

## **ICMR-RCN meeting on Antimicrobial Resistance**

### ***Understanding Challenges and Identifying Potential Solutions***

***November 10 -11, 2016***

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The Indo-Norway workshop on Antimicrobial Resistance was organized in succession with the bilateral discussions which took place in Tromsø in 2013, hosted by University of Tromsø. The Tromsø workshop was attended by Indian Council of Medical Research (ICMR) scientists and experts to discuss the potential research areas of mutual interest and cooperation. The Indo-Norwegian Cooperation on AMR was strengthened in October 2014, with a signing of MoU between ICMR and Research Council of Norway (RCN). In the current workshop, over 25 Indian scientists from various hospitals, and research institutes, were working in human and veterinary AMR space, were invited to participate. 24 Norwegian scientists with expertise in human, veterinary and environment AMR took part in the workshop. The New Delhi workshop provided a platform for brainstorming between Indian and Norwegian researchers to find potential research partners in the research areas agreed under the cooperation.

The two days workshop was planned to address four major areas: Overview of national strategies and research on AMR, surveillance of AMR and antibiotic use, diagnostics and therapeutics solutions for AMR, AMR in tuberculosis, and Transmission of AMR in environment. A comprehensive overview of the presentations and discussions is presented below:

#### **Overview of national strategies and research on AMR**

Dr. Gunnar Skov Simonsen presented the antibiotic policy of Norway and discussed the joint research initiatives between Norway, other European countries and researchers from other countries globally. Dr. Gunnar presented the overview of Norwegian healthcare and regulation of prescription in Norway. He mentioned that in Norway, antibiotics are available by prescription only and prescription drugs are not advertised to the general public, and for prescription of antibiotics physicians and veterinarians follow the same guidelines. The Norwegian national strategy for 2015-2020 to tackle AMR was jointly developed by Ministry of Health, Ministry of Fisheries, Ministry of Agriculture and Food and Ministry of Climate and Environment. The national AMR strategy defines goals for the government and for specific sectors such as health, food producing animals and household pets, fisheries and aquaculture, and climate and environment. The overall objectives of the national strategy are to reduce total use of antibiotics (by 30% in population), reduce prescription of antibiotics from current 450 to 250 per 1000 inhabitants/year, antibiotic resistant bacteria reservoir mapping in relevant animal and plants, reducing antibiotic use

in terrestrial animals by minimum 10% and in pets by at least 30%. For fisheries, the antibiotics usage is targeted to be either the same or lower by 2020, also, it is proposed to initiate mapping of resistant bacteria in specific environments in animals, water and soil. Dr. Simonsen also presented highlights of the New Drugs 4 Bad Bugs initiative (ND4BB) and Joint Programming Initiative on Antimicrobial Resistance (jpiamr, [www.jpamr.eu](http://www.jpamr.eu)).

Dr. Anuj Sharma presented the World Health Organization (WHO) strategy for AMR.

Dr. Shome from NIVEDI provided a summary on the policies for use of antibiotics in animals in India. Dr. Shome emphasized that nine out of the fourteen classes of drugs which are used in humans are also used in animals. Further, he discussed that the specifications from regulatory bodies such as Bureau of Indian Standards (BIS), includes restriction in systemic acting antibiotic, Food Safety & Standards guidelines discuss Maximum Residue Limit (MRL) of 4 antibiotic in sea food and prohibition of certain antibiotics for export products only, while the National Policy on containment of antimicrobial resistance, 2011 published by MoHFW, does not emphasize the need for surveillance of resistance in animals and related food chain.

Dr. Kamini Walia, a senior scientist at Indian Council of Medical Research (ICMR) presented ICMR's initiative Antimicrobial Resistance Surveillance and Research Network (AMRSN) which was started in 2013. She presented some of the highlights of the data collected from the four nodal centers under AMRSN.

Dr. Sunil Gupta, Additional Director of National Center for Disease Control (NCDC) presented antibiotic policy of India. He said that the main drivers of AMR in India are: uncontrolled use of antibiotics in human and in veterinary sector, inadequate regulations (Schedule H only for human use, limited regulations for food animals, however, No regulations in Non food animals), very little national data of antimicrobial use and inadequate interaction among clinicians and laboratory experts. Dr. Gupta presented the network recently established by NCDC which has included 10 labs in the first phase and aims at strengthening a total of 30 labs in state medical colleges in a phased manner. He informed the participants that NCDC formulated the National Policy for AMR containment formulated in 2011 and is currently in the process of preparing a national action plan on AMR.

### **Surveillance of AMR and antibiotic use**

Dr. Marianne Sunde, a senior researcher at the Norwegian Veterinary Institute, presented the animal AMR surveillance in Norway. She informed the participants about NORM-VET, the Norwegian monitoring program for antimicrobial resistance in the veterinary sector, which is running since 2000. NORM-VET is monitoring resistance trends in different bacterial populations through susceptibility testing and is also monitoring antimicrobial

use through sales/registry veterinary prescriptions. According to the NORM-VET, there is low prevalence of AMR in most animal species, high prevalence of ESBL/AmpC and quinolone resistance in *E. coli* in broilers.

Dr. GunnarSkov Simonsen in his presentation on surveillance discussed that in Norway, surveillance data includes routine data, NORM surveys, MSIS notification and data from reference labs. The data presented showed that the *Salmonella* Enteritidis and *Campylobacter jejuni* are most resistant to nalidixic acid. The number of Carbapenemase producing Enterobacteriaceae and Carbapenemase producing Enterobacteriaceae is continuously increasing since 2007.

Dr. Anita Kotwani, Professor at the V. P. Chest Institute, discussed a pilot project on community-based surveillance of antibiotic use & resistance, which was conducted at five sites (3 in India and 2 in South Africa), during 2002-2005. The project (survey) was also conducted from December 2007- Nov 2008. The survey revealed that 39% patients visiting public facilities and private retail pharmacies received antibiotic; 43% patients at private clinics got an antibiotic.

Dr. HegeSalvassen Blix in her presentation elaborated that there are large variations among various countries in the volume and pattern of use of antibiotics in animals, in healthcare systems, disease patterns, therapeutic traditions, dosing and duration of treatment, which need to be collected, analyzed, compared and interpreted.

Dr. Morten Lindbaek, professor in general practice, leader of Antibiotic Centre for Primary Care, shared his experiences from intervention studies on antibiotic use in clinical practice. Dr. Ingrid Smith presented her talk on antimicrobial stewardship (AMS), prescription patterns and digital tools. She highlighted that AMS programs should be implemented in hospitals, which in Norwegian context will be important in order to reduce the antibiotic use by 30% till 2020. She discussed that the challenge with digital tools is that the IT systems do not support clinical work flow and integrated care pathways, lack functionality for clinical decision support and quality management and their lack of structured information prevents automatic data availability.

Dr. PriscilliaRupali presented the India experience on the use of AMSP in hospitals. In her presentation, Dr. Rupali discussed clinical cases which were accurately treated due to the intervention of the Infection Control team of the hospital.

### **Diagnostics and therapeutics solutions for AMR**

Dr. Kristin Hegstad presented her work on identification of virulence factors from clinically important human pathogens, refine and validate them, design and synthesize ligands for target interaction and identify biological targets of these novel compounds. Using this

approach, Dr. Hegstad's team has identified in two Tir-E proteins in *Enterococcus faecium* which are highly prevalent in clinical isolates and expressed in blood of the patients, and they interfere with Toll-like receptor 2 signalling and are important for the bacteria's survival.

Dr. Gaurav Batra, Assistant Professor at Translational Health Science and Technology Institute, presented a multiplexed point of care diagnostic strip that he and his team are developing for detecting specific pathogen associated with acute febrile illness. The test is aimed to provide core-lab performance in a form suitable for the point-of-care.

Dr. Pål Rongved, Professor at the University of Oslo, presented his work under the project ZinChel discovery, under which his team is working on a new strategy to identify new antimicrobials against resistant bacteria based on chemistry.

Dr. Otterlei, presented her work on antibacterial peptides labeled as APIM-peptides which are shown to have a vital role in regulating cellular stress/DNA repair in mammalian cells and also possess broad antibacterial activity against both Gram positive and Gram negative bacteria.

Dr. Jan Egil Afset spoke on the virulence factors in diarrheagenic *E. coli*. (DEC). He discussed that antibiotics are not recommended for the treatment of diarrhoea caused by DEC, but is used often. He suggested that the role of DEC as risk factor for antibiotic resistance should be studied more thoroughly, including the molecular link between virulence and antibiotic resistance.

Dr. Anne Tondervik, a Senior Scientist at SINTEF (Stiftelsen for industriell og teknisk forskning), educated the participants about the technology platforms that are available with SINTEF and the projects that they are undertaking. She showed that SINTEF has various technology platforms for high throughput screening, and other high end techniques used at SINTEF for bioprospecting, development of new bioactive compounds by strain engineering and discovery of new clusters for synthesis of bioactive compounds.

### **AMR in tuberculosis**

Dr. Uma Devi presented the current scenario of AMR in tuberculosis and potential ways to tackle drug resistance in tuberculosis. She discussed that of the 10.4 million new TB cases globally, of which the cure rate of treated MDR-TB patients was an estimated 52% while for XDRTB patients, the treatment success rate was only 28%. She highlighted that research in TB is moving towards using Bacterial genomics as a diagnostic tool in drug-resistant TB.

Dr. Avinash Sonawane presented the role of the glycoproteins of the cell wall of *Mycobacterium tuberculosis* in its pathogenesis and as potential drug targets. He discussed

peptidoglycan amidase (Rv0024) glycoprotein which was found to induce biofilm formation and drug resistance and mimG glycoprotein which was found to be involved in tuberculosis development in Zebrafish.

Dr. Tone Tonjum in her presentation explained that *M. tuberculosis* does not have plasmid, so it cannot efficiently transfer resistance genes horizontally. She discussed that RecG, a helicase, is a potential drug target as it has role in several DNA transaction pathways.

### **Transmission of AMR in environment**

Yngvild Wasteson, suggested a paradigm shift in the conventional approach through one health in a way that if the control measures are applied in animal population, it will result in management of disease and infections in humans. In EU, antibiotics as growth promoters in animal feed has been banned since Jan 1, 2016, still increased use of strongest antibiotics in European farms at record levels has been reported. He emphasized that AMR sustains in animal (food producing and pets) and environmental reservoirs (marine sediments and sewage) and is transmitted through food or through direct human-animal contacts.

Dr. V. Balaji, in his presentation highlighted that multiple records show the evidence for transmission of AMR from livestock to humans. ESBL is one among the most common, followed by VRE, MRSA and colistin resistant gram negative organisms. Several scenarios occur in the genetic transport of AMR genes from animal to human environments. The endogenous AMR genes in animals are transported unchanged to humans or the genetic structure passes through one or more different hosts, ending in a new host (humans).

### **Remarks by Ambassador Kamsvag and Dr. Soumy Swaminathan**

**Ambassador Kamsvag** highlighted the importance of the knowledge based decision making. He expressed his concern on rising AMR and communicated that the area is receiving growing political attention as 50,000 lives are lost each year to AMR alone of which HIV and TB are the serious issues. Ambassador Kamsvag opined that free and independent research is needed in this area and there is growing international interest to collaborate with India in research. Norway has invested heavily in AMR, policy and knowledge and research. Indian and Norwegian scientists have worked together in the past in the areas of mutual interest. Norway is proud to be part of this initiative. National bilateral programs are key to advances in science and research. He expressed his commitment to the initiative and said that Norway is willing to be pioneer in AMR. Ambassador Kamsvag was enthusiastic about the fact that the two countries are joining forces to address the challenge of AMR which will benefit global community and was convinced that the collaboration will bear fruit.

**Dr. Soumya Swaminathan**, Secretary DHR, DG ICMR, talked about the national initiatives taken to tackle AMR. She informed the participants about the Red Line Campaign, under which the antibiotic packs are labeled with a Red Line to encourage their judicious usage. Dr. Swaminathan said that ICMR is collaborating with ICAR to strengthen AMR research towards One Health. She opined that the available treatments should be a step ahead of the bacteria, so the researchers have to focus also on alternative therapies such as new peptide and molecules as antimicrobial agents. Antimicrobial Stewardship Programs have proven to control the AMR directly. Therefore, Dr. Swaminathan maintained that AMSP should be one of the cornerstones in controlling AMR. She highlighted that tuberculosis (TB) especially MDR and XDR TB is a huge problem. In order to counter the growing threat of AMR, engagement of partners from ministries and donors is essential and it is important that all the stakeholders work in synergy. Advances in sequencing with less cost are allowing the researchers to discover the underlying mechanism of resistance to antimicrobials. She said that innovation and collaboration can do a lot of advancement and empowerment. Earlier detection and targeted treatment can avert AMR or significantly reduce the emergence of AMR. She was enthusiastic about the outcome of the RCN-ICMR collaboration and specified that the conference should be followed up with a call.

### **Group Work**

The participants were distributed in four groups based on their areas of expertise under the matchmaking event. The participants were allowed to discuss together about their work amongst themselves and present their discussion and future plan. The four broad areas were identified as:

- Surveillance of antibiotic use and interventions (Group 1)
- Surveillance for resistance and transmission (Group 2)
- Diagnostics and Therapeutics (Group 3)
- Tuberculosis (Group 4)

**Group 1 (Surveillance of antibiotic use and interventions)** proposed two overall objectives for designing collaborative proposals:

- i) Mapping of antibiotic use in India and in Norway through description of use in primary care, hospital, human/animal, both total use and pattern of use.
- ii) Implement interventions such as education of the health care professionals and general public about AMR; provide guidelines for hospitals and primary care, development and use of indicators and implementation of guidelines.

**Group 2 (Surveillance for resistance and transmission)** proposed the following overall area of research:

i) One Health approach to delineate AMR dynamics in defined ecosystems in India and Norway” with an aim to study the pattern of antibiotic resistance among common bacteria in defined eco-system.

The group suggested that the outcome of the study will be development of a one health platform, development of SoPs, establishment of AMR surveillance networks, data on AMR dynamics in defined ecosystem, establishment of public health system and capacity building of human resources and exchange of scholars between the two countries.

**Group 3 (Diagnostics and Therapeutics)** came up with three major areas of research:

i) Assessment and understanding the molecular mechanisms involved in antibiotic resistance as well as other drug targets such as virulence factors focusing on ESKAPE pathogens.

ii) Detection of antibiotic resistance and pathogen specific diagnostics for evidence based treatment and

iii) Novel therapeutic strategies against MDR pathogens particularly the hard to kill ESKAPE pathogens (novel antibiotics as well as inhibitors of determinants of MDR)

**Group 4 (Tuberculosis)** suggested that though the proposed area of discussion was specific, nevertheless the participants decided to propose broader topics which could be applied both for tuberculosis research as well as other infections. The group identified four broad areas under which they would suggest proposals:

1. Surveillance of AMR as a phenotype of mutagenicity
2. Environmental and animal reservoirs of mycobacteria in a One Health perspective
3. Efforts to shorten treatment duration, therapeutic AMR vaccines
4. Rapid and sensitive diagnostics of AMR and host responses related to AMR
5. Improved diagnostics: point of care tests; diagnostic and prognostic biomarkers; biomarkers to monitor latent TB, detect dormant mycobacteria and persisters; monitor the efficacy of TB therapy
6. New drug targets/screening strategies/novel delivery systems
7. Optimising the use of approved and repurposed drugs
8. Evolution of drug resistance in *M. tuberculosis*
9. Molecular mechanisms of AMR development
10. Microbial host ecology including the impact of microbiomes in a One health perspective

**Concluding session: Dr Rashmi Arora and Dr Swarup Sarkar WHO**

There is a need to strengthen research in AMR and ICMR-RCN collaboration can go a long way in achieving the same. There is a need to increase funds available for research in AMR. It is important that the research which is being funded should make a strong case for increased funding in future.

The two day event ended with presentation of vote of thanks by Dr Kamini Walia.