding the use of antibiotics in livestock.
  - Establish intersectoral coordination committee with experts from various sectors.
  - Develop regulations on usage of antimicrobials in poultry and other animals as well as the requisite labelling requirements in food.

- **For promoting rational use of drugs various strategies suggested are:**
    - Educational strategy: Training, printing materials, media-based approach
    - Managerial strategy: Monitoring & supervision, generic substitution, patient cost sharing (economic incentives) etc
    - Regulatory strategy: Enforcement, sanction, drug withdrawal, market control etc
    - Formulation & implementation of an antibiotic policy
    - With quality assured laboratory data in real time develop antibiotic policies that are standard national / local treatment guidelines advocating evidence based immunotherapy or combination therapy. This must include consideration of spectrum of antibiotics, pharmacokinetics / pharmacodynamics, adverse effects monitoring, cost and special needs of individual patient groups

- **For strengthening diagnostics for antimicrobial resistance monitoring the strategies are**
- Appropriate diagnostic tools already known should be selected as well as new ones developed for rapid identification of pathogens for AMR surveillance.

- Robust quality assurance system should be implemented that could be carried out by a “neutral” central institute.

MEMBERS OF TASK FORCE

1. Dr. R.K. Srivastava, *DGHS* - ***Chairperson***
2. Prof. Ranjit Roy Chaudhury, *Member, Board of Governors, M.C.I.*
3. Dr. N.K. Ganguly, *President, JIPMER, New Delhi*
4. Dr. S.K. Bramhachari, *Director General, CSIR, New Delhi*
5. Dr. Surender Singh, *Drugs Controller General of India, New Delhi*
6. Dr. Randeep Guleria, *Prof. of Medicine, AIIMS, New Delhi*
7. Dr. Ajit Sinha, HoD, *Deptt of Surgery, Safdarjung Hospital, New Delhi*
8. Dr. Usha Gupta, *Sr. Consultant, Clinical Pharmacology, Fortis Hospital, NOIDA*
9. Dr. Manish Kakkar, *Public Health Foundation of India, New Delhi*
10. Dr. Camilla Rodrigues, *Consultant, Lab Medicine, PD Hinduja Hospital, Mumbai*
11. Dr. Chand Wattal, *Chairperson, Clinical Microbiology, Sir Ganga Ram Hospital, New Delhi*
12. Dr. Anita Kotwani, *Associate Prof., Pharmacology, VP Chest Institute, Delhi*
13. Director *NCDC, Delhi* - ***Member Secretary***

TERMS OF REFERENCE
OF THE TASK FORCE COMMITTEE

1. Review the current situation regarding manufacture, use and misuse of antibiotics in the country.

2. Design for creation of a National Surveillance System for antibiotic resistance.

3. Studies documenting prescription patterns and establish a monitoring system for the same.

4. Enforce and enhance regulatory provisions for use of antibiotics in human veterinary and industrial use.

5. Specific intervention measures such as rational use of antibiotics and antibiotic policies in hospitals which can be implemented, as early as possible.

6. Diagnostic Methods pertaining to antimicrobial Resistance Monitoring

BACKGROUND

1. Aims of the National Antimicrobial Policy

a) Understanding emergence and spread of antimicrobial resistance and the factors influencing it

b) Establish a nationwide well coordinated antimicrobial program with well defined and interlinked responsibilities and functions of different arms of the program

c) Rationalizing the usage of available antimicrobials

d) Reducing antibiotic selection pressures by appropriate control measures

e) Promotion of discovery of newer and effective antimicrobials based on current knowledge of resistance mechanisms

f) Rapid and accurate diagnosis of infections and infectious diseases

1.1 Action points

General

1. Establish government commitment and support for nation-wide antimicrobial program and within it the policy & set up national focal point for collaborations & compilation.

2. Establish a National Alliance for prevention and control of antimicrobial resistance

3. Institute a surveillance system that captures the emerging resistance, seeks and envisions trends in it's spread and correlates with utilization of antimicrobial agents in community as health care set ups

4. Promote rational usage of antimicrobial agents

5. Strengthen infection prevention and control measures- healthcare associated and community based

6. Support research in developing newer antimicrobial agents and improving usage of available ones, based on pharmacological properties

7. Educate, train and motivate all stake holders in rational and appropriate usage of antimicrobials and its regulation

8. Establish a Quality System and a National registry for Antimicrobial resistance for bacteria, fungi and viruses at national focal point.

9. Co-development of antimicrobial agents with pharmaceuticals and leaving the distribution, sales and promotion with the government

1.2 Implementation

1. Establishing a Surveillance Program

- Establish that all Hospital/ health care set up should have an Infection control officer with well defined role and responsibilities

- Formation of a Local Infection control team

- Protocols on antimicrobial testing to be formulated and distributed in a categorized manner- primary/secondary tertiary health care set ups/standalone labs with/without automation

- Interpretive criteria- e.g. CLSI/BSAC etc. to be standardized as per our needs and adopted nationwide

- Software generation for data feeding and analysis

- Collection of Data from Microbiology laboratory for both health care setups and community

- Collection of Data from Pharmacy for both health care setups and community

- Collection of Data from pharmaceuticals-sale by distributors and sale by retailers to be compared

- Quality Control programs to be promoted and adopted EQAS to be set up at well established institutes

2. Promotion of Rational Usage of Antimicrobials

A. Personnel involved:

- Local hospital/health care setup Infection prevention and Control Officer and Infection Control professionals

B. Action points

- Local health care set up Antimicrobial policy to be drawn by each health care setup

- Training modules on rational prescription to be created
- Training of Undergraduate and postgraduate medical, dental, nursing, veterinary and pharmacy
- Training and awareness of General Practitioners and Specialists
- CMEs and workshops for all concerned
- Banning non therapeutic usage in animals and farms
- Pharmacists involvement
- Ban over-the-counter (OTC) sale of antimicrobials - **Schedule H1**
- Adherence on all levels to be sent in annually to the State director who shall put this data to the central director

3. Infection Prevention and Control Program

Establish and Strengthen Infection Control Programs

- In both Health care set ups
- Infection Control Plan and policy for tertiary care hospital
- Infection control Committee to be set up in all health care institutions
- Infection Control Team
- Standard Operating Procedures (SOPs)
- Immunization and vaccination of vaccine preventable diseases

4. Research in Antimicrobials

- Government sponsored, public-private partnership (PPP) model or pharmaceutical industry collaboration with govt. and private health care setups
- Budget allotment, grants to be set aside
- Community based research
- Health care setup based research
- Veterinary research

- Agriculture, fisheries, farms to be included

- Rapid diagnostics researched and promoted

- Regulatory mechanisms to be in place for prioritizing research

- National Commitment in the form of Antimicrobial Policy and later on legislation Formation of Advisory Body

- Formation of Steering Committee under the advisory body

- Targets for all involved to be set up for tertiary care hospitals Deadlines to be formulated and implemented

- Software to be generated & evaluated

5. Monitoring and evaluation

QC checks
Audits
Feedbacks to Advisory body
Review of Action Plan annually
New actionable for implementation to be developed regularly & give feed back

ToR-1: *Review the current situation regarding manufacture, use and misuse of antibiotics in the country*

The quality of the drugs imported, manufactured and sold in the country is regulated under the provisions of Drugs and Cosmetics Act, 1940 and Rules made there under. The Act visualize the regulatory control over the drugs imported in to the country by the Central Government while the manufacture, sale and distribution of drugs is primarily regulated by the State Drug Control Authorities appointed by the State Governments. The manufacture and sale of the drugs is regulated through a system of licensing and inspection by the Licensing Authorities.

The Central Drugs Standard Control Organization (CDSCO), headed by the Drugs Controller General (India) in the Directorate General of Health Services, is concerned with the regulatory control over the quality of drugs, cosmetics and certain notified medical devices under the Drugs and Cosmetics Act, 1940 and rules made there under. The organization has its head quarters at Food and Drug Bhawan, Kotla Road, Near ITO, New Delhi-110002 and has six zonal offices, two sub zonal offices, seven sea ports/Airports offices and six laboratories under its control.

1.1 Functions of CDSCO

a) Approval of new drugs including vaccines to be introduced in the country.

b) Permission to conduct clinical trials.

c) Registration and control on the quality of imported drugs and notified medical devices.

d) Institutionalise regulatory measures and recommend amendments to the Drugs and Cosmetics Act and Rules made there under.

e) Prescribing regulatory procedures and standards for drugs, cosmetics, diagnostic reagents and medical devices.

f) Approval of License as Central License Approving Authority for manufacture of large volume potentials, sera and vaccines, biotechnology products, medical devices and operation of blood banks and manufacture of blood products.

g) Coordinating the activities of the States and advising them on matters relating to uniform administration of the Act and Rules in the country.

State Drugs Control Organization is appointed by the State/Union Territory Governments to regulate the manufacture and sale of Drugs and Cosmetics.

1.2 Functions of State Drug Control Authorities

a) Licensing of Manufacturing Site for Drugs including API and Finished Formulation

b) Licensing of Establishment for sale or distribution of Drugs

c) Approval of Drug Testing Laboratories

d) Monitoring of Quality of Drugs and Cosmetics marketed in the country

e) Investigation and prosecution in respect of contravention of legal provision

f) Recall of sub-standard drugs

1.3 Mechanism for Enforcement of the Act in Respect of Sale and Manufacture of Drugs

The manufacture and sale of drugs is a licensed activity under the Drugs and Cosmetics Act, 1940 and the licensees are required to comply with the provision of the Act and the conditions of the licence. The Act specifies offences and penalties for violations of the provisions of the Act.

The licences for sale of drug (wholesale or retail) are granted by the State Licensing

Authorities. The licences are required to comply with the condition of licence as provided under Rule 65 of the Drugs and Cosmetics Rules. Some of the salient conditions are as under:

I. The supply, otherwise than by way of wholesale dealing of any drug supplied on the prescription of a Registered Medical Practitioner should be effected only by or under the personal supervision of a registered pharmacists.

II. The supply of any drug on a prescription of a registered medical practitioner should be recorded at the time of supply in a prescription register specially maintained for the purpose and the serial number of entry in this regard shall be entered on the prescription. The following particulars should be entered in the register-

a) The date of supply.
b) The name and address of the prescriber.
c) Name and address of the patient.
d) The name of the drug or preparation and the quantity.
e) Batch number and date of expiry.
f) Signature of the registered pharmacists.

The licences should maintain an Inspection Book to enable an Inspector to record his impression and defects noticed.

Schedule H of the drug provide a list of the drug which are required to be sold on the prescription of a registered medical practitioner and the manufacturer is required to label the drug with the symbol Rx and with the following words:

'Schedule H drug - warning: To be sold by retail on the prescription of a Registered Medical Practitioner only'.

The Drugs and Cosmetics Act provide penalty for manufacture, sale etc. of drugs in contravention in Act or the Rule made there under. Drug Inspector appointed under the Act is empowered to institute prosecutions in respect of breaches of the Act and Rules there under.

Schedule M to the Drugs and Cosmetics Rules provides requirements for Good Manufacturing Practices and requirements of plant and equipment for manufacture of drugs. It specify in detail the requirements of premises, surroundings, personnel, sanitation, storage of raw materials, documentation and records, self inspections and quality control systems and site master files etc. The manufacturer should comply with the requirements of Schedule M under the conditions of the license.

The manufacturer should provide and maintain adequate staff, premises, plant and machinery for manufacture of drugs under the conditions of license for manufacture of drugs. He should maintain records of manufacture including the testing of raw material and finished products**.** Each batch of the product should to be tested by the manufacturer either in their quality control laboratory or any laboratory approved by the Licensing Authority before releasing the product into market.

A Drug Inspector appointed by the respective Governments should to inspect not less than once a year all establishment licensed for manufacture or sale within the area assigned to him and to satisfy himself that the conditions of license are being observed. He may draw samples of a drugs or cosmetics from the manufacturing or sale premises, where he has reason to doubt the quality of drug, in a prescribed manner and send them for test and analysis to the Government analyst to check the quality.

The manufacturer should allow an inspector to inspect all registers and records maintained by him and to take samples of manufactured products, if required, and provides such information as required for the purpose of ascertaining whether the provisions of the Act and Rules there under have been observed. The inspection may be conducted by one or more inspectors to examine the premises, plant, appliances and process of manufacture, professional qualifications of technical staff and capability of the manufacturer to comply with the requirements of Good Manufacturing Practices and

requirements of plant and equipment before a license is granted.

1.4 Proposed Actions to monitor Sale of Antibiotics

- **Schedule H** of the drug and cosmetics act contains a list of **536 drugs** which are required to be dispensed on the prescriptions of a registered medical practitioner. In order to have separate regulation to check unauthorized sale of antibiotics, a separate schedule as **Schedule H1** may be introduced under the Drugs and Cosmetics Rules to regulate sale of antibiotics exclusively. Corresponding provisions under the Rules could be framed for their implementation. A provision could be incorporated for spot suspensions /cancellation of the sale licence for contravention of the provision of Schedule H1. Drug Inspectors in the Zonal and sub-zonal offices of CDSCO along with the State Drug Inspectors may conduct surprise raids at the chemist shops to ensure that the provision of the Drugs and Cosmetics Rules especially in respect of Schedule H1 are strictly complied by the licensees.
- *A system of colour coding of **third generation antibiotics and all newer molecules like Carbapenems (Ertapenem, Imipenem, Meropenem), Tigecycline, Daptomycin** may be put in place restricting their access to only tertiary hospitals.*
- *Appropriate steps should also be taken to curtail the availability of fixed dose combination of antibiotics in the market, by and large combinations should be discouraged except for naturally interactive ones like Co-trimoxazole, Amoxyclav, etc.*
- *A similar review needs to be carried out on the composition of topical antibiotics*
- The drug testing laboratories in the country should be strengthened in terms of infrastructure, number and also training of drug inspectors.

- Incentives should be given to pharmacies for not selling antibiotics without prescription and appropriate regulation for the same should be formulated.

1.5 Proposed action for development of newer antimicrobials

- The universities and prominent research institutes in the country should be encouraged by appropriate incentives to develop newer antimicrobials. In this regard, a National Technical Advisory Group on development of Newer Antimicrobials may be established.

ToR-2: *Design for creation of a National Surveillance System for Antimicrobial Resistance*

2.1 Background:

Antimicrobial resistance in pathogens causing important infectious diseases is a matter of great public health concern globally, as well as in India. A major factor responsible for this is the widespread use and availability of practically all antimicrobials over the counter for human as well as animal consumption.

Though, there are definite policies / standard treatment guidelines for appropriate use of antimicrobials in specific national health programmes e. g**. RNTCP (Revised National Tuberculosis Control Programme), NACP (National AIDS Control Programme), NVBDCP (National Vector Borne Disease Control Programme)**, the same are not available for other diseases of public health importance like enteric fever, diarrhoea / dysentery, pneumonia, etc.

Reliable Indian data on antimicrobial resistance (**AMR)** for important pathogens of public health importance is an essential pre-requisite for developing appropriate guidelines for use of antimicrobials. Currently, there is no accepted national database of antimicrobial resistance in different pathogens except for those where there is a specific national health programme.

Despite many microbiology laboratories (in both public as well as private sector) performing routine antibiotic susceptibility testing **(AST**) of at least bacterial pathogens, the data is neither analysed regularly nor disseminated for use by clinicians / public health experts / programme managers. Quality control and data sharing by these laboratories are other important issues that need attention.

Analysis of the AST results from laboratories in India reveals an increasing trend of development of resistance to commonly used antimicrobials in pathogens of public health importance like *Salmonella spps, Shigella spps*, *V. cholerae*, *Staph aureus*, Gonococcus, Meningococcus, *Klebsiella spps, Mycobacterium tuberculosis*, HIV, and others.

There are a few examples of successful networking of laboratories carrying out antimicrobial sensitivity testing of gonococcus in the country under the **GASP** (**Gonococcal antimicrobial susceptibility programme**) with regional STD laboratory at Safdarjung Hospital, New Delhi being the referral laboratory.

Evidence from the experience of countries like UK, Sweden and other European 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.

2.2 Types of AMR surveillance:

Three types of surveillance can be done for AMR - **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 specially in our country. 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.

Sentinel surveillance for AMR

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 is needed. This seems to be the best approach for our country. One or more central institutions under the Ministry of Health may be the coordinating centre(s) at the national level depending on the size of the laboratory network.

2.3 Design for AMR surveillance

2.3.1 **Identification of the pathogens / diseases of public health importance for surveillance**

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.

First phase (Non fastidious bacterial pathogens)

1. Following Gram Negative Bacilli (should **address Extended Spectrum β-lactamases [ESBLs] and Metallo β-lactamases [MBLs], including NDM-1)** may be included.
   - Pseudomonas aeruginosa
   - Acinetobacter spps
   - Klebsiella pneumoniae
   - *Esch. coli*

2. Staphylococcus aureus (should address Methicillin Resistant *Staph aureus* - **MRSA) Second phase in addition to the above the following organism surveillance will be added:**
   - Enterococci specially VRE (Vancomycin Resistant Enterococci)
   - Salmonella , Shigella sp and *Vibrio cholerae*
   - *Streptococcus pneumoniae*, and *H. influenzae*

2.3.2 Creating a network of AST laboratories

Surveillance networks at different levels of healthcare system should be set up with unified protocols and 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 laboratory should preferably be a part of a large hospital having different types of facilities Outdoor and Indoor, ICU, Operation theatres, etc.
- 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 antimicrobial susceptibility testing techniques and should be carrying out AST 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 NABL accredited specially 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.

- *We may also identify a central reference centre for Characterization and epidemiological study of resistance factors in microbial pathogens*
- In the **first phase**, the following three central Govt. Hospital in Delhi will be included for AMR surveillance.

    - Sucheta Kriplani Hospital (SKH) & Lady Hardinge Medical College (LHMC), New Delhi
    - Dr Ram Manohar Lohia (RML) Hospital, New Delhi
    - Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital, New Delhi
- Subsequently, in a phased manner, the surveillance network should be linked with existing special networks such as one for resistance monitoring in malaria, pneumonia or low-respiratory tract infection, tuberculosis and HIV etc.

2.3.3 Standardize methodology for microbial identification and AST

- Develop standardized **AST** (Antimicrobial Susceptibility Testing) methodology including identification of antimicrobials to be tested and reported for each identified pathogen for AMR surveillance

- Develop detailed Standard Operating Procedure (**SOPs**) for microbial identification and AST based on current **CLSI** (Clinical Laboratory Standards Institute) guidelines; the same may be made available to all the testing laboratories.

- Though the network laboratories would be recommended to do the AST by **Disc diffusion** test using **Modified Kirby Bauer method** ,those following other standard methods e.g. **Stokes method** or doing MIC testing by methods like '**E' test**, automated systems may also be included provided they are following appropriate Quality control measures. Laboratories should also be having expertise to do **MRSA, ESBL and Carbapenemase (Modified Hodge test / Imipenem + EDTA E test)** testing. Carbapenem resistant isolates may be stocked and sent to a designated central laboratory for further molecular analysis (For **NDM-1 etc).** The identified central laboratory should be equipped with facilities to analyze mutations and Single Nucleotide Polymorphisms (SNPs) along with deep sequencing and DNA fingerprinting to identify strains with differential activities.

- DNA-based technologies should be included wherever possible at it will not only identify the organism, but will also give a glimpse of resistance.

- **Reporting of results**: AST results should be reported on a predestined format/template in terms of percentage sensitivity/resistance/ intermediate sensitivity with a clear denominator. Only isolates numbering **more than 10** should be used for the purpose of reporting, the data should also indicate the location and the site/source of the pathogen. Attempts should also be made to incorporate the history of use of antimicrobials in the given subject. The data can

be entered using excel sheet on a predesigned template taking into account the following parameters to generate surveillance data of OPD,WARD &ICU with validity period:

- 1. Identify organism
- 2. Segregate as per Grams Reaction: Gram positive/ Gram Negative organism
- 3.Source : Blood, Urine, Respiratory, Pus / body fluids
- 4. Percent sensitivity to the CLSI designated antibiotics
- The above data is used in formulating the surveillance results as per the following template:

Hospital surveillance data (Jan-Dec of x year)			**Validity of these data: Dec x + 1 yr**		
S. No	*Most common pathogens*	*% prevalence*	*S. No.*	*Most sensitive antibiotics in descending order*	–
1	–	–	1	–	–
2	–	–	2	–	–
3	–	–	3	–	–
4	–	–	4	–	–
5	–	–	5	–	–

2.3.4 **Strengthen Quality Systems in the network laboratories**

- Standardization of lab variables like qualities of antibiotic discs, different methodologies, different interpretation criteria, etc will help to generate reliable data on AMR.

- Institution of uniform testing methodology supported by availability of quality reagents and a robust quality assurance system (internal quality control and external quality assurance).

- **EQA** (External Quality Assurance) for the network laboratories in the country should be established & this work can be assigned to one or more reputed institutions in the country who are already having infrastructure for quality assurance for AST testing

2.3.5 AST Data analysis

- Many laboratories are carrying out the analysis of AMR data manually or using Excel software. Few laboratories use **WHONET 5** for AST data reporting and analysis.
- The network laboratories should compile & analyzed data on regular basis & send the data quarterly to designated central coordinating institution.
- There is a need of developing a user friendly tool / software for AST data compilation and analysis.

2.3.6 Dissemination of AMR data

- 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 centre, regularly on a quarterly **(once in 3 months**) basis.
- The data 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.

2.3.7 Development of National Repository of Bacterial strains / cultures

There is also a strong need to establish a national repository of standard bacterial strains required for quality control of AST as well as repository of drug resistant strains (including molecular components like DNA / plasmids) isolated from the different

network laboratories. Already, Institute of Microbial technology **(IMTECH),** Chandigarh has the requisite infrastructure and expertise to do the same. The responsibility can be assigned to this institute for maintaining the repository of cultures and also supplying the same to the network laboratories as per the need/demand. In addition to IMTECH, other institutes can be identified for the purpose.

2.4 Operationalization of the Action plan for AMR surveillance:

2.4.1 A one (1) day **sensitization workshop** for the senior microbiologists of the network laboratories

2.4.2 A 2-3 days **training workshop** for junior microbiologist/ data reporting personnel on various aspects of AST specially quality control and data analysis/ transmission.

2.4.3 Followed by regular monitoring and review meetings once in 6/12 months

2.5 Research in AMR Surveillance

2.5.1: New and simple surveillance tools with the capability to detect AMR at the lowest capable health centre should be developed and its ability to track the infection should be established.

2.5.2: All surveillance activities should be linked with epidemiological studies particularly surveillance around relevant vaccination programs.

2.5.3: A National Health Policy Unit should be entrusted with analysis of the surveillance data and provide advisory for framing of policies for use of antibiotics according to region, nation or hotspots.

ToR-3: *Studies documenting prescription patterns and establishing a monitoring system for the same*

3.1 Introduction

The current worldwide increase in antimicrobial resistance and, simultaneously, the downward trend in the development of new antibiotics have serious public health and economic implications. The increased antimicrobial resistance (AMR) is a result of many factors, but the foremost cause is the overall volume of antibiotic consumption, particularly for indications that do not require such therapy.

About 80% of antibiotics are used in the community and the rest are used in hospitals. It is estimated that 20-50% of all antibiotics use is inappropriate, resulting in an increased risk of adverse side effects, higher costs of therapy and higher rate of antimicrobial resistance of community pathogen.

3.1.1 Need for surveillance of antibiotic use in the community

Enhanced antibiotic surveillance is one of the strategies is one of the strategies to guide control of antibiotic overuse or misuse. This is because the ability to study population-based pattern of antimicrobial use provides a more comprehensive understanding of how the physician and patient use these agents. Promoting appropriate use of antibiotics through various interventions will help stop unnecessary prescribing and misuse of antibiotics. For suitable interventions to be carried out in the community it is essential to know the extent of antimicrobial use and pattern of antimicrobials in the population.

In a number of developed country settings, extensive programmes have been developed to track patterns of AMR and antibiotic use over time. Most developing countries do not have systems for routinely monitoring AMR. Measuring AMR rates on the basis of hospital isolates and having in-patients antibiotic policy as is presently done in few hospitals, is inadequate for understanding the burden of increasing AMR on the community.

3.1.2 Situation in India

Data on the use of antimicrobial agent at the population level are lacking in India as we do not have any database for the consumption of antimicrobials (antibiotics) in the community. This is mainly because in India, unlike many developed countries, prescriptions are kept by the patient and not with the pharmacist and antibiotics may be obtained with or without a prescription. Therefore, determining consumption of antibiotic use or trends in antibiotic use is problematic, more so in private sector, since there are no prescription records. Hence, there was an utmost need to develop a methodology that can measure consumption and trends in antibiotic use in the community.

3.1.3 Methodology for surveillance of antibiotic use in the community

Recently a methodology was established for surveillance of antibiotic use in the community for out-patients. The methodology used was bulk purchased data and conducting exit interviews of patients buying any antibiotic at private retail pharmacies in New Delhi.[1] The methodology was replicated and extended in public and private sector. This study of surveillance of antibiotic use in the community (December 2007-November 2008) utilized the established methodology of patient exit interviews at three types of facilities: 20 private retail pharmacies, 10 public sector facilities, and 20 private clinics to obtain a complete picture over a year in New Delhi. The Anatomical Therapeutic Chemical (ATC) classification and the Defined Daily Dose (DDD) measurement units were assigned to the data. 39% of the patients had encountered with at least one antibiotic at private retail pharmacies and public facilities whereas 43% of patients visiting private clinics were prescribed antibiotics. Consumption pattern of antibiotics were similar at private retail pharmacies and private clinics where fluoroquinolones, cephalosporins, and extended spectrum penicillins were the three commonly prescribed groups of antibiotics. At public facilities, fluoroquinolones, penicillins, macrolides, tetracyclines, cephalosporins and co-trimoxazole group of

[1] Kotwani A, Holloway K, Chaudhury R R. Methodology for surveillance of antimicrobials use among out-patient in Delhi. Indian Journal of Medical Research 2009;

antibiotic class were used in this descending order. Newer members from each class of antibiotics were prescribed.

Based on this methodology and experience in conducting drug utilization and rational use of medicines studies, surveillance of antimicrobials will be conducted in selected hospitals of India in a phase manner. T**he first phase of the study will be conducted in three tertiary care hospitals under central government in Delhi.**

3.2 Objectives

- To study the consumption of various antibiotics in tertiary care public hospitals in Delhi **under central government**
- To study the trends in antibiotic use in these hospitals of Delhi
- Data generated will be used for intervention studies for rational use of antibiotics.
- Later on, the network should also include peripheral heath facilities as well as pharmacies to obtain community based data on antimicrobial usage.
- Auditing of the pharmacies in the hospital, prescription of the practitioner as well as the pharmacies in the cities, districts and villages should be audited through a random selection basis.

3.3. Methodology

The first phase of the study will be conducted in NCT, Delhi and at tertiary care level of health care. Study will have a multi-disciplinary advisory committee of experts who will meet at regular intervals and their inputs will be helpful for implementation of the study.

3.3.1 Facilities included:

1. Sucheta Kriplani Hospital, New Delhi
2. R. M. L. Hospital, New Delhi
3. Safdarjung Hospital. New Delhi

3.3.2 Study design and duration

Prospective study for approximate 3 months but will be continued as surveillance. Fourth month data will be analysed for overall consumption and trends of antibiotic use.

3.3.3 Data collection methodology

In-patients

Consumption of antibiotics in various departments: Data on antibiotic consumption will be collected from all the important departments like, medicine, surgery, gynaecology, orthopaedics, ICU, etc.

a. **Data collection from medical store:** Total consumption of all antibiotics used/consumed will be collected every month from in-patient indent/issued to each department.

b. **Prescription data:** Prescription audit of approximate 10% of total in-patient in each department for each month will be done. For this data collectors will randomly pick 10% of prescriptions for the previous month and note down the details including the condition for which antibiotic was prescribed.

Outcome measures: Consumption of each group of antibiotic will be defined in terms of total number of DDDs using the WHO ATC/DDD system[2]. Consumption will be expressed as DDD/100 bed/day.

Out-patients

a. **Exit interview:** Exit interviews will be carried out at the pharmacy of public hospital and for each special clinic operating in the public hospitals.

For private hospital data collectors will do exit interview for each speciality in their OPD days and time.

Exit Interviews – Exit interviews of the patient receiving any antibiotic at the chosen hospital/department/special clinic would be done. Two trained data collectors will carry out exit interviews outside the pharmacy of hospital. One counts all the patients visiting the pharmacy during the period of data collection

[2] World Health Organization. The anatomical therapeutic chemical classification system

and checked whether they receive any antibiotic medicine. If the prescription has any antibiotic she/he will refer to the other data collector standing/sitting nearby and will interview the patient receiving an antibiotic as referred by his/her colleague. A pre-designed Performa will be used to collect data. The data collected would be

- Total number of drugs prescribed in the prescription
- Number of antibiotic(s) in the prescription
- Name of the antibiotic as prescribed
- Antibiotic prescribed as generic or trade name
- Strength, dose and duration of antibiotic prescribed
- Total amount prescribed
- Total amount purchased/dispensed
- Name, dose and duration of antibiotic dispensed
- Nutritional (body weight)/ HIV status (anonymous) etc.

Thirty exit interviews per month from each special clinic would be done and from general pharmacy 600 exit interviews will be done. For this required number of exit interviews to be conducted data collectors should visit 4-5 times the same facility/clinic to get a comprehensive picture.

Outcome measures: Percentage of patients receiving antibiotics would be found out. Results would be expressed as DDD/100 patients. The denominator for exit interviews data is the number of patients attending the pharmacy/clinic during the time taken to do the target number of exit interviews.

3.3.4 Data entry and data analysis

A sophisticated software programme will be developed for entering the data and double entry will be done to check for errors.

Data obtained will be analyzed to show monthly patterns of use and consumption of various group of antibiotic in all three public hospitals. Data will be compared

between hospitals, between various departments using different methodologies. A detailed secondary analysis will be done to find trends of antibiotic use.

A meeting to disseminate the results of the study will be held at the end (4 months) for all the stakeholders and participants of the study.

3.3.5 Implementation

Govt. of India, Ministry of Health will be coordinating the study with advisory committee/ task force .Project coordinator and the surveillance team set up for the purpose in the selected tertiary care hospitals will implement the surveillance of antimicrobials.

3.3.6 Personnel required for the project

- Project coordinator
- Research Officer
- Office assistant 1
- Data collectors - 6
- Office attendant 1
- Software computer programmer
- Bio Statistician
- Data entry personnel

3.3.7 Partners from each hospital

- M. S. of each hospital
- Officer who will coordinate the study from each hospital
- Sister-in Charge
- Pharmacy in-charge

ToR-4 : *Enforce and Enhance regulatory provisions for use of antibiotics in human, veterinary and industrial use*

4.1 Regulatory provisions for use of antibiotics in veterinary and industrial use

In livestock production, antibiotics are dispensed to animals for a number of different reasons viz. therapeutic treatment, disease prophylaxis and growth promotion. The administration of antibiotics against bacterial populations is a significant driving force for selection of resistant forms of bacteria, which can spread from one organism to another. There is therefore an important question of whether the use of antibiotics in animal food production poses a threat to human health. In particular, the worry is that resistant forms of bacteria may spread from animals and/or the environment (ground water / surface water / soil) to humans.

4.1.1 The effects of use of antibiotics in food animals on human health

There is a broad scientific consensus that the use of antibiotics in livestock, on some occasions, has detrimental effect on human health. The use of the antibiotic avoparcin as a growth promoter in food animals in Europe resulted in the development and amplification of Vancomycin-Resistant Enterococci (VRE) and subsequent colonization in human intestine. Vancomycin-resistance is a cause of concern because vancomycin is used as a last-line antibiotic for some hospital-acquired infections due to enterococci and staphylococci that have become resistant to the more commonly used antibiotics.

The use of antibiotic enerofloxacin was approved for use in food production animals in many countries. The use of this antibiotic in food animals has resulted in the development of ciprofloxacin-resistant strains of *Salmonella* spp. and *Campylobacter* spp. These resistant bacteria have subsequently caused human infections. The use of animal feed supplements with the antibiotic tylosin has led to the development of

erythromycin-resistant streptococci and staphylococci not only in the animals but also in their handlers.

WHO held a conference on use of antimicrobials issue and concluded that there is sufficient evidence showing that "the major transmission pathway for resistant bacteria is from food animals to humans" and has led to "increased frequency of treatment failure (in some cases deaths) and increased severity of infections". In their recommendations, WHO specifically called for stricter legislation to minimize antimicrobial usage in livestock because as it may pose a significant risk to the human health.

In 1997, the WHO's report on `The medical impact of antimicrobial use in food animals' highlighted several causes where transfer of resistance from animals to human had occurred. It can happen through: direct contact with animals; the consumption of meat; drinking contaminated water or the transfer of genes between animal and human bacteria. The best known examples are the food borne pathogenic bacteria viz. *Salmonella* and *Campylobacter* and the commensal bacteria like *Enterococcus*. Scientific data has shown that resistance of these bacteria to routine antimicrobial treatment in humans is often a consequence of the use of certain antimicrobials in agriculture.

4.1.2 International Regulations

Driven by a concern for human health, Denmark initiated in 1995 a process to end the use of antibiotics as growth promoters in livestock production. This process involved both voluntary and legislative elements, which led to a total ban on use of antimicrobial growth promoters in Denmark since the end of 1999.

Recognizing that antibiotic-resistance poses such a serious health threat, the European Union (EU) has banned the use of growth promoting antibiotics (specially those which are also used in human medicine) in animal feed. In December 1997, the EU banned the **Animal Growth-Promoter** (AGP) avoparcin in all its member states. In July 1997, the EU banned another four AGPs (tylosin, spiramycin, bacitracin and virginiamycin) because they belonged to classes of antimicrobial drugs used in human medicine.

Although the United States has yet to pass such a far-reaching policy decision about antibiotics in livestock production, the Food & Drug Administration (FDA) did ban one class of antibiotics used in poultry. Based on studies showing that high levels of fluoroquinolones in poultry led to drug resistance in humans, the FDA finally decided in 2005 to prohibit the use of fluoroquinolones in animal husbandry

4.1.3 Indian Scenario

In India, the antibiotics are used widely in food animals as growth promoters and to prevent and treat infections. Non-therapeutic usage of antibiotics has been especially common in poultry production. However, cuurently there is no regulatory provision regarding the use of antibiotics in livestock.

The Prevention of Food Adulteration Rules, 1995-part XVIII: Antibiotic and other Pharmacologically Active Substances, regulates the use of antibiotics and other pharmacologically active substances as given below:

The amount of antibiotics for sea foods including shrimps, prawns or any other variety of fish and fishery products, shall not exceed the prescribed tolerance limit (mg/Kg[ppm]) as mentioned below:

a. Tetracycline (0.1)
b. Oxytetracycline (0.1)
c. Trimethoprim (0.05)
d. Oxolinic acid (0.3)

The use of any of the following antibiotics and other pharmacologically active substances shall be prohibited in any unit processing sea foods including shrimps, prawns or any other variety of fish and fishery products: All Nitrofurans, Chloramphenicol, Neomycin, Nalidixic Acid, Sulphamethoxazole, Aristolochia spp. and preparations thereof, Chloroform, Chlorpromazine, Colchicine, Dapsone, Dimetridazole, Metronidazole,

Ronidazole, Ipronidazole, other Nitroimidazoles, Clenbuterol, Diethylstilbistrol, Sulphonamide drugs, Fluoroquinolones and Glycopeptides

4.2 Proposed Action Plan:

4.2.1 Establishment of inter-sectoral coordination committee comprising experts from the following agencies:

- Central Council for Scientific and Industrial Research (CSIR) (**Chairperson: DG, CSIR)**
- Ministry of Health and Family Welfare
- Ministry of Agriculture
    i. Indian Council for Agricultural Research
    ii. Department of Animal Husbandry
- Food Safety and Standards Authority of India (FSSAI)
- Agricultural and Processed Food Products Export Development Authority (APEDA)
- Marine Products Export Development Authority (MPEDA)
- Drug Controller General of India **(Member Secretary**)

4.2.2 The inter-sectoral coordination committee may undertake the following activities:

- Review of available data regarding the use of antimicrobials.
- Generation of data by undertaking studies on the use of antimicrobials as Animal Growth-Promoters.
- Specify the antibiotics for use in Livestock
- Review of current laws on use of AGPs in other countries and feasibility of their implementation in India.
- Development of regulations on usage of antimicrobials in poultry and other animals as well as the requisite labelling requirements in food.

- Review of Prevention of Food Adulteration Rules, 1995-part XVIII: Antibiotic and other pharmacologically active substances, if required, to enhance the scope (inclusion of other food products and antimicrobials).
- Any other related issue.

4.3 Regulatory provisions for use of antibiotics in Human use

The regulations regarding manufacture, use and prevention of misuse of antibiotics for humans and animals in India are governed by the Drug Controller General of India with the help of State Drug Controllers.

The current situation regarding "manufacture, use, misuse of antibiotics in the country" has been covered under ToR-I. The same also applies for the use of antibiotics in livestock.

The recommendations made by the subgroup constituted for ToR-I, which is headed by DCG (I) would also be applicable for human and animal component of ToR-IV.

ToR-5 : *Specific intervention measures such as rational use of antibiotics and antibiotic policies in hospitals*

5.1 Rational Use of Drugs

Over the last 60 years, bacteria &in particular those pathogenic to humans have evolved towards antimicrobial drug resistance. Antimicrobial resistance is an issue of great significance for public health at the global level. Antibiotics are considered as wondered drug, but its irrational use & often inappropriate prescriptions makes it as abused drugs sometimes. The pathogens causing acute illness are showing resistance to antibiotics & pose a great threat to public health. Thus it is a fact that wide spread practices of medically ineffective and economically inefficient use of medicines has become a serious public health threat in many countries, jeopardizing quality of care, wastage of limited resources ,access to essential medicines and development of antibiotic resistance .

Despite of existing policies, programs in different countries in various stages of implementation, sustainable effective interventions are lacking with significant impact in many of the countries including some part of India.

Overuse, under-use, and misuse of medicines & antimicrobials remains a world wide hazard, as has been reported in the literature - over 15 billion injections per year, half un-sterile, many unneeded, 25-75% of antibiotic prescriptions inappropriate, 50% of people worldwide fail to take medicines correctly (Health quick 2003).

Misuse and overuse of antibiotics, overuse and unsafe use of injections has been reported in Southeast Asian countries. All over the world 30-60% of PHC patients receive antibiotics which may be twice a s high as it may be clinically required. Large number of viral URTI and diarrhoea are treated with antibiotics in the world and inappropriate use is also being used in teaching hospitals all over the world.

Examples of irrational drug use are as follows:

- No drug needed e.g. unnecessary & ineffective antimicrobials or antidiarrhoeals given instead of Oral Rehydration Solution.
- Unsafe drugs e.g. Analgin (Dipyrone) banned in most developed countries, is used in many developing countries.
- Under use of available effective drugs e.g. ORS not used effectively.
- Ineffective drugs & drugs with doubtful efficacy e.g. unnecessary excessive use of tonics & multivitamin preparations
- Incorrect use of drugs e.g. overuse of Injections
- Wrong drugs used in unwarranted situations

Rational use of drug involves using the correct drug with appropriate indication i.e. the reason to prescribe the drug should be based on sound clinical consideration appropriate drug should be administered keeping in mind the safety, suitability, efficacy and cost. Apart from this the duration and administration of drug should also be done appropriately. Drug administration should also take into consideration the chances of drug reaction. Correct prescription and patient adherence to the treatment should also be considered.

5.2 Interventions

- A mandated multi-disciplinary national body should be established to coordinate medicines use policy
- Developing evidence-based clinical guidelines in a participatory way that are easy to implement and reinforced by prescription audit, etc
- An essential medicines list should be developed
- To form a national drug and therapeutics committees
- Problem-based pharmacotherapy training should be undertaken at regular intervals
- Continuing in-service medical education (CME) is a requirement for licensure of health professionals

- Continuous supervision, audit and feedback should be done
- Independent medicine information to be coordinated by the pharmacist
- Public education about medicines
- Appropriate and enforced regulation by drug controller of India
- While procuring antibiotics, efforts should be made to procure generics only with appropriate quality checks before bulk purchases.

The following three strategies should be followed to improve drug use:

- Educational strategy: Training, printing materials, media-based approach discourage self medication by the general public.
- Managerial strategy: Monitoring & supervision, generic substitution, patient cost sharing (economic incentives) etc
- Regulatory strategy: enforcement, sanction, drug withdrawal, market control etc

5.3 Protocol

To recommend **specific intervention** measures such as rational use of antibiotics and antibiotic policies in hospitals which can be implemented as early as possible.

Intervention Measures:

- Formulation of antibiotic policy
- Education and Training of all prescribers
- Implementation of infection Control guidelines

5.3.1 Formulation & implementation of an antibiotic policy

With quality assured laboratory data in real time develop antibiotic policies that are standard national / local treatment guidelines advocating evidence based immunotherapy or combination therapy. This must include consideration of spectrum of antibiotics, pharmacokinetics / pharmacodynamics, adverse effects, cost and special needs of individual patient groups.

5.3.2 Formulation:

Step I:

- Compile Local Hospital data based. on AMR
- Site of infection
- Geographic Variations (ICUs / Wards / Surgical Site Infections etc.)
- *Percent Distribution of organisms*
- *Percent Susceptibility to identified antibiotics*

Step II:

Put the data in given template:

- Site of Infection, Type of Infection.
- Causative pathogens.
- Recent 12 month antimicrobial data.
- Capture pathogens contributing to 80-90% of infections.
- Capture the susceptibility of antimicrobials from highest to lowest.
- Pneumonia
- IAI
- UTI
- BSI
- SSTI
- Surgical Prophylaxis.

Step III

- Put in database, based on site of infection?
- Data will be separate for Ward and ICU isolates

- 5 most common pathogens be identified and most antibiotics in decreasing order of sensitivity also be identified. Refer ToR-2 (Page no. 19 to 21) For details
- Generate the Validity period (X+1yr)

Hospital surveillance data (Jan-Dec of X year)			**Validity of these data: Dec X+1yr**		
S. No	***Most common pathogens***	***% prevalence***	***S. No.***	***Most sensitive antibiotics in descending order***	–
1	–	–	1	–	–
2	–	–	2	–	–
3	–	–	3	–	–
4	–	–	4	–	–
5	–	–	5	–	–

5.4 Implementation:

Defining patient type: ***Do Risk Stratification for each patient's type***

	TYPE 1	**TYPE2**	**TYPE 3**
Health Care Contact	No	Yes	Prolonged
Procedures	No	Minimum	Major invasive procedures
Antibiotic Rx History	No in last 90 days	Yes in last 90 days	Repeat multiple antibiotics
Patients Characteristics	Young – No co-morbid conditions	Elderly Few co-morbid conditions	Immuno-compromised +/- many co-morbid conditions

Possible Causative Pathogen	No MDRs Pathogens susceptible to common antibiotics	ESBLs / MRSA	ESBLs + Pseudomonas + MRSA

For example, an antibiotic policy for blood stream infections (BSI)

Blood Stream Infections (BSIs) Antibiotic Protocol: ICU *(valid upto June,2009)*

ICU MICROBIOLOGY DATA *(Total no. of isolates = 171)*

Most Common Pathogens	%	Antibiotics Susceptibility	%
Acinetobacter (n=48)	*28%*	*Colistin / Imipenem (=Amikacin) / Cef/Sul / Piptazo*	*98%; 9%; 6%; 2%*
Klebsiella (n=43)	*25%*	*Imipenem (~Ertapenem) / Amikacin / Piptazo / Cef/Sul*	*97%; 43%; 33%; 21%*
E.coli (n=24)	*14%*	*Imipenem (~Ertapenem) / Amikacin / Piptazo (=Cef/Sul)*	*100%; 92%; 67%*
Pseudomonas (n=20)	*12%*	*Colistin / Pip/Taz / Imipenem / Cef/Sul (=Amikacin)*	*91%; 62%; 29%; 27%*
Staph CNS(n=16)	*9%*	*Vancomycin (~Teicoplanin)*	*100%*

Patient Type 1 (CAI)	Patient Type 2 (HAI)	Patient Type 3 (NI)
No contact with health care system	*Contact with health care system (e.g. recent hospital admission, nursing home, dialysis) without invasive procedure*	*Long hospitalization and or invasive procedures*
No prior antibiotic treatment	*Recent antibiotic therapy*	*Recent & multiple antibiotic therapies*
Patient young with few co-morbid conditions	*Patient old with multiple co-morbidities.*	*Cystic fibrosis, structural lung disease, advanced AIDS, neutropenia, other severe immunodeficiency.*
Send Sample for Culture	***Send Sample for Culture***	***Send Sample for Culture***
PRESUMPTIVE THERAPY	**PRESUMPTIVE THERAPY**	**PRESUMPTIVE THERAPY**
Ampicillin/ Ampicillin-sulbactam/ Amoxi-Clavulanate Ceftriaxone Ciprofloxacin*	Ertapenem/Tigecycline** ± Vancomycin/ Teicoplanin	Colistin+Imipenem+Sulbactam ± Vancomycin or teicoplanin
After Culture Report	***After Culture Report***	***After Culture Report***
Continue Treatment	***Continue Treatment***	***Continue Treatment***
S.typhi: Continue the treatment	ESBL +ve Klebsiella / E.coli: Continue treatment with monotherapy	Susceptible PA/AB /MRSA: Continue treatment as monotherapy
Stop "De-Escalate "	***Stop "De-Escalate "***	***Stop "De-Escalate "***
Continue monotherapy	Non ESBL Enterobacteriaceae, De-Escalate & Treat it as patients type 1	ESBL Positive Enterobacteriaceae, De-Escalate and treat as Patients Type 2
Consider Escalation	***Consider Escalation***	***Consider Escalation***
ESBL +ve Enterobacteriaceae including Salmonella: Escalate and treat as patient type 2	PA/AB: Escalate and treat as Patient Type 3; in case of MRSA add Vancomycin or Teicoplanin	MDR-PA or AB: Continue 3 Drug Colistin + Imipenem + Sulbactam

*Avoid Ciprofloxacin since it has potent antipseudomonal activity

Note: Patient Type 4 can also be added in special circumstances where suspicion of fungal (Candida) infection is highly suspect

5.4.1 Set up an Antibiotic Management Team (AMT)

This is a Multi disciplinary team with experts in: Infectious diseases, Internal medicine, Intensive care, Surgery, Paediatrics, Clinical microbiology, Pharmacology and Hospital pharmacy.

The functions of the AMT are

- Develop the hospital antimicrobial policy both from existing policy (if any) and evidence based guidelines and adapt to suit local circumstances.

5.4.2 The policy should be for presumptive / empiric therapy and prophylactic therapy

(i) Presumptive/ Empiric antibiotic policy

The policy should be simple, clear, non-controversial, clinically relevant, flexible and applicable to day-to-day practice and available in user friendly format. It should also include optimal selection dosage, route of administration, duration, alternatives for allergic to first-line agents; adjusted dosage for patients with impaired renal functions.

The policy should risk stratify patients if this has not been done by the antimicrobial surveillance

Previous history of antimicrobials or current antibiotics along with patient co morbidities may play a role in final prescribing.

Note: Case index ratio has not been addressed at present (will be done subsequently).

5.4.3 The presumptive / empiric policy should set the levels for prescribing antibiotics:

- First choice antibiotics: Can be prescribed by all doctors
- Restricted list of antibiotics: Only after permission from HoD or AMT representative
- Reserve antibiotics: Only after permission from AMT member

Presumptive therapy only applicable for 48 hrs after that the therapy needs to be converted into a definitive therapy (de-escalation step) based on evidence whether clinical or microbiological. AMT should interact with the unit that prescribes more than two antibiotics and satisfy them to the correctness of the regimen.

5.4.4 Prophylactic antibiotic policy

Procedure for which antibiotic are needed should be posted in Operating Room with Optimal agents, dosage, timing, route and duration of administration e.g. Inj Cefuroxime 1.5 gm I/V before induction of anaesthesia, repeat another dose if procedure extends beyond 4 hrs.

Prophylactic antibiotics should be given for a short duration, free of side effects and relatively inexpensive and should not be used as a therapy

5.4.5 De-escalation for targeted therapy should also be a vital aspect of the policy after microbiology reports are available

5.5 Constructive feedback of policy prior to implementation

After formulation of the presumptive / empiric & prophylactic policies they should be circulated to receive constructive feedback. Policy should be reviewed by respected peers who are not the members of the AMT, but are also experts in the relevant field .Ownership should be complete.

5.6 Monitor implementation: we may form Drug and Therapeutics Committee which may carry out the following:

5.6.1 Basis for approval of new drugs: The DTC has to fix criteria for the approval of new drugs. Those criteria include safety, efficacy, availability and cost of the medication.

5.6.2 Fixing of three brands per generic: The DTC may decide to keep a maximum of three brands of an approved generic.

5.6.3 Banning of harmful drugs in the Hospital: The DTC can ban the use of few harmful drugs like Phenylpropanolamine (PPA) and Nimesulide in the hospital.

5.6.4 Removal of irrational fixed dose combinations from the hospital drug list: The committee can remove few irrational fixed dose combinations from the hospital drug list.

These combinations include the fixed dose combination of ampicillin with cloxacillin, amoxicillin with cloxacillin etc.

5.6.5 Development of over the counter (OTC) drug list: Hospital DTC should develop the OTC drug list for the Hospital. This OTC drug list should also contain the quantity to be dispensed

5.7 Assess outcome of Intervention: as below

A monthly update of antibiotic consumption of a unit is sent with a comparison of other units in the institute this highlights any excess, for e.g. a monthly update on antibiotic prescribed can be shared with the doctors of their speciality:

Unit: Cardiology

- Your unit prescribed 117 DDD/100 bed-days
- Average for all specialties: 189 DDD/100 bed-days
- Average for your specialty: 133 DDD/100 bed-days
- 3 % of units in this hospital prescribe fewer DDDs of antibiotics per 100 bed-days than your unit

DDDs are a standardized measure of drug consumption used by WHO: They represent the average daily maintenance dose of a drug used for its main indication in adults

Table 1. Breakdown of antibiotic use by class (in DDDs/100 bed-days). When your unit's prescribing rate for an antibiotic class is above the average for all units in this study, it is shown in red

Antibiotic class	Your unit's prescribing rate	Average for all specialties	Average for Cardiology
Penicillins	7	1	1
Cephalosporins	29	89	26
BL BLIs	41	35	50
Quinolones	18	15	32
Aminoglycosides	4	20	4
Macrolides	9	7	12
Clindamycin	3	7	3
Carbapenems	4	6	2
Glycopeptides	1	5	4

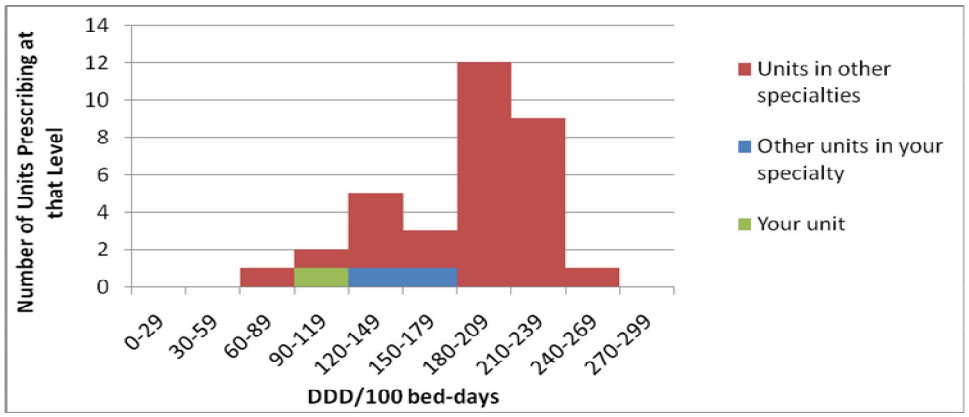

Figure 1 - The distribution of prescribing rates. The green is your unit and blue rectangles represent other units in your specialty and the red rectangles represent all units in other specialties of the hospital. Similarly this should be made for each unit at a particular hospital

Note: Confidential: circulation to unit only

5.7.1 Update and revise

The policy should be updates every year based on local surveillance of antimicrobial susceptibility data, clinical practice and local circumstances

5.7.2 Set prescription audit targets

5.8 Education

Train and educate doctors at all levels for usage of this antibiotic policy.

Ensure training on types of organisms in each type of infection and the ideal choice should be in the form of weekly CMEs seminars etc., in the beginning of the launch of the antibiotic policy.

5.9 Implementation of Infection Control Guidelines

Ensure Infection prevention guidelines to prevent cross transmission of resistant pathogens (guidelines for good infection control practice and SOPs should be circulated including waste disposal guidelines to prevent release of antimicrobials in the environment through human excreta and other body fluids)

After the IC guidelines are adopted regular point Surveillance Audit are essential aspects to ensure implementation

- **Preoperative prophylaxis:** Surgeons should regularly follow up on feasibility of not giving oral antibiotics on post-op day 2-5 after perioperative antibiotics on day one.

- **Audit:** should be the collective responsibility of the members of the AMT. For this the microbiologist of the hospital can take ward rounds at least once a week and do spot or point surveillance.

- Cost related issues to be decided by the committee set up in each hospital for antibiotic policy.

Reference to the other Terms of Reference can be given where ever necessary.

ToR-6 : *Diagnostic methods pertaining to Antimicrobial Resistance Monitoring*

Appropriate diagnostic tools already known should be selected as well as new ones developed for rapid identification of pathogens for AMR surveillance.

Robust quality assurance system should be implemented that could be carried out by a “neutral” central institute.

If needed, linkages should be established with some of the existing institutes for strengthening quality assurance. This strengthening of quality assurance should span animal health, industrial surveillance and environmental surveillance.

Environmental surveillance should be an interface between veterinary, industrial and human health.

7. *Conclusions*

- It is imperative that all the clinicians understand the principles and standard methods of antibiotic susceptibility tests. They should also insist on the laboratory to follow these recommended procedures to generate antibiotic susceptibility test reports that are quality assured. Antimicrobial susceptibility data generated based on consistent reproducible and comparable data between different laboratories will produce better outcomes and help in developing region-wise antibiograms.

- All the tertiary care hospitals (public or private) need to develop their SOP's and guidelines as per the national guidelines and implement in their setting.

- The guidelines in the hospital to be reviewed every 6 months; national guidelines to be reviewed on yearly basis.

Public Private Partnership:

- All health care facilities need to implement the Antibiotic Policy which should be one of the components of hospital infection control guidelines & share the data with national agency.

8. *Important Abbreviations*

AGP	:	Animal Growth-Promoter
AMR	:	Antimicrobial Resistance
APEDA	:	Agricultural and Processed Food Products Export Development Authority
AST	:	Antibiotic Susceptibility Testing
ATC	:	Anatomical Therapeutic Chemical
BSI	:	Blood Stream Infection
CDSCO	:	Central Drugs Standard Control Organization
CLSI	:	Clinical Laboratory Standard Institute
CME	:	Continuing Medical Examination
DCGI	:	Drug Controller General India
DDD	:	Defined Daily Dose
DTC	:	Drug Therapeutics Committee
EQA	:	External Quality Assurance
ESBL	:	Extended Spectrum Beta Lactamase
EU	:	European Union
FDA	:	Food & Drug Administration
FSSAI	:	Food Safety & Standards Authority of India
GASP	:	Gonococcal Antimicrobial Susceptibility Programme
IAI	:	Intra-abdominal Infection
ICU	:	Intensive Care Unit
MBL	:	Metallo-β-Lactamase
MDR	:	Multi Drug Resistance
MPEDA	:	Marine Products Export Development Authority
MRSA	:	Methicillin Resistant Staphylococcus Aureus
NACP	:	National AIDS Control Programme
NDM	:	New Delhi Metallo-β-Lactamase
NVBDCP	:	National Vector Borne Disease Control Programme
ORS	:	Oral Rehydration Therapy

RNTCP	:	Revised National Tuberculosis Control Programme
SOP	:	Standard Operating Procedure
SSTI	:	Skin and Soft Tissue Infection
ToR	:	Terms of Reference
URTI	:	Upper Respiratory Tract Infection
UTI	:	Urinary Tract Infection
VRE	:	Vancomycin Resistant Enterococcus