ANTIMICROBIAL RESISTANCE (AMR) RESEARCH AND INNOVATION: ADDRESSING INDIA’S PRIORITIES

7 December 2016, New Delhi, India
Meeting Report

This one day gathering of 40 experts and stakeholders in the field of drug resistant infections was jointly organised/co-hosted by the Indian Council of Medical Research (ICMR) and the Global Antibiotic Research and Development Partnership (GARDP, a recently launched joint initiative of the Drugs for Neglected Diseases initiative [DNDi] and the World Health Organization [WHO]). The meeting aimed to advance the understanding of the most pressing antimicrobial resistance-related medical needs, research and development (R&D) gaps, and evaluate the potential to address the same through collaboration opportunities in India. It specifically aimed at ensuring that key priorities and gaps were brought forward through a participative programme, and that recommendations be made in three areas (see under ‘Priorities’ in breakout sessions):

- Public health AMR priorities in India: surveillance, treatments, diagnostics
- Clinical research for antibiotic treatments in and for India: potential for regional collaboration and clinical trial networks
- Drug discovery: needs, challenges, opportunities

The meeting included discussions on a wide range of subjects including infections and patient groups, national regulations, diagnostics, and surveillance factors. It also explored how to capitalize on existing networks in the antibiotic R&D landscape in India. A key issue raised by all was the need for a research consortium or platform in India with key national and international partners to address the various aspects of antimicrobial resistance through regular meetings.

Indian Council of Medical Research (ICMR), Priority Areas of Research for AMR: Dr Soumya Swaminathan, Secretary, Department of Health Research & Director General, ICMR

This important meeting organized by DNDi and ICMR brings together private and public sector experts - clinicians, pharmacologists, academics, and industry partners to explore existing and potential collaborations which can steer research in antimicrobial resistance (AMR).

Indian institutes such as the ICMR, the Council of Scientific and Industrial Research (CSIR), and the Department of Biotechnology (DBT) have complementary strengths. CSIR has capacity in early stage drug discovery (e.g. medicinal plants, preclinical testing). DBT institutes such as its Bangalore cluster have carried out work on the mechanisms of many pathogenic organisms. ICMR has translational and clinical research capacity. It has structured an AMR surveillance network that includes four tertiary hospitals, soon to expand to include 15 more hospitals, both public and private. The network is focussing on six pathogen groups, which have high rates of drug resistance and are responsible for hospital acquired infections, including in neonates and leading to death. ICMR is working closely with the Ministry of Health and WHO to implement an AMR stewardship programme in hospitals. Early clinical trials are required for existing as well as new drug combinations, and repurposing of existing drugs is needed. New approaches are required for the use of non-antibiotics and for synergistic ways of enhancing existing antibiotics. Finally, a network
of institutes that can undertake clinical trials is needed, and ICMR is committed to developing this capacity. This network of public and private hospitals with capacity for the highest standard of quality for clinical trials will need to focus on difficult infections whether in neonates, paediatrics, or in intensive care units.

Professor K Vijay Raghavan, Secretary, DBT

Antimicrobial resistance highlights the ongoing biomedical research debate in India regarding how complex problems are addressed. Early stage research has a deep impact on society. There is an expectation that science will provide a solution to every problem, and when that does not happen a policy response is demanded. In a country with multiple government agencies, there is a need for active coordination, allowing work to be carried out in relevant domains yet without hindering creativity and diversity. DBT has funded a significant amount of work on drug resistance and has built genetics and microbiology capacity to explore its origins. DBT has successfully engaged in tuberculosis research and drug discovery in general, such as with the UK Medical Research Council.

There is still a need for large scale drug discovery and vaccine research efforts, which are planned for the coming year in collaboration with the World Bank, with research centres across the country. India’s drug discovery efforts would be greatly reinforced through collaboration between ICMR, Indian Council of Agricultural Research (ICAR), and CSIR – which all have enormous capability and talent. The DBT needs to provide support to different components of drug pipelines in a dynamic way so as to integrate the ecosystem. It is now important to start a consortium which effectively moves from discussion to action.

Dr Jagdish Prasad, Director General of Health Services

Antimicrobial resistance is an important issue for India and the world as a whole, and collaborations such as those with GARDP/DNDi provide a platform for research with many partners worldwide. In India, it is important for the groups active in the field of AMR to meet regularly to share developments and bring in new thinking on drug discovery. We also need more standardization and harmonization of the ways that clinicians prescribe drugs; this is challenging because, in absence of standard treatment guidelines, individual clinicians may have very different ways of treating the same disease.

An AMR platform could also contribute to concrete policy on AMR. We must address drug combinations which are currently being prescribed with no clinical trial data supporting their use, and also support research on old antibiotics to determine if their pharmacokinetics and pharmacodynamics (PK/PD) are adequate. Given the problem of resistance because of the mutation rate of bacteria, it is now the time to investigate new approaches to the biochemical action of drugs.

Dr V. G. Somani, Deputy Drug Controller

Promotional and actual usage practice, in addition to hygiene, pollution, awareness and surveillance, must be addressed. A number of medicines for case management and post-surgical coverage are given by medical practitioners without any testing. Practitioners and manufacturers need to be motivated.
The drug development pipeline is dry because companies have a tendency to make broad spectrum antibiotics and not to work on resistant strains, as the market for these drugs is very small, resulting in big gaps. It is suggested that consortium like this can fill the gaps, however the groups have to be very active and motivated, with regular monitoring plans in place.  

**Dr Henk Bekedam, WHO representative to India**

Today, a simple infection can lead to a life-threatening situation due to resistance to antibiotics. However, there are enormous research opportunities on AMR which is encouraging. There is a need to understand antibiotics globally in terms of usage, awareness, knowledge, and practice. It is necessary to start from the basics, such as hand hygiene, and raise awareness regarding safe surgery and injection safety in order to curb the problem of AMR. Also, we need to understand population demand for antibiotics; in Asia it has been shown that doctors earn a lot of money by prescribing antibiotics. Farmers believe there is a need to use antibiotics, which is also a big problem. We therefore need to strategize based on knowledge and existing evidence. More than 100 hospitals in India conduct AMR monitoring, but data needs to be centralized. Prescription audits could be considered to ensure optimal use of antibiotics and to monitor supply and demand. India will be using a national health protection scheme, which will cover about 400 million people, so a strong emphasis should be placed on monitoring.

It is essential to take up the research agenda through a consortium to understand what is happening. A research consortium would also be useful to address a variety of currently unaddressed issues such as environmental pollution.

**Global Antibiotic Research and Development Partnership, New Approach to Delivering Innovations of Public Health Importance**

**Dr Manica Balasegaram, Director, GARDP/DNDi**

The Global Antibiotic Research and Development Partnership (GARDP) arose from two parallel processes – the World Health Organization’s work on its Global Action Plan on AMR and the Drugs for Neglected Diseases initiative’s work on its new business plan, which includes AMR. A joint WHO-DNDi initiative, GARDP was launched in May 2016 during the World Health Assembly. Its scope is global, and its vision is that R&D will ensure that everyone in need of antibiotics receives effective, appropriate and affordable treatment. GARDP is a non-profit R&D organization and will embed sustainable access – linking innovation, stewardship, and patient access to treatment – in all of its work, which will be conducted within a true public and private partnership model.
GARDP will prioritize its work through intersecting priority pathogens, diseases/syndromes, and underserved populations. Its objectives for 2023 are to develop and deliver up to five new treatments, build a robust pipeline of preclinical and clinical candidates, and actively promote appropriate use of antibiotics, sustainable access, and long-term R&D financing.

**Break-Out Sessions: Introduction**

**Dr Raman Gangakhedkar, National Research Institute (Pune)**

In general, health outcomes rely on three important stakeholder groups: patients, providers, and policy makers. Given that 10 million deaths due to AMR are estimated by 2050, we need to have better surveillance data (80 out of 194 countries do not have data for AMR and, where it is available, it may be incomplete and/or outdated). Overall, there is a lack of a public health (collective) perspective and too much emphasis on the individual. Key pathogens/infections to focus on include: *Escherichia coli*, *Klebsiella pneumonia*, *Staphylococcus aureus*, *Non-typhoidal Salmonella*, *Shigella*, and *Neisseria gonorrhoea*, and the more notorious HIV, *Mycobacterium tuberculosis* and *Malaria*.

Geographical boundaries are no limitation and human mobility cannot be controlled. There is a great need to emphasize AMR surveillance, antibiotic use in combinations, and the pipeline of antibiotics. Healthcare providers tend to be complacent, and ignorance among patients is leading to inappropriate use of antibiotics.

**Breakout Group 1: Public Health AMR Priorities in India – Surveillance, Treatments, Diagnostics**

*Facilitated by Dr Kamini Walia, ICMR*

This group covered not just priority setting for R&D but also surveillance of human and non-human antibiotic use. There is a need to focus on surveillance in order to feed into R&D prioritization, and the Indian government can play a significant role in setting and funding R&D priorities at country level, in line with global priorities. Locally available data needs to be used to adapt global guidelines to the local context, linking to R&D to ensure evidence based policies. Surveillance data is also valuable for adapting and customizing guidelines at regional and international levels. Surveillance, however, is limited to tertiary level hospitals, and does not distinguish between hospital acquired and community acquired infection, owing to various indigenous challenges peculiar to the Indian healthcare system. In reality, hospital acquired infections are often treated in the community. R&D should prioritize hospital acquired infections.

Priority pathogens as per the available data include *Escherichia coli*, *Shigella*, *Klebsiella*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter cloacae*, but also fungal infections such as *Candida* and *Aspergillus*. Complicated hospital acquired pneumonia/ventilator
associated pneumonia (HAP-VAP) and urinary tract infections (UTIs) also require attention. Dosing, duration, combinations, paediatric use of antibiotics and optimum use of existing antibiotics (and here community needs can be considered) are important areas which need attention. *Shigella* and non-typhoidal *Salmonella* were also highlighted. *Gonorrhoea* is currently not a priority in India, but there may be a need for an alternative treatment in the near future; some monitoring in the private sector has shown resistance. Biofilm infections need to be looked at, for example for UTIs. Beyond drug R&D, availability and access of existing drugs is an important problem. For diagnostics, rapid molecular-based tests could guide the use of antibiotics, while a point of care test could reduce global antibiotic consumption.

**Breakout Group 2: Clinical Research for Antibiotic Treatments and Drug Combinations**

*Facilitated by Dr Suman Rijal, DNDi India & Dr Ramesh Argawal, AIIMS*

There is a need for an overarching multidisciplinary consortium of existing networks, including the veterinary and agricultural sectors, WHO, Indian ministries, and a drug development network. A multidisciplinary drug development and research network would provide knowledge and resources for clinical trials, microbiology, and stewardship. While a primary goal of this research network would be to carry out clinical trials, which is a long-term endeavour, it should also include components of surveillance, where appropriate, and prevention. There is a clear need to adopt some of the principles of surveillance and stewardship into the network of many different sites and institutes. There is a need to map key government institutes that have the expertise and capacity to do PK/PD studies and to include those with potential for biobanking and data management. The reluctance of individual institutes to share data is a barrier to overcome. ICMR can play a role through its data sharing policy, and capacity must be built in the public and private sectors. Two important regulatory requirements - compensation requirements for Serious Adverse Events (SAEs) and insurance coverage - should be taken into consideration, especially for clinical trials in disease areas with high mortality. The National Institute of AIDS and National Institute for Cholera and Enteric Diseases have vast networks for trials and have biobanking capacity. It is envisaged that this network should be inclusive (not only clinicians and not confined to one area) with the aim of providing credible data for the use of new antibiotic treatments, whether this be new drugs or combinations of drugs.

Additional discussion took place concerning unjustified fixed-dose combinations (FDCs) of antibiotics in India, which should be taken into careful consideration when considering trials on drug combinations. In this case the regulatory pathway is different and further clarification on this issue must be sought with DCGI and ICMR.

**Breakout Group 3: Drug Discovery: Needs, Challenges, Opportunities**

*Facilitated by Dr Jean-Pierre Paccaud, GARDP/DNDi & Dr Shirshendu Mukherjee, DBT-BIRAC-BMGF-Wellcome Trust*

In India, while there is a great deal of capacity in early stage research, private sector contributions are relatively limited, with only a handful of companies embracing the field, because of three major
hindrances: the science is challenging; long-term drug development has to be financed, which hinders even larger companies from entering the field; and economic incentives are absent or slow to materialize. There are probably about a dozen active public institutions, including the Central Drug Research Institute (CDRI). CDRI has undertaken anti-infective research, while others generally focus on early stage drug screening. In general, translational work is missing from the drug R&D landscape. Getting from a hit to a lead, and then to a validated product on the market is a challenge in the absence of a well-defined pathway and financial resources/incentives.

GARDP business models were discussed, notably how to address access and stewardship together. For example, while the public sector can control distribution, the private sector needs a return on investment. The landscape is changing, and regulatory authorities are considering changes in their approach, so it is important to interact with regulatory authorities. Recently passed regulation in the US (Critical Care Act of 2016) is promising, in that regulators are starting to look at new pathways and thresholds of acceptance for antibiotics so that drugs can be made available to patients in the shortest possible time. The Indian regulatory environment also needs to be on the same page as FDA, EMA etc. in terms of how they review NDA’s for antibiotics, and needs to treat this area as a large and urgent unmet need.

It is important to fill the translation gap, proposals for diagnosis and innovation should be translated into products. Nonetheless, most of the required R&D capacity is available in India. A mapping of public and private sector R&D actors in the field of antibiotics in India is key. India has one of the largest disease burdens in the AMR space, and has to step up funding of R&D to promote both drug discovery/development and the development of spot-diagnostics. New PPP initiatives such as CARB-X (lead by BARDA, UK-AMR, Wellcome Trust) are excellent examples of how governments are stepping in to fund the discovery and development of antibiotics. India must take this problem very seriously and allocate significant resources to promote the development of new antibiotics, including grants and entry-level rewards for small and medium-sized enterprises. Without these incentives, drug development in AMR will simply not happen, and India will need to wait for foreign markets to create such drugs, resulting in big challenges in affordability and accessibility.

Companies and grant agencies in India could partner with organizations such as GARD-p and Wellcome Trust to institute grants and market-entry level rewards for SME’s doing R&D in this area.

Concluding Remarks: Dr Kamini Walia and Dr Manica Balasegaram

ICMR is committed to strengthening AMR surveillance and antimicrobial stewardship, and is developing standard operating procedures. Many laboratories are working on the development of new antibiotic molecules but are unable to move forward - there is a need for a clear development pathway for them to progress through the pipeline. There is a need for epidemiological data both in human and animal health,
and to gain an understanding of the dynamics of pathogen transmission. ICMR endeavours to bring stakeholders together from human, environmental, and animal sectors.

ICMR and GARDP recognize that AMR in India is a major public health issue, and that there is a great need to focus on R&D, sustainability, and stewardship. To be effective, there is a need to do more than R&D, to prioritize, and consider how to effectively use surveillance data. GARDP is committed to moving forward with implementing programmes rapidly, and aims to ensure, with the collaboration of ICMR, that work begins in India in areas that are deemed to be a priority for the country.