INTRODUCTION: ANTIMICROBIAL RESISTANCE – A SERIOUS THREAT FOR HUMANITY

DR JEAN CARLET, PRESIDENT, WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE (WAAAR)

Antimicrobial resistance, as defined by the World Health Organization (WHO), includes all forms of resistance to medicines on the part of viral, parasitic, fungal or bacterial infections. It is also a natural phenomenon. Resistance genes have been found in samples that are millions of years old or in animals which have never been in touch with humans. The overuse of antibiotics has accelerated the phenomenon. Immediately after the discovery of penicillin, Fleming alerted us to the risk of resistance to this drug, in particular, if the dosage was too low to cure.

Antibiotic resistance has increased dramatically in the last 20 years, and very few new products have been discovered, with almost no drug with any new mechanisms of action. Therefore, we are in a very dangerous and fragile situation. Morbidity and mortality from bacterial infections resistant to antibiotics is already very high and make impressive reading. The Centers for Diseases Control and Prevention estimated that 2 million patients are infected by bacterial infections resistant to one or more antibiotics, and that 23,000 patients die from drug resistance every year. The European Centre for Diseases Prevention and Control (ECDC) found similar numbers, with a mortality of 25,000 per year. A recent simulation by the Rand Corporation estimated that 10 million people worldwide could die from resistant micro-organisms in 2050, which is more than from cancer, and that the cumulative costs from now to 2050 could climb up to US$ 100 trillion.

Antibiotics resistance is heavily correlated with the consumption of antibiotics, in human and animal health, in husbandry and agriculture. We have been using far too many antibiotics in the last few decades, in particular to fatten food animals faster. We have used antibiotics in a very liberal and uncontrolled manner, and we have been unable to protect the treasure that they represent. There are huge differences in the way countries use antibiotics. For example, in Europe, the Scandinavian countries, or the Netherlands, use few antibiotics, and consequently have very low levels of resistance. On the contrary, countries like Greece, France, and Italy are heavy users. Italy and Greece have a dramatic level of antibiotic resistance, in particular for *enterobacteriacae* harbouring carbapenemases. Many other countries, like India, China and the Americas are heavy users, and still use antibiotics as growth promoters. The same huge differences are seen in animal production related use as shown in the ESVAC network.

Resistance affects both Gram-positive and Gram-negative bacteria. Although some important progress has been made for drug resistant *Staphylococcus Aureus* MRSA, this Gram-positive micro-organism remains a serious issue in many countries in particular the United States. There are huge differences between countries concerning vancomycin-resistant *enterococci*. Epidemic outbreaks happen in several countries, but with a very low prevalence. In other ones like the United States, resistance is already totally endemic with a very high prevalence.

The antibiotic resistance of Gram-negative bacteria has increased dramatically in the last two decades and poses a serious challenge as almost no new antibiotics active against them has been made available in the last few years, representing a dramatic public health threat. *Enterobacteriaceae* harbouring extended spectrum beta lactamases are nowadays our number one public enemy. Prevalence can reach 80% in certain countries. Consumption of carbapenems is increasing sharply worldwide, which increases antibiotic resistance pressure on this agent. The prevalence of enterobacteriaceae harbouring carbapenemases is increasing in many countries,

like Greece and Italy in Europe, India, China and several Asian countries, the Middle East and North African countries. These multi-resistant bugs pose very difficult therapeutic problems. To treat those infections, people must use colistine, an old and relatively toxic drug, tigecyclin, or various combinations which have been poorly studied. Micro-organisms resistant to every antibiotic are frequently involved in invasive infections, with a very poor prognosis.

What can we do to tackle this dramatic problem? As emphasized recently by WHO in its "global action plan", the problem is global, and the programme must be global, and international. We must act simultanously at all levels: human health, food production and the environment in a "one health" philosophy. It must involve developed and developing countries. Governments and non-governmental organizations can and should cooperate.

The World Alliance Against Antibiotic Resistance (WAAAR) was initiated, in 2011, in order to motivate politicians, policy-makers, health-care professionals and consumers to take antibiotic resistance very seriously. Today, WAAAR brings 730 members together, and is supported by 90 medical societies and 55 organizations worldwide. In June 2014 a solemn declaration "The Paris Declaration" was launched and widely disseminated. The Paris Declatation contains 10 propositions for action.

Well known personalities have been very active and have initiated concrete actions in the last few months, such as Margaret Chan at WHO, Dame Sally Davis and David Cameron in the United Kingdom and Barack Obama in the United States. They stressed the public health issue represented by antibiotic resistance, and the urgency of the problem. Task forces have been created in the United States and in the United Kingdom. In France, Marisol Touraine, Minister of Health, decided to initiate a National Task Force on the Preservation of Antibiotics. Important resources will be devoted to this issue in the United States and the United Kingdom (US$ 1.2 billion and £250 million respectively).

Garance Upham, from the Board of WAAAR and Associate Editor of AMR Control 2015, has put together this publication for key decision-makers who would want a quick overview of the most salient issues.

About AMR Control 2015

AMR Control 2015 gathers more than 20 outstanding authors who wrote instructive chapters covering a broad range of topics and concepts.

Global overview of antimicrobial resistance.

A world leader in the drive to control AMR, **Dame Sally Davies, Chief Medical Officer of England**, presents here a succinct overview of the need for action: "Individual nations have recognized the importance of antimicrobial resistance as a health issue, but countries have different needs and priorities. In many parts of the world, those with treatable infections lack access to antibiotics, particularly in rural areas. Here the challenge is to improve access without making the drugs so readily available that they can be used inappropriately, the so-called paradox of controlling drug resistance."

The United Kingdom has been a leader among high income countries. In 2013, the United Kingdom published an ambitious strategy to combat antimicrobial resistance by focusing activities around three strategic aims to: 1) Improve the knowledge and understanding of antimicrobial resistance; 2) Conserve and steward the effectiveness of existing treatments; 3) Stimulate the development of new antibiotics, diagnostics and novel therapies.

Economic and business models

Antibiotic innovation – Some lessons from the WHO processes on public health, innovation and intellectual property. This very comprehensive overview, from the Norwegian Institute of Public Health Professors **Jens Plathe and John-Arne Røttingen** provides us with a well-informed overview of business models, inspired by the experience of WHO's Consultative Expert Working Group on Research and Development (CEWG), which the second author had chaired. The authors ask how can you combine reduction of "excess use" with "equitable access"? Are the usual market mechanisms appropriate? What is the right reward for innovation? How can IPR be mobilized and harnessed in ways that contribute to a feasible economic reward model for sustainable access to effective antibiotics and in this respect what experiences can be drawn from the field of neglected diseases generally and from the recommendations proposed by the CEWG under the auspices of WHO? The authors conduct a very thorough analysis of the wide array of innovative solutions such as new forms of IP licensing practices, patent pools and open source R&D collaboration models which can be used as building blocks, in combination with measures such as pooled funds, direct grants, prizes and access maximizing pricing, in designing a comprehensive global framework for new antibiotics that strengthens innovation, secures access and promotes rational use.

Creating an Intergovernmental Consortium for New Antibiotics. **WHO Assistant Director-General Marie-Paule**

Kieny has given a lot of thoughts to the kind of new development models which would carry the features necessary to satisfy the need to reward R&D with the need for access but not excess in human antibiotics use. The author proposes an "Intergovernmental Consortium for New Antibiotics" that would feature: 1) mostly public sector funded research and clinical trials; 2) grants to small and medium-size innovative companies or universities to develop new products; 3) milestone and end prizes to reward innovation; 4) patent pools to bring together Intellectual Property Rights generated by public sector funded research and 5) production and marketing agreements for a needs-based number of treatments per year. A lot of emphasis is put on "decoupling" R&D rewards from financial returns from the market. Various End Prize and Milestone Prize systems of rewards are presented which would favour LMIC university research and small innovative companies everywhere, and might benefit all parties. In fact several large pharmaceutical firms CEOs have come to express interest in such a solution.

Monitoring, surveillance and national plans

Surveillance and Monitoring of Antimicrobial Resistance. US Centers for Disease Control Director for AMR, **Professor Steve Solomon, with Dr Kashef Ijaz**, unlike many norm setting institutions or public health specialists, write from the standpoint of how low-income countries can be partners in the global effort. For example, on the need for Improving laboratory capacity: "The ability of laboratories to accurately and consistently identify pathogens and their antibiotic susceptibility varies greatly. Trained personnel are the single most important asset in any laboratory. On-site technical assistance, sending staff for off-site training and education, online training courses and laboratory "twinning" are all strategies that have been used to successfully improve laboratory capacity…" Further down he writes "Prioritize which bacteria are most important to track" which is so important in view of the kitchen sink approach to bacterial resistance which is a tendency in some resource poor countries after years of not looking at all. Then "Prioritize and standardize epidemiological data collection…" His contribution is remarkably useful at a time when the WHO AMR draft action plan requires each government to establish a national plan. He traces the path of the best way to really implement AMR control on a global scale.

Antimicrobial Resistance Control in Asia. From South Korea, **Professor Jae-Hoon Song,** a member of STAG (the WHO initiated expert working group on AMR), takes us through the six major action plans to control and prevent AMR in the Asian region can provide Asian countries: 1) Strengthen the surveillance of AMR and antibiotics use; 2) Improve awareness of AMR; 3) Promote appropriate uses of antimicrobial agents; 4) Strengthen hospital infection control and 5) Promote vaccination against bacterial infections; 6) Strengthen the national infrastructures and international efforts".

Under the third action plan, Professor Song writes: "One of the most important policies to control antibiotic abuse is the separation of prescribing from dispensing antibiotics by law, which can prevent general public purchase over-the-counter antibiotics without doctor's prescription. Antibiotic uses in animal husbandry should be also monitored and regulated with appropriate regulations."

The Actions of China in Antimicrobial-Resistance Containment. Since 2011 China has embarked on an ambitious programme for "rational antibiotic use", reports **Professor Yonghong Xiao** of the Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases. What is striking is that the same levels of antibiotic drug resistance are found in all regions and settings even though the regions are widely different in terms of socioeconomic development. The author notes that (as in Africa) there is a tendency among doctors and prescribers aware of resistance to prescribe … the latest, newest antibiotic medicines which is an important fact fuelling resistance. It is at the time of the SARS outbreak in 2003 that China's MoH asks for the establishment of infectious disease units, whose responsibility included antibacterial resistance. The MoH "Institutionalizes clinical pharmacists in hospitals" with more than 50 training centres. This is quite a model for low- and middle-income countries where the role of well-trained pharmacists is a key – yet neglected – element in proper antibiotics usage. Measured outcomes showed significant reduction in irrational antibiotic drug usage between 2010 and 2012, and the national campaign reported significant success in both tertiary and secondary hospitals. But, we are made to understand, China is a huge country and a lot remains to be done, at a time when hospital management might not be aligned with national priorities and there is a weakening of public investments in health.

A middle-income country model national AMR Plan: South Africa. A very comprehensive model programme on AMR control has been put together by the Republic of South Africa, described by **Professor Marc Mendelson and Precious Matsoso** in South Africa, the report highlights reinforcement of infection prevention and control within

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health-care structures, and comprises just about all the recommended features, including flu vaccination to decreasing the superfluous use of antibiotics in the flu season. The South African Strategy Framework features: "Optimization of surveillance and early detection of AMR with a watch on: 1) Antimicrobial resistance patterns; 2) Antimicrobial consumption; 3) Antimicrobial drug quality; 4) Medication errors." Overall the RSA program is a model of the kind for a middle income country.

Prescription control in human health. **Professor Céline Pulcini**, of France's Nancy University Hospital and a pioneer innovator in her field, discusses what is called antibiotic stewardship. The main component of this technique is mostly the control of the prescriptions. The paper describes the main measures that could be implemented and discuss the potential limitations and barriers to implementation of those restrictive antibiotic stewardship strategies.

Antimirobial resistance and the environment

The role of sanitation in the development and spread of AMR. The article from **Professor Timothy Walsh**, UK's Cardiff University and **Professor Antoine Andremont**, is set to challenge many perceived notions on AMR Control. One sentence for example says: "The link between sanitation, or lack thereof, and antimicrobial resistance (AMR) is primarily to do with two factors: the level of antibiotic resistant bacteria in a person's gut, and 2, the level of AMR in the environment. The argument that resistance starts in a hospital and then so called "spreads into the community or environment" is often inaccurate and most certainly naive." From there the authors, both of them experts in the field, explain the situation regarding bacterial resistance spread in the environment and call for adequate investment in water and sanitation, with a particular focus on emerging countries, short of which national and international efforts on AMR might fail. Dr Timothy Walsh is internationally known for having discovered the New Delhi NDM-1 resistance gene with a team of collaborators, a gene which has now travelled worldwide and could ignite global pandemics of diarrheal diseases.

Confronting antimicrobial disease

Diagnostic solutions critical to limit antimicrobial resistance development.

Time has come for more investments and more expenditures in diagnostics, in every way, postulate **Dr Catharina Boehme** (Foundation for Innovative Diagnostics), **Mark Kessel**, and **Professor Ilona Kickbush**: Accurate, precise, diagnostic tools ought to be considered as crucial as medicines, the necessary companion. Too many doctors in well to do countries bypass precise diagnostic to put patients on antibiotics indiscriminately. Too many LMIC hospitals systematically give "a shot of antibiotics" to a patient coming up with diarrhea, for example, in regions where parasitic and viral pathogens causing diarrhea are widespread.

The graphs of antibiotic consumption goes up with the flu season in the Northern Hemisphere and back down while the Southern Hemisphere graph goes up in summer. Antibiotic overuse will not be brought under control without more acute diagnosis with proper tools and national insurance schemes would do better to fund systematic investigation rather than drug overuse.

Diagnostic use is in the public interest and ought to be better supported. FIND develops path for partnerships and operates with WHO to that effect. "The world health community has been increasingly sounding a clarion call for taking action against the dangers of AMR, and it has become clear that we cannot rely solely on new drugs or vaccines emerging from the development pipeline, but need a multifaceted and global response to combat AMR."

Infection prevention and control – Patient safety a key objective for AMR control

"Is patient safety important for AMR Control?" Is the question discussed by a USAID team with **Professor Rashad Massoud, Danika Barry, Sonali Vaid, Samson M Haumba, Nokuthula Mdluli Kuhlase**). According to USAID "patient safety" starting with the prevention and control of infection in health care settings, is a crucial component of any AMR control programme, internationally and nationally. This article takes us through the USAID outstanding effort in this area and their partnering with low-income countries, in this case Zambia.

"Reducing unnecessary infections reduces potential

antibiotic use, thus slowing the spread of antibiotic susceptible and antibiotic resistant organisms. Furthermore, HAIs include occupational experienced by health workers, as well as patients. Health worker safety is a key component of infection control, and has impacts on health worker numbers, morale, retention and a host of other factors. Thus, infection control is critical not only for patient safety, but for provider safety, and should be central to any health systems strengthening effort."

Multidrug resistant tuberculosis monitoring in India

"Systematic surveillance for TB drug resistance is the best way to document its presence and has been very difficult to establish in most of the high burden countries, the major obstacle to the expansion of routine surveillance activities has been the lack of laboratory capacity needed to detect resistance" writes Assistant Director General of the TB programme for the Indian government Department of Health, **Dr. Kuldeep Singh Sachdeva,** (with **Dr S Anand** and **Dr Ranjani Ramachandran** of WHO-India, who tells the story of how his services were able to undertake monitoring in India.

Professor Sachdeva discusses the issue of anti-tuberculosis drug resistance surveillance. Presently 60% of all countries in the world have implemented surveillance activities that have been disseminated by WHO. The new diagnostic methods, which are far more rapid, and routine surveillance linked to patient care can be implemented nowadays even in developing countries. Several countries, in particular, India have reported drug-resistance through their own surveys, sometimes national. India is moving toward a systematic surveillance of drug resistance and is moving toward universal DST by 2019.

HIV resistance to antiretrovirals another key issue of AMR management

From South Africa, Professor **Gary Maartens,** Head of Clinical Pharmacology, University of Cape Town, South Africa; **Professor Lyn Morris,** HIV Virology laboratories at the National Institute for Communicable Diseases, **Dr Gillian Hunt,** senior research scientist, Centre for HIV and STI and **Professor François Venter,** Wits Reproductive Health and HIV Institute (RHI) review the management of HIV resistance in a high burden country. With over 6 million persons living with HIV, South Africa has, on record, the highest number of patients to whom the country offers antiretroviral treatment. The RSA is truly a model country today considering that it is not a high-resource country, and that it also has, historically, a high levels of tuberculosis. They write that: "Significant strides have been made in improving the quality of care for HIV-infected people in resource-limited settings. However, 1) We need surveillance; 2) We do not fully understand the consequence for public health programmes of HIV DR – transmitted or acquired; 3) Better tracking of patients is needed and 4) New generations of drugs may change the way we do business."

Nothing possible without civil society's input!

From civil society, we have two contributions: CDDEP Director **Hellen Gelband,** reports on the Center for Disease Dynamics, Economics & Policy partnership with LMIC: "The Partnership operates to bring a set of new voices to the antibiotic resistance issue and to establishing local capacity to develop and help to implement evidence-based policies in eight LMICs from Africa and Asia", while our WAAAR collaborator, Dr Abdul Ghafur explains his Mumbai Declaration initiative, an India wide coalition which has been extremely effective, in that it convinced authorities to stop over the counter sales of medicines.

Alternatives to antibiotics

Phages research

Phagoburn: an EU Research programme. **Professor Patrick Jault**, French Military Health Services and **Jérôme Gabard**, Pherecydes Pharma, gives us an account of a specific clinical research "Phagoburn", funded by the European Union, on the use of viruses specific to bacteria (phages) to combat bacterial infection so dangerous on burn wounds, the type of research which might well open our arsenal to treat antibiotic resistant infections.

Phage therapy: Could viruses help resolve the worldwide antibiotic crisis? The article from **Professor Daniel de Vos** and **Dr Jean-Paul Pirnay**, both with the Belgian Military Hospital research, gives a background on phages as therapy and stresses the epistemological hurdles in its acceptance for mainstream medicine. Phage therapies could be part of a patient-centred highly individualised medicine of the future and could be profitably used also in association with antibiotics in both human and animal medicines. While the regulatory framework for medicines is ill adapted to phage therapies and would need to be modified, and in part for that reason, the vast expansion of interest for phages, especially since 2000, involved on the one hand the Defence establishment – with the rebuilding the Eliava Centre in Georgia (to deal with the Anthrax scare – and on the other hand, a vast expansion of very innovative food industries use of phages to prevent bacterial growth in processed food.

The European Medicine Agency in London, is actually

planning a meeting on phages and regulatory mechanisms early June 2015.

Animal Husbandry's role in AMR

Costs and benefits of antimicrobial use in livestock. Could animal husbandry do without antibiotics? **Aude Teillant**, researcher at Princeton's Environmental Institute, discusses the costs and benefits of antimicrobial use in livestock. She is co-author of the OECD just released first study on global consumption of antibiotics in food producing industries. Aude Teillant writes for *AMR Control*: An estimated 14,788 tons of antimicrobials were sold for use in animals (both food-producing animals and companion animals for disease treatment and sub-therapeutic use) in 2013 in the United States, including 4,434 tons of ionophores, a class of antimicrobials used only in veterinary medicine. (...) In comparison, an estimated 3,290 tons of antimicrobials were sold during 2011 for human use." Most antibiotics are not for medical care for animals, but solely to make animals fatter: antibiotic growth promoters, yet she writes, latest scientific studies show that, in fact, these growth promoters are no longer considered effective, while global animal-food industries are expected to increase by 70% by 2030. What are law makers waiting for? In 2006 the EU banned AGPs, the US FDA only "recommends it".