AMR CONTROL 2015

OVERCOMING GLOBAL ANTIMICROBIAL RESISTANCE

EDITOR-IN-CHIEF: DR JEAN CARLET, PRESIDENT, WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE
ASSOCIATE EDITOR: GARANCE UPHAM, WAAAR

GLOBAL OVERVIEW OF ANTIMICROBIAL RESISTANCE • ECONOMIC AND BUSINESS MODELS
SURVEILLANCE AND MONITORING OF ANTIMICROBIAL RESISTANCE
ANTIMICROBIAL RESISTANCE AND THE ENVIRONMENT • CONFRONTING
ANTIMICROBIAL RESISTANCE • ALTERNATIVES TO ANTIBIOTICS
ANIMAL HUSBANDRY'S ROLE IN ANTIMICROBIAL RESISTANCE

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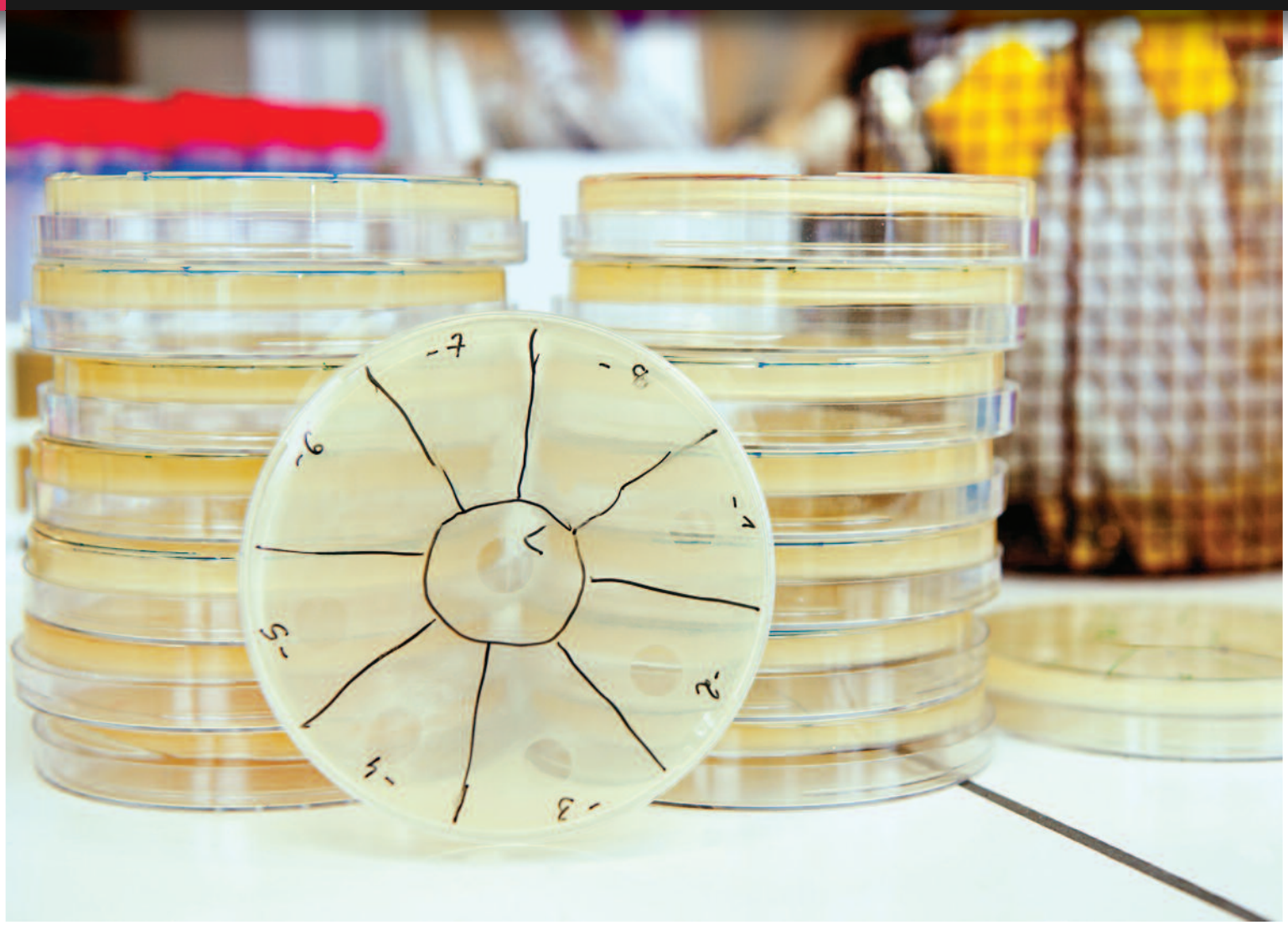

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CONTENTS

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".

GLOBAL OVERVIEW

A GLOBAL OVERVIEW OF ANTIMICROBIAL RESISTANCE

DAME SALLY DAVIES (TOP), CHIEF MEDICAL OFFICER FOR ENGLAND; CHAIR, UK CLINICAL RESEARCH COLLABORATION AND THE WORLD HEALTH ORGANIZATION SPECIALIST TECHNICAL ADVISORY GROUP ON ANTIMICROBIAL RESISTANCE AND WHO EXECUTIVE BOARD MEMBER; **JOHN WATSON** (MIDDLE), DEPUTY CHIEF MEDICAL OFFICER FOR ENGLAND AND **LAURA SHALLCROSS** (BOTTOM), CLINICAL LECTURER, DEPARTMENT OF INFECTION & POPULATION HEALTH, UNIVERSITY COLLEGE LONDON, UK

Antibiotics, with their ability to save the lives of people with severe infections, have revolutionised medicine in the last 70 years. They now underpin major elements of modern treatments, such as bowel surgery, organ transplantation and cancer therapy, as well as curing most of the bacterial infections that cause common problems such as sore throat. From the start, however, microbes developed resistance to antibiotics (and other antimicrobials active against viruses and fungi) through evolutionary changes. Antibiotic resistance is now a global problem as an increasing proportion of microbes can no longer be treated effectively by readily available antibiotics. Overuse, and inappropriate use, of antibiotics in humans and animals has been the main driver for the development of resistance and this has occurred in countries all around the world.

The threat of antimicrobial resistance can only be tackled through international collaboration and by working across human and animal health sectors. Our global organizations are rising to the challenge with a recent World Health Assembly resolution and a World Health Organization (WHO) Global Action Plan, but we must act now to preserve the benefits to modern medicine that antibiotics have provided, and avoid a return to a pre-antibiotic era.

Microbes have been engaged in an evolutionary battle with the humans and animals they infect since the dawn of time. Every time a new antimicrobial is developed resistance follows, sometimes swiftly, and this occurs for all antimicrobials (anti-bacterial, anti-viral and anti-fungal therapies). Resistant bacteria pose the greatest threat to human health.

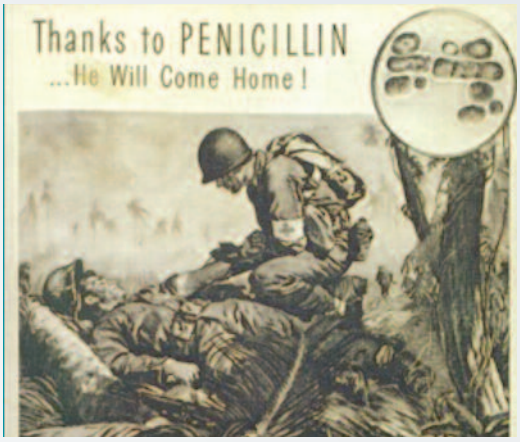
When Alexander Fleming accepted his Nobel Prize for the discovery of penicillin in 1945, he foretold the development of antimicrobial resistance: *(1)*

"I would like to sound one note of warning…It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

Despite these warnings, from 1943 onwards penicillin was widely marketed as a wonder drug in tablets, syrups and throat lozenges (reference to images). Resistant strains were soon noted in hospitals and by 1950, 60% of the bacterium *Staphylococcus aureus* isolates were resistant to penicillin *(2)*. Soon a familiar pattern emerged: a new drug was introduced and resistance followed, either quickly with the bacterium *Staphylococcus aureus*, or more slowly with *Streptococcus pneumonia* (both common causes of infections). At this time resistance did not pose a serious threat to health because there was a steady supply of new antimicrobials. These drugs were marketed by the pharmaceutical industry and used extensively by health professionals in both human and animal populations, placing selection pressure on bacterial populations and hastening the emergence of drug resistant strains.

Most of the antibiotic classes currently in use were identified in the golden era of antibiotic discovery between 1945 and 1960 and only four new classes have antibiotic have been discovered in the past 50 years *(3)*. With the exception of a few small and medium size biotech enterprises but few larger pharmaceutical companies, there is little work going on to discover new antimicrobials to replace those that are fast becoming ineffective. The technical challenge in developing new antimicrobials is substantial, but the barrier to research and development is economic. Bringing a new drug to market is estimated to cost around one billion US dollars which cannot be recouped at the prices that health systems expect to pay

Figure 1: Examples of early marketing for antibiotics



Source: National World War 2 Museum – New Orleans

Source: Unknown

Most of the antibiotic classes currently in use were identified in the golden era of antibiotic discovery between 1945 and 1960 and only four new classes have antibiotic have been discovered in the past 50 years

for antimicrobials. This issue is complicated further by the public health imperative to hold new antibiotics in reserve for those patients most at risk rather than allowing widespread use that selects the development of resistance.

In recent years the major focus in many countries has been on reducing methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* infections (CDI), because these infections cause substantial morbidity and mortality, primarily amongst patients in hospitals or in long-term care facilities. During this period, the total burden of drug resistant infections has increased, particularly amongst "gram-negative" bacteria such as *E. coli*. Resistance threatens the effectiveness of the carbapenem class of antibiotics, which are widely regarded as the treatment of last resort for severe infections and particularly those caused by gram-negative bacteria. Drug resistance in gonorrhoea, a sexually transmitted infection, has also increased in recent years in England and could become untreatable. In the United States, the Centers for Disease Control and Prevention have updated their empirical treatment guidance for gonorrhoea three times since 2003 because resistant strains have become sufficiently prevalent in the population to compromise the effectiveness of each successive recommended antibiotic regimen *(4)*. Worldwide there is increasing resistance to other antimicrobials such as those used to treat HIV/AIDS, tuberculosis and malaria, impacting heavily on developing countries and increasing morbidity, mortality, the duration of treatment and costs.

The single most important factor driving resistance is antimicrobial use, particularly in humans but also in animals. Antibiotics are among the most commonly prescribed drugs in human medicine and their use continues to rise, partly driven by inappropriate prescriptions for minor viral infections, such as coughs or colds, where they confer no benefit. In some countries, the availability of antibiotics over the counter, falsified and counterfeit drugs and inadequate dosing as a result of prescription of wrong dose, wrong duration or the

Milestone Prizes entail recognition of very early discovery – before the definitive proof of principle of the innovation. These intermediate prizes should be sized so that they would be attractive to academia from applied or fundamental research fields. It would also attract small and medium size enterprises (SMEs), including from LMICs

wrong drug, all select for the development of resistance. In animals, antimicrobials are used to prevent, control and treat disease, and in some countries antibiotics are used as growth promoters. This practice has been banned in Europe and recommended against in the United States. There is still much to be done to ensure appropriate use and conservation (or stewardship) of antimicrobials across both animal and human health sectors.

The human and economic costs of antimicrobial resistance are compelling. Antimicrobial resistance is estimated to cause at least 23,000 deaths per year in the United States and 25,000 deaths per year in Europe *(5,6)*. The economic impact of antimicrobial resistance has been estimated to be 0.4–1.6% of GDP in the United States where antimicrobial resistance has been estimated to cost up to US$ 20 billion in excess direct health-care costs, with additional costs for society for lost productivity as high as US$ 35 billion per year *(5)*.

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. Counterfeit and substandard drugs pose a threat worldwide but this is a particular issue in developing countries where regulation is lacking in effectiveness, and antibiotics and anti-parasitic agents are the most frequently counterfeited drugs *(7)*.

Some high-income countries have identified the need to take drastic action against antimicrobial resistance. In the United Kingdom, for example, an ambitious strategy to combat antimicrobial resistance was published in 2013 *(8)*, with the goal of slowing the development and spread of 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.

Antimicrobial resistance – a global problem

Antimicrobial resistance (AMR) is a global problem that cannot be solved by a single country working in isolation. International travel allows people to spread their infections from one country to another, including those with drug resistant infections. An effective response to AMR demands collaboration across international borders and across health professional boundaries, the relevant regulatory agencies and their enforcement arms. Since 1998 there have been a series of World Health Assembly (WHA) resolutions on AMR, paving the way for the 2001 WHO global strategy for the containment of antimicrobial resistance and the 2011 EU AMR strategic action plan. In May 2014 a further WHA resolution on AMR was passed, which builds on previous WHO initiatives but now gives the WHO a mandate to develop a global action plan in 2015, legitimising action by WHO on behalf of member states. Achieving change at the rate required to impact on AMR requires political will and global action, working across the human and animal health sectors through international partnership known as the "One Health" approach.

Different countries have different needs and priorities related to AMR. The draft WHO Global Action Plan has been developed with five strategic objectives which provide member states with the flexibility to set out the priority actions that need to be taken in their country and respond in a step-wise manner to meet both local needs and global priorities. The first objective relates to communication, education and training, to improve awareness and understanding of AMR. The second is to strengthen the knowledge and evidence base through surveillance and research. A further objective is to reduce the incidence of infection through effective hygiene and infection prevention. The final two objectives concern the optimization of antimicrobial use in human and animal health and the development of the economic case for sustainable investment in combatting AMR, taking account of the needs of low- and high-income countries.

Communication, education and training

To reverse the increasing rates of AMR will require major

behavioural change across all swathes of society, from professionals in health and other sectors, governments, organisations, patients and the public. None of this will happen if people are not aware of the harm of misusing antibiotics and dire consequences of not taking action. We must find ways to communicate AMR messages to a wide range of audiences, including social media as well as educational and social marketing tools, as a route for advocacy. We should educate children about infections and antibiotic use and embed AMR and antimicrobial stewardship as a core part of education, training and accreditation for professionals working in human health, veterinary medicine and agriculture.

Surveillance, research and development

The first step in tackling AMR is to understand the burden of disease due to drug resistant infections. This requires active surveillance and research. Hospitals need laboratories that can determine rapidly if patients have an infection, identity the organism and determine the sensitivity and whether there is resistance to antibiotics. This data needs to be collected at local, regional and national level, and then to be collated globally in order to track changes in rates of antibiotic resistance over time and between countries. It is also important to monitor the sales and use of antibiotics, not only from hospitals, but also in the community and their use in the veterinary and agricultural sectors. Present surveillance systems for AMR are fragmented with major gaps in information. Better surveillance will make it possible to better to target resources where they are most needed and monitor the impact of interventions aimed at reducing AMR.

Despite much increased effort over recent years, our understanding of the mechanisms that underlie development of AMR at a molecular, patient and population level remains limited. There is need for much more work including research to develop drugs and new vaccines, and large scale population based studies to evaluate the effectiveness of a range of interventions including those targeted at people's behaviour.

Preventing infection and promoting good hygiene

We must do all we can to prevent infection in the first place. This includes strong public health or hygiene measures such as the separation of potable water from sewage (in countries where this is a problem), and infection control, particularly scrupulous hand-washing in food preparation We need to focus on improving infection control, particularly in hospitals where the majority of serious and difficult to treat infections are treated and where there is widespread opportunity for drug-resistant infections to spread between patients. Vaccination can play a key role in preventing infection, not only in humans but also in veterinary medicine, and is one of the most effective public health interventions.

Optimizing antimicrobial use in humans and animals

We must conserve the antibiotics we have, a process referred to as "stewardship". The right antibiotic should be used at the right dose for the right time period and, if appropriate, in the right combination. We need to stop prescribing antibiotics for viral infections such as coughs and colds where they have no effect. This would be much easier if there were rapid diagnostic technologies to help to target antibiotics to those who really need them. Antibiotics should not be available over-the-counter (as they are in some countries) or over-the-web, but only on prescription from a health practitioner (doctor, veterinarian, dentist, nurse or pharmacist) who follows national guidance informed by the local laboratory surveillance programmes.

Sustainable development

Current levels of investment in infrastructure and resources to tackle AMR are inadequate in most parts of the world, with a clear need for training and capacity building. The costs of remedying this are both significant and long-term and are likely to present a barrier to action, particularly in low-income countries. The development of new drugs and diagnostics is likely to be best addressed by developing new processes to stimulate investment in R&D, such as uncoupling the cost of investment from volume of sales to ensure that new drugs remain effective, are available in high- and low-income countries according to need and are managed within a suitable framework of stewardship.

Conclusions

The threat of antimicrobial resistance is shared by all countries. The challenges in combatting AMR vary from country to country but some priorities for action are common to all. We need to re-double our efforts to ensure effective hygiene and infection control. The antibiotics we have need to be conserved while we reinvigorate research and development to deliver new rapid diagnostics and innovative antimicrobials.

None of this will be possible unless professionals, public and policy-makers understand the threat and agree to work together to solve this problem. Our global organizations are starting to rise to the challenge, with WHO developing a global action plan and supporting countries in developing their own plans. We must keep this high on the political agenda because without concerted action, we risk losing the many

benefits of modern medicine that we have been made possible by antimicrobial agents in the last 70 years.

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References

1. World Health Organization. WHO Global Strategy for containment of Antimicrobial resistance. 2001. http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf [Last accessed 1-7-2014].
2. Levy SB. The antibiotic paradox - how miracle drugs are destroying the miracle. 1992
3. Wright GD. The antibiotic resistome: the nexus of chemical and genetic diversity. *Nat Rev Microbiol* 2007 Mar;5(3):175-86.
4. Centers for Disease Control and Prevention. Antibiotic Resistant Gonorrhoea - basic information. 2013. http://www.cdc.gov/std/gonorrhea/arg/basic.htm . 2013. [Last accessed 24-11-2014]
5. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/ , [Last accessed 24-11-14].
6. ECDC/EMEA Joint Technical report. The bacterial challenge: time to react. 2009. http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf . [Last accessed 24-11-2014]
7. Frankish H. WHO steps up campaign on counterfeit drugs. *Lancet* 2003 Nov 22;362(9397):1730.
8. Department of Health. UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018. https://www gov uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018 https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018. [Last accessed 24-11-2014]

ECONOMIC AND BUSINESS MODELS

ANTIBIOTIC INNOVATION– SOME LESSONS FROM THE WHO PROCESSES ON PUBLIC HEALTH, INNOVATION AND INTELLECTUAL PROPERTY

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In this article we discuss the relevance for development of new antibiotics from the main conclusions of the report of the Consultative Expert Working Group on Research and Development (CEWG). This report is part of a work stream that was initiated by the WHO in 2003, leading to the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property Rights in 2009. Subsequently, the CEWG Report was published in 2012. It assessed a number of proposals that aim to strengthen global financing and coordination of R&D for diseases disproportionately affecting developing countries, the so-called neglected diseases.

Specifically, we ask: how can intellectual property rights (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 in particular? We conclude that innovative IPR licensing practices and open source R&D collaboration models can be used as buildings block, together with interventions such as pooled funds, direct grants, prizes, and access maximizing pricing, in designing a comprehensive framework for new antibiotics that strengthens innovation, secures universal access and promotes rational use.

Practitioners, policy-makers and researchers within the field of global health may have grown accustomed to the sad fact that, frequently, drugs that are directly needed by vulnerable patients are not being developed due to lack of profitability or to markets with low purchasing power. With emerging antibiotic resistance and the concurrent lean antibiotics R&D pipelines the striking feature is likely not the novelty of that challenge, but the fact that in this specific case the potential victims to the public health threat are not only poor people in faraway countries, but also patients and consumers in high-income countries.

On the other hand, a different problem in the antibiotics field is that excess use compounds the all too familiar problem of lack of access. Irrational use of antibiotics leads to quicker evolution of resistance in pathogenic (and non-pathogenic, so called normal flora) bacteria than would otherwise be the case.

The all too small trickle of candidate antibiotic drugs in the pipelines calls for new economic reward models to incentivize innovation. However, such reward models should not only ensure a sufficient return on investment to the drug developer since somebody has to cover the costs. They should also, in an integrated and coherent way, ensure equitable access to new antibiotics on a global scale to those that truly need them, as well as ensure their rational use. Together these measures could secure sustainable access to effective antibiotics in the years to come.

Despite persistent unmet needs for drugs, vaccines,

diagnostics and other essential health commodities and technologies in low- and middle-income countries, there have been encouraging interventions and initiatives to strengthen and promote R&D efforts targeting neglected diseases. We believe some of the experiences in the field of neglected diseases are very relevant to discussions about how to resolve the currently unfolding antibiotics crisis. Nevertheless, in the following we will explain that there are important differences between neglected diseases and infections caused by emerging resistant bacteria, which impedes direct transfer of experience, solutions and economic models from the one to the other.

Thus, the main question to be discussed in this article is: how can IPR be mobilized and harnessed in ways that contribute to a feasible economic reward model for sustainable access to effective and appropriate antibiotics, and in this respect what experiences can be drawn from the field of neglected diseases generally and from the recommendations proposed by the Consultative Expert Working Group on Research and Development (CEWG) under the auspices of WHO.

First, we will discuss similarities and differences between diseases caused by resistant bacteria and neglected diseases in order to provide a general idea of the extent to which experiences with different interventions in neglected diseases are transferrable to the antibiotics field. We then give a brief account of the process leading up to the publication of the CEWG report. Lastly, we discuss six selected proposals that were recommended in the report in light of their relevance for antibiotics innovation and stewardship, while simultaneously introducing a few other relevant ideas.

Diseases caused by resistant bacteria are Type I diseases

In global health discourse diseases for which appropriate treatment is lacking are termed "neglected diseases". We use the following classification to illustrate some schematic points.

Type III diseases are those that are overwhelmingly or exclusively incident in developing countries, such as bilharzia (schistosomiasis) and ebola *(1)* (p 18). For many Type III diseases the main problem is that appropriate treatments simply do not exist, basically because of lack of purchasing power on part of the potential patients, or the governments in their countries of residence, means that incentives for R&D are weak.

Type II diseases are incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries, such as hepatitis, tuberculosis and HIV. For many Type II diseases treatments exist, but in many cases drug patenting facilitates monopoly prices which means that patented medicines are out of reach for poorer populations.

Type I includes diseases that are incident in both rich and poor countries, with large numbers of vulnerable populations in each, and thereby not "neglected" as such. In this typology most antibiotic resistant infections fall within the Type I category, being as it is a truly global challenge. For instance, the UN Commission on Life Saving Commodities for Women and Children listed injectable antibiotics to treat sepsis in newborns as one of the 13 most important commodities addressing leading avoidable causes of death during pregnancy, childbirth and childhood *(2)*.

Apart from the geographical distribution the other important difference between antibiotic resistant infections (Type I) and Type III diseases is the nature of the market failure. While in Type III developing and manufacturing appropriate medicines are not profitable, with antibiotics there should realistically be sufficient purchasing power in high-income countries to achieve a positive bottom line. The problem is rather that the opportunity costs to the innovating companies are too high given other more profitable disease areas *(3)*.

A common problem in infectious diseases of all three types is of course the emergence of antimicrobial resistance. In antibiotics resistance develops as a function of the distributed volumes, thereby limiting their profitability. Moreover, given that users/agencies will seek to ration an antibiotic drug in order to avoid development of resistance and hence preserve its effectiveness, there is also an element of financial risk and unpredictability in antibiotics R&D investment decisions.

It is important to note, however, that high-income countries are better equipped for combatting and controlling infectious diseases than low-income countries in terms of sanitation, public health measures, immunization programmes and health-care systems. In this way also Type I infectious diseases impact more strongly on poor people in low-income countries than on people in high-income countries.

To sum up, interventions on the antibiotics field should incentivize innovation and ensure global access, much like what CEWG set out to achieve in Type II and III diseases. In addition, appropriate interventions should prevent excessive use.

The CEWG Report

The Consultative Expert Working Group on Research and

Table 1: **The 15 groups of proposals for stimulating R&D assessed by the CEWG. Adapted from *(1)*. The six groups that best met the evaluation criteria are in bold italics**

Proposals assessed by the CEWG	
Global framework on research and development	***Open approaches to research and development and innovation***
Removal of data exclusivity	***Milestone prizes and end prizes***
Direct grants to companies	Purchase or procurement agreements
Green intellectual property	Priority review voucher
Health Impact Fund	Regulatory harmonization
Orphan drug legislation	Tax breaks for companies
Patent pools	Transferable intellectual property rights
Pooled funds	

Development (CEWG) Report represents the end result of a cascade of resolutions and reports that was initiated at the 56th World Health Assembly (WHA) in 2003, where the World Health Organization (WHO) Secretariat presented a report on intellectual property, innovation and public health, whose main focus was on the need for looking at mechanisms for stimulating innovation and at the relationship between intellectual property rights and public health *(4)*. Nine years later, following two resolutions and a report by an international commission *(5)* and a negotiated global strategy and action plan *(6)* and one working group *(7)*, in 2012 the CEWG Report was published under the auspices of WHO[1]. The report assesses a range of different proposals for strengthening financing and coordination of R&D for neglected diseases.

The main task of the CEWG was to "to examine current financing and coordination of research and development, as well as proposals for new and innovative sources of financing to stimulate research and development" for neglected diseases, by building on the above mentioned previous processes and reports. More than 100 proposals from the previous reports and proposals solicited from different stakeholders that were considered to be within the mandate of the group were reviewed and grouped into 15 main categories (see Table 1), of which six were considered to best meet the evaluation criteria. In the following, we will discuss all of the six while adding some ideas that were not included in the CEWG assessment.

Delinking and decoupling

In order to finance R&D related to Type III diseases the CEWG report argues for delinking revenues and R&D costs, while in antibiotics we also wish to decouple revenues and volumes. What does this mean?

The basic pharmaceutical company business model consists in covering initial R&D costs by generating downstream revenues based on high prices facilitated by monopoly market power through patents. Delinking R&D costs from revenues and price means to cover the R&D costs by other means, for instance by public sector interventions. For Type III diseases Product Development Partnerships are but one delinking mechanism.

Similarly, the business model entails having manufacturing costs covered by maintaining a revenue stream based on high volumes. In antibiotics, however, even if R&D costs are delinked, drug stewardship (and indeed, resistance development) might limit sales to the extent that not even manufacturing costs are covered since many new antibiotics will be shelved for third or fourth line treatment. In addition, there is agreement for the need to avoid financial incentives for oversale, overuse or overprescription. Hence the need for also decoupling revenues from volumes, i.e. somehow the manufacturing costs must be covered independently of the sold quantities.

Cut short, the need for stewardship in antibiotics adds decoupling to the delinking requirement. The CEWG report did not see delinking as a proposal per se; instead it was used as one out of nine criteria for evaluating the different proposals[2].

Open approaches to research and development and innovation

The CEWG report gives an overall positive, but yet conditional, assessment of the Open approaches, which includes the following five interventions and measures.

Open innovation is an R&D strategy that aims at sourcing knowledge and information across organizational boundaries, commonly by establishing research networks and other means of collaborative operational procedures. Precompetitive R&D platforms are a subset of open

[1] One of the present authors (JAR) chaired the CEWG.

[2] The other criteria were: public health impact, efficiency/cost effectiveness, technical feasibility, financial feasibility, intellectual property, access, governance and accountability, and capacity building.

innovation, and refer to collaborative efforts at developing technologies that are not intended to be patented as such, but which aim to overcome problems in the overall research process in any given field. One example is the DRIVE-AB project, which aims at developing an economic reward model for antibiotics innovation and stewardship[3].

In our view, these two ways of organizing R&D have great potential for stimulating antibiotics R&D. We believe public funds should be used to finance innovation models that source R&D efforts from a multitude of commercial and non-commercial entities, much like the operational procedures for many of the Product Development Partnerships (PDPs). Indeed, our impression is that several PDPs actually practise open innovation, albeit without necessarily self-declaring to do so.

In its strictest sense, open source in its original version from the computer software industry does not translate directly into drug development, primarily because of the differences in managing copyrighted software source code on the one hand and patented molecules on the other. However, in the adapted version introduced by the CEWG open source drug discovery entails an open approach to IP, that is, making data and papers publicly available, and allowing IP rights to be used freely by collaborators (and others) by customized licenses or the use of public domain.

The CEWG viewed the potential of the Open approaches to lie in reduced R&D costs, possibilities for delinking, and more collaboration and broad participation in R&D processes. They are technically feasible, and seem to be particularly applicable in earlier stages of the development process. The qualification is that these Open approaches have been implemented and tested to a limited degree only, so that evidence on their feasibility and efficiency is still somewhat scant. In sum, despite addressing access issues mostly in indirect ways, Open approaches were considered to meet many of the assessment criteria in contributing to R&D.

We believe that up to the clinical trial level an antibiotic drug development process can be facilitated by open source measures in combination with other interventions *(8)*.

However, in antibiotics specifically one aspect of the IP issue is turned inside out, as it were. In Type II diseases transfer of IP rights to generic manufacturers commonly appears as a measure to introduce competition and hence price reductions, which in turn contributes to universal access *(9)*. However, in antibiotics unrestricted generic manufacturing and sales may hold the potential to undermine rational use. Or, controlling IP rights to new antibiotics can be a key instrument for effective stewardship, at least in the short to medium term, i.e. the duration of the patent protection. Such IP rights could be acquired by an international public entity for instance by way of a patent buy-out, and sub-licencees would be obliged to comply with defined conservation or stewardship measures. Thus, in the absence of a strong and well-functioning global framework or regulation for antibiotic stewardship, universal access may need to be ensured by other means than free generic manufacturing and sales. We wish to underscore, however, that using IP rights as a stewardship instrument immediately raises many concerns including the highly critical issue of who is supposed to control those rights. Most likely, a publicly controlled entity would be most appropriate. We also wish to reiterate that global stewardship by IP control must be implemented with participation by an international range of stakeholders, including representatives from different countries; that imposes stewardship regimes that are appropriate for the different national and regional contexts; and that are linked to other interventions to improve access and rational use.

These lines of thinking link directly to the last proposal that the CEWG considered under the Open approaches headline, namely equitable licensing, which is a set of defined strategies for managing IP rights. This set of principles for IP licensing for global access aims at increasing access to pharmaceuticals by facilitating generic manufacturing, technology transfer and further research. Within this framework[4] "at-cost" provisioning is considered a second best alternative to generic provisioning. Translated into a hypothetical situation in which IP is being used as a stewardship instrument, conditional non-exclusive licensing appears to be a strategy for achieving the dual goals of access without excess. The non-exclusivity would facilitate universal access, while the conditions would seek to avoid excess. In short, this would be a model for restricted and supervised generic manufacturing.

An access interlude – tiered pricing

In the absence of (restricted) generic manufacturing there is one alternative measure available for promoting universal access that the CEWG considered to be outside of its mandate since it does not directly incentivize innovation. On the global vaccine markets suppliers have offered vaccines at tiered prices, or differential prices. In parallel, consumers have established pooled procurement mechanisms, most

[3] The DRIVE-AB projects involves more than 20 organizations, including industry partners. The present authors are active partners. See http://drive-ab.eu/

[4] http://uaem.org/cms/assets/uploads/2013/03/GlobalAccessLicensingFrameworkv2.pdf

notably those operated by the UNICEF Supply Division (SD) and the Pan American Health Organization's Revolving Fund (PAHO RF), and this combination of market behaviour by monopolies on the supply side and monopsonies on the demand side has resulted in prices for many off-patent vaccines approaching marginal manufacturing cost in developing country markets *(10)*. It is important to note, however, that in principle tiered prices is a profit maximizing measure employed by the supplier which, in the absence of counteracting measures on part of the consumers such as for instance pooled procurement, will entail perfect price discrimination, and the opportunity for selling at monopoly prices in both high-income and low-income markets, albeit at a lower price in the latter. This means that low-income country purchasers get a lower price than what would be the case if the product was sold at a uniform price, but the low-income country price is still higher than what would have been the case in the presence of generic competition, for instance.

Thus, although tiered pricing of new antibiotics might generate a certain revenue stream in high-income markets while to some degree increasing access in low-income markets, universal access requires additional measures on part of consumers or third parties.

The conditional non-exclusivity licensing model above could be complemented with the IP holding entity marketing antibiotics at different prices in different markets, but by setting prices that maximize access in line with responsible use instead of maximizing profits, i.e. implementing principles for access maximizing pricing. We decidedly do not recommend using prices at the point of care to limit the use of a new antibiotic, since uneven purchasing powers of the different users would make this an overly blunt, imprecise and inequitable instrument.

Compounding the access issue is the fact that most likely new second and third line antibiotics will not be oral but injectable. In particular, in low-income settings intravenous drugs can be a challenge, as can the stability of the formulation. Thus, universal access to these antibiotics will not only depend on affording the drug itself, but might also require universal access to functional health facilities and hospitals as well as trained providers; a far cry from current realities in many low- and middle-income countries *(11)*. We also see universal access to point of care diagnostics as indispensable tools for rational use.

Patent pools

Typically, patent pools are formed by patent holders whenever the technology in question is subject to patenting by several patent holders in a way that makes it difficult for each of them to determine how to implement the technology in manufacturing without infringing, or appearing to infringe, on the other patents holders' claims. Such a situation is quite common in the electronics and telecommunication industries with complex products.

The CEWG gave a high rating to the three patent pools that were assessed, of which one will be mentioned here[5]. Specifically, CEWG assessed the Medicines Patent Pool (MPP), funded by UNITAID,[6] as one of the model examples in this category. MPP deals with patents related to products for treatment of HIV/AIDS. This therapeutic area is dominated by combination therapies, that is, most drugs used in the treatment regimens consist of several patented chemical components, and commonly these patents are distributed among several different companies and entities. Thus, for an entity developing combination HIV/AIDS drugs negotiating licenses with all the relevant patent holders can involve both high administrative costs and a high degree of uncertainty and risk.

Taking the CEWG assessment as a point of departure, to what extent are patent pools relevant and feasible in designing economic reward models for incentivizing antibiotics innovation, and in securing access and rational use? In antibiotics, the above mentioned risk and cost reducing properties of a patent pool seem to be evoked first and foremost whenever the drug in question consists of several patented molecules or compounds owned by different entities, or if for some reason licensing of several process patents should be required to set up the manufacturing process of a single molecule drug or otherwise combine technologies, or if there are patented technologies that are necessary further upstream in the innovation process. Nevertheless, given that cross-resistance might occur between different antibiotic drugs within a class, it could be appropriate to jointly manage the IP rights within each class by way of a patent pool. And to our knowledge there is nothing to prevent the MPP from also managing IP rights for antibiotics.

Next, we will be looking at the three CEWG proposals that are relevant for the delinking/decoupling argument mentioned above, namely direct grants to companies, milestone prizes and end prizes, and pooled funds.

Direct grants to companies

The basic idea under this heading is to provide public funding to small and medium sized enterprises in "innovative"

[5] The other two were the Pool or Open Innovation, established by GlaxoSmithKline, and the Re:Search, launched by WIPO.

[6] For more information about UNITAID please see http://www.unitaid.eu/

developing countries, much like the United States Small Business Innovation Research Initiative (SBIR)[7] operated by the National Institutes of Health. Even though such funding is likely to be aimed at the early stages of drug development processes, the CEWG report cited evidence from the United States suggesting that there can be significant public health impact of such interventions.

We believe that biotech and "one-product" start-up companies worldwide having antibiotics and bacterial diagnostics in their pipeline can be effectively supported by such schemes. Indeed, the New Drugs for Bad Bugs programme (ND4BB) under the Innovative Medicines Initiative (IMI)[8] and the Biomedical Advanced Research and Development Authority (BARDA)[9] grants of the US Department of Health and Human Services fall within this category. Grants can be awarded on conditions related to rational and equitable marketing of the final product, and to licensing strategy. In this sense, direct grants can contribute to both delinking and decoupling. However, to our knowledge, neither IMI nor BARDA have incorporated conditions like this in their funding models.

Milestone prizes and end prizes

Such prizes are rewards for successful completion of a specified set of R&D objectives. They can be linked to specific milestones in the R&D process, or to a Target Product Profile of a desired end product. The CEWG report points out the advantage of paying for success only, and of having the option of imposing specific licensing conditions on the award winner, including a patent buy-out as suggested above. As such, they have considerable potential for delinkage, but they require careful set up of governance institutions and clear rules and eligibility criteria to work properly. Moreover, conditions related to IP could contribute to decoupling.

In antibiotics, prizes for point-of-care diagnostics were recommended in a recent Report to the President of the United States by the Council of Advisors on Science and Technology *(12)*, and indeed, the Longitude Prize 2014, which opened in November 2014, awards £10 million to inventors of a cost-effective, accurate, rapid and easy-to-use test for bacterial infections that will allow health professionals worldwide to administer the right antibiotics at the right time[10].

In our view, the flip side of the advantage of the no-cure-no-pay principle is that much of the risk needs to be carried by the product developing entity alone, which means that cash-constrained companies might not be incentivized. This is not in line with many actors arguing for risk sharing models in antibiotics development *(13)*. This is less of a disadvantage with milestone prizes than with end prizes, however. Bearing the above CEWG caveats in mind, we believe prizes, much like any other intervention discussed here, may work well in concert with other reward mechanisms.

Pooled funds

This group of proposals in the CEWG report is based on the common idea of having one entity managing funds from multiple stakeholders and donors by allocating grants to designated R&D purposes, be it Product Development Partnerships, small and medium sized enterprises (in developed and developing countries), pharmaceutical companies, research institutions, or any other kind of relevant entity. Although these intervention ideas need some further elaboration and development, their potential strength would have to be proven in terms of their ability to generate additional funding in innovative and sustainable ways.

Given the global scope of the antibiotics crisis, the relevance of pooled funds is quite obvious. From a more microeconomic perspective pooling is also a requirement for decoupling and delinking since moving away from only relying on unit based revenue streams means that purchasing power needs to be pooled at one level to aggregate demand, at least at the health system or health insurer level. This pooling will also be able to facilitate pooling at the national or supranational levels. Pooled funding could both delink revenues from R&D costs and decouple revenues from volumes. Decoupling would take place for instance by using pooled funds to pay a manufacturer for the production costs independently of the volumes actually purchased through e.g. a service level agreement where the manufacturer guarantees provision of a volume within a boundary. Such a set-up would fit well with the sixth and last CEWG proposal to be dealt with in this article.

Global Framework on Research and Development

The CEWG considered a Global R&D Framework to be ambitious, but also to have the virtues of transparency, participation, effectiveness in governance, global coordination of R&D, and generation and allocation of funds.

[7] http://sbir.nih.gov/

[8] The above mentioned DRIVE-AB project (p) is funded by IMI. See http://www.imi.europa.eu/.

[9] See http://www.phe.gov/about/barda/Pages/default.aspx

[10] See http://www.longitudeprize.org/. One of the present authors (JAR) is in the advisory group of the Longitude Prize 2014.

In our view, a global framework in antibiotics would have the primary purpose of ensuring responsible use. Funding for antibiotics R&D will most likely be provided by high income countries, so we see a true Global Framework first and foremost providing the resources necessary for securing decoupling. In this way, a Global Framework could have provisions for how to market, dispense, distribute and prescribe antibiotics in ways that both limit resistance development and increase access. Such a framework could be part of a more comprehensive package of measures.

A Global Framework can then be supported by a more limited multi-country-based agreement where a coalition of committed states could pool their resources to contribute to pooled funds for antibiotic development and require this to happen under the globally agreed framework that first and foremost handles responsible use.

Conclusion

The performance of the traditional reward model of selling patented drugs at monopoly prices is not satisfactory in terms of providing needed drugs against neglected diseases and antibiotics against common bacterial infections. The traditional model is both failing to bring new antibiotics to the marketplace at a satisfactory rate and to ensure a sufficiently rational use of existing and future antibiotics.

There are interesting and relevant lessons to be drawn from the field of neglected diseases in global health discourse, both in the form of practical experiences such as PDPs and in the form of reports and analytical efforts and policy discussions such as the CEWG and its follow up. However, there are important differences between "traditional", mostly tropical, Type II and III neglected diseases on the one hand and antibiotic resistant infections of Type I on the other which call for caution in translating those lessons from the former field to the latter.

For instance, although generic manufacturing can facilitate access, it may also facilitate excess, since it does not ensure rational use. Contrary to the case of Type II and III diseases, controlling IP rights can be important in implementing a non-paternalistic, participatory, transparent and context sensitive regime for rational use of new antibiotics. Along this line of thinking a public patent owning agency and any licensees can market patented antibiotics on conditions that would secure rational use, for instance by requiring prescriptions or similar arrangements based on defined diagnostic criteria only. IP protection may not be the only way, though, as sustainable solutions also need to address the post patent expiry period.

Indeed, we do not assume that any of the following proposed interventions can possibly solve the antibiotics crisis in a satisfactory way in isolation. The point to be made here is rather that innovative IP licensing practices, patent pools and open source R&D collaboration models can be used as building blocks, in combination with measures such 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. One of the great challenges ahead is to develop models for operationalizing and implementing a comprehensive and coherent set of appropriate measures.

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References

1. WHO. Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination. Geneva: World Health Organization, 2012.
2. UNFPA. UN Commission on Life Saving Commodities for Women and Children. Commissioners'Report New York: United Nations Population Fund; 2012 [cited 2014 28 October]. Available from: http://www.unfpa.org/public/home/publications/pid/12042.
3. Sertkaya A, Eyraud J, Birkenbach A, Franz C, Ackerley N, Overton V, et al. Analytical Framework for Examining the Value of Antibacterial Products: Eastern Research Group, Inc., report commissioned by the US Department of Health and Human Services; 2014 [cited 2014 31 October]. Available from: http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm.
4. WHO. Intellectual property rights, innovation and public health. Report by the Secretariat Geneva: World Health Organization; 2003 [cited 2014 13 October]. Available from: http://apps.who.int/gb/archive/pdf_files/WHA56/.
5. WHO. Public health, innovation and intellectual property rights Geneva: Report of the Commission on Intellectual Property Rights, Innovation and Public Health. World Health Organization; 2006 [cited 2014 10 November]. Available from: http://www.who.int/intellectualproperty/documents/thereport/ENPublicHealthReport.pdf?ua=1.
6. WHO. Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property Geneva: World Health Organization; 2011 [cited 2014 10 November]. Available from: http://www.who.int/phi/publications/Global_Strategy_Plan_Action.pdf.
7. WHO. Research and Development - Coordination and Financing Geneva: Report of the World Health Organization Expert Working Group on Research and Development Financing; 2010 [cited 2014 24 December]. Available from: http://www.who.int/phi/documents/ewg_report/en/.
8. Årdal C, Røttingen J-A, Alstadsæter A. Common characteristics of open source software development and applicability for drug discovery: a systematic review. *Health Research Policy and Systems.* 2011;9(36).
9. Moon S, Jambert E, Childs M, von Schoen-Angerer T. A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries. *Globalization and Health.* 2011;7(1):39.
10. Plahte J. Tiered pricing of vaccines: a win-win-win situation, not a subsidy. *The Lancet Infectious Diseases.* 2005;5(1):58-63.
11. Bigdeli M, Peters DH, Wagner AK. Medicines in Health Systems: Advancing access, affordability and appropriate use Geneva: Alliance for Health Policy and Systems Research, World Health Organization; 2014 [cited 2014 10 November]. Available from: http://www.who.int/alliance-hpsr/resources/ATMFlagshipReport.pdf?ua=1.
12. PCAST. Report to the President on Combating Antibiotic Resistance Washington DC: President's Council of Advisors on Science and Technology; 2014 [cited 2014 10 November]. Available from: http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf.
13. So AD, Ruiz-Esparza Q, Gupta N, Cars O. 3Rs for innovating novel antibiotics: sharing resources, risks, and rewards. *British Medical Journal.* 2012;344(e1782).

CREATING AN INTERGOVERNMENTAL CONSORTIUM FOR NEW ANTIBIOTICS: A NEW DEVELOPMENT MODEL

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All countries in the world are facing increasing levels of resistance to existing antibiotic treatments. In recent decades, only two new classes of antibiotics have come to market, although around 60 derivatives of existing classes are in the pipeline, of which few are targeting Gram-negative bacteria. The creation of a new system of rewards for innovation and development of new antibacterial drugs has come to the fore as a matter of urgency.

The world needs to develop the means to bring about new antibacterial products, while working in parallel on strong regulations on the availability and use of the new drugs in human and/or veterinary medicine, in order to prevent the occurrence of resistance.

We present here the concept of an "intergovernmental consortium for new antibiotics", a new development model to promote and finance R&D and production of medicines against bacterial infections. Such a new model could have the following features:

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;
5) production and marketing agreements for a needs-based number of treatments per year;
6) an intergovernmental consortium to manage the distribution and preservation of new antibiotics.

The above 1), 2) and 3) elements have potential for decoupling rewards for research from product sales revenues.

Introduction: Public health needs in the "post-antibiotic" era

"The world is moving towards a post-antibiotic era in which common infections will once again kill" declared World Health Organization's Director-General, Dr Margaret Chan *(1)*.

Antibiotic resistant bacterial infections affect 5 million patients hospitalized every year in the wealthiest parts of the world – United States and European Union, and kill 50,000 patients, figures rising, the situation is indeed serious *(1)*. Advanced medical practices such as transplantations and cancer treatments are impossible without working antibiotics. Years of medical practices could be put in jeopardy, and tomorrow a minor bicycle injury could mean death, as was the case a century ago. Conclusive research shows that countries with lesser levels of economic development face the same problem.

In general, bacterial diseases still contribute heavily to the global burden of disease; they are a major factor in mother-child morbidity and mortality, strike heavily at young children and young adults. Drug resistance has been inexorably climbing in low- and middle-income countries (LMICs), as has been now documented for more than a decade *(2)*. Neonatal sepsis, pneumonia, tuberculosis and meningitis are examples among many where bacterial resistance has been identified. Pneumonia is the most common cause for adults being hospitalized in sub-Saharan Africa – 4 million episodes – and accounts for 200,000 deaths a year *(3)*. A hospital study in Tanzania showed that

Gram-negative sepsis in children had a mortality rate twice that of malarial infection *(4)*. Nearly a quarter of *Streptococcus pneumoniae* strains are reportedly resistant to three classes of antibiotics *(5)*.

Across Africa and Asia, the resistance of bacillary dysentery in children to ciprofloxacin – the treatment recommended by WHO – has risen from negligible to 30% in a decade *(6)*. Drug resistance to gonorrhea has arisen in waves, first to fluoroquinolones, then to cefixime, and more recently to azithromycin *(7)*. While a protective vaccine exists for some of these conditions, many must rely on antibiotic treatment *(8)*.

Low-income populations, which have access to antibiotics mainly through cheaper generics will be at risk from the rise of bacterial infections resistant to first- and second-line treatments as third-line treatments of which no generic versions is available due to patent protection will often be unaffordable.

Antibiotic resistant pathogens recognize no political borders or frontiers and represent a very important global risk. It has been identified as such by the WHO *(9)*, the G8 *(10)*, the World Economic Forum *(11)*, and many governments of countries from all income levels, from the United States administration to the United Kingdom authorities, and from China to India or South Africa, as well as by large constituted networks of scientific societies and committed individuals *(12, 13)*. Indeed, the rise and spread of a bacterial gene which confers resistance to a broad range of antibiotics, first discovered in United Kingdom patients returning from India, identified in the wastewater of New Delhi, and named "NDM-1" (New Delhi Metallo-beta-lactamase-1), has now been identified with alarm all around the world: in China, Pakistan, the United States and European countries. NDM-1 has been identified in 18 countries from all continents over the span of one year. As the gene travels via human gut microbiota, the epidemiological consequences are awesome: global outbreaks of totally antibiotic resistant diarrheal and other diseases are looming *(14)*.

The need for a new innovation model

The objective of this proposal is to suggest a new model for research, development and distribution of new classes of antibiotics.

Everywhere national plans for rational use of antibiotics and to mobilize societies against resistance are coming into being. Antimicrobial resistance is now a key topic at the World Health Assembly, and has been the topic of many inter-ministerial meetings *(15)* as well as national emergency announcements since June 2014 *(16)* .

Low-income populations, which have access to antibiotics mainly through cheaper generics will be at risk from the rise of bacterial infections resistant to first- and second-line treatments as third-line treatments of which no generic versions is available due to patent protection will often be unaffordable.

In the array of antimicrobials antibiotics occupy a unique place from the standpoint of research and development needs and implications.

We do not get the antibiotics we need

It has now been publically acknowledged by all public and private stakeholders that the R&D pipeline for novel classes of antibiotics has faltered *(17, 18, 19)*.

There are several explanations for this state of affairs:

- Low hanging fruits have already been collected: easily developed molecules with antibacterial properties have already been investigated, generally from stored compounds by the large pharmaceutical companies. "New" antibiotics are more difficult to identify and develop, and hence more costly to bring to market.
- Public pharmaceutical research is often strapped for funding in many countries, while small and medium size innovators may lack access to sufficient funding.
- Market prospects are better in other areas. Antibiotics are short course treatments and do not compare well as an R&D investment with drugs for lifelong ailments such as hypercholesterolemia, diabetes or other noncommunicable diseases.
- The need to maintain the effectiveness of any really new antibiotic by restricting its use to patients with ailments not responding to treatments, diminishes the financial rewards that any private entity would expect from investing in R&D. In fact new antibacterial entities may be considered rare and precious resources.
- Mechanisms should and will be put in place to prevent widespread use of antibiotics in human health.
- Clinical development today would need to be conducted on patients with antibiotic resistant infections and the

lives of a hypothetical placebo group would be at risk, raising difficult ethical questions.

- Newer products may not be allowed for use in animal health (which represents over 50% of global sales today).

As in the case of diseases of poverty or neglected diseases, the market alone does not assure sufficient investment in research and is not needs driven, thus not necessarily focusing on the products that are most needed.

The bottlenecks are not just financial, but also of a scientific and regulatory nature. The drive to discover new drugs should be accompanied with a commitment by all countries to make sure the new antibiotics will be used sparingly so they will remain effective for some years since any large scale indiscriminate use would, in fact, spur natural bacterial resistant mechanisms overnight.

The commitments of countries should also include access for all patients in need, independent of financial status, anywhere in the world.

Therefore we are facing the need to reconcile developer incentives with the preservation of the resource.

New and innovative approaches and mechanisms to support the financing and coordination of R&D

There are several viable ways to foster R&D for innovation. Of particular interest are the mechanisms 1–3 described below, as they are potentially a means of delinking R&D from marketing a product, which would be crucial to resolving the antibiotic challenge in the interest of all. In a Chatham House seminar paper, law professor Kevin Outterson wrote : "Antibiotic delinkage may offer the most promising avenue for a sustainable, global approach. Delinkage recognizes that rewarding producers and sellers on the basis of volume is fundamentally inappropriate" *(20)*. Outterson lists all the diverse schemes proposed recently and states that a significant number of CEOs from the pharmaceutical industry have come to endorse the idea. Among the WHO demonstration projects presented early 2014, an Antibiotic Innovative Funding Mechanism (AIFM) was selected by the European Union region *(21)*.

1. Public-sector funded research and clinical trials

The history of medical research shows that public sector-funded research has consistently played a key role in discovery of medical products. For the research of new antibiotics, the knowledge of traditional healers would need to be tapped for potential new classes of compounds, and attention should be brought to natural substances. Indeed, between 1982 and 2002, 70 of the 90 antibiotics reaching market came from natural product sources *(22)* . In this regard, it should be noted the biodiversity needed to search for potentially effective natural substances is often richer in low-income countries.

Historically, a European example of publicly-funded inter-country collaboration is CERN, the European Centre for Nuclear Research, which continues to bring together scientists from all of Europe, even at the height of the Cold War, to study the origin of our universe. CERN was the cradle of the World Wide Web, the "www", which we all use daily today. A March 2014 Geneva Graduate Institute event on antimicrobial resistance concluded that such a publically funded "CERN-like" research centre could be envisaged as a way to strengthen research and innovation for new antibiotics, although a major difference is that antibiotic research does not require the same huge infrastructure as the research carried out in CERN. Another interesting model of an international publicly-funded research institution is the International Agency for Research on Cancer (IARC). IARC is a specialized agency of WHO, established by a resolution, but independently governed and supported by regular budget contributions paid by participating countries and extra-budgetary resources secured through competitive grants from funding agencies.

Clinical trials will be required to assess safety and efficacy. This is considered the most "costly" part of the pipeline approach to drug production by industry. Therefore public funding for clinical trials would be important to speed up the trials, make sure they are ethically correct, that they are transparent, and open to scrutiny so as to avoid drugs with little innovation.

2. Grants to small and medium size innovative companies or universities

Grants are a common mechanism through which funding is allocated for research projects. In the case of antimicrobials, grants could be set up by public entities for small or large companies to assist in perfecting and optimizing the new antibiotics.

3. A Prize system

Prizes can be of two sorts: End Prizes and Milestone-intermediate Prizes. WIPO recently included a discussion on innovation inducement prizes and delinking at its Committee on Development and Intellectual Property (CDIP) Fourteenth Session *(23)*. Some high-income countries are envisioning this option on a national basis. In the United States, the President's Council of Advisors on Science and Technology, (PCAST) September 2014, latest document on antibiotic resistance has

a whole chapter on de-linking and envisions a large "financial reward", a Prize: "Under such schemes, a successful developer of an antibiotic that addresses an important public health need would receive a financial reward that is not directly tied to the usage of the drug" *(24)*. In the Chatham House seminar paper, Professor Outterson lists all the diverse "prize" schemes. Among the WHO demonstration projects presented early in 2014, was the Antibiotic Innovative Funding Mechanism (AIFM) prize.

In the history of scientific discoveries, a close look demonstrates that cooperation and serendipity nourish scientific discovery. Major outcomes came from public endeavours when scientists were left to search for solutions, without administrative restrictions. It is also the case that major breakthroughs did not emerge from spontaneous generation in one genial brain, but rather grew from the fertile seeding of innovations, "incremental milestones" findings of many innovators which provided the terrain in which the "genial" mind could make the breakthrough. Hence, perhaps, most important to consider are "milestone" or interim, incremental result prizes in the quest to find innovative antibiotics.

This feature is important for many small biotech enterprises or research departments in universities who, by themselves, may not have the capacities to bring a product to fruition but which are frequently imaginative breeding nests for innovations.

Milestone Prizes entail recognition of very early discovery – before the definitive proof of principle of the innovation. These intermediate prizes should be sized so that they would be attractive to academia from applied or fundamental research fields. It would also attract small and medium size enterprises (SMEs), including from LMICs. It should be expected that entities entering the Milestone Prize contests would accept – in case they win a reward – to give a right of first refusal on their intellectual property rights to the publically managed intergovernmental consortium.

The UK Longitude Prize of £10 million, which was voted by the public in 2014 to go towards diagnostics to help identify antibiotic resistant infections and to assist in the rational use of antibiotics, is a good example of an "End Prize" *(25)*. The United States' President's Council of Advisors on Science and Technology PCAST envisions very high level End Prizes to be offered by the United States government for the discovery of novel antibiotics *(26)*.

End Prizes should entail a very high financial reward for a fully developed antibacterial drug. It should be expected that entities entering the End Prize contests would accept – in case they win the reward – to assign intellectual property right to the publicly managed intergovernmental consortium.

4. Pooling patents to bring together intellectual property rights generated by public sector funded research

In effect, all the rights to inventions which successfully obtained a Milestone Prize and the outcome product of the End Prize would end up into a publically managed patent pool that would be set up by the consortium. Historically patent pools have been in existence for quite a while. The best known is FD Roosevelt forcing two competing plane manufacturers to merge their intellectual property *(27)*, so that the United States could build an air force capability to enter World War II.

The Medicine Patent Pool (MPP) Foundation that was set up with the support by UNITAID, is a prime example of what a patent pool is all about and how it works. Using patent pools to facilitate access to medicines was an idea spearheaded by a number of nongovernmental organizations (NGOs), including Knowledge Ecology International (KEI) and the international NGO Médecins sans Frontières (MSF) who initiated a campaign for a patent pool back in 2006, and applauded when the MPP was launched in 2009, while continuing to demand that access for all had to be the driving motive. The MPP advocacy description stipulates that patent pools allow for easy access to latest medicines for LMIC poor populations; facilitating low-cost manufacturers production of new medicines easily and rapidly; and the pooling of innovations to develop combination therapies. The MPP was considered a model pool by the WHO "Consultative expert working group on research and development: financing and coordination." (CEWG), in its April 2012 report.

Another example of pooling scientific knowledge and making available research results is the new Re:Search of the World Intellectual Property Organization (WIPO) *(28)*.

The consortium would manage the pooled intellectual property and provide licenses to countries that allow for the manufacturing of the new antibiotics. Conditions for obtaining a license would be such as authorized production would not result in indiscriminate large scale distribution of the new antibiotics, in order to prevent rapid onset of resistance. Indeed, self-regulation by users and prescribers would not result in elimination of overuse and misuse of new antibiotics, judging from past and present experience. Such license conditions could be for example restriction of use for human medicine, limited production, sales to authorized entities (such as hospitals) only.

5. Production and marketing agreements

Purchase agreements with private industry could be put in place for the production of a set number of treatments per

year to be allocated to all countries, according to needs, under an agreement that they would monitor use and restrict utilization to agreed health-care settings (such as secondary or tertiary level hospitals, for example).

This would exclude direct commercialization of the product in private pharmacies and prescription for indications where other therapeutic interventions are available. These conditions would ensure preservation of the new drugs.

6. An intergovernmental consortium to manage distribution and preservation of new antibiotics

This programme would be managed primarily through an intergovernmental consortium which would provide both financing and oversight. Operationalization could be the responsibility of an entity that could be modeled as a non-profit public pharmaceutical company as exists on national level in various countries. This entity would also be responsible for registering the new product in individual countries.

The proposed intergovernmental consortium would have the following four objectives: promotion of innovation, access to all in need, controlled use for better preservation, and inclusiveness.

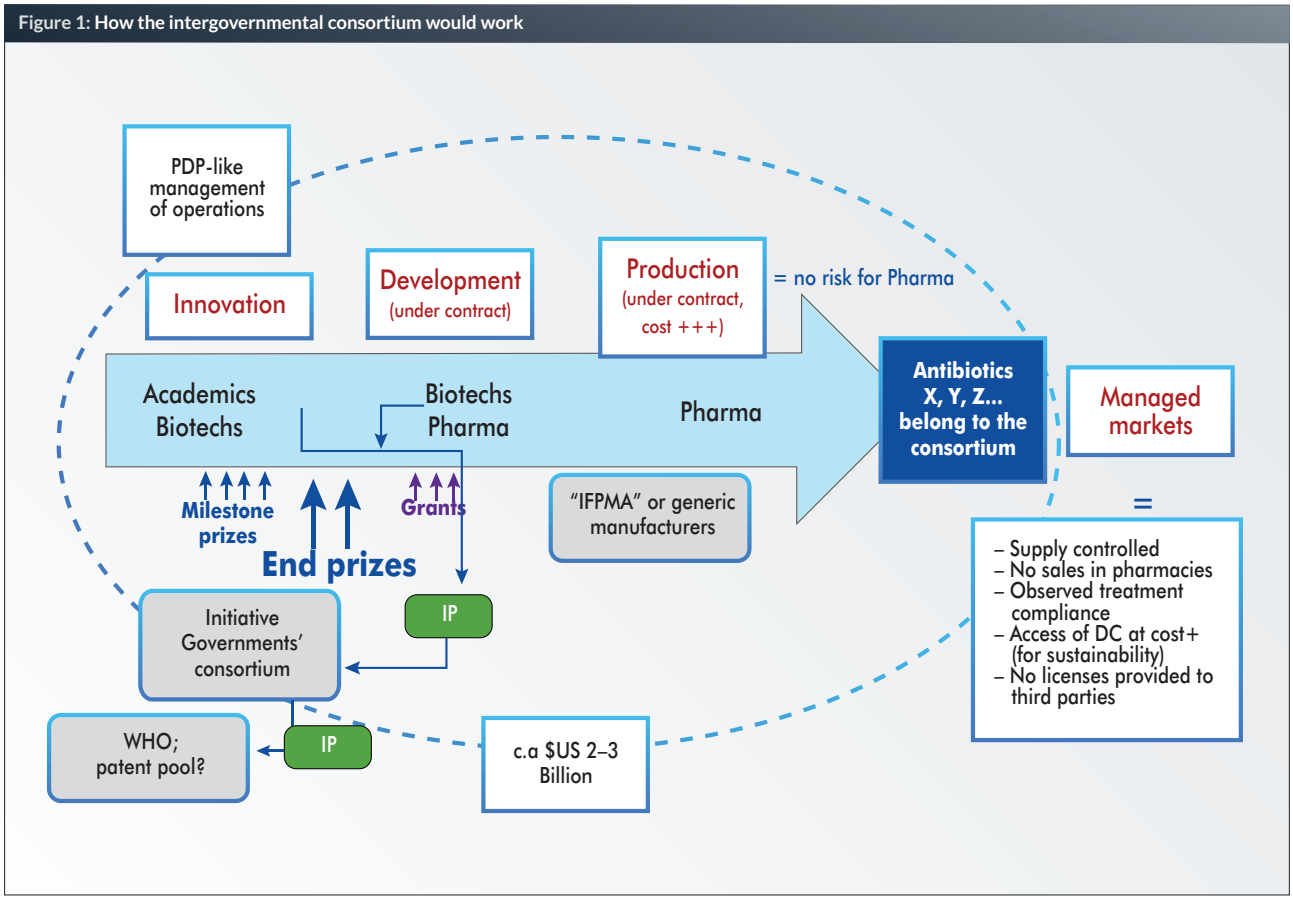
Promotion of innovation:

- Public funding of scientific research should be encouraged. The United States has the largest health research public sector-funding in the world, followed by Western Europe as a whole *(29)*. Having understood the value of research and innovation for economic growth, China is about to catch up and overtake the United States *(30)*. Other countries such as Brazil, Singapore, South Korea and India also have considerable investments in pharmaceutical R&D.
- The framework would increase the potential and the means for fundamental discoveries in new antibiotics, since it would separate basic research funding from clinical trial funding and management (a huge part of the costs of bringing products to the table), as well as from production and marketing costs.
- Grants and prizes would be a crucial asset: the twenty-first century is exploding with scientific and technical capacities, tapping this potential widely and openly would greatly favour fundamental breakthroughs in new antibiotics.

Access to all in need:

- The capacity to prevent disability and death from

Figure 1: How the intergovernmental consortium would work



infectious diseases, everywhere, should be a Global Public Good; all countries would have access to the new antibiotics on a needs-basis at an affordable price under the proposed intergovernmental consortium.

Controlled use for better preservation:

- All partners to the consortium would have to adhere to standards of responsible use to delay the development of resistance. Countries would have to set up national plans for preservation.
- Strict means to control dispensation would be needed at all levels in all countries, including access to latest state of the art diagnostics.
- No licenses would be provided for veterinary use, in order to avoid and the current overuse of antibiotics in the food industry.

Inclusiveness:

- Low-income countries have a lot of potential to contribute to innovation in antibiotics, notably but not solely, by the search for new natural resources or the tapping of traditional knowledge.
- Most discovery and innovative concepts arise in academia and small biotech enterprises. Multinational pharmaceutical companies often buy up small innovating firms or license inventions from universities. Innovations are spurred by scientific freedom, unshackled by demands of short term profitability or bureaucratic oversight.
- Middle-income countries have undergone very fast expansion of their capacities in pharmaceutical research and high-level biotech industry generally; their contribution to any new antibiotic development project would be important *(31)*.

The consortium would be funded by governments and other public sector entities, to which philanthropic foundations could be added. A considerable financial commitment (possibly in tens of US$ billions) over a 15 year period would be needed. The current estimated cost of developing one new drug is between US$ 5 billion *(32)* and 500 million *(33)*.

The core concept here is the need for a type of institution which would enter into a dynamic interplay with the scientific innovative capabilities of the many actors and which would creatively feedback innovative products into society *(34)*.

Finally, "prevention comes first!"

"Prevention first. Every infection prevented is one that needs no treatment!", according to the WHO Draft global action plan on antimicrobial resistance *(35)*. The drive to find and produce new antibiotics should be accompanied with much stronger efforts for prevention than is currently the case, in order to reduce the number of patients who might contract drug resistant infections from the environment, within health systems, and hence need treatments. There is a need for:

- 1- much stronger and more efficient prevention of hospital acquired infections;
- 2- prevention and monitoring to prevent AMR entering the food chain;
- 3- surveillance, monitoring of water and waste, as well as global investments to improve LMICs water and sanitation systems *(36)*.

As the Ebola crisis has demonstrated, there is an urgent need for strong investment in infection prevention and control in the health systems of low-income countries, including in situation where there is no market for advanced technologies in the prevention of in-health centre transmission of infections.

Newer antibiotics would be most efficient in a global environment in which preventative measures had been taken as outlined above, it would give the new drugs a longer life span.

While the drive for antibiotics R&D is most urgent, other research avenues, some which have began to be explored *(37, 38)* others in the wings, should not be forgotten, and some might benefit from some of the options presented here for a newer, more modern R&D model for the common public good of benefit to all. •

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References

1. US CDC Threat Report 2013: Antibiotic / Antimicrobial Resistance. http://www.cdc.gov/drugresistance/threat-report-2013/ (accessed on January 10, 2015)
2. Antimicrobial Resistance in Developing Countries Sosa, A. de J., Byarugaba, D.K., Amabile, C., Hsueh, P.-R., Kariuki, S., Okeke, I.N. (Eds.), 2010, XXIII, 554 p. Springer.
3. Zar, H. J., S. A. Madhi, S. J. Aston, and S. B. Gordon. "Pneumonia in Low- and Middle-Income Countries: Progress and Challenges." *Thorax* (2013): 1-5.
4. Blomberg B, Manji KP, Urassa WK, et al. Antimicrobial resistance predicts death in Tanzanian children with bloodstream infections: a prospective cohort study. *BMC Infectious Diseases* 2007; 7:43.
5. Laxminarayan R, Bhutta ZA, Duse A, et al. "Chapter 55: Drug Resistance," in Jamison DT, editor, Disease Control Priorities in Developing Countries, 2nd edition. New York: *Oxford University Press*, 2006.
6. Gu, Bing, et al. "Comparison of the Prevalence and Changing Resistance to Nalidixic Acid and Ciprofloxacin of Shigella between Europe–America and Asia–Africa from 1998 to 2009." *International Journal of Antimicrobial Agents* 40.1 (2012): 9-17.
7. Deguchi, Takashi, et al. "Emergence and Spread of Drug Resistant Neisseria Gonorrhoeae." *The Journal of Urology* 184 (2010): 851-58.
8. Brenzel L, Wolfson LJ, Fox-Rushby J, Miller M, Halsey NA. Chapter 20: Vaccine-Preventable Diseases. Disease Control Priorities in Developing Countries (2nd Edition), ed. ed.New York: Oxford University Press, 2006, p. 397.
9. World Health Organization. The evolving threat of antimicrobial resistance: Options for action. Geneva, Switzerland: WHO, 2012. Available at: http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf (accessed on January 10, 2015).
10. Cookson C. G8 ministers pledge to act on bacterial antibiotic resistance. Financial Times, June 13, 2013. http://www.ft.com/cms/s/0/172341bc-d428-11e2-a464-00144feab7de.html#axzz2gfdBG33I (accessed on January 10, 2015)
11. Howell L, editor. Global Risks 2013, Eighth Edition. Geneva, Switzerland: World Economic Forum, 2013
12. The Declaration of WAAAR - World Alliance Against Antibiotic Resistance, June 23, 2014, signed by 700 personalities from the medical world and a 100 scientific societies. http://www.ac2bmr.fr/index.php/fr/declaration-waaar (accessed on January 10, 2015)
13. Ghafur A, Mathai D, Muruganathan A, Jayalal JA, Kant R, Chaudhary D, Prabhash K, Abraham OC, Gopalakrishnan R, Ramasubramanian V, Shah SN, Pardeshi R, Huilgol A, Kapil A, Gill J, Singh S, Rissam HS, Todi S, Hegde BM, Parikh P. "The Chennai Declaration" Recommendations of "A roadmap- to tackle the challenge of antimicrobial resistance" - A joint meeting of medical societies of India. Indian J Cancer [Epub ahead of print] [cited 2013 Jul 15]. http://www.indianjcancer.com/preprintarticle.asp?id=104065 (accessed on January 10, 2015)
14. Walsh T., et al. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *The Lancet*, Vol 11, 5, May 2011. http://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2811%2970059-7/abstract (accessed on January 10, 2015) Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Kumarasamy K., Toleman M., Walsh T., http://www.ncbi.nlm.nih.gov/pmc/ articles/PMC2933358/ (accessed on January 10, 2015)
15. The Hague, The Netherlands, Ministerial meeting Antibiotic Resistance, 25-26 June 2014 http://www.who.int/drugresistance/netherlands_meeting_june_2014/en/ (accessed on January 10, 2015); and Oslo, Norway, Norwegian Institute of Public Health, Nov.13-14 2014 "Commitments to the responsible use of antimicrobials", meeting organized by the group "Diplomacy and Health" (Brazil, France, Indonesia, Norway, South Africa http://www.fhi.no/artikler/?id=112149 (accessed on January 10, 2015)
16. Press release: (UK) Prime Minister warns of global threat of antibiotic resistance, source, First published: 2 July 2014 https://www.gov.uk/government/news/prime-minister-warns-of-global-threat-of-antibiotic-resistance (accessed on January 10, 2015). The White House Blog http://www.whitehouse.gov/blog/2014/09/18/new-executive-actions-combat-antibiotic-resistance-and-protect-public-health (accessed on January 10, 2015)
17. APUA Newsletter - Newsletter Vol. 30 No. 1. New Antibiotic Development: Barriers and Opportunities in 2012. Spellberg, B. http://www.tufts.edu/med/apua/news/news-newsletter-vol-30-no-1-2.shtml (accessed on January 10, 2015)
18. Peláez, F., The historical delivery of antibiotics from microbial natural products – Can history repeat?, Biochemical Pharmacology, 2006, http://www.sciencedirect.com/science/article/pii/S0006295205006611 (accessed on January 10, 2015)
19. So AD, Gupta N, Brahmachari S, et al. Towards new business models for R&D for novel antibiotics. Drug Resistance Updates 2011; 14:88-94. On page 89, "Seventy screens conducted by GlaxoSmithKline (GSK) from 1995 to 2001 (67 HTS, three whole-cell) produced five lead compounds, representing a mere 7% success rate. GSK's experience is corroborated by Pfizer's 6.5% success rate in producing lead compounds (personal communication Paul Miller, Pfizer)."
20. New Business Models for Sustainable Antibiotics, Chatham House report, Outterson K., February 2014 http://www.chathamhouse.org/sites/files/chathamhouse/public/Research/Global%20Health/0214SustainableAntibiotics.pdf (accessed on January 10, 2015)
21. Antibiotics Innovation Funding Mechanism (AIFM), a proposal shortlisted for demonstration project by WHO's EURO region http://keionline.org/node/1832 (accessed on January 10, 2015). A funding mechanism in the AIFM is a special tax levied on the use of the new antibiotics, as a way to replenish the fund for prizes and to monitor and curb drug use.
22. Peláez, F., Op. cit.
23. Committee on Development and Intellectual Property, Fourteenth Session, Geneva, November 10 to 14, 2014. World Intellectual Property Organization, 19 Sept. 2014, http://www.wipo.int/edocs/mdocs/mdocs/en/cdip_14/cdip_14_inf_12.pdf (accessed on January 10, 2015)
24. USA Sept. 18, 2014. Report to the President on combating antibiotic resistance, Executive Office of the President President's Council of Advisors on Science and Technology (PCAST) September 2014 http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf (accessed on January 10, 2015). And, "New Executive Actions to Combat Antibiotic Resistance and Protect Public Health"
25. http://longitudeprize.org/challenge/antibiotics (accessed on January 10, 2015)
26. PCAST, USA Op. cit.
27. Harry T. Dykman, Patent Licensing within The Manufacturer's Aircraft Association (MAA), 46 J. PAT. OFF. SOC'Y 646, 648 (1964)
28. http://www.wipo.int/research/en/ (accessed on January 10, 2015)
29. Global Forum for Health Research, Monitoring Financial Flows for Health Research, MA Burke, SA Matlin, JJ Monot, yearly reports and meetings with the WHO. http://announcementsfiles.cohred.org/gfhr_pub/M.htm (accessed on January 10, 2015).
30. Kristiansen C, America is losing biomedical research leadership to Asia, NIH - Fogarty International Center, Global Health Matters newsletter, January / February 2014 | Volume 13, Issue 1. http://www.fic.nih.gov/News/GlobalHealthMatters/january-february-2014/Pages/spending-investment-biomedical-research-development.aspx (accessed on January 10, 2015).
31. UNCTAD, Technology and Innovation Report 2012, Innovation, Technology and South-South collaboration, Gehl Sampath P,
32. http://www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/ (accessed on January 10, 2015).
33. http://ca-biomed.org/pdf/media-kit/fact-sheets/cbradrugdevelop.pdf (accessed on January 10, 2015).
34. According to the concept of the role of institutions in the expansion of science and discoveries dear to the American Norwegian economic Thorstein Veblen.
35. WHO, Draft global action plan on antimicrobial resistance, 12 Dec. 2014, EB136/20
36. The tripartite collaboration WHO, FAO and OIE are developing standards for the presence of antimicrobial agents and their residues in the environment, especially in water, wastewater and food (including aquatic and terrestrial animal feed).
37. Phage therapy: the Escherichia coli experience, Harald Bruessow, Nestle´s Research Centre, *Microbiology* (2005), 151, 2133–2140. http://mic.sgmjournals.org/content/151/7/2133. (accessed on January 10, 2015)
38. European Union funded research on use of phages (viruses of bacteria) for patients burn wound bacterial infections. http://www.phagoburn.eu/ (accessed on January 10, 2015). Phage therapies are also presently investigated extensively for animal health to

MONITORING, SURVEILLANCE AND NATIONAL PLANS

SURVEILLANCE AND MONITORING OF ANTIMICROBIAL RESISTANCE (AMR)

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Antibiotic resistance is a global problem of increasing significance that takes a costly toll on lives and the health-care economy around the world. It is beyond the ability of any one country to prevent, detect and control antimicrobial resistance (AMR) within its own borders without ongoing engagement of regional and global partners. Challenges to detecting, monitoring and controlling AMR infections are found in all settings and in every country. Improvements are necessary in three areas of surveillance capacity: data collection and data sources, data management, analysis and interpretation; and information reporting, dissemination, communication and use. Focused and targeted international cooperation will be vital to contain and control AMR. A number of ongoing and planned initiatives show a clear path forward to achieve that collaborative success.

Antibiotic resistance is a global problem of increasing significance that takes a costly toll on lives and the health-care economy around the world *(1)*. In May 2014, a resolution passed by the 67th World Health Assembly (WHA) identified antimicrobial resistance (AMR) as "a heavy and growing burden on high-, middle- and low-income countries, requiring urgent action at national, regional and global levels" and called for the development of a draft global action plan to combat antimicrobial resistance to be presented in one year to the 68th WHA *(2)*." In addition to high mortality (multi-drug resistant TB alone killed an estimated 210,000 people *(3)* in 2013), AMR may cost the world's economy as much as 1.6% of global gross domestic product *(4)*.

It is beyond the ability of any one country to prevent, detect and control AMR within its own borders without ongoing engagement of regional and global partners *(5)*. Highly mobile populations, the ease of ever-growing international travel and trade, high density populations, the growth of industrial agricultural practices, environmental changes, continuous pathogen evolution, and increasingly complex health-care treatments have all increased the potential for the emergence and rapid dissemination of new or variant forms of known pathogens, and present an array of new challenges to clinicians, microbiologists and public health officials.

Surveillance and monitoring of antibiotic resistant bacteria is essential for detecting and controlling outbreaks, identifying populations most at risk, designing and evaluating intervention strategies, and focusing the use of scarce resources so that they can be used most efficiently and effectively to prevent illness and save lives *(6, 7)*. However, challenges to detecting, monitoring and controlling AMR infections are found in all settings and in every country.

Awareness of the problem of AMR by medical and veterinary public health officials and clinicians as well as technical capacity for detection and monitoring of these pathogens vary greatly among and within countries. Because AMR can spread widely and rapidly, accurate tracking of infections and resistant strains is of the highest importance. Surveillance data must be comparable – laboratories need to be using valid and reliable testing methods, collection of isolates should be appropriately representative for the purposes of the surveillance activity, and reporting must be complete and consistent from facilities and laboratories which do report. At present, the varied capacity and practices in different countries pose a serious obstacle to the usefulness of international surveillance, particularly from countries with limited resources *(1)*. A coordinated network approach will be a key element to generating AMR data of quality and comparability that would support effective control strategies across countries.

General principles and needs

Surveillance can serve a number of purposes in combating antibiotic resistance. Surveillance serves as an early warning

system for the emergence and spread of new forms of resistance, can provide valuable information about geographic variations in incidence and prevalence of resistant pathogens and identify populations at risk. This information is vital to developing public health interventions, prioritizing resistance problems, and efficiently deploying limited resources to implement those interventions. Surveillance then becomes the tool that is used to evaluate the success of those interventions.

Surveillance programmes should be simple, flexible, representative of populations at risk, provide timely information for situational awareness and decision-making, be acceptable to both the data providers and audiences for the analyzed and interpreted information produced by the system, and assure that data is accurate and reliable, and sustainable over time.

Successful global efforts to establish surveillance for TB, malaria and HIV have demonstrated the utility and value of national and international systems and can be used as blueprints and reference points for developing the necessary components of national and international surveillance for antibiotic resistance. *(1)*

Challenges to implementing effective surveillance

Identifying, tracking and monitoring the emergence and spread of antibiotic-resistant bacteria poses a number of challenges in both higher-income as well as in low- and middle-income countries (LMICs). Accessing reliable, accurate data requires recognition of an infection, adequate culturing and handling of specimens, transportation to a laboratory equipped to perform the appropriate testing and an assurance that such tests can be performed correctly and consistently meet quality control standards. Then, the data must be made available in a form that can be transmitted to a central repository of data, aggregated with data from other reporting sites and analyzed and interpreted. Ideally, clinical patient data would accompany microbiologic data to allow for necessary epidemiology assessment. Finally, the analyzed and interpreted information needs to be disseminated in formats that can be easily understood and applied by diverse audiences for both clinical and public health purposes *(6, 7)*. Barriers to even the most basic types of surveillance systems will clearly exist in settings where the health-care and public health infrastructure is inadequate due to limited resources. A lack of resources may result in gaps at more than one stage in the surveillance process – from the inability to obtain appropriate cultures to constraints on processing and laboratory testing to the lack of effective reporting mechanisms. A paucity of trained professionals, including health-care providers, pharmacists, microbiologists and epidemiologists in LMICs is a particular problem in creating a surveillance infrastructure. The ready over-the-counter availability of antibiotics in many countries, combined with the lack of trained health personnel and laboratory capacity encourages self-treatment and at best empirical treatment, at times with drugs which are counterfeit or adulterated *(8)*. Treatment is most likely to be empirical and syndromic where laboratory facilities are most limited.

Data collection and data sources

Effective surveillance and monitoring starts with identifying reliable data sources and optimizing data collection. Both laboratory data, including at a minimum microbial identification and antibiotic susceptibility, and epidemiologic data, including basic demographic, treatment and outcome data on patients, are needed. Data that are used for surveillance purposes are generally obtained from routine clinical laboratory testing patient records. These data are often collected from hospitals and may not be representative of the actual disease burden in a particular community or country. In addition, laboratory methods are often variable, especially in low-resource settings, and the accuracy and reliability of laboratory data has been questioned, even in developed countries. Specific areas to address include:

- **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. Ongoing evaluation and testing programmes are important activities to maintain and assure laboratory competence. Not all countries will be able to maintain needed laboratory capacity, suggesting a need for the establishment of regional reference centres to support specialized and reference testing.
- **Prioritize which bacteria are most important to track.** For public health purposes, not every form of bacterial resistance can be monitored with the same level of attention. WHO has identified seven resistant pathogens ("bug-drug combinations") as priorities for surveillance and reporting *(11)*. The CDC has identified 18 pathogens of public health concern in the United States and placed those pathogens into three categories

relative to the need for urgent public health action to combat them *(9)*. Each country may have its own set of priority pathogens, but focusing on an agreed-upon set of priority bacteria with specific resistance profiles will help assure that the data necessary to facilitate collaborative global efforts to prevent and control antibiotic resistance can be integrated and that data collection is sustainable.

- **Prioritize and standardize epidemiologic data collection.** Not all data is of equal value in assessing risks and designing and evaluating interventions to prevent the emergence and spread of bacterial resistance. In areas where electronic data may be available, being parsimonious in selecting key variables to monitor will simplify data management and analyses and enhance the timeliness of reporting. In settings where paper records need to be reviewed and tallied, minimizing the collection burden to those data most relevant for the specific needs of the prevention programme will similarly facilitate sustainability of an efficient and effective programme.
- **Harmonization of standards for identification and susceptibility testing.** Laboratories need to be using common standards and criteria for identification of bacterial resistance. Aggregation of data from different laboratories within a country and comparison of data between countries is vital for effective surveillance but is hampered if definitions or laboratory standards vary. However, due to variations in health systems and regulatory environments, achieving fully harmonized standards can be a challenge even in higher-income countries.
- **Increasing the use of laboratory testing for resistance in clinical specimens.** In order to identify resistant bacteria in the laboratory, doctors and health-care workers must correctly obtain necessary clinical specimens and send them to a laboratory which can perform the testing. The likelihood of this happening varies tremendously among clinical settings, between lower-resource and higher-resource settings and among clinical syndromes. For example, routine susceptibility testing for *Neisseria gonorrhoeae*, the bacteria causing gonorrhea, is rarely done in clinical settings even in higher resource environments. Maximizing the appropriate culturing of clinical specimens will greatly improve the representativeness of surveillance data.
- **Promoting and disseminating innovation.** Developing and promoting the use of new, low-cost technologies to improve laboratory and surveillance capacity to detect, identify and characterize antimicrobial resistance threats. Such technologies can potentially provide comparable information across national and regional boundaries and may include rapid diagnostic tests, kits, and techniques for detecting drug resistant pathogens that can be utilized in developing countries, rural areas, and settings where routine susceptibility testing would normally be unavailable or unreliable. The GeneXpert and related technologies, and the manner in which they have been applied to TB surveillance and control, is one example of the potential value of such innovative approaches *(11)*.

Data management, analysis and interpretation

Within each country, data on antibiotic resistance needs to be centrally stored, managed, analyzed and interpreted to provide the information that will be used for public health purposes. Data needs to be transmitted from the source – the laboratory and the clinical setting where patient information is kept – to a central site and the data may need to be translated into a standard electronic format if it has not been collected and transmitted in that format. The data needs to be analyzed to fulfill the key objectives of antibiotic resistance surveillance – tracking the incidence and prevalence of high-priority pathogens by person, place and time – and making those data available in an easily interpretable form for quick public action as well as for decision-makers to plan medium-term and long-term strategy. Analyzing and interpreting antibiotic resistance data is particularly challenging because of the many different types of bacteria involved and their diverse epidemiology, the variety of different resistance mechanisms and the complexity of integrating and interpreting the clinical, epidemiologic and laboratory data. Focusing on a smaller number of priority resistance threats helps but does not fully solve these difficulties. Specific areas to address include:

- **Taking advantage of rapid technological change to bolster infrastructure for data management and analysis.** The increasing availability of wireless cellphone networks and the enhanced capacities of handheld devices, including smartphones and tablets, offer opportunities to revolutionize data collection, transmission, management and analysis. Cell phone networks have been incorporated successfully in public health initiatives in a number of settings in low-resource countries. It would be good to have the data encrypted if possible to protect confidentiality *(12, 13)*.
- **Increasing the availability of trained personnel to**

manage, analyze and interpret data. Distance learning, on-site technical assistance, training courses and mentoring are all methods which have proven successful in a variety of settings. Collaborations involving individual countries, international partners, and donors are needed to increase capacity for AMR surveillance, to include data collection, analysis and interpretation, and reporting. Also, working with ministries of health and utilizing fellows or residents from the Field Epidemiology Training Program would be helpful to address the availability of trained personnel.

- **Setting up standardized, interoperable IT platforms.** Simplicity is also the key here. The more complicated the software and greater the number of variables involved, the harder it will be to establish easy data sharing and aggregation across countries and regions.

Information reporting, dissemination, communication and use

The value of information derived from public health surveillance depends on the uses to which it is put. Surveillance information needs to be made available to a variety of audiences in ways that those audiences can most readily understand and employ for their needs and purposes. Public officials use surveillance for situational awareness, to target prevention and control efforts where they are most needed, design and evaluate intervention strategies and monitor the success of public health efforts. Of particular importance in LMICs is the need to focus limited resources on the populations most at risk and thus maximize the effectiveness of every public health investment. Health professionals need to know local resistance patterns to make the best antibiotic choices in clinical settings. Decision-makers and legislators need to understand the nature, scope and magnitude of the antibiotic resistance problems within their scope or responsibility or jurisdictions so that they may be more likely to support public health efforts to combat those problems. The general public, as consumers of health care and members of communities affected by resistance problems need to receive information about resistance to enable their participation in prevention and control efforts, such as receiving immunizations and reducing demand for unnecessary antibiotics.

Specific areas to address include:

- **Strengthen systems for international real-time communication of critical health events.** This is consistent with efforts to promote the fulfilment of countries' obligations associated with the International Health Regulations *(14, 15)*. It can also build upon efforts initiated by the Transatlantic Task Force on Antimicrobial Resistance as part of collaborations between the European Union and the United States *(10)*.
- **Leverage and build upon existing international partnerships.** A number of effective global partnerships under the auspices of the United Nations, such as the Codex Alimentarius *(16)* as a collaboration between WHO and the Food and Agriculture Organization (FAO), as well as other organizations such as the World Organisation for Animal Health (OIE) *(17)*, and the Global Fund demonstrate the effectiveness of cooperative efforts to address specific health problems. Many of these groups and others are already engaged in combating antimicrobial resistance. Continuing to promote shared goals and objectives among such groups will increase the likelihood of successful outcomes for the many projects and initiatives underway and planned.
- **Education and information dissemination to the public.** AMR is one of the most complex problems in all of public health and medicine. The threat posed by the emergence and spread of "superbugs" is less well understood than it is for some epidemic and pandemic diseases which spread widely in communities at risk. Health-care professionals around the world often lack the information they need to fully understand the scope and breadth of the problem in their own localities or countries or the interconnectedness of the rising global pandemic of antimicrobial resistance. Communicating the basic biologic and microbiologic facts more broadly and with greater clarity and dispelling misinformation on this topic is a vital step in accelerating and sustaining the permanent global response that will be necessary to contain this threat.

Examples of current activities

A number of activities are underway which address the need for enhancing global surveillance of antimicrobial resistance and offer examples of the wide array of potential solutions to the challenges of tracking and monitoring resistant pathogens.

The recently announced Global Health Security Agenda *(19)* sets forth a series of "Action Packages" to further preparedness and response to infectious disease threats. Several of these Action Packages address needs for combating antimicrobial resistance. One set of activities, specifically targeting antimicrobial resistance *(20)* calls for collaboration among the World Health Organization, the FAO and the OIE to:

"develop an integrated and global package of activities to

combat antimicrobial resistance, spanning human, animal, agricultural, food and environmental aspects (i.e. a one-health approach), including: a) Each country has its own national comprehensive plan to combat antimicrobial resistance; b) Strengthen surveillance and laboratory capacity at the national and international level following agreed international standards developed in the framework of the Global Action plan, considering existing standards and; c) Improved conservation of existing treatments and collaboration to support the sustainable development of new antibiotics, alternative treatments, preventive measures and rapid, point-of-care diagnostics, including systems to preserve new antibiotics."

This effort will also engage countries in "twinning" *(21)* activities, promoting cooperation between higher income and lower and middle income countries. Related packages call for improvements in laboratory capacity and real-time surveillance.

Pilot projects demonstrating the value of international collaboration, which serve as models for implementation of the GHSA Action Packages have been conducted in Uganda *(22)* and Vietnam *(23)*. In both countries, an emphasis on strengthening laboratory capacity and increasing the timeliness of reporting of specified health events showed how strengthening public health infrastructures are necessary and potentially achievable goals. Although not directly aimed at AMR, except for multidrug resistant tuberculosis on Uganda, the principles demonstrated in these projects are directly applicable to the needs of the international network that will be required for detection, prevention and control of the spread of resistant pathogens.

Other examples of successful programmes to enhance laboratory capacity which can serve as models for work in a variety of settings include projects in Guatemala *(24)*, Nepal *(25)*, China (26), and six countries in the Middle East and Central Asia *(27)*.

In addition, CDC's Global Disease Detection Program *(28)*, conducting programmes in 10 countries around the world to develop and strengthen the global capacity to address infectious disease threats. Selected examples of these efforts include:

- In Bangladesh, studying antimicrobial resistance pathogens from patients with diarrheal disease and in environmental samples of river water and hospital effluents.
- In Kazakhstan, collaborating with WHO to produce an antimicrobial resistance toolkit for low- and middle-income countries conduct situation analyses of antimicrobial resistance and its determinants.
- In India, is working with the national Integrated Disease Surveillance Program to initiate routine laboratory surveillance for acute diarrheal disease pathogens (*Salmonella*, *Shigella*, and *Vibrio species*) in two states.
- In Guatemala, studying antimicrobial resistance in blood culture isolates for six key patterns: methicillin-resistant *S. aureus*, vancomycin resistant-enterococci; multi-drug resistant *Acinetobacter*; cephalosporin-resistant *Klebsiella*; and *carbapenem*-resistant *Klebsiella* and *E. coli*.
- In Egypt, working with surveillance programmes for health-care-associated infections and antimicrobial resistance in acute care hospitals for three pathogens of the WHO pathogens of concern: *Escherichia coli* (resistance to 3rd generation cephalosporins and fluoroquinolones); *Klebsiella pneumonia* (resistance to 3rd generation cephalosporins and carbapenems); and methicillin-resistant *Staphylococcus aureus*.

Summary

Efforts to prevent the spread of antimicrobial-resistant bacteria build on the foundation of proven public health strategies: immunization, infection control, protecting the food supply, and preventing person-to-person spread through screening, treatment and education. All of these strategies rely on accurate and reliable surveillance data. The recently released United States National Strategy for Combating Antibiotic-Resistant Bacteria *(5)* has as one of five goals to "Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development". Along with support for the WHO Global Action Plan and the Global Health Security Agenda, this clear recognition of and commitment to international collaboration and cooperation is a cause for optimism in the fight against this ever-growing world-wide threat of antimicrobial resistance. •

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

References

1. World Health Organization. . Antimicrobial Resistance. Global Report on Surveillance. Geneva 2014. http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1 (accessed December 1, 2014)
2. World Health Organization. Resolutions of the 67th World Health Assembly, WHA 67.25. http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R25-en.pdf?ua=1 (accessed December 1, 2014)
3. World Health Organization. WHO Global Tuberculosis Report 2014. http://www.who.int/tb/publications/factsheet_global.pdf (accessed December 1, 2014
4. World Health Organization. Global action plan on antimicrobial resistance Draft for consultation with Member States October 2014 http://www.who.int/drugresistance/AMR_DRAFT_GAP_1_Oct_2014_for_MS_consultation.pdf?ua=1 (accessed December 1, 2014)
5. National Strategy for Combating Antibiotic Resistant Bacteria, September 2014 http://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf (accessed December 1, 2014)
6. O'Brien TF, Stelling J. Integrated Multilevel Surveillance of the World's Infecting Microbes and Their Resistance to Antimicrobial Agents. *Clin Microbiol Rev*. 2011 Apr;24(2):281-95.
7. Grundmann H, Klugman KP, Walsh T, Ramon-Pardo P, Sigauque B, Khan W, et al. A framework for global surveillance of antibiotic resistance. *Drug resistance updates: reviews and commentaries in antimicrobial and anticancer chemotherapy*. 2011 Apr;14(2):79-87.
8. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. *The Lancet Infectious diseases*. 2013 Dec;13(12):1057-98..
9. Centers for Disease Control and Prevention. Antibiotic Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/index.html (accessed December 1, 2014)
10. Transatlantic Taskforce on Antimicrobial Resistance: Progress report May 2014 http://www.cdc.gov/drugresistance/tatfar/index.html (accessed December 1, 2014)
11. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement. Geneva, Switzerland: World Health Organization; 2011. (http://apps.who.int/iris/handle/10665/44586, accessed December 8, 2014)
12. Rosewell A, Ropa B, Randall H, Dagina R, Hurim S, Bieb S, et al. Mobile phone-based syndromic surveillance system, Papua New Guinea. Emerg Infect Dis. 2013 Nov;19(11):1811-8.
13. Nonaka D, Pongvongsa T, Nishimoto F, Nansounthavong P, Hongwei J, Vongsouvanh A, et al. Successful mobile phone network-based approach to integration of the health care system in rural Laos: strengthening lay health worker performance. *Rural and remote health*. 2014;14:2588.
14. Ijaz K, Kasowski E, Arthur RR, Angulo FJ, Dowell SF. International Health Regulations--what gets measured gets done. Emerg Infect Dis. 2012 Jul;18(7):1054-7. PubMed PMID: 22709593. Pubmed Central PMCID: PMC3376826. Epub 2012/06/20. eng.
15. World Health Organization. International Health Regulations, 2005. 2nd edition. http://whqlibdoc.who.int/publications/2008/9789241580410_eng.pdf?ua=1 (accessed December 1, 2014)
16. http://www.codexalimentarius.org/ (accessed December 1, 2014)
17. http://www.oie.int/ (accessed December 1, 2014)
18. http://www.theglobalfund.org/en/ (accessed December 1, 2014)

1.9 http://www.cdc.gov/globalhealth/security/pdf/ghsa-action-packages_24-september-2014.pdf (accessed December 1, 2014)

20. http://www.cdc.gov/globalhealth/security/antimicrobial_resistance.htm (accessed December 1, 2014)
21. Erlacher-Vindel E1, Brockner GK, Vallat B The OIE concept of laboratory twinning. Dev Biol (Basel). 2007;128:115-9.
22. MMWR 2014;63:73-76
23. MMWR 2014;63:77-80
24. Benoit SR, Lopez B, Arvelo W, Henao O, Parsons MB, Reyes L, et al. Burden of laboratory-confirmed Campylobacter infections in Guatemala 2008-2012: results from a facility-based surveillance system. *Journal of epidemiology and global health*. 2014 Mar;4(1):51-9.
25. Malla S, Dumre SP, Shakya G, Kansakar P, Rai B, Hossain A, et al. The challenges and successes of implementing a sustainable antimicrobial resistance surveillance programme in Nepal. *BMC public health*. 2014;14:269. .
26. Shengjie Yi, Jing Xie, Nan Liu , et al Emergence and Prevalence of Non-H2S-Producing Salmonella enterica Serovar Senftenberg Isolates Belonging to Novel Sequence Type 1751 in China *J. Clin. Microbiol.* July 2014 vol. 52 no. 7 2557-2565
27. Rahman BA, Wasfy MO, Maksoud MA, Hanna N, Dueger E, House B. Multi-drug resistance and reduced susceptibility to ciprofloxacin among Salmonella enterica serovar Typhi isolates from the Middle East and Central Asia. New Microbes and New Infections 2014;2(4):88-92.
28. http://www.cdc.gov/globalhealth/gdder/gdd/default.htm (accessed December 1, 2014)

ANTIMICROBIAL RESISTANCE CONTROL IN ASIA

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Antimicrobial resistance (AMR) is a very critical health-care, social and economic problem worldwide. In particular, the Asian region shows the seriousness of the AMR problem due to its high prevalence rates of AMR in major bacterial pathogens and lack of effective efforts to combat AMR. Although AMR should be considered the national priority, it has not been recognized as an important health-care issue in most Asian countries. Given the clinical and socioeconomic impact of AMR, comprehensive strategies and action plans based on the national efforts and international collaboration are urgently required to control and prevent AMR in the region.

Treatment of infectious diseases is becoming more difficult due to widespread emergence of antimicrobial resistance (AMR) in major pathogens, particularly in bacteria, which results in treatment failure, prolonged illness, disability and greater risk of death. AMR is considered responsible annually for >23,000 deaths in the United States, 25,000 deaths in the European Union and >38,000 deaths in Thailand *(1)*. AMR can spread rapidly between patients, regions, and countries. Recently, New Delhi metallo-β-lactamase-1 (NDM-1)-producing bacteria which originated from India in 2008 have spread throughout the world *(2, 3)*. Since AMR can spread across the borders, this is not a local problem but an international issue. Furthermore, AMR can cause enormous economic loss. Overall societal costs for AMR are estimated to be US$ 35 billion as direct and indirect cost in the United States, € 1.5 billion in the European Union, and US$ 1.3 billion in Thailand *(1)*. Given that most of the low- and middle-income countries which might have even more serious problems of antibiotic abuse and AMR do not have the data. The global impact of AMR on clinical, social, and economic aspects is unprecedented.

Current situation of AMR in the Asian region

Based on the published reports, the Asian region is evidently an epicenter of AMR globally with the highest prevalence of resistance in major bacterial pathogens (Table 1) *(4-8)*. Multi-drug-resistant pathogens have been widely disseminated both in hospitals and in the communities in many Asian countries. For instance, *Streptococcus pneumoniae* which is the most common pathogen of community-acquired pneumonia, shows an extremely high prevalence rate to macrolide antibiotics in Asian countries (Fig. 1) *(5, 9-12)*. Unusually high prevalence rates of AMR in major bacterial pathogens in Asian countries are affected by several factors.

Figure 1: Prevalence of *Streptococcus pneumoniae* resistant to macrolide in Korea, Taiwan, and Vietnam (2008–2009); USA (2007–2009); Canada (2008); Belgium (2007–2009); and Germany (2008)

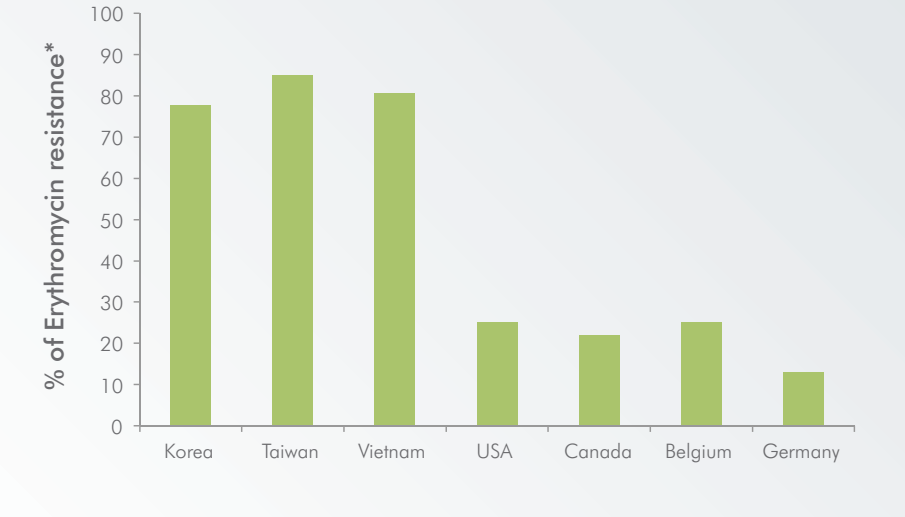


Figure 2: **Current status of Asian Network for Surveillance of Resistant Pathogens (ANSORP)**

The most important reason is antibiotic abuse and misuse both in the clinical practice and in animal husbandry in Asian countries. Although antibiotics are universally abused throughout the world, these special therapeutic agents are very frequently and widely abused in the Asian region where antibiotics can be purchased as over-the-counter drugs in many countries. Counterfeit antibiotics are another inducer of AMR: 78% of counterfeit antibiotics are made in Southeast Asian countries where 44% of these drugs are consumed *(13)*. Antibiotics are also widely abused in animal husbandry in many Asian countries. In China, the use of antibiotics for disease treatment and as growth promoters in animals is unmonitored which leads to the overuse of antibiotics and may pose a risk to human health worldwide due to the scale of the livestock industry and the largest volume of antibiotics is produced and consumed in China *(14)*. Once AMR emerges, these resistant pathogens can easily and rapidly spread unless effective control measures are implemented. However, inadequate health-care infrastructures and infection control programmes in most of the low- and middle-income Asian countries prevent effective control and prevention of the emergence and spread of AMR.

Strategies and action plans to control AMR in Asia

International efforts to combat AMR in Asia

International efforts to perform surveillance of AMR and to prepare the international strategies have been pursued only by limited groups and organizations in the Asian region despite the critical situation of AMR. In 1996, the Asian Network for Surveillance of Resistant Pathogens (ANSORP) was organized by Asian physicians (organizer: Professor Jae-Hoon Song, Korea) to perform international surveillance of AMR in the Asian region (www.ansorp.org). ANSORP has collaborated internationally to identify the problems of AMR in major bacterial pathogens by activating 113 hospitals in 65 cities in 14 Asian countries/areas (Fig. 2). In order to support the ANSORP activities and other programmes, the Asia Pacific Foundation for Infectious Diseases (APFID) was founded in 1999 which organizes and

Table 1: **Prevalence of resistance in major bacterial pathogens**

Pathogen	Disease	Antibiotic	Resistance[1] %	Focus area
Community				
Streptococcus pneumoniae	CAP[2]	Macrolide	73%	Asia
Escherichia coli	UTI[3]	3rd cephalosporins	95%	Asia
Salmonella Typhi	Enteric infection	Ciprofloxacin	84%	Asia
Hospital				
Staphylococcus aureus	HAP[4], bacteremia	Methicillin	82%	Asia
E. coli	HAP, bacteremia	Ciprofloxacin	96%	Asia
Klebsiella pneumoniae	HAP, bacteremia	3rd cephalosporins	81%	Asia
Pseudomonas aeruginosa	HAP	Carbapenem	30%	Asia
Acinetobacter baumanii	HAP	Carbapenem	68%	Asia

[1] *Highest reported prevalence of resistance to prototype antibiotics*
[2] *CAP ; Community-acquired pneumonia*
[3] *UTI ; Urinary tract infection*
[4] *HAP ; Hospital-acquired pneumonia*

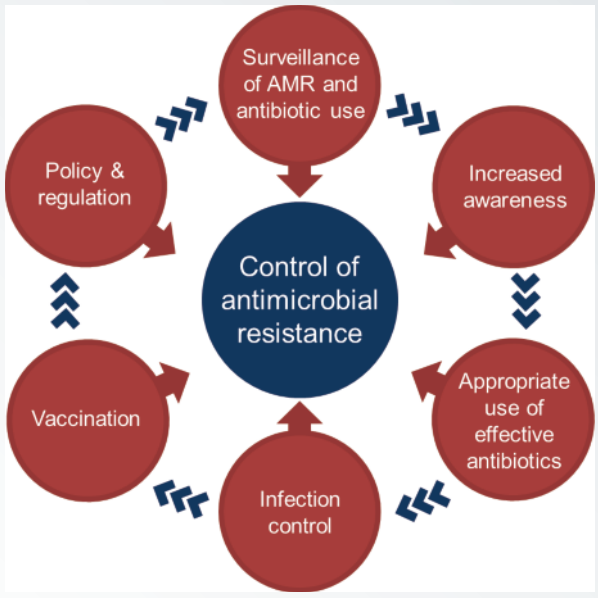
supports various international efforts to combat infectious disease threats, particularly infections caused by drug-resistant bacteria in the Asia-Pacific region. APFID has been operating four major international programmes; international surveillance of AMR by ANSORP since 1996, international communication of scientific issues by ISAAR (International Symposium on Antimicrobial Agents and Resistance) since 1997, international microbial collection by ABB (Asian Bacterial Bank) since 1996, and international campaign for AMR by Campaign 4 since 2014. APFID and ANSORP have been actively collaborating with the World Health Organization (WHO), Asia Pacific Economic Cooperation (APEC), regional academic societies and health-care organizations in individual countries to prepare international strategies and action plans as well as to establish a platform for effective control and prevention of AMR in the region.

Strategies and action plans for AMR control in Asia

APFID has proposed the international strategies to control and prevent AMR in the Asia-Pacific region in collaboration with APEC as the "APEC guideline to tackle antimicrobial resistance in the Asia-Pacific region" in 2014 *(15)*. The guidelines includes six strategic action plans (Fig. 3):

- Strengthen national and international surveillance activities to identify the problems and issues of AMR and monitoring of antibiotic uses.
- Improve awareness of AMR through campaigns, education and training.

Figure 3: **Six strategic action plans to control and prevent antimicrobial resistance in Asia**



Surveillance of AMR tracks changes in microbial populations, permits the early detection of resistant strains of public health importance, and supports the prompt notification and investigation of outbreaks

- Promote appropriate uses of antimicrobial agents in human and animal husbandry.
- Strengthen hospital infection control and prevention.
- Promote vaccination programmes to reduce the incidence of bacterial infections.
- Strengthen the national infrastructures and international efforts to combat AMR.

Action plan 1: Strengthen the surveillance of AMR and antibiotics use

Surveillance of AMR is essential for identifying current problems by providing information on the magnitude and trends in AMR. Surveillance of AMR tracks changes in microbial populations, permits the early detection of resistant strains of public health importance, and supports the prompt notification and investigation of outbreaks. Surveillance findings are needed to inform clinical therapy decisions and to guide policy recommendations. First of all, the national surveillance of AMR should be urgently established in every country in the region. The microbiology laboratory procedures, data collection, and data reporting should be qualified and standardized. Moreover, the international surveillance of AMR in the Asian region should be established because AMR can spread across the borders. ANSORP has been contributing to collecting and reporting the AMR in the Asian region through international collaboration for the past two decades *(5, 6, 16, 17)*. Surveillance is also needed for monitoring the effect of interventions. Monitoring of antibiotic use is also very important because inappropriate taking of antibiotics is the most basic driving force for the emergence of AMR. Given that Asian countries have a very serious problem with antibiotic abuse/misuse not only in patients but also in animal husbandry as well as

the issues of counterfeit antibiotics, monitoring of antibiotic use is very crucial for proper control and prevention of AMR.

Action plan 2: Improve awareness of AMR

Lack of awareness and knowledge about AMR prevents Asian countries preparing comprehensive strategies to combat AMR. Also, it is one of the main reasons for the inappropriate use of antibiotics. A recent survey in Asia showed that most Asian countries do not have adequate knowledge about AMR or the appropriate use of antibiotics among the general public and health-care professionals *(18, 19)*. However, there has been no adequate educational and campaigning activities for this issue in most Asian countries. APFID is preparing the first international campaign programme – "Campaign 4" – to improve awareness of AMR in the Asian region. Campaign 4 is aiming to deliver four key messages to four major target groups:

- 1) Take prescribed antibiotics only;
- 2) Take antibiotics exactly as prescribed;
- 3) Do not take left-over antibiotics; and
- 4) Do not take antibiotics for the common cold.

The four target groups are the general public (patients), health-care professionals (prescribers), the pharmaceutical industry (providers) and health-care policy-makers. Campaign 4 will be introduced to Asian countries soon using videoclips, leaflets, educational conferences/symposia, media promotions, and e-learning programmes (www.campaign4.org). This campaign will be introduced to Asian countries in collaboration with APEC, WHO and local academic societies as well as public health systems in individual countries. International conferences or meetings are also effective in providing updated information on AMR in the region. ISAAR (www.isaar.org) has been working to disseminate the state-of-the-art knowledge and information on AMR and emerging infectious disease threats biennially since 1997.

Given the rapid increases in extensively-drug-resistant (XDR) or pan drug-resistant (PDR) pathogens throughout the world, the development of new antibiotics that can be effective against these pathogens is critically required

Action plan 3: Promote appropriate uses of antimicrobial agents

Because antibiotic abuse or misuse is the most important factor in the emergence of AMR, appropriate use of antibiotics is the first and basic step for prevention and control of AMR. Given the dearth of new antibiotics in recent decades, appropriate use of the current antibiotics is of the utmost importance. Prudent use of antibiotics should be achieved both at the hospital level and at the national level. In the hospitals, antimicrobial stewardship programmes should be implemented into clinical practice. At the national level, collection of data on the use of antibiotics in humans and animal husbandry, legal control of purchasing and prescribing antibiotics, and governmental regulation to ensure production, licensing, distribution and quality assurance of antibiotics are crucial in Asian countries.

Given the rapid increases in extensively-drug-resistant (XDR) or pan drug-resistant (PDR) pathogens throughout the world, the development of new antibiotics that can be effective against these pathogens is critically required. Since the discovery of new antibiotics is not a major interest for most pharmaceutical companies, however, it should be solved through international collaboration by political, scientific and industrial systems.

Action plan 4: Strengthen hospital infection control

Health-care-associated infections, often caused by antimicrobial resistant bacteria, are an important cause of increased mortality and morbidity. Infection control and prevention in health-care facilities is an effective way to curb AMR by preventing the spread of resistant bacteria within the hospital. Hospital infection control is important not only for the control of AMR in hospitals but also to prevent the emergence of AMR in the community because resistant pathogens can spread out from the hospital to the community. Infection control programmes in health-care facilities in the Asian region should be improved by establishing a secure infrastructure consisting of infection control professionals, continuous support by the hospital leadership, adequate support from the clinical microbiology laboratory and multifaceted education and reinforcement of policies. The antimicrobial stewardship programme (ASP) is another critical component of hospital infection control programmes for preventing the emergence of AMR in hospitals.

Action plan 5: Promote vaccination against bacterial infections

With growing burden of AMR worldwide, fewer antibiotic options are left against resistant pathogens. Preventing the

Given that most Asian countries have serious problems with AMR but weak infrastructures and inadequate responses to meet this threat, AMR should be considered even more important for this region and be urgently managed

occurrence of infection by vaccination would eliminate the need for antibiotic use and can reduce the risk of emerging AMR in bacterial pathogens. Currently, vaccines have been developed for various bacterial pathogens including typhoid fever, cholera, tuberculosis, diphtheria, tetanus, pertussis, *S. pneumoniae*, *Haemophilus influenzae* type b and *meningococci*. Vaccines targeting MDR pathogens such as *S. aureus or P. aeruginosa* are also being developed *(20)*. Among these bacterial vaccines, pneumococcal conjugate vaccine (PCV) is the most representative example of vaccine that can reduce the prevalence of AMR in *S. pneumoniae* by reducing the incidence of pneumococcal infections. Therefore, national and international efforts should be exerted to promote the vaccination programmes available against bacterial infections.

Action plan 6: Strengthen the national infrastructures and international efforts

Control of AMR should be a "national priority" since AMR is a more serious health-care issue than any other single infectious disease with regard to the clinical and economic impact. Given that most Asian countries have serious problems with AMR but weak infrastructures and inadequate responses to meet this threat, AMR should be considered even more important for this region and be urgently managed. National policies and action plans for control of AMR should be based on a multidisciplinary approach consisting of medical, legal, social, economic and public measures. The most important national policies are establishing relevant policies and regulations for production, quality control, circulation and use of antibiotics, nationwide surveillance of AMR, evaluation of the clinical and economic impact of AMR, and public implementation of various interventional measures. One of the most important policies to control antibiotic abuse is the separation of prescribing from dispensing antibiotics by law, which can prevent the general public purchasing over-the-counter antibiotics without a doctor's prescription. Antibiotic uses in animal husbandry should also be monitored and regulated by appropriate regulations. In addition to national efforts, international collaboration is also crucial with regard to international surveillance, improving awareness, prevention of counterfeit drugs, development of new antibiotics, and exchanges of information. In the Asia region, private organizations such as APFID/ANSORP, public health-care systems such as the Center for Disease Control and Prevention (CDC) or ministry of health in individual countries and international organizations such as WHO (WHO Western Pacific Region, WPRO and WHO South-East Asian Region (SEARO) or APEC should collaborate to create effective control and prevention of AMR in the region. Given that many Asian countries do not have adequate financial and human resources to improve their health-care infrastructures to control AMR, it would be important in the Asian region to establish an international coalition to combat AMR.

Conclusion

Given a growing crisis of AMR worldwide, particularly in the Asian region, strenuous efforts to tackle AMR should be urgently implemented through international and multisectoral collaboration. This is very crucial because effective prevention and control of AMR can be achieved only by multifaceted international collaborations based on strong national and international initiatives. The six major action plans to control and prevent AMR in the Asian region can provide Asian countries with the guide to establishing the strategies to address the growing threats of AMR and can contribute to reducing the economic and clinical burden of AMR in the Asian region. •

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References

1. Global Risks 2013 Eighth Edition. Geneva, Switzerland: World Economic Forum, 2013.
2. Kumarasamy KK1, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, Chaudhary U, Doumith M, Giske CG, Irfan S, Krishnan P, Kumar AV, Maharjan S, Mushtaq S, Noorie T, Paterson DL, Pearson A, Perry C, Pike R, Rao B, Ray U, Sarma JB, Sharma M, Sheridan E, Thirunarayan MA, Turton J, Upadhyay S, Warner M, Welfare W, Livermore DM, Woodford N. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis.* 10(9):597-602, 2010.
3. Berrazeg M, Diene S, Medjahed L, Parola P, Drissi M, Raoult D, Rolain J. New Delhi Metallo-beta-lactamase around the world: an eReview using Google Maps. *Euro Surveill.* 19(20), 2014.
4. Antimicrobial resistance : Global report on surveillance. Geneva, Switzerland: World Health Organization, 2014.
5. Kim SH, Song JH, Chung DR, Thamlikitkul V, Yang Y, Wang H, Lu M, So TM, Hsueh PR, Yasin RM, Carlos CC, Pham HV, Lalitha MK, Shimono N, Perera J, Shibl AM, Baek JY, Kang CI, Ko KS, Peck KR; ANSORP Study Group. Changing trends in antimicrobial resistance and serotypes of Streptococcus pneumoniae isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *Antimicrob Agents Chemother.* 56(3):1418-1426, 2012.
6. Chung DR, Song JH, Kim SH, Thamlikitkul V, Huang SG, Wang H, So TM, Yasin RM, Hsueh PR, Carlos CC, Hsu LY, Buntaran L, Lalitha MK, Kim MJ, Choi JY, Kim SI, Ko KS, Kang CI, Peck KR; Asian Network for Surveillance of Resistant Pathogens Study Group. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. *Am J Respir Crit Care Med.* 184(12):1409-1417, 2011.
7. Singhal L, Gupta PK, Kale P, Gautam V, Ray P. Trends in antimicrobial susceptibility of Salmonella Typhi from North India (2001-2012). *Indian J Med Microbiol.* 32(2):149-152, 2014.
8. Kang CI, Song JH. Antimicrobial resistance in Asia: current epidemiology and clinical implications. *Infect Chemother.* 45(1):22-31, 2013
9. Link-Gelles R, Thomas A, Lynfield R, Petit S, Schaffner W, Harrison L, Farley MM, Aragon D, Nicols M, Kirley PD, Zansky S, Jorgensen J, Juni BA, Jackson D, Moore MR, Lipsitch M. Geographic and temporal trends in antimicrobial nonsusceptibility in Streptococcus pneumoniae in the post-vaccine era in the United States. *J Infect Dis.* 208(8):1266-1273, 2013.
10. Wierzbowski AK, Karlowsky JA, Adam HJ, Nichol KA, Hoban DJ, Zhanel GG; Canadian Antimicrobial Resistance Alliance. Evolution and molecular characterization of macrolide-resistant Streptococcus pneumoniae in Canada between 1998 and 2008. *J Antimicrob Chemother.* 69(1):59-66, 2014.
11. Lismond A, Carbonnelle S, Verhaegen J, Schatt P, De Bel A, Jordens P, Jacobs F, Dediste A, Verschuren F, Huang TD, Tulkens PM, Glupczynski Y, Van Bambeke F. Antimicrobial susceptibility of Streptococcus pneumoniae isolates from vaccinated and non-vaccinated patients with a clinically confirmed diagnosis of community-acquired pneumonia in Belgium. *Int J Antimicrob Agents.* 39(3):208-216, 2012.
12. Imöhl M, Reinert RR, Mutscher C, van der Linden M. Macrolide susceptibility and serotype specific macrolide resistance of invasive isolates of Streptococcus pneumoniae in Germany from 1992 to 2008. *BMC Microbiol.* 10:299, 2010.
13. Delepierre A, Gayot A, Carpentier A. Update on counterfeit antibiotics worldwide; public health risks. *Med Mal Infect.* 42(6):247-255, 2012.
14. Zhu YG, Johnson TA, Su JQ, Qiao M, Guo GX, Stedtfeld RD, Hashsham SA, Tiedje JM. Diverse and abundant antibiotic resistance genes in Chinese swine farms. *Proc Natl Acad Sci* USA. 110(9):3435-3440, 2013.
15. APEC guideline to tackle antimicrobial resistance in the Asia-Pacific region. Seoul, Korea: Asia Pacific Economic Cooperation (APEC), 2014.
16. Song JH, Hsueh PR, Chung DR, Ko KS, Kang CI, Peck KR, Yeom JS, Kim SW, Chang HH, Kim YS, Jung SI, Son JS, So TM, Lalitha MK, Yang Y, Huang SG, Wang H, Lu Q, Carlos CC, Perera JA, Chiu CH, Liu JW, Chongthaleong A, Thamlikitkul V, Van PH; ANSORP Study Group. Spread of methicillin-resistant Staphylococcus aureus between the community and the hospitals in Asian countries: an ANSORP study. *J Antimicrob Chemother.* 66(5):1061-1069, 2011.
17. Song JH, Lee NY, Ichiyama S, Yoshida R, Hirakata Y, Fu W, Chongthaleong A, Aswapokee N, Chiu CH, Lalitha MK, Thomas K, Perera J, Yee TT, Jamal F, Warsa UC, Vinh BX, Jacobs MR, Appelbaum PC, Pai CH. Spread of drug-resistant Streptococcus pneumoniae in Asian countries. *Clin Infect Dis.* 28(6):1206-1211, 1999
18. Proceedings of the 1st APEC Expert Forum for "International initiatives to control antimicrobial resistance in the Asia-Pacific region". Seoul, Korea: APEC, 2011.
19. Ganguly NK, Arora NK, Chandy SJ, Fairoze MN, Gill JP, Gupta U, Hossain S, Joglekar S, Joshi PC, Kakkar M, Kotwani A, Rattan A, Sudarshan H, Thomas K, Wattal C, Easton A, Laxminarayan R; Global Antibiotic Resistance Partnership (GARP) - India Working Group. Rationalizing antibiotic use to limit antibiotic resistance in India. *Indian J Med Res.* 134:281-294, 2011.
20. Medicines in Development for Vaccines : 2012 Report. Washington, DC, USA: Pharmaceutical Research and Manufacturers of America (PhRMA), 2012.

THE ACTIONS OF CHINA IN CONTAINING ANTIMICROBIAL RESISTANCE

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Bacterial resistance is a serious problem in China. In 2011, the Chinese government began a three-year special campaign for rational antibiotic use centred on the "Administrative Regulations for the Clinical Use of Antibiotics", which integrated successful domestic and international experiences and defined all aspects of antibiotic use in hospitals. The regulations outline the roles, responsibilities and liabilities of health administrative authorities, medical institutions, hospital task forces and all categories of health-care professionals in detail. It also proposed antibiotic stewardship as a basic management concept and asked medical institutions to build professional teams, implement staff training, and establish and improve the technological systems supporting rational antibiotics use. Some indicators were defined and targets set for institutions. Surveillance from tertiary hospitals between 2010 and 2012 showed that the proportion of outpatients receiving prescriptions for antibiotics decreased from 22% to 14.7%, and that of inpatients decreased from 68.9% to 54%, and the use of antibiotic prophylaxis in surgical procedures decreased from 95% to 44.6%. Massive governmental effort and regulatory support could improve antibiotic use in a large country like China in a relatively short time.

Bacterial resistance is a serious problem in China *(1)*. Surveillance data show that the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in clinical isolates in tertiary hospitals is approximately 50% and that more than 80% of *S. aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* were resistant to macrolides and clindamycin. Among Gram-negative bacteria, approximately 70% of *Escherichia coli* isolates were resistant to ciprofloxacin and approximately 60% were resistant to third-generation cephalosporins. Glucose nonfermenting Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, and Burkholderia spp. were the second most frequent clinical isolates. Carbapenem-resistance was seen in 20%–35% of *P. aeruginosa* and in more than 50% of Acinetobacter baumannii. Although China is a vast country with large regional differences in socioeconomic development, there were no significant differences in bacterial resistance among the various geographical regions *(1, 2)*. Bacterial resistance has created a serious socioeconomic burden throughout China *(3)*, and the prevalence of resistant strains of several bacteria with public health importance continues to increase or remain at high levels (Fig. 1).

Antibiotics have been the most frequently used medicines in Chinese health-care facilities, and account for approximately 20% of all drug sales by general hospitals. Inappropriate use of antibiotics has also been very common in health-care settings. The overall proportion of outpatients prescribed antibiotics in 2002–2012 was 50.3%, and was 47.1%, 49.2% and 53.4% in tertiary, secondary and primary care institutions, respectively *(4)*. Surveillance data from 15 tertiary hospitals in four central cities in China in 2007 indicated that 49.1% of nonsurgical and 94.6% of surgical inpatients received antibiotic therapy or prophylaxis *(5)*. The situation in rural clinics was even more serious. In those settings, 48.4% of prescriptions for outpatients in western China in 2008 were for antibiotics, and the prescribing physicians preferred broad spectrum and newly marketed agents, such as cephalosporins or fluoroquinolones *(6)*. Such extensive use of broad spectrum antibiotics is likely to accelerate the development of bacterial resistance *(7)*.

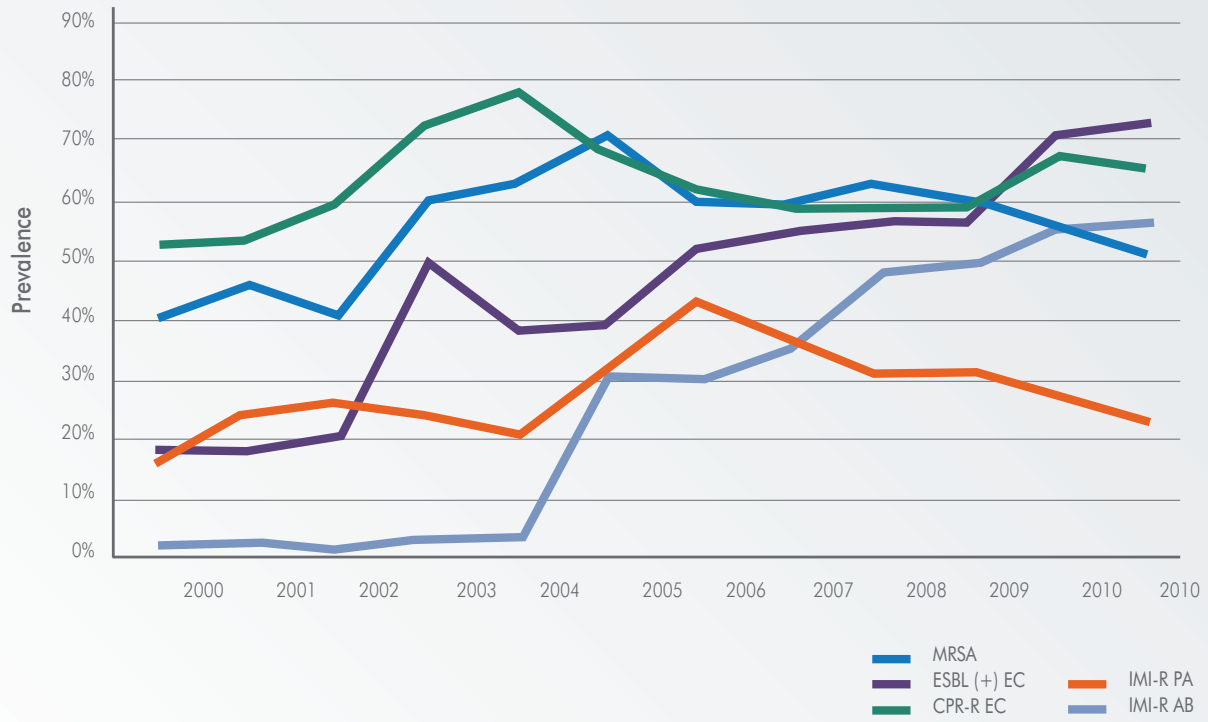
Table 1: **Content and purposes of the national antibiotics stewardship system in China**

Field	Time	Policies and actions	Main activities and goals
1. Talent team	2003	Set up infectious disease units in hospitals	• Diagnosis and treatment of infectious diseases • Antibiotic stewardship and control of drug resistance • Dealing with emerging & re-emerging infectious diseases
	2007	Launch pilot programmes for clinical pharmacists	• Consult on medicinal treatment • Prescription review and feedback • Therapeutic drug monitoring • Patient consultation of drug use
	2008	Organize the Expert Committee of Drug Rational Use of the Ministry of Health	• Counseling the government for drug rational use • Making recommendations and strategies for drug rational use • Investigation & monitoring of drug use • Training & education for rational drug use
2. Legislation and policies	2002	Temporary Rules for Pharmaceutical Affairs in Health-care Institutions	• Establishing clinical pharmacist system in health-care institutions • Setting up drug therapeutics committee (DTC) in hospitals • Regulating the full-procedure management of medicine in hospitals • Pharmacovigilance
	2006	Administrative Regulations for Nosocomial Infections	• Assigning responsibility of nosocomial infection control in each health-care sector • Monitoring, supervision and control strategies on control of nosocomial infection and antimicrobial resistance • Legal responsibility for violating the regulations
	2007	Administrative Regulations for Prescription	• Accrediting prescription rights for physicians • Standardizing prescription procedures • Monitoring and supervising prescriptions •Legal responsibility for violating the regulations
	2012	Administrative Regulations for Clinical Use of Antibiotics (see also Table 2)	• Assigning personal, institutional and governmental liability in antibiotic use • Strategies and support systems for rational use of antibiotics • Administrative penalties and legal responsibilities for violating the regulations
3. Technological specification and guidance	2004	Principles for the clinical use of antimicrobials	• Principles of antimicrobial rational use • Formulary restriction for antimicrobials • Pharmacological characteristics of primary antimicrobials and recommendations of antimicrobial therapies for common infections
	2009	Notification on strengthening management of clinical use of antibiotics	• Hierarchical management on antibiotics • Monitoring and alerts of drug-resistant bacteria • Antibiotic prophylaxis in surgical procedures • Benchmarking of fluoroquinolone use
	2010	Guidance in diagnosis and therapy of pan-drug resistant *Enterobacteriaceae* infections	• Diagnosis and therapy of infections caused by the NDM-1-producing bacteria
	2011	Guidance for the prevention and control of multi-drug resistant bacterial infections	• Strengthening measures to prevent and control MDR nosocomial infections • Monitoring MDR nosocomial infections • Rational use of antibiotics
	2009, 2012	National formulary & National formulary (pediatric edition)	• National model formulary
	2009, 2012	National essential drug list (Elementary edition) & National essential drug list (2012 edition)	• National essential drug lists containing 205 and 317 pharmaceuticals, respectively
	2013	National guidelines for antimicrobial therapy	• Empiric therapy for infectious diseases • Target therapy for microbial infections • Pharmacological characteristics and safety of antibiotics • Special points for antimicrobial therapy of pediatric infections
4. Surveillance	2006	Surveillance network for the use of antibiotics in health-care institutions	• The national monitoring network for antimicrobial use in hospitals (mainly in tertiary & secondary hospitals)
	2006	Ministry of Health National Antimicrobial Resistance Investigation Net (Mohnarin)	• The national monitoring network for antibiotic resistance in hospitals (mainly in tertiary & secondary hospitals)
5. Education and training	2007	Training course for clinical pharmacists	• There are more than 50 training sites, and more than 2,000 pharmacists have been trained to improve competency

Table 1: **Content and purposes of the national antibiotics stewardship system in China (continued)**

Field	Time	Policies and actions	Main activities and goals
5. Education and training (continued)	2008	National training programme for clinicians in the rational use of antibiotics	Training 40,000 physicians in three years in basic theories and strategies of antibiotic use
	2009	Training programme for clinical microbiologists	Training 500 microbiologists from primary health-care institutions on theory and 100 microbiologists on site in practice during three years
	2010	Training course for physicians from primary health-care setting on the rational use of medicines	Training 20,000 physicians in five years on basic knowledge of rational antibiotic use

Figure 1: **Resistance trends in the predominant antimicrobial-resistant bacteria in China from 2000 to 2011 (MRSA, Methicillin-resistant *Staphylococcus aureus*; ESBL (+) EC, extended-spectrum β-lactamase producing *Escherichia coli*; CPR-R EC, ciprofloxacin-resistant *Escherichia coli*; IMI-R PA, imipenem-resistant *Pseudomonas aeruginosa*; IMI-R AB, imipenem-resistant *Acinetobacter baumannii*).**



The national antibiotics stewardship system in China

The system includes five different fields, as shown in Table 1.

1. The Talent Team: building the capacity for the rational use of antimicrobial agents.

Infectious disease units in hospitals

After the outbreak of SARS in 2003, the Ministry of Health (MoH) asked medical institutions around the country to establish infectious diseases units to take responsibility for treating a variety of infectious diseases, the prevention and control of antibacterial resistance, and managing emerging infectious diseases. Most tertiary and some secondary hospitals have established these units, but their effectiveness needs to be strengthened because most infectious disease physicians are still interested in, and occupied by, the management of common communicable diseases, such as viral hepatitis, tuberculosis and AIDS *(8)*.

Institutionalizing clinical pharmacists in hospitals

In 2002, the MoH issued "Temporary Rules for Pharmaceutical Affairs in Healthcare Institutions", which required medical institutions to implement systems and personnel, including clinical pharmacists. Since then, more than 50 clinical pharmacist training centres have been established around the country. By this time, all tertiary hospitals and more than 50% of secondary hospitals already had clinical pharmacists, who engaged in patient drug

Table 2: **Content of the "Administrative Regulations for Clinical Use of Antibiotics**

Subjects	Responsibility	Tasks	The manner of the work	Penalty for violation
Ministry of Health (MoH)	• National management of clinical use of antibiotics	• Making policies • Setting targets • Supervising and inspecting	• Making and issuing policies • Periodically setting management targets • Setting up national surveillance networks of antibacterial resistance and antibacterial use • Punishing local subsidiaries or MoH-owned health-care institutions that violate laws or policies	
Local health administrative authorities	• Implementing the regulations and policies of MoH • Supervising the use of antibacterials in local health-care institutions	• Specifying the policies of MoH • Defining the antibiotic category list • Supervising and inspecting	• Formulating and issuing the antibiotic category list • Supervising hospital antibiotic formularies • Supervising and inspecting antibiotic use in health-care institutions • Setting up the local surveillance networks • Punishing local health institutions that violate laws and policies	• MoH will punish its local subsidiaries that violate the law or policies or are guilty of nonfeasance with criticism, warnings, demotion, or dismissing staff
Health-care institutions	• Practicing the rational use of antibiotics in institutions	• Following the laws and policies issued by MoH • Achieving the targets set by MoH	• Formulary restriction of antibiotics and accrediting physician antibiotic prescribing rights • Selection and procurement of antibiotics • Development of information systems on the rational use of antibiotics • Setting targets for clinical departments • Review and feedback of antibiotic prescriptions • Medical staff and patient education • Posting antibiotic use and prescription review reports • Removing financial incentives for antibiotic use • Punishing personnel who violate policies	Health-care authorities will punish the institutions or its administrators failing to comply with regulations through: • nonconformity to facility quality control • lowering the academic grade of the institution • warning or dismissing the administrative staff
Physicians	• Following the rational use of antibiotics in daily practice • Infectious disease physicians are members of hospital antibiotic management teams	• Patient therapy with rational antibiotic use	• Accredit prescription rights of antibiotics with different antibiotic indications • Rational treatment of patients with infectious diseases • Taking continuing medical education courses on rational use of antibiotics	People who violate policies will be punished by: • economic penalties • lowering the level of antibiotics prescription rights • suspending antibiotic prescription rights • suspending the career promotion • revoking physician's license • legal liability to severe outcome
Pharmacists	• The management and review of the use of antibiotics • Members of the hospital antibiotic management team	• Antibiotic dispensing • Antibiotic prescription review and feedback	• Antibiotic dispensing • Antibiotic use consultations • Antibiotic prescription review and feedback • Public education	Persons who violate policies will be punished by: • economic penalties • suspension of drug-dispensing qualification • suspension of career promotions • legal liability to severe outcome
Microbiologists	• Pathogen isolation and resistance surveillance • Members of the hospital antibiotic management team	• Microbiological diagnosis of infections • Drug-resistance surveillance	• Pathogen isolation and susceptibility testing • Antibiotic use consultations • Participating in national or regional resistance surveillance • Providing regular reporting on hospital-resistance surveillance	Person to violate policies will be punished by: • economic penalties • suspension of career promotions • administrative penalties, such as criticism or warning

therapy, therapeutic drug monitoring and patient medication counseling. They were also responsible for the management of rational drug use and prescription review *(9–11)*.

Organizing the Expert Committee for Rational Drug Use

To strengthen the management of rational drug use, the MoH set up the Expert Committee for Drug Rational Use (ECDRU) in October 2008. The main task of the ECDRU is to develop national rational drug use strategies, objectives and work protocols, to develop proposals for the national implementation of rational drug use practices, to study and formulate the clinical rational drug use measures and standards, and to organize education and training for drug rational use *(12)*.

2. Regulatory mechanisms: Issuing rules and regulations for the rational antibiotic use and control of antibiotic resistance

From 2002 onwards, the Chinese MoH issued the following regulatory file for promoting drug rational use:

- (Temporary) Rules for Pharmaceutical Affairs in Healthcare Institutions *(13,14)*;
- Regulations for Nosocomial Infections *(15)*;
- Administrative Regulations for Prescriptions *(16)*;
- Administrative Regulations for Clinical Use of Antibiotics *(17)*.

3. Technical specifications of antibiotic rational use

From 2004 onwards, the Chinese MoH issued the following technical guidelines and principles for promoting antibacterial agent rational use:

- Principles for the clinical use of antimicrobials and its supplementary rules *(18,19)*;
- Guidance for specific infections *(20)*;
- National Formulary and National Formulary (Pediatric Edition) *(21)*;
- National Essential Drugs List (2009 Elementary Edition and 2012 Edition) *(22,23)*;
- National Guidelines for Antimicrobial Therapy *(24)*.

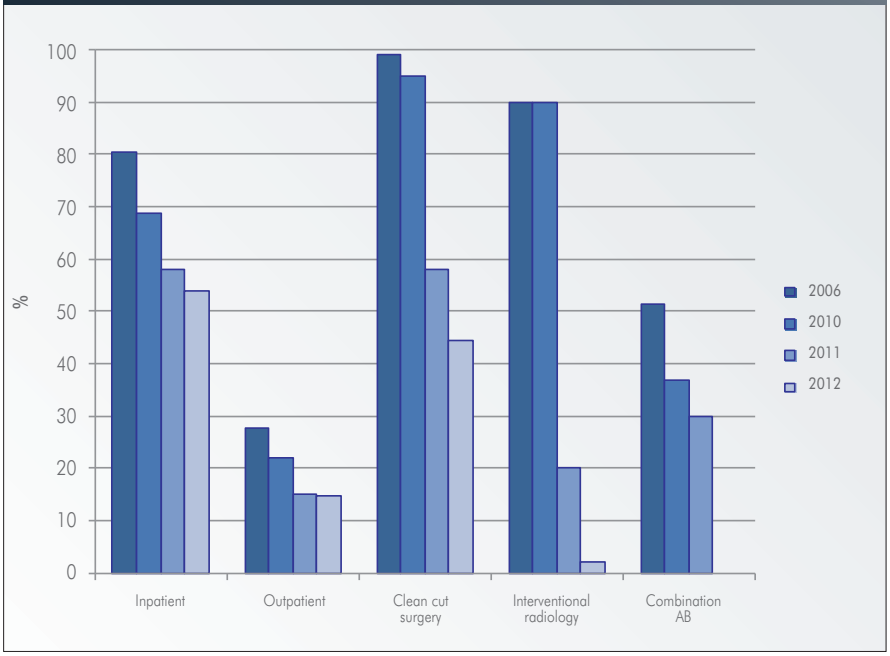
4. Antimicrobials consumption and bacterial resistance surveillance

In 2005, the MoH established hospital antibiotic consumption surveillance and bacterial resistance surveillance networks to link the prevalence of bacterial resistance to the rational use of antibacterials in medical institutions. Up to now, the member hospitals in the networks have expanded to more than 1,300, and include more than 800 tertiary hospitals and more than 500 secondary hospitals, and two-thirds of the provinces have networks that include all the tertiary and major county medical institutions *(25, 26)*.

5. Education and training for rational antibiotic use

In recent years, national health administration authorities have led training programmes and continuing education courses in rational antibiotic use, including clinical pharmacist training, clinician antibiotic training and clinical microbiologist training for primary health-care practitioners that have enrolled more than 72,500 people in total.

Figure 2: **Comparison of antibiotic prescription rates in various services before and after the special campaign**



National special campaigns to promote antibiotic rational use

In 2011, the MoH launched a three-year national campaign for antibiotic rational use in association with these health-care reforms. Considering international successes in fostering the rational use of antibiotics, the government used antibiotic formulary restriction as a core strategy, set management targets, conducted education and training and recommended rational antibiotic-use strategies to hospitals. The authorities then conducted

Textbox 1: Major strategies and targets of the annual special campaigns for rational antibiotic use from 2011 to 2013

Step 1: Initiation (before May)

1. MoH issues protocol for the special campaign
2. MoH sets major targets and strategies:
   a) Set up task force in health-care institutions (a professional working team: infectious disease physicians, clinical pharmacists and microbiologists);
   b) Enforcing formulary restriction in health-care institutions;
   c) Clinician training and antibiotic prescription rights accreditation in grades;
   d) Building up electronic prescription systems in institutions;
   e) Antibiotic resistance and utilization surveillance, prescription review;
   f) Major targets for the campaign;
      i. Antibacterial agents being stocked less than 50 or 35 in tertiary or secondary hospitals, respectively;
      ii. Prescriptions with antibiotics for outpatients being < 20% ;
      iii. Prescriptions with antibiotics for emergency patients being < 40%;
      iv. Antibiotic-use rate for inpatients being < 60%;
      v. Antibiotic prophylaxis use for surgical procedures being < 30%, and regimen rationality > 80%;
      vi. Antibiotic utilizing intensity for inpatients being < 40DDD/100 patient days;
      vii. Microbiological testing rate before antibacterial therapy being > 35% (in 2011) or > 50% (in 2012).

Step 2: Implementation (the whole year)

1. Actions of local health administrative authorities:
   a) Setting up directory for antimicrobial formulary restriction;
   b) Formulating detailed rules for the campaign.
2. Actions in health-care institutions:
   a) Setting up task force;
   b) Conducting clinician training and antibiotic prescription rights accreditation in grade;
   c) Setting antibiotic prescription privileges for each clinician in the prescription system;
   d) Generating antibiotic formularies;
   e) Setting up individual antibiotic target values for each clinical unit;
   f) Professionals following antibiotics management strategy in daily work;
   g) Carrying out supervision and monitoring of the use of antibiotics;
   h) Antibiotic-resistance monitoring at institutions;
   i) Antibiotic prescription review and feedback;
   j) Penalizing clinicians and pharmacists for violating regulations.

Step 3: Supervision and summary (September to December)

1. MoH supervises tertiary hospitals in central cities, and local health authorities supervise the others.
2. Composition of the supervision team (about five people): management staff, infectious disease physician, clinical microbiologist, clinical pharmacist and information specialist.
3. Focus of supervision;
   a) Actions of task force for rational antibiotic use;
   b) Measurement for promoting antibiotic rational use;
   c) Implementation of formulary restriction;
   d) Utilization of antibiotics in the institution;
   e) Target values;
   f) Technology support system: talents, surveillance and information system.
4. Reporting the results of supervision;
   a) Feedback of the results to hospitals;
   b) Medical institutions and their responsible persons with poor implementation or serious violation of regulation would be penalized;
   c) Partial results will be available to the public.

supervisions and inspections to push the campaign forward by the end of each year, and any medical institutions and administrators, physicians and pharmacists who violated the regulations or failed to meet targets were penalized. The special campaign laid the foundation for establishing the sustainable development of rational antibiotics use and control of bacterial resistance control (see Textbox 1) *(27, 28)*.

Effects to date

Data from the hospital antibiotic consumption surveillance network in 2012 indicated that inappropriate use of antibiotics had significantly decreased (Fig. 2) *(29)*. At the national level, the proportion of outpatients receiving antibiotic prescriptions dropped from 22% to 14.7% from 2010 to 2012. Similarly, the proportion of inpatients receiving antibiotics decreased from 68.9% to 54%, antibiotic prophylaxis in surgical procedures decreased from 95% to 44.6%, and combined antibiotic treatment with two or more agents decreased from 37% to 30%. The special campaign was obviously successful in both tertiary and secondary hospitals. A tertiary hospital in Hangzhou in eastern China reported that the prescription of antibiotics in emergency service patients, outpatients and inpatients declined from 58.4%, 39.6% and 68.9% to 46.3%, 22% and 39.2%, respectively. Inpatient antibiotic utilization intensity dropped from 65.6 DDD per 100 hospital days to 39.2 *(30)*; the situation in

other regions of China was the same. A general hospital in Sichuan in western China witnessed decreases of 9.5% in hospital antibiotic sales, 15% in outpatient antibiotic prescriptions and 14.7% in inpatient antibiotic use. Inpatient antibiotic utilization intensity decreased by 44 DDD/100 patient days and antibiotic prophylaxis in surgical procedures decreased by 20.4% *(31)*. The achievement in secondary hospitals was also exciting. A hospital in Shanghai reported that the inpatient antibiotic-use rate, antibiotic surgical prophylaxis and inpatient utilization intensity were 60.2%, 78.4% and 60 DDD/100 patient days in early 2011 and had fallen to 55.3%, 42.6% and 35 DDD/100 patient days, respectively, by September 2012 *(32)*. Another county hospital in Guangzhou found that outpatient antibiotic prescriptions, inpatient antibiotic use and antibiotic surgical prophylaxis were 38.5%, 70.1%, and 80.1% in 2010 and 18.2%, 56.4%, and 29.9% in 2012, respectively *(33)*.

Summary

During past decades, the Chinese authorities have established a national antibiotic stewardship system, but the efficacy in promoting antimicrobial rational use was very weak because the rules, guidelines and surveillance were not mandatory. Inappropriate use of antibiotics in health-care institutions remained a common phenomenon. Beginning in 2011 with a new round of health-care reform in China, the MoH issued new legislation and implemented a special campaign to promote the rational use of antibiotics. The new strategies included antibiotic formulary restriction in hospitals, setting up a task force, and law liability assignment. After three years, a substantial change has been observed in most of the hospitals; national and hospital surveillance data indicate that antibiotic use in health-care institutions has improved in quality and the quantity used has been reduced *(33–38)*. Considering the conflict between hospital operating practices and insufficient governmental investment, additional new sustainable strategies for expanding the achievement of rational antibiotic use in China should still be explored *(34)*. •

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References

1. Xiao YH, Giske CG, Wei ZQ, Shen P, Hedinni A, Li LJ. Epidemiology and characteristics of antimicrobial resistance in China. *Drug Resist Updat* 2011; 14(4-5):236-250.
2. Xiao YH, Shen P, Wei ZQ, Chen YB, Kong HS, Yang Q, et al. Mohnarin report of 2011: monitoring of bacterial resistance in China. *Chin J Nosocomiol* 2012; 22(22):4946-4949
3. Yang L, Xiao YH, Wang J, Zheng YD, Yan Q, Hou F, et al. Impact of Antimicrobial resistance on hospitalization costs. *China Journal of Pharmaceutical Economics* 2009, 1:16-21
4. Yin XX, Song FJ, Gong YH, Tu XC, Wang YX Cao SY, et al. A systematic review of antibiotic utilization in China. *J Antimicrob Chemother* 2013,68(11):2445-2452
5. Jin CM, Xiao AL, Yan L, Chen G. Investigation and analysis on antibacterial drug use in four cities of China. *Chin J Pharmacovigil* 2011,8(4):216-219
6. Dong LF, Yan H, Wang DL. Antibiotic prescribing patterns in village health clinics across 10 provinces of Western China. *J Antimicrob Chemother* 2008, 62:410-415
7. Bell BG, Schellevis F, Stobberinggh E, Goossen H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis* 2014, 14:13.
8. Ministry of Health of China .The notice on setting-up infectious disease unit in second-level and above general hospital. Ministry of health, 2004. Available from: http://www.moh.gov.cn/mohbgt/pw10410/200804/27131.shtml. [accessed 10 March 2013]
9. Ministry of Health of China, the State Administration of Traditional Chinese Medicine. Temporary Rules for Pharmaceutical Affairs in Healthcare Institutions. Ministry of Health, 2002. Available from: http://www.moh.gov.cn/mohyzs/s3577 /200804/18787.shtml. [accessed 10 March 2013]
10. Ministry of Health of China; Rules for Pharmaceutical Affairs in Healthcare Institutions. Ministry of Health, 2011. Available from: http://www.moh.gov.cn/mohyzs/s3586/201102/50581.shtml. [accessed 10 March 2013]
11. Ministry of Health of China. The notice on carrying out clinical pharmacist pilot work. Ministry of Health, 2008. Available from: http://www.moh.gov.cn/mohyzs/s3577/200804/18775.shtml. [accessed 10 March 2013]
12. Ministry of Health of China. The notice on establishing Ministry of Health committee of experts on rational drug use. Ministry of Health; 2012. Available from:http://www.moh.gov.cn/mohyzs/s9980/201206/0cfca0147618458585a6b83fe194d5ad.shtml. [accessed 10 March 2013]
13. Ministry of Health of China. Administrative regulation for nosocomial infections. Ministry of Health, 2006. Available from: http://www.moh.gov.cn/mohyzs/s3576/200804/29294.shtml. [accessed 10 March 2013]
14. Ministry of Health of China. Administrative Regulations for Prescription. Ministry of Health, 2007. Available from: http://www.moh.gov.cn/mohbgt/pw10704/200804 /18855.shtml. [accessed 10 March 2013]
15. Ministry of Health of China. Administrative Regulations of Clinical Use of Antibiotics. Ministry of Health, 2012. Available from: http://www.moh.gov.cn/mohyzs/s3584/201205/54645.shtml. [accessed 10 March 2013]
16. Ministry of Health of China. Principles for the clinical use of antimicrobials. Ministry of health, 2004. Available from: http://www.moh.gov.cn/mohyzs/s3573/200804/18544.shtml. [accessed 10 March 2013]
17. Ministry of Health of China. The notice to strengthen antibiotics management. Ministry of Health, 2009. Available from: http://www.moh.gov.cn/mohbgt/s9508/200903/39723.shtml. [accessed 10 March 2013]
18. Ministry of Health of China. Guidance in diagnose and therapy of NDM-1 producing pan-drug resistance Enterobacteriaceae infections (trial version). Ministry of Health. 2010. Available from: . http://www.moh.gov.cn/mohyzs/s8233/201010/49274.shtml. [accessed 10 March 2013]
19. Ministry of Health of China. National Formulary (2010 edition). Available from: http://www.moh.gov.cn/mohbgt/s10696/201002/45875.shtml. [accessed 10 March 2013]
20. Ministry of Health of China. National Essential Drugs List (edition for elementary institutions) (2009). Available from: http://www.moh.gov.cn/mohbgt/s9512/200908/42506.shtml. [accessed 10 March 2013]
21. Ministry of Health of China. National Essential Drugs List (2012 edition) (2012). Available from:http://www.moh.gov.cn/wsb/pwsyw/201303/f01fcc9623284509953620abc2ab189e.shtml. [accessed 10 March 2013]
22. He LX, Xiao YH, Xu YC, Li ZL, Lu Q. National antibiotic treatment guidelines (first edition). People's Medical Publishing House; Beijing, 2013
23. Xiao YH. Introduction of Mohnarin (Ministry of Health National Antimicrobial Resistance Investigation Net). *Chin J Antibiot* 2008; 10:577-578
24. MOH Center for Antibacterial Surveillance. Available from: http://y.chinadtc.org.cn/program/index.php [Accessed 10 March 2013].
25. Xiao YH. The current status of clinical application of antimicrobial agents in China and consideration on the rational drug use. *Chin Licensed Pharmacist* 2011; 4:4-9.
26. Tang SL, Meng QY, Chen L, Bekedam H, Evans T, Whitehead M. Tackling the challenges to health equity in China. *Lancet* 2008; 372(9648):1439-1501.
27. Ministry of Health of China. 2011 national special rectification activities program of clinical use of antibiotics (2011). Available from: http://www.moh.gov.cn/mohyzs/s3586/201104/51376.shtml. [accessed 10 March 2013]
28. Ministry of Health of China. 2012 national special rectification activities program of clinical use of antibiotics (2012). Available from: http://www.moh.gov.cn/mohyzs/s3586/201203/54251.shtml. [accessed 10 March 2013]
29. Ministry of Health of China. Press conference of Ministry of Health in May 8, 2012. Available from: http://www.moh.gov.cn/mohbgt/s3582/201205/54651.shtml. [accessed 10 March 2013]
30. Li JY, Chen L, Luo Y, Wang G, Ye HJ. Comparison of antibiotic use before and after the antibiotic special campaign (Chinese). *Herald of Med*, 2013,32(6):802-804
31. Xiao SL, Luo LH, Huang YL. Comparative analysis of antibiotics use before and after its special rectification in our hospital (Chinese). *J Luzhou Med College*, 2013, 36(1):84-86
32. Zheng T, Du DP, Liu D, Xie HJ. Analysis of the inpatients usage of antimicrobial agents between 2011 and 2012(Chinese). *Shanghai Med*. 2013,34(4):40-242
33. Pang TY, Luo LW, Pang DM. Efficacy analysis of antibiotic special campaign in our hospital (Chinese). *Pharmaceut Front* 2012,10:57-58
34. Xiao Y, Zhang J, Zheng B, Zhao L, Li S, Li LJ. Changes in Chinese policies to promote the rational use of antibiotics. PLoS Med, 2013, 10(11): e1001556. doi:10.1371/journal.pmed.1001556

THE SOUTH AFRICAN ANTIMICROBIAL RESISTANCE STRATEGY FRAMEWORK

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South Africa faces an overwhelming burden of infectious diseases at the heart of the HIV and tuberculosis pandemic. Largely unnoticed, the rise of antibiotic resistance in our country is now highly visible and tangible to health-care professionals and the public alike. With outbreaks of MDR bacteria closing wards and causing high morbidity and mortality, a strong response as part of the WHO Global Action Plan is required. The adoption of the Antimicrobial Resistance National Strategy Framework is the first step in this response, and can be seen as a blueprint for other middle-income countries. Furthermore, many of the interventions described here are applicable across health resource settings.

Infections constitute South Africa's greatest burden of disease *(1)*. The collision of two pandemics, HIV (12.2% of the population, 6.4 million persons in 2012) *(2)* and tuberculosis (prevalence of ~1,000/100,000 population) *(3)* has dominated the health landscape for over 20 years. In the second national burden of disease study (1997–2009), HIV was responsible for the highest number of deaths (31.2%), ahead of cerebrovascular disease (6.2%), tuberculosis (5.4%), lower respiratory tract infection (5.2%) and ischaemic heart disease (4.4%) *(1)*. Despite nearing elimination, malaria too continues in three of South Africa's nine provinces, and neglected tropical diseases, predominantly schistosomiasis, are a major, yet largely undocumented, burden in many parts of the country. Three quarters of schoolchildren at a junior school in Mbashe district of the Eastern Cape Province were found to have *S. haematobium* in urine *(4)*.

The true burden of bacterial infection (HIV- and non-HIV related) in South Africa remains incompletely documented due a high level of empiric management and an overall paucity of samples being sent for laboratory diagnosis. Although reduction in bacterial disease burden has occurred for some infections *(5)* as a result of South Africa's extended programme of immunization, respiratory, enteric and meningitis-related disease remain the predominant causes of bacterial infection in the country *(6)*. The true burden of fungal infection too is poorly understood, although a greater level of understanding of the burden of deep fungal infection in HIV through enhanced surveillance of cryptococcosis and the identification of new fungal species in the South African population *(7)* is increasing our understanding.

It follows, that with such a high burden of infection, an equally high burden of antimicrobial use occurs and hence, antimicrobial resistance. Over 2.5 million South Africans currently receive antiretroviral therapy (ART), with a significant increase expected once the criteria for initiation eases from CD4 T lymphocyte count of <350, to <500 cells/mm^3. Current rates of transmitted resistance to first line ART remain low in some provinces (<5% in Gauteng and Western Cape), yet are increasing in others (5–15% in KwaZulu Natal, Free State and Eastern Cape), and are predicted to rise as rollout of ART continues *(8)*. A level of 10–17% has been documented in more mature epidemics in developed countries *(9)*. The World Health Organization estimates between 400,000–600,000 cases of tuberculosis occurred in 2012, multi-drug-resistant (MDR) tuberculosis cases comprising 1.8% of new cases and 6.7% of retreatment cases respectively *(3, 10)*. Heightened surveillance for extensively-drug-resistant (XDR) tuberculosis is increasing our understanding of true extent of drug-resistant

Table 1: Antibiotic resistance profiles in human and animal health in South Africa

Human Health

	Resistance profile	Comments
Gram-positive	Methicillin-resistant *Staphylococcus aureus* (MRSA)	>50% of all hospital-acquired *S. aureus* isolated from the blood of sick patients in public hospitals in 2010 were MRSA.[i] MRSA accounted for three quarters of all hospital-acquired *S. aureus* infections in a large tertiary level paediatric hospital.[ii]
	Vancomycin-resistant Enterococci (VRE)	In 2012, there were large outbreaks of VRE in public and private hospitals in South Africa. *Enterococcus faecium* bloodstream isolates from the private sector between Jan–Jun 2012 showed variable sensitivity to vancomycin ranging between 33–100% depending on geographical location.[iii]
Gram-negative	ESBL-producing Bacteria	In studies from 2010 and 2012, up to 75% of *K. pneumoniae* isolated from the blood of hospitalised patients were ESBL.iv
	Carbapenemase-producing Enterobacteriaceae (CPE)	16.2% (115/711) of carbapenem non-susceptible Enterobacteriaceae in private sector contained a carbapenemase producing gene.[v] CPE are now widespread across public and private hospitals in South Africa

Animal Health

There is little published data on resistance rates for bacteria in food animals, and even less in companion animals. High rates of tetracycline and sulphonamide resistance in *E. coli*, *Enterococcus spp* and *Salmonella enterica* was highlighted in the South African National Veterinary Surveillance and Monitoring Programme for Resistance to Antimicrobial Drugs (SANVAD) that studied infections between 2002-2004.[vi]

[i] *Bamford et al. SAJEI 2011;26:243-250*
[ii] *Naidoo et al. PLoS One. 2013 8(10): e78396*
[iii] *SASCM Laboratory Surveillance data, Private Sector, Jan-Jun 2012*
[iv] *Bamford et al. S Afr J Epidemiol& Infect 2011;26:243-250. And GERMS-SA Annual Report 2012*
[v] *National Institute for Communicable Diseases. Communicable Diseases Communiqué 2014;13(8):6-7*
[vi] *Henton et al. S Afr J Med 2011;101(8): 583-6*

tuberculosis in South Africa. Drug resistance in both HIV and tuberculosis is already managed within their respective national programmes and HIV resistance in South Africa is discussed elsewhere in this publication.

Despite a national public surveillance programme for bacteria causing specific respiratory, gastrointestinal and central nervous system infections, there are significant gaps in our knowledge of drug resistance in bacteria other than tuberculosis (hereafter termed bacterial resistance) in South Africa. Currently, we are largely unable to identify patterns of community compared to hospital-acquired bacterial resistance due to a lack of linkage between laboratory and clinical data systems. The information available from public and private laboratory surveillance suggests very high levels of MDR-bacterial infections in hospitalized patients (Table 1). In terms of antibiotic consumption, South Africa, as one of the BRICS nations, has recently been highlighted as a major contributor to the global increase in antibiotic use *(11)*. However, detailed surveillance of antibiotic consumption at provincial, local, district and institutional levels is lacking, as integrated information systems that link pharmacy with laboratory and clinical data are not in place.

The initial response to rising antibiotic resistance levels in South Africa

In 2011, the Global Antibiotic Resistance Partnership–South Africa (GARP–SA) performed a situational analysis of antibiotic resistance (ABR) in South Africa *(12)*. A clear need for action was identified and for this reason, and in response to an increasing number of outbreaks of MDR-bacterial infections in health-care institutions, the South African Antibiotic Stewardship Programme (SAASP) *(13)* was formed under the auspices of the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA). SAASP comprises members from public and private sectors, bringing together the necessary skills set of infectious disease physicians and paediatricians, veterinarians, microbiologists, IPC practitioners, pharmacists,

Figure 1: Pillars of the South African Antimicrobial Resistance Strategy Framework

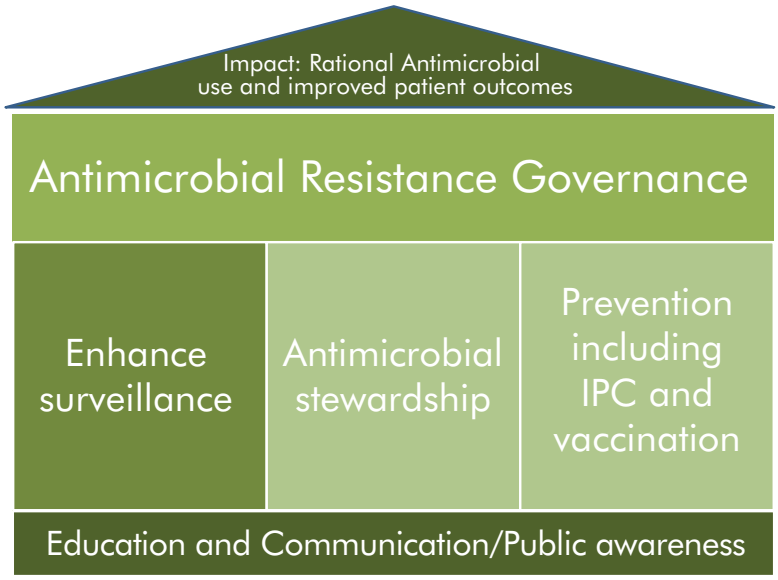


Figure 2: Multidisciplinary intersectoral Ministerial Advisory Committee on Antimicrobial Resistance

pharmacologists, intensivists, surgeons, epidemiologists and quality improvement experts. Its objectives are to promote appropriate antibiotic prescribing, education and engagement with (and in support of) the National Department of Health, as the effector arm of the ABR response. Advocacy by SAASP coupled with encouragement from WHO for Member States to develop a national plan to combat AMR, has resulted in the development of the national strategy framework for AMR.

The South African Antimicrobial Resistance Strategy Framework

Antimicrobial surveillance and reporting, antimicrobial stewardship (AMS) and improved infection prevention and control (IPC) form the three pillars of the national AMR strategy framework (Fig. 1). Under-pinning these, are plans to strengthen existing health systems, educate the workforce and public, and to stimulate local research and development into therapeutics, diagnostics and preventative measures. The framework describes a strong governance model to ensure success of each measure, and is supported by a rich legislative framework (Table 2).

Governance

Antimicrobial stewardship, which is cross-cutting within departments, programmes, hospitals and districts, needs to be positioned at a high level within a National Department of Health, where leadership can be provided to influence policy development and implementation. A multi-disciplinary, intersectoral Ministerial Advisory Committee (MAC) comprised of key stakeholders (Fig. 2), provides oversight for central interventions, to:

- Enhance national surveillance and reporting systems for MDR pathogens and AMR in the human health and agriculture sectors;
- Guide the selection of antimicrobials in the Essential Medicine List based on resistance patterns;
- Provide leadership and guidance to implement effective systems of AMS at national, provincial, state and institutional level;
- Define improvements in prevention strategies focusing on IPC and enhanced vaccination programmes;
- Advise on core curricula for AMR, patient advocacy and awareness campaigns to reduce the inappropriate use of antimicrobials in human and animal health.

At the operational level, governance is provided through Provincial structures, which monitor pharmaceuticals and therapeutics, AMS and IPC. Institutional CEOs and District Managers govern AMR activities at the coalface. A set of

Table 2: **Legislative framework for the South African AMR strategy**

The Constitution of South Africa (Constitution)	Guides the substantive content of all laws and policies through its Bill of Rights. The Constitution provides for health policy and practices that respond to the needs of South Africans. In terms of Section 27 of the Constitution access to health care in itself is a basic human right. All reasonable measures must be taken to ensure that this right is protected, promoted, and fulfilled within the limits of available resources.
The National Health Act (Act 61 of 2003)	Provides the framework for a structured uniform health system within South Africa. The Act specifically provides for the establishment of "a system of co-operative governance and management of health services, within national guidelines, norms and standards, in which each province, municipality and health district must address questions of health policy and delivery of quality health care services".
The Medicines and Related Substances Act (Act 101 of 1965)	Provides the legislative framework to ensure that medicines are safe, efficacious and of good quality. It also provides for control of veterinary medicines in such a way as to ensure that they are produced, distributed and used without compromising human and animal health. Antimicrobials intended for use in animals and registered under Act 101 can only be administered or prescribed by a veterinarian.
The Public Finance Management Act (Act 1 of 1999)	Ensures that all revenue, expenditure, assets and liabilities of all levels of governments are managed efficiently and effectively and provides for the responsibilities of persons entrusted with financial management to support, among others, sustainable access to health care and medicines.
The National Drug Policy (NDP)	Health objectives are to ensure the availability and accessibility of essential drugs to all citizens, to ensure the safety, efficacy and quality of drugs, to promote the rational use of drugs by prescribers, dispensers and patients through provision of the necessary training, education and information and to promote the concept of individual responsibility for health, preventive care and informed decision making.
The Fertilizers, Farm, Feeds, Agricultural Remedies and Stock Remedies Act (Act 36 of 1947)	Governs the use of antimicrobials for growth promotion and prophylaxis/metaphylaxis, and the purchase of antimicrobials over the counter (OTC) by the lay public (chiefly farmers). The National Department of Agriculture, Forestry and Fisheries has a responsibility to ensure that farmers have access to veterinary drugs for disease control and improved food production and to safeguard man by monitoring residues (including antibiotics) in products of food-producing animals, preventing zoonoses and controlling notifiable diseases.
The Health Profession Act (Act 56 of 1974)	Provides for control over the education, training and registration for and practicing of health professions registered under this act.
The Veterinary And Para-Veterinary Professions Act (Act 19 of 1982)	Provision for the compounding and or dispensing of any medicine which is prescribed by the veterinarian for use in the treatment of an animal which is under his or her professional care

national core standards has been developed for both AMS and IPC to ensure a standardized approach. Every institution will have an AMR committee and AMS team(s) to effect good practice and oversee appropriate antimicrobial prescribing.

Optimization of surveillance and early detection of AMR

Surveillance of four components of AMR is to be strengthened within the strategy framework:

- Antimicrobial resistance patterns;
- Antimicrobial consumption;
- Antimicrobial drug quality;
- Medication errors.

A centralized data warehouse (CDW) will collate public and private national resistance data. Specific drug resistance patterns are to become statutorily notifiable. This will include both statutory notifications of resistance patterns for common bacterial infections that are already at high prevalence such as methicillin resistant *Staphylococcus aureus* (MRSA) and extended spectrum beta-lactamase (ESBL) producing bacteria, and sentinel notification of the most serious resistant MDR bacteria currently at low prevalence, e.g. carbapenemase-producing Gram-negative

Table 3: **Antimicrobial Stewardship Toolkit**

Intervention	Comment
Antibiotic Prescription Chart	Stand alone or incorporated into the Provincial or institutional prescription chart
AMS Ward Round	Each institution and district will have its own AMS team(s) to perform ward rounds. The composition of participants will vary depending of level of health-care and human resources. The nucleus of the AMS team should be a prescriber "champion" and a pharmacist
Antibiotic prescribing guidelines	Essential Medicines List, Structured Treatment Guidelines and the SAASP antibiotic prescribing guidelines will provide direction to prescribers
Antibiotic prescribing license	Along the same lines as Advanced Trauma (or Cardiac) Life Support courses, which are mandatory for certain medical practices, a compulsory antibiotic prescribing course which mandates passing to be allowed prescribing rights is under discussion with the Health Professions Council of South Africa and providers. A biennial, renewable, web-based qualification is envisaged.
"Train the Trainer" AMR residential courses	A two-week residential course combining theory and AMS ward rounds target under-served Provinces, which do not have an AMS programme running. This provides an opportunity to rapidly up skill AMR "champions"
Restrictive interventions	Restrictive interventions show inter-Provincial, intra-Provincial and inter-institutional variation. Formulary restriction and pre-authorisation are options for health care programmes within institutions

bacteria. Sentinel reporting will act as an early warning system for AMR outbreaks.

In addition, CDW data has been de-duplicated and transformed to generate an electronic tuberculosis and drug resistant tuberculosis surveillance system for monitoring trends in disease burden *(14)*.

The National Institute for Communicable Diseases (NICD) conducts surveillance for human bacterial and fungal diseases of public health importance. Such surveillance platforms have already demonstrated significant declines in invasive pneumococcal disease cases caused by bacteria resistant to one or more antibiotics, a very valuable added benefit of immunization *(5)*. Performing susceptibility testing on submitted invasive fungal pathogens such as Cryptococcus and Candida, and tracking antifungal resistance patterns is an important component of NICD surveillance. While antifungal resistance in Cryptococcus remains very unusual, azole resistance in bloodstream Candida isolates has emerged as a major problem in some parts of South Africa *(15)*.

A recent addition to NICD's surveillance platform is the prospective sentinel surveillance programme for Xpert MTB/Rif diagnosed rifampicin resistant tuberculosis cases. This is being expanded to include integrated tuberculosis/HIV surveillance. An early warning system for detection of recent transmission clusters and outbreaks with predictive geospatial capability in selected, high burden, drug-resistant districts is also being piloted.

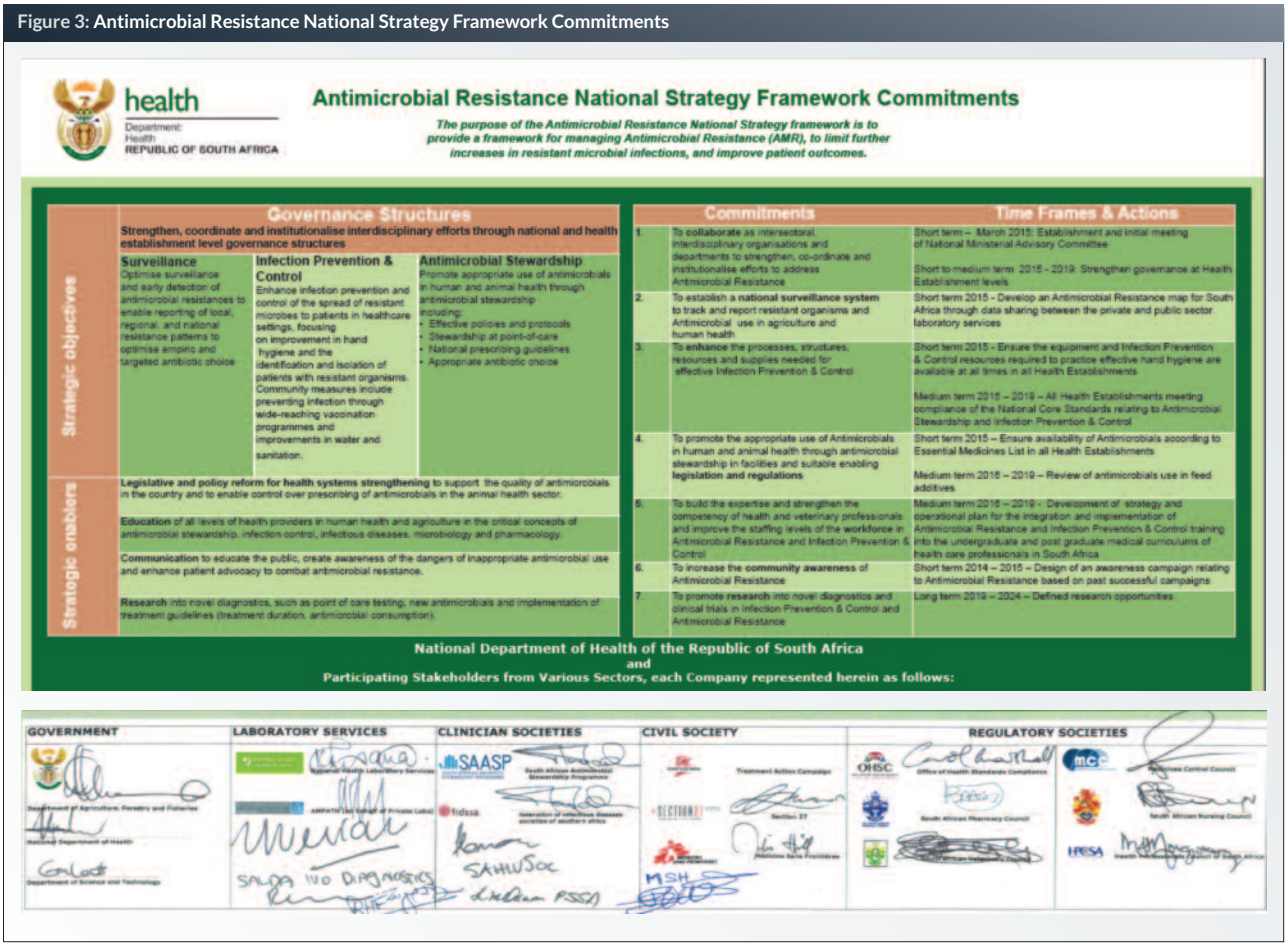
Surveillance and reporting of bacterial resistance in feed and companion animals is an equally important component of the national strategy framework. Prior to 2007, a surveillance programme active in all nine of South Africa's provinces was reporting data. However, the programme lost funding and was discontinued. This will be resurrected in conjunction with the Faculty of Veterinary Sciences at University of Pretoria and the Department of Agriculture, Forestry and Fisheries (DAFF).

In line with World Health Assembly resolution 67.25 *(16)*, South Africa is forging international collaborations to strengthen surveillance and reporting. An antimicrobial resistance map of the country is being developed as a collaborative project between the Center for Diseases Dynamics, Economics and Policy (CDDEP), SAASP, NICD and the South African Society for Clinical Microbiology. In addition, a Commonwealth twinning project with Public Health England is planned to strengthen laboratory support within South Africa.

Promotion of appropriate use of antimicrobials in human and animal health

Uninterrupted access to affordable antimicrobials means adopting appropriate prescribing practice. The quality of

Figure 3: **Antimicrobial Resistance National Strategy Framework Commitments**



medicines will be strengthened through the use of laboratory systems to monitor quality assays and pharmacovigilance reporting systems monitored by the Medicines Control Council, which will also include veterinary medicines.

The strategy framework aims to institutionalize AMS, not only through the adoption of national core standards, but by incorporating AMS activities into job descriptions, performance appraisals and continuing professional education activities. The national development of an integrated information technology system to link pharmacy, laboratory and clinical information is similarly vital in this regard. An audit of patient information systems at primary care level revealed that only 22 out of 37 systems in all nine provinces were functional and operational, but could be scaled up (unpublished observations). A similar audit is underway at hospital level.

A series of antimicrobial stewardship interventions are being put in place as part of the strategy framework (Table 3). Central to these is the AMS ward round, which has been shown to reduce antibiotic prescribing in South Africa, without affecting patient safety *(17)*. Coupled with dedicated antibiotic prescription charts, these activities focus attention on antimicrobial prescribing and is an effective means of transferring skills to trainees. Information on appropriate prescribing in the form of the South African Essential Medicines List and Standard Treatment Guidelines has been augmented by an algorithmic clinical guideline on appropriate antimicrobial prescribing *(18)*.

Enhance infection prevention and control (IPC)

Prevention of infection through wide-reaching vaccination programmes and improvements in water and sanitation are important prevention strategies to reduce AMR. South Africa's extended programme of immunization will be augmented by increased coverage of influenza vaccination, which has been shown elsewhere to reduce influenza-associated antibiotic prescribing *(19)* and by fast-tracking expanded immunization of pneumococcal conjugate vaccination in high-risk adults. In the context of South Africa, this includes HIV-infected adults.

A key enabler to effective IPC includes sufficient, suitably qualified, and competent IPC practitioners (IPCPs) with defined core competencies. Human resource planning to meet international norms for IPCPs in South Africa is a required component of the strategy framework. Although

Table 4: **Strategic enablers towards the antimicrobial resistance national strategy framework.**

Intervention	Comment
Legislative and policy reform for health systems	AMS and IPC national core standards are prescribed as regulated standards that accompany the National Health Act, and the promulgation of the Office of Health Standards Compliance (OHSC). OHSC inspectors will ensure compliance countrywide.
Education and Workforce Development	DAFF are undertaking a comprehensive review ofthe Stock Remedies Act 36 of 1947, which regulates the use of antimicrobial feed additives (AFAs) used for growth promotion, and those used for metaphylaxis. Impact studies on the phasing out of AFAs with respect to food security and production are to be undertaken, so that the use of antimicrobials in food production may be aligned with international norms and standards.
	Annual reporting of antimicrobial use in animal health will be instituted under the direction of DAFF.
	In collaboration with the Department of Education, curricula for school learners, medical and paramedical undergraduates, as well as post-graduate continuing professional development programmes will be reviewed to augment AMR content.
	Targets for human resource development, especially in terms of IPCPs and pharmacists are important enablers to the rollout of AMR programmes nationally, as are the required number of Infectious Diseases specialists and Microbiologists needed to support the national strategy. Current levels are inadequate.
Communication	Capitalizing on heightened awareness of infectious disease transmission in the wake of the Ebola epidemic, a national hand hygiene campaign has begun to inform the public of simple infection prevention measures. Annual influenza vaccination campaigns will be strengthened to include messaging around antibiotic use.
Research	Initial priorities will include studies on the impact of proposed changes to prescribing practices in the animal feed sector, piloting electronicprescribing and integration of pharmacy/clinical and laboratory data systems to inform rational antibiotic prescribing.
	South Africa has a long tradition of excellence in research. The recent characterization of a novel antimalarial drug,*(18)* which is currently in phase I trials highlights the role of academia.The Biovac Institute*, a private-public partnership between the South African Government and the Biovac consortium will play a vital role in manufacturing affordable quality vaccines for South Africa, the continent,and the developing world.

**The Biovac Institute. http://www.biovac.co.za*

more challenging, interventions to mobilize communities with respect to basic infection prevention and hand hygiene are currently underway as part of a private-public partnership with local celebrities *(20)*. As world attention is currently focused on transmission of Ebola in West Africa, community awareness around infection and transmission has been heightened, and offers a receptive audience for health messaging around infection prevention.

Strategic enablers of appropriate antimicrobial prescribing

We recognize four strategic enablers to achieve our objectives; legislative and policy reform for health systems strengthening, education, communication and research (Table 4). These enablers form an integral part of the strategy framework, which was presented to a national AMR Summit held in Johannesburg on 16 October 2014. The Antimicrobial Resistance National Strategy Framework Commitments (Fig. 3) were formally adopted by Government departments and all relevant stakeholders at the Summit

Summary

South Africa faces an overwhelming burden of infectious diseases at the heart of the HIV and tuberculosis pandemics. Largely unnoticed, the rise of antibiotic resistance in our

country is now highly visible and tangible to health-care professionals and the public alike. With outbreaks of MDR-bacteria closing wards and causing high morbidity and mortality, a strong response as part of the WHO Global Action Plan is required. The adoption of the Antimicrobial Resistance National Strategy Framework is the first step in this response, and can be seen as a blueprint for other middle-income countries. Furthermore, many of the interventions described here are applicable across health resource settings.

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References

1. Pillay-van Wyk V, Msemburi W, Laubscher R, et al. Second national burden of disease study South Africa: national and subnational mortality trends, 1997-2009. *Lancet* 2013;381:S113. Doi:10.1016/S0140-6736(13)61367-7
2. Shisana O,Rehle T, Simbayi LC, et al. (2014). South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town, HSRC Press.
3. WHO Global Tuberculosis Report 2014. Accessed at http://www.who.int/tb/publications/global_report/en/
4. Meents EF & Boyles TH. Schistosoma haematobium prevalence in school children in the rural Eastern Cape Province, South Africa. *South Afr J Epidemiol Infect* 2010;25(4):28-29
5. Von Gottberg A, de Gouveia L, Templa S,.et al. Effects of vaccination on invasive pneumococcal disease in South Africa. N Engl J Med 2014;371(20):1889-99. Doi: 10.1056/NEJMoa140194.
6. GERMS-SA Annual Report 2013. Available from: http://www.nicd.ac.za/assets/files/2012%20GERMS-SA%20Annual%20Report.pdf
7. Kenyon C, Bonorchis K, Corcoran C, et al. A dimorphic fungus causing infection in South Africa. *N Engl J Med*. 2013:369!15):1416-24. Doi: 10.1056/NEJMoa1215460.
8. Hunt G, Ledwaba J, Salimo A, Kalimashe M, Singh B, Puren A and Morris L. Surveillance of transmitted HIV-1 drug resistance in 5 provinces in South Africa in 2011. *Communicable Diseases Surveillance Bulletin*, 2013: 11(4); 122-124.
9. World Health Organization. *The HIV drug resistance report*, 2012. Geneva, Switzerland.
10. World Health Organization. Tuberculosis country profile, South Africa. http://www.who.int/tb/country/data/profiles/en/
11. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, Laxminarayan R. Global antibiotic consumption 2000 to 2010: an analysis of national pharamaceutical sales data. *Lancet Infect Dis* 2014;14:742-50.
12. Winters C, Gellband H. Part 1. The Global Antibiotic Resistance Partnership (GARP). *S. Afr J Med.* 2011;101(8):566-7
13. South African Antibiotic Stewardship Programme. Accessed at http://www.fidssa.co.za/A_SAASP_Home.asp
14. Koornhof H, Ihekweazu C, Erasmus L and Coetzee G. Update on Corporate Data Warehouse-derived MDR– and XDR-TB statistics for eight provinces in South Africa, January 2007 to 30th June 2011 Communicable Diseases Surveillance Bulletin. 2011 9(3): 68-72
15. GERMS-SA Annual Report 2013. Accessed on 23rd December 2014. Available from: httpp://www.nicd.ac.za/assets/files/GERMS-SA%202013% 20Annual%20Report.pdf
16. World Health Assembly Resolution WHA 67.25. Antimicrobial Resistance. Accessed at http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R25-en.pdf on 1st December 2014
17. Boyles TH, Whitelaw A, Bamford C, Moodley M, Bonorchis K, Morris V, Rawoot N, Naicker V, Lusakiewicz I, Black J, Stead D, Lesosky M, Raubenheimer P, Dlamini S, Mendelson M. Antibiotic stewardship ward rounds and a dedicated prescription chart reduce antibiotic consumption and pharmacy costs without affecting inpatient mortality or re-admission rates. *PLoS One*. 2013 Dec 9;8(12):e79747. doi: 10.1371/journal.pone.0079747. eCollection 2013. PMID: 24348995 [PubMed - in process]
18. South African Antibiotic Stewardship Programme. A Pocket guide to antibiotic prescribing for adults in South Africa, 2014. Accessed at http://www.fidssa.co.za/images/SAASP_Antibiotic_Guidelines_2014.pdf on 1st December 2014
19. Kwong JC, Maaten S, Upshur RE, Patrick DM, Marra F. The effect of universal influenza immunization on antibiotic prescriptions: an ecological study. *Clin Infect Dis.* 2009k49(5):750-6. Doi: 10.1086/605087
20. Minister Aaron Motsoaledi launches hand wash campaign, 24 Nov. Accessed on 23rd December 2014 at http://www.gov.za/minister-aaron-motsoaledi-launches-hand-wash-campaign-24-nov

TACKLING ANTIMICROBIAL RESISTANCE THROUGH PRESCRIPTION CONTROL IN HUMAN HEALTH

CÉLINE PULCINI, CHU DE NANCY, SERVICE DE MALADIES INFECTIEUSES, NANCY, FRANCE; UNIVERSITÉ DE LORRAINE, UNIVERSITÉ PARIS DESCARTES AND WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE

Antibiotic resistance is on the rise worldwide, as are antibiotic prescriptions. Antibiotic stewardship programmes are urgently needed in all settings, if we are to tackle bacterial resistance. Prescription control is one of the strategies used in antibiotic stewardship programmes. This article describes the main measures that could be implemented, and discusses the potential limitations and barriers to implementation of restrictive antibiotic stewardship strategies.

Antibiotic resistance is a growing international threat, and is gaining more and more attention *(1, 2)*. The causal link between antibiotic use and bacterial resistance is well known *(3, 4)*. We need to reduce antibiotic use if we are to tackle bacterial resistance, all the more since antibiotic use is on the rise worldwide *(5)* and because up to half of antibiotic prescriptions are considered to be either unnecessary or inappropriate *(6-8)*.

We need to break the "vicious" circle: antibiotic overuse/misuse -> growing antibiotic resistance -> increased use of broad-spectrum antibiotics -> more selection of resistant bacteria. Antibiotics must be considered as special drugs, due to the collective impact of antibiotic resistance, and these precious drugs must be protected. Unnecessary prescriptions must be reduced to a minimum, and narrow-spectrum antibiotics must be preferred to broad-spectrum antibiotics whenever possible, for the shortest possible duration.

What is an antibiotic stewardship programme?

According to the Infectious Diseases Society of America (IDSA), the definition of antibiotic stewardship includes: optimizing the indication, selection, dosing, route of administration and duration of antibiotic therapy to maximize clinical cure or prevention of infection while limiting the collateral damage of antibiotic use, including toxicity, selection of pathogenic organisms (such as *Clostridium difficile*) and the emergence of resistance *(8)*. Antibiotic stewardship programmes are multifaceted, associating educative/persuasive and restrictive measures, including prescription control, as well as organizational/structure measures (Table 1). In the hospital setting, a recent meta-analysis supports the use of restrictive interventions when the need is urgent (e.g. a multi-resistant bacteria outbreak), but suggests that persuasive and restrictive interventions are equally effective after six months *(9)*. In both outpatient and inpatient settings, multifaceted programmes are considered to be more effective than a single-component intervention *(9, 10)*.

Antibiotic stewardship programmes have been shown to improve the appropriateness of antibiotic use, reduce patient morbidity and mortality, decrease antibiotic use and costs, and reduce bacterial resistance and *C. difficile* infections, both in the outpatient and the inpatient settings *(6, 7, 9-11)*.

Who are the actors in prescription control ?

Antibiotic prescriptions are usually controlled by infectious diseases specialists, clinical pharmacists, clinical microbiologists, and/or clinicians with a training in infectious diseases *(12)*. Adequate training and clinical expertise are crucial, as well as communication and teaching skills *(6, 13)*. The organization of prescription control varies between

Table 1: **Main antibiotic stewardship strategies recommended in the literature for hospital settings**

Restrictive measures	- Hospital formulary with a limited number of antibiotics - Antibiotic order form - Automatic stop order - Formulary restriction and pre-authorization
Passive educational measures	- Local antibiotic guidelines - Educational sessions
Active persuasive / educational interventions	- Clinical rounds discussing cases - Prospective audit and feedback - Academic detailing
Structure/ organizational measures	- Multidisciplinary antibiotic stewardship teams (pharmacist, infectious diseases specialist, microbiologist, infection control specialist) - Consultancy service (infectious diseases, microbiology, pharmacy) - Computerized-decision support system - Regulating contacts with pharmaceutical representatives

countries and even between hospitals and structures *(12, 14)*.

In some countries, such as France, the role of the "antibiotic expert" is clearly defined (role, competencies, time to be spent) and is part of the accreditation process of hospitals, but no specific funding has been allocated to this mission (http://www.sante.gouv.fr/IMG/pdf/12_286t0.pdf). In a cross-sectional survey involving 74 hospitals in France, time dedicated by the antibiotic expert was significantly associated with a decrease in fluoroquinolone use *(15)*. Whether the antibiotic expert should be an infectious disease specialist or not is a matter of debate and depends on local resources *(6)*. It is likely that a multidisciplinary antibiotic stewardship team, involving ideally at least an infectious diseases specialist, a clinical microbiologist and a clinical pharmacist, is likely to achieve more significant results than an antibiotic expert on his/her own *(6, 8, 16, 17)*.

Nurses are more and more involved in antibiotic stewardship programmes *(12)*. Regarding prescription control, they could play a significant role for certain strategies, for example IV-oral switch or helping in triggering the review of antibiotic prescriptions *(18, 19)*.

Strategies for prescription control in hospitals

Most hospitals define a list of antibiotics that are available to the prescribers (hospital formulary). This was the case in 90% of the hospitals in the 2012 international survey conducted by ESGAP (the European Society of Clinical Microbiology and Infectious Diseases Study Group for Antibiotic Policies), even though this picture is likely to be an optimistic one, since the study was probably biased towards the most motivated hospitals, and since it was based on declarative data *(8, 9, 12)*. A formulary is a list of antibiotics that have been approved for use in a hospital. Formularies are useful in influencing prescribing behaviour by controlling access to particular drugs (e.g. use is approved only for a particular department, for patients with a particular condition, or where other options are contraindicated). These restricted drugs require approval by nominated experts who are members of the antibiotic stewardship team *(17)*.

In some countries, such as France, the role of the "antibiotic expert" is clearly defined (role, competencies, time to be spent) and is part of the accreditation process of hospitals

Antibiotic order forms, i.e., a standardized form that is filled in by the prescriber in order to get the antibiotic from the pharmacy, are also very common *(8, 9, 12)*.

Automatic stop orders can also be implemented in order to limit the duration of treatments, and to force the prescriber into reviewing his/her antibiotic prescription; they were in place in 46% of the hospitals in the 2012 ESGAP international survey *(8, 9, 12)*. This means that the pharmacy delivers the treatment for a short period of time (e.g. three days) for each antibiotic order form.

Automatic therapeutic substitutions can also be in place at the pharmacy level (e.g. dispensing cefotaxime instead of ceftriaxone, since cefotaxime is thought to select less resistant bacteria than ceftriaxone).

Restricted prescriptions require expert approval for the pharmacy to dispense the treatment; this system was in place in 81% of the hospitals in the 2012 ESGAP international survey *(12)*. Expert approval is usually needed for broad-spectrum and expensive antibiotics (e.g. carbapenems, daptomycin, fidaxomicin). Approval may be required pre-prescription (pre-authorization), or post-prescription within a specified time period, for example 48 hours (post-prescription review). Pre-authorization is sometimes needed to allow the dispensing of the first dose of treatment, but most of the time, it takes place just after first dose, to avoid delayed administration of the first dose of

Ideally, all prescriptions should be looked at, since there are no reliable predictors of antibiotic misuse. The best strategy depends, however, on the local context and resources

antibiotic. Pre-authorization requires 24-hour coverage and real-time expert advice *(12)*. Post-prescription review of antibiotic prescriptions by an expert appears to be more effective than review by the prescriber on his/her own *(6, 9, 20)*. In Turkey, the introduction of a new health-care regulation in 2003 requiring mandatory approval of specific parenteral IV antibiotics by dedicated infectious diseases specialists found some health-economic benefits *(21)*, which have been shown by others *(9, 17)*.

Experts can also provide unsolicited advice for certain situations, for example positive microbiological samples (multi-resistant bacteria, positive blood cultures) *(6, 9, 12)*, giving more opportunities to review antibiotic prescriptions. In some hospitals, systematic review of all antibiotic prescriptions are planned regularly in certain units (e.g. twice weekly rounds in intensive care units) *(12)*. All expert reviews provide an opportunity for additional education as well as feedback on the episode of care.

Table 2 gives practical examples of restrictive measures that could be implemented in hospitals, and that have been successfully tested by the author *(22)*.

Ideally, all prescriptions should be looked at, since there are no reliable predictors of antibiotic misuse. The best strategy depends, however, on the local context and resources. Electronic medical records and electronic prescribing obviously facilitate prescription control, but they are not implemented in all hospitals *(12)*. Sophisticated electronic antimicrobial approval systems have been implemented in some hospitals and look promising *(17, 23)*.

Most experts recommend that the antibiotic stewardship programme should reside within the hospital's quality improvement and patient safety governance structure and should be included within the hospital's quality and safety strategic plan, thereby facilitating its implementation *(17)*. As antibiotic stewardship is an important component of patient safety, its performance indicators should be measured and publicly reported, and hospitals and hospital executives should be accountable for these *(17)*. Structure indicators for hospital antibiotic stewardship programmes have recently been validated across European hospitals *(24)*.

Table 2: **Practical examples of restrictive measures that could be implemented in a hospital**

Hospital formulary	List of antibiotics available in the hospital with a specific list for restricted broad-spectrum antibiotics
Nominative antibiotic order form	Specific form to be filled in to get antibiotics from the pharmacy
Automatic stop order	The pharmacist delivers treatment for three days only, forcing the prescriber to review the prescription For surgical prophylaxis, the pharmacy delivers one day of treatment only
Expert approval	For all the following situations: • Restricted broad-spectrum antibiotics, before day three (post prescription review) and at day seven; • Multi-resistant bacteria (list to be defined); • Positive blood cultures; • Regular rounds of the antibiotic expert with systematic advice on all antibiotic prescriptions in some units (especially in those with high antibiotic use).

One of the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) objectives is indeed to develop a common structure and process indicators for hospital antibiotic stewardship programmes (http://www.cdc.gov/drugresistance/pdf/TATFAR-Progress_report_2014.pdf).

In France and in Australia, for example, antibiotic stewardship has become a criterion for the accreditation of health services. In particular, hospitals are required to have an antibiotic stewardship programme in place and measureable clinical standards for stewardship (http://www.sante.gouv.fr/IMG/pdf/12_286t0.pdf and http://www.safetyandquality.gov.au/our-work/healthcare-associated-infection/antimicrobial-stewardship/) *(14, 17)*.

Strategies for prescription control in the outpatient setting

Controlling antibiotic prescriptions in the outpatient setting is even more challenging, since relationships between prescribers and an antibiotic stewardship team are uncommon.

To start controlling prescriptions, over-the-counter prescriptions must be banned (i.e. the pharmacist cannot deliver an antibiotic without a nominative prescription), and this is not the case in all countries *(2)*.

Antibiotic formularies, i.e. the list of antibiotics that can be prescribed in the outpatient setting, should be available, in order to limit the prescription of some broad-spectrum antibiotics. The list needs however to be updated regularly,

to take into account current guidelines and resistance data.

Specific antibiotic order forms (i.e. forms dedicated to antibiotic prescriptions only), automatic stop orders and automatic therapeutic substitutions could also be used, but they are quite uncommon.

Expert approval is much more difficult to organize in the outpatient setting, and few countries have implemented such a strategy. In Australia, for example, the use of fluoroquinolones has long been restricted by guidelines favouring alternative options and the limitation of prescription subsidies for this antibiotic class by the Pharmaceutical Benefits Scheme to very specific indications are recognized by the guidelines *(25)*.

Structural and organizational strategies can also be used. For example, in Slovenia, primary care prescribers pay a fine if certain antibiotic prescriptions (amoxicillin-clavulanic acid, fluoroquinolones, macrolides, third-generation cephalosporins) do not comply with existing national guidelines. The Slovene National Health Insurance is auditing medical records in order to enforce this policy (M Cizman and B Beovic, personal communication) *(26, 27)*.

The example of Denmark also demonstrates how, at the national level, the authorities have a powerful tool in their reimbursement policy. Antibiotics are reimbursed differently, according to national decisions and this policy impacts significantly on prescribing *(28)*.

Strategies for prescription control in long-term care facilities

The same strategies could also be used in long-term care facilities *(7, 29, 30)*. However, antibiotic stewardship programmes in long-term care facilities tend to be less well-organized and less-resourced than in the hospital setting *(7, 29, 30)*. National performance indicators for antibiotic stewardship in European long-term care facilities have recently been validated *(31)*.

Limitations of and barriers to prescription control

Prescription control should be associated with educative and persuasive measures, within a multifaceted antibiotic stewardship programme *(8, 9)*. This approach is more effective, and is also likely to lessen the barriers to prescription control from the prescribers. It is indeed well known that a prescription control approach on its own can lead to adaptation strategies from prescribers bypassing the restriction *(32)*. There is no "magic bullet", meaning that no single antibiotic stewardship model will deliver optimal antibiotic prescribing in every context. In addition to selecting the strategies that have the best efficacy, the antibiotic stewardship team needs to consider which strategies are most likely to be successful in their specific context and how best to implement them *(17)*.

Prescription control needs dedicated resources, since it is a time-consuming activity. In the ESGAP international survey conducted among 660 hospitals in 2012, less than 20% of hospitals had dedicated funding in place for their antibiotic stewardship team *(12)*. Opposition from prescribers can also be an issue and that cannot be solved without strong institutional support *(12)*. When expert approval is in place, the clinician in charge of the patient is usually free to comply, or not, with suggestions made by the expert, because of legal responsibility issues. The quality of the relationship between the expert and the clinician is therefore crucial to ensure a good level of compliance. Finally, since expert approval does not always involve a bedside consultation, the quality of exchanged information (by phone, fax, mail) has a direct impact on the quality of the given advice *(33)*. Traceability of all exchanged information is needed.

Conclusion

Given the worldwide antibiotic resistance crisis, implementing antibiotic stewardship programmes in all settings is an emergency *(12, 34, 35)*. Prescription control is one aspect of these programmes, and can be very useful to improve antibiotic prescribing; however, restrictive measures are currently not in place in all countries, and neither are they implemented in all settings *(7, 12, 14, 29, 30, 34, 36)*. Establishing an international framework for antibiotic stewardship is urgently needed, as are regulatory measures enforcing the implementation of antibiotic stewardship programmes, including restrictive measures *(12, 34, 35)*. •

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References

1. World Health Organization. Antimicrobial resistance - Global report on surveillance. 2014. Available at: http://www.who.int/drugresistance/documents/surveillancereport/en/
2. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. *Lancet Infect Dis.* 2013;13(12):1057-98
3. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis.* 2014;14:13
4. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet.* 2007;369(9560):482-90
5. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis.* 2014;14(8):742-50
6. Pulcini C, Botelho-Nevers E, Dyar OJ, Harbarth S. The impact of infectious disease specialists on antibiotic prescribing in hospitals. *Clin Microbiol Infect.* 2014. [E-published ahead of print].
7. Dyar OJ, Pagani L, Pulcini C. Strategies and Challenges of Antimicrobial Stewardship in Long-Term Care Facilities. *Clin Microbiol Infect.* 2014. [In press].
8. Dellit TH, Owens RC, McGowan JE, Jr., Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis.* 2007;44(2):159-77.
9. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev.* 2013;4:CD003543.
10. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev.* 2005(4):CD003539.
11. Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. *J Antimicrob Chemother.* 2014;69(7):1748-54.
12. Howard P, Pulcini C, Levy Hara G, West RM, Gould IM, Harbarth S, et al. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals *J Antimicrob Chemother.* 2014. [In press].
13. Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. *Virulence.* 2013;4(2):192-202.
14. Huttner B, Harbarth S, Nathwani D. Success stories of implementation of antimicrobial stewardship: a narrative review. *Clin Microbiol Infect.* 2014. [E-published ahead of print].
15. Dumartin C, Rogues AM, Amadeo B, Pefau M, Venier AG, Parneix P, et al. Antibiotic usage in south-western French hospitals: trends and association with antibiotic stewardship measures. *J Antimicrob Chemother.* 2011;66(7):1631-7.
16. Standiford HC, Chan S, Tripoli M, Weekes E, Forrest GN. Antimicrobial stewardship at a large tertiary care academic medical center: cost analysis before, during, and after a 7-year program. *Infect Control Hosp Epidemiol.* 2012;33(4):338-45.
17. Australian Commission on Safety and Quality in Healthcare. Antimicrobial stewardship in Australian hospitals. 2011. Available at: http://www.safetyandquality.gov.au/our-work/healthcare-associated-infection/antimicrobial-stewardship/book/
18. Fleet E, Gopal Rao G, Patel B, Cookson B, Charlett A, Bowman C, et al. Impact of implementation of a novel antimicrobial stewardship tool on antibiotic use in nursing homes: a prospective cluster randomized control pilot study. *J Antimicrob Chemother.* 2014;69(8):2265-73.
19. Gillespie E, Rodrigues A, Wright L, Williams N, Stuart RL. Improving antibiotic stewardship by involving nurses. *Am J Infect Control.* 2013;41(4):365-7.
20. Lesprit P, Landelle C, Girou E, Brun-Buisson C. Reassessment of intravenous antibiotic therapy using a reminder or direct counselling. *J Antimicrob Chemother.* 2010;65(4):789-95.
21. Arda B, Sipahi OR, Yamazhan T, Tasbakan M, Pullukcu H, Tunger A, et al. Short-term effect of antibiotic control policy on the usage patterns and cost of antimicrobials, mortality, nosocomial infection rates and antibacterial resistance. *J Infect.* 2007;55(1):41-8.
22. Mondain V, Lieutier F, Dumas S, Gaudart A, Fosse T, Roger PM, et al. An antibiotic stewardship program in a French teaching hospital. *Med Mal Infect.* 2013;43(1):17-21.
23. Buising KL, Thursky KA, Robertson MB, Black JF, Street AC, Richards MJ, et al. Electronic antibiotic stewardship--reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting. *J Antimicrob Chemother.* 2008;62(3):608-16.
24. Buyle FM, Metz-Gercek S, Mechtler R, Kern WV, Robays H, Vogelaers D, et al. Development and validation of potential structure indicators for evaluating antimicrobial stewardship programmes in European hospitals. *Eur J Clin Microbiol* Infect *Dis.* 2013;32(9):1161-70.
25. Cheng AC, Turnidge J, Collignon P, Looke D, Barton M, Gottlieb T. Control of fluoroquinolone resistance through successful regulation, Australia. *Emerg Infect Dis.* 2012;18(9):1453-60.
26. Cizman M, Beovic B, Krcmery V, Barsic B, Tamm E, Ludwig E, et al. Antibiotic policies in Central Eastern Europe. *Int J Antimicrob Agents.* 2004;24(3):199-204.
27. Cizman M, Srovin T, Pokorn M, Cad Pecar S, Battelino S. Analysis of the causes and consequences of decreased antibiotic consumption over the last 5 years in Slovenia. *J Antimicrob Chemother.* 2005;55(5):758-63.
28. Sorensen TL, Monnet D. Control of antibiotic use in the community: the Danish experience. Infect Control Hosp Epidemiol. 2000;21(6):387-9.
29. Moro ML, Gagliotti C. Antimicrobial resistance and stewardship in long-term care settings. *Future Microbiol.* 2013;8(8):1011-25.
30. Rhee SM, Stone ND. Antimicrobial stewardship in long-term care facilities. *Infect Dis Clin North Am.* 2014;28(2):237-46.
31. Cookson B, Mackenzie D, Kafatos G, Jans B, Latour K, Moro ML, et al. Development and assessment of national performance indicators for infection prevention and control and antimicrobial stewardship in European long-term care facilities. *J Hosp Infect.* 2013;85(1):45-53.
32. Burke JP. Antibiotic resistance--squeezing the balloon? *JAMA.* 1998;280(14):1270-1.
33. Linkin DR, Paris S, Fishman NO, Metlay JP, Lautenbach E. Inaccurate communications in telephone calls to an antimicrobial stewardship program. *Infect Control Hosp Epidemiol.* 2006;27(7):688-94.
34. Carlet J, Piddock LJ, Pulcini C. Antibiotic resistance: A geopolitical issue. *Clin Microbiol Infect.* 2014. [E-published ahead of print].
35. Carlet J, Jarlier V, Harbarth S, Voss A, Goossens H, Pittet D. Ready for a world without antibiotics? The Pensieres Antibiotic Resistance Call to Action. *Antimicrob Resist Infect Control.* 2012;1(1):11.
36. Huttner B, Goossens H, Verheij T, Harbarth S. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *Lancet Infect Dis.* 2010;10(1):17-31.

ANTIMICROBIAL RESISTANCE AND THE ENVIRONMENT

THE ROLE OF SANITATION IN THE DEVELOPMENT AND SPREAD OF ANTIMICROBIAL RESISTANCE

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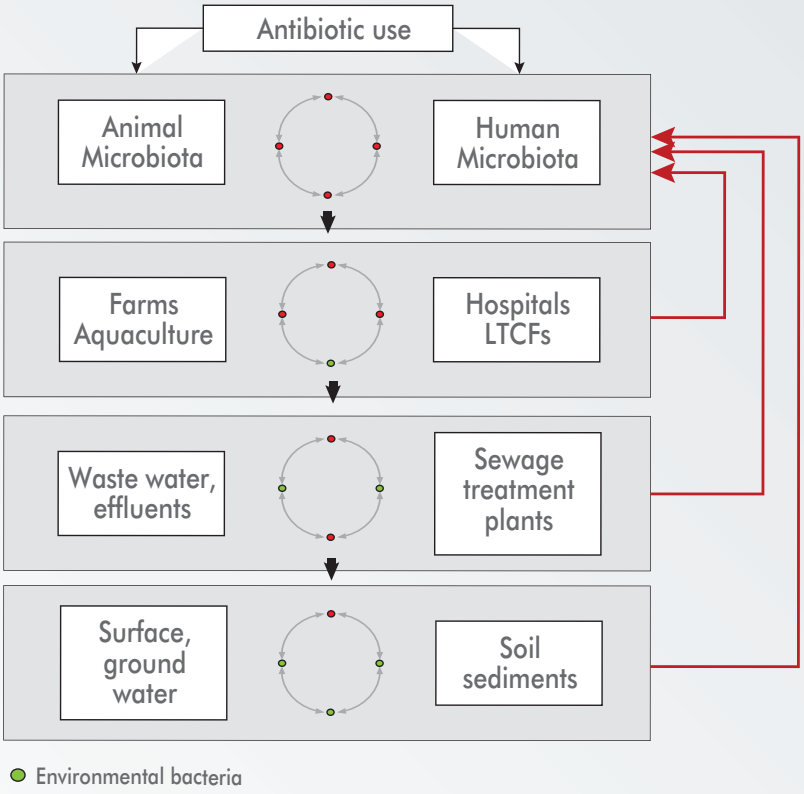
Many studies on antibiotic resistance (AR) focus on hospital infections yet in developing countries where sanitation is so poor, the continuous recycling of antibiotic resistant bacteria in poor communities invariably impacts on the health of those communities, the life span of the individual and represents a financial burden. More studies are urgently needed examining the risk factors for carriage of AR bacteria and their impact on human infections and wellbeing. Greater political commitment is required and a global awareness campaign encapsulating a "one world health" message, as, invariably, it is an issue that has global ramifications.

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 the level of AMR in the environment. The argument that resistance starts in a hospital and then spreads into the community or environment is often inaccurate and most certainly naïve. There is little evidence that few, if any, new antibiotic resistance mechanisms (ARMs) were acquired by bacteria in health settings yet there is some substantial evidence that clinically relevant bacteria have acquired ARMs from environmental bacteria typified by the sequestration of the CTM-X-15 gene by E. coli from environmental *Kluyvera* spp. and has now become the globally dominant extended spectrum β-lactamase *(1–4)*.

There is a significant documented problem of AMR occurring between animal, human and environmental sectors, including water bodies and soil (Fig. 1). Antibiotic resistant bacteria (and the antibiotics themselves) are excreted with effluents and sewage into the environment, and from there re-contaminate humans and animals via drinking water or food. This does not only concern antibiotic resistant bacteria but also antibiotics entering the eco-system mediating direct resistance and collateral damage. Once antibiotics enter the ecosystems, they can influence bacterial populations *(5)*, and correspondingly influence potable water *(6, 7)*. Accordingly, critics have commented on the long-term impact of antibiotic remnants in aquatic and semi-aquatic environments *(8–10)*. India produces about 40% of the world's antibiotics and has been commended by WHO for supplying the world with miracle drugs but the contamination in the Indian (and generally throughout South Asia) environment with antibiotics is immense. Antibiotics can enter sewerage treatment plants (STPs) through human excretion, farm animals and the direct disposal of medical and industrial wastes. Some antibiotics are removed through the degradation and sorption to biosolids during treatment plant processes, such as the secondary and tertiary stages *(11)*, but not all antibiotics are completely removed *(12)*. Studies by Al-Ahmad et al. (2009) and Wiethan et al. (2000) suggest that bacteria, which have already shown resistance to antibiotics, will not necessarily have a selective advantage in sewage treatment *(13, 14)*.

Of greatest concern is the production and gross environmental contamination with fluoroquinolones (e.g. ciprofloxacin), once considered the perfect antibiotic. Studies have shown therapeutic levels of ciprofloxacin in Indian rivers and if the elegant studies of Beaber and colleagues are extrapolated to South Asia, this would indicate a colossal level of gene transfer happening in and between bacteria in this part of the world *(15)*. This antibiotic load or pressure is further exacerbated by the levels of poorly degraded antibiotics contained in peoples normal flora that either enter sewerage treatment plants or worryingly, through open defecation.

Figure 1: The main digestive or environmental reservoirs of AMR to which the worldwide human community belongs and is also exposed



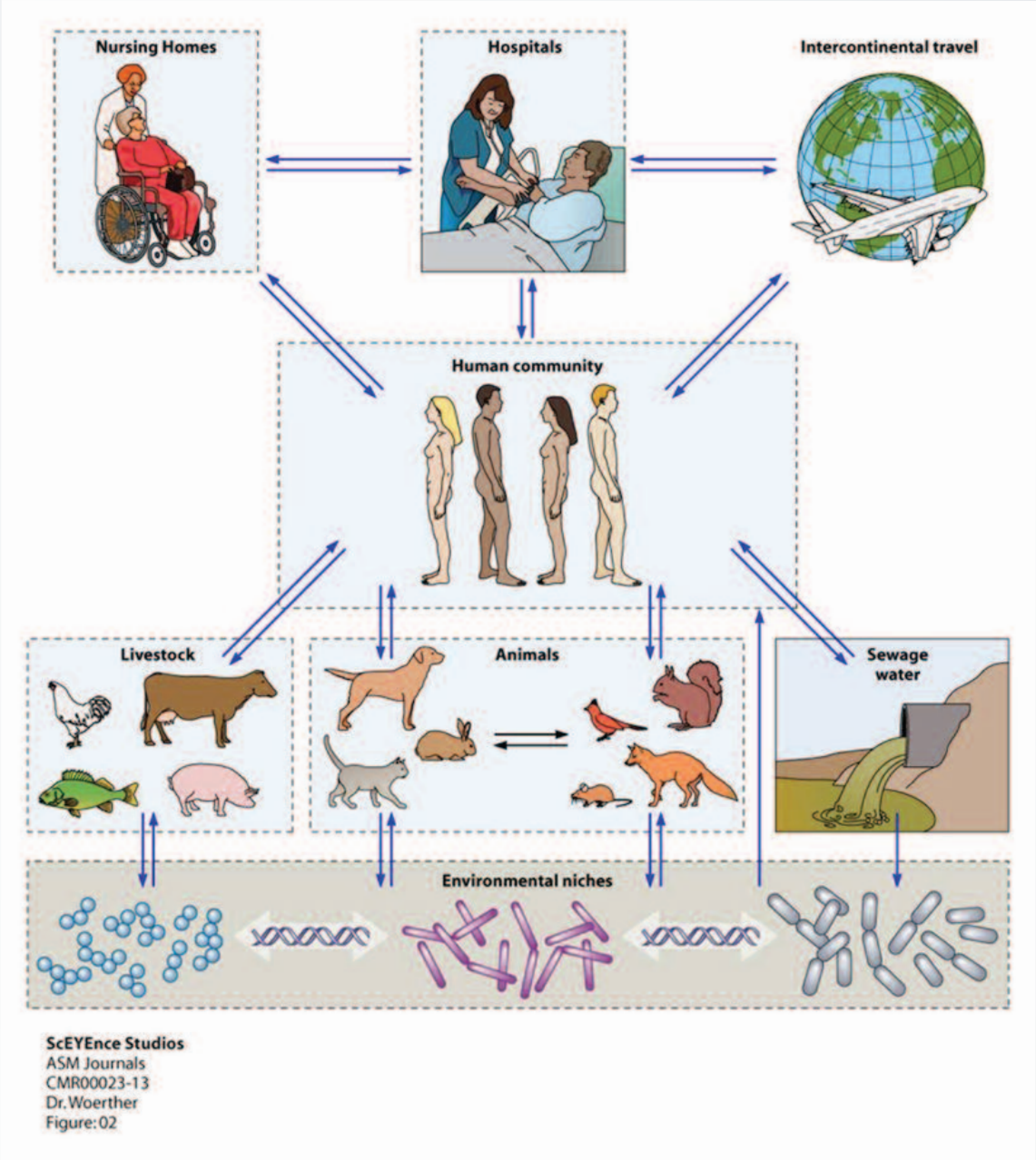
The major interrelations between human and animal activities and the water system are obvious in many parts of the world. Above is a representation of the main digestive or environmental reservoirs of AMR to which the worldwide human community belongs and is also exposed. Each independent reservoir is included in a dashed black outline, inside which cross-transmission may occur. Arrows show the flux of ESBL-E from one reservoir to another. Environmental niches comprise mainly water, soils and plants, where genetic material exchanges between bacteria of digestive and/or environmental origin occur. From Woerther PL et al. Clin. Microb. Rev. 2013 (3).

Aside from the chemical pollution caused by antibiotics, invariably they will increase the development and subsequent spread of antibiotic resistant bacteria (ARB) and antibiotic resistant genes (ARGs) – particularly those associated with mobile genetic elements i.e. DNA structures that mediate the transfer of resistance genes between bacteria e.g. plasmids *(6, 17)*. (Fig. 2). Large amounts of antibiotics are released into municipal waste due to the incomplete metabolism (e.g. fluoroquinolones) of humans or due to disposal of unused antibiotics resulting in the detection of ARBs and ARGs *(18-23)*. In India a simple point of prevalence study involving 171 seepage samples and 50 tap water samples from New Delhi detected ^{bla}NDM-1 in two of 50 drinking-water samples and 51 of 171 seepage samples. Bacteria containing ^{bla}NDM-1 included *Shigella boydii* and *Vibrio cholera* and the gene was shown to be carried on plasmids that can be easily transmissible between unrelated bacteria. Worryingly, the transfer of the plasmids was more common at 30°C than at 25°C or 37°C which corresponded to the mean annual temperature of New Delhi indicating that transfer of resistance genes can readily transfer in human waste and treatment plants in South Asia *(16)*.

Aside from the chemical pollution caused by antibiotics, invariably they will increase the development and subsequent spread of antibiotic resistant bacteria (ARB) and antibiotic resistant genes (ARGs)

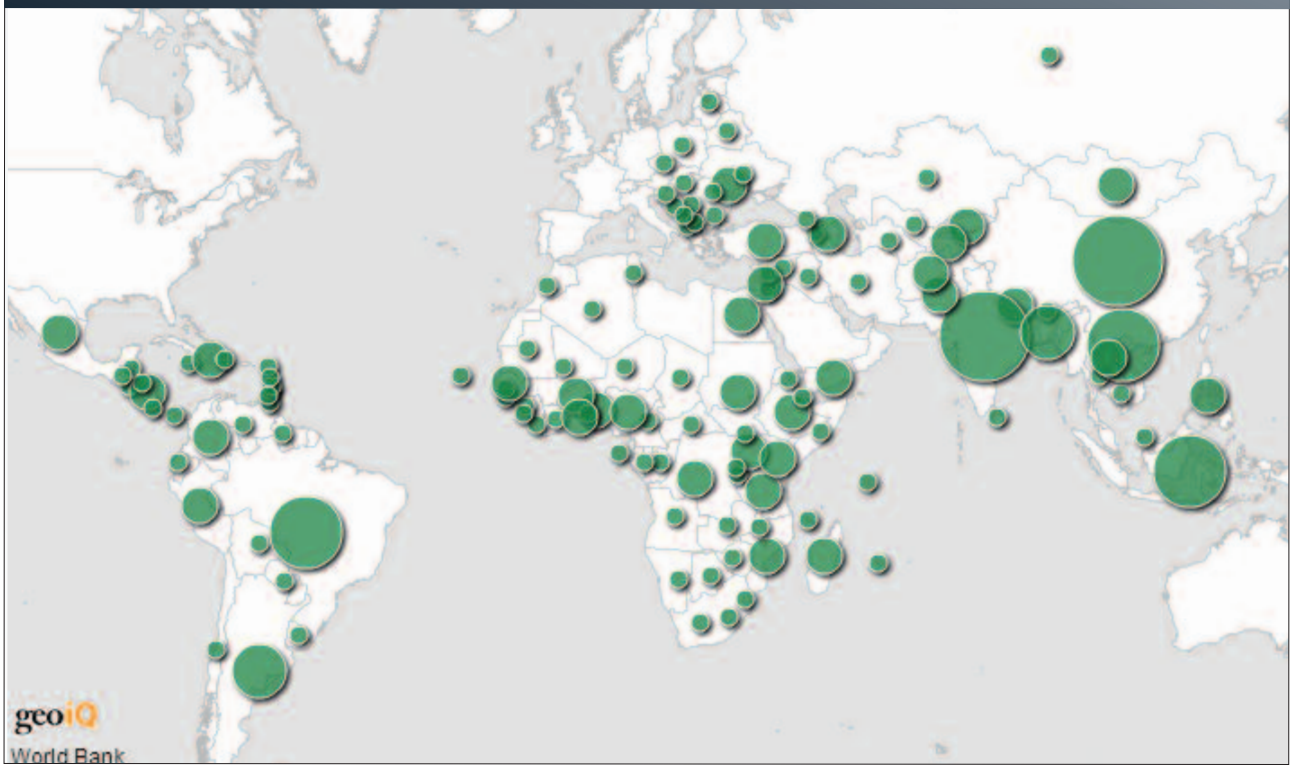
The spread of resistance in an eco-system occurs proportionally to the lack of sanitation, as shown by the contamination in the South Asian environment with not only

Figure 2: The four reactors for the antibiotic-promoted genetic evolution



extended-spectrum beta-lactamases but also carbapenemase-producing Enterobacteriaceae. But Western countries are also affected by the problem, as shown by the cases of MRSA on pig farms in Holland and neighbouring countries or in the deadly cases in Germany involving the multi-resistant E. coli O104:H4 strain. It is also highly suspected that ESBL E. coli that cause infections in humans are acquired, at least in part, through the food chain. However, there is very little known as to the true level of contamination with antibiotic resistant bacteria between humans and animals via the surrounding environment or the food chain. Environmental contamination in developing counties directly affects the level of cleanliness in food products and therefore treatment of both animal and human

Figure 3: World Bank map of countries with critically high sanitation needs – the larger the circle, the greater the need



sewerage becomes critical.

Whilst it has been known for some time that Enterococci, particular VRE, from the environment has impacted on the fecal carriage and ultimately infections in humans; the notion that human waste could impact significantly on human health has been particularly enhanced by multi-drug resistant Enterobacteriaceae. The fact that all humans and animals usually carry *E. coli* as part of their fecal flora and that this organism causes the majority of community acquired disease; mainly arising from endogenous sources, demonstrates their significance. Humans and animals are walking microcosms and can carry between 10–100 trillion bacteria and 1010-12 bacteria/gram of feces. Thus the management of waste at a human and animal level is essential in lessening the burden of environmental AMR bacteria that can cause untreatable infections in the community.

Although animal waste is a constant concern, there is a lack of adequate sewage systems in countries such as India, Bangladesh, Pakistan, China, African and South American countries to deal with human and animal's waste. Moreover, in South Asia (India, Pakistan and Bangladesh) and many parts of Africa the vast majority of people eat with their fingers and are reliant on domestic cleaning agents to prevent cross-contamination. In many households in these countries there are precious few cleaning agents and the eating surfaces are possibly contaminated with fecal

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bacteria and thus the constant recycling from humans to the environment and visa versa is destined to continue ad perpetuum. In the "West" and in SE Asia where chopsticks are used to consume food there is at least a physical barrier between the environment and the oral cavity. Few studies have studied the impact of eating with your hands and its subsequent impact on the AMR load in the gut compared with the immediate environment.

The WHO-UNICEF Joint Monitoring Program (JMP) for Water and Sanitation, which tracks progress towards the water and sanitation targets of the Millennium Development Goals, estimates that 36% of the world's population, or 2.5 billion people, lack access to an improved sanitation facility, defined by the JMP as "one that hygienically separates human excreta from human contact" *(24)*. This situation

Currently, it is public funding or charitable funds that support such schemes and it is a sad fact that invariably demand outweighs the financial resources – often national governments do not see this issue as a priority and almost certainly fail to understand the indelible link between sanitation and the containment of human pathogens

means that a large proportion of the world's people live at risk of contamination of their environment by human fecal matter (Fig. 3). UN figures show that approximately 700 million Indian people alone lack sanitation and that by 2020 China will have to process 500 billion tons/year of human waste. In Europe we have very little data on environmental contamination and its effects on antibiotic resistance particularly from the newer regions. Despite these worrying facts, sewerage treatment struggles to meet demands in rural areas in China, the Pakistani government have announced cut-backs in public funding for sanitation, and the Indian sewage system will continually lag behind through serious under-investment (Fig. 3). Currently, it is public funding or charitable funds that support such schemes and it is a sad fact that invariably demand outweighs the financial resources – often national governments do not see this issue as a priority and almost certainly fail to understand the indelible link between sanitation and the containment of human pathogens. Environmental risk factors for the dissemination of AMR bacteria have not been adequately assessed and while ad-hoc studies have examined the effects of antibiotic contamination on AMR, these are small-point prevalence surveys and lack structure to identify risk factors e.g. flooding. Food contamination, particularly in relation with environmental contamination, is another area that has lacked a systematic analysis particularly with regard to local markets and exported meat into Europe. The role of animals in AMR in these countries also remains underexplored.

Data from small studies and preliminary data from larger studies estimate that in the India/Pakistan alone over 200 million people carry carbapenemase-positive as normal flora and thus the potential for highly resistant strains to be continually recycled throughout and inter-communities is immense (Walsh, unpublished data). Whilst portable sewerage treatments are being piloted in these areas lacking sanitation, there is not a systematic publicly funded programme seriously addressing these issues or the impact this will have on the environment, animals, food contamination and potable water with regard to AMR. Reducing pathogen load or destroying plasmid DNA in the environment will significantly lessen the burden of MDR in communities and correspondingly in hospitals, and reduce the health and financial burden in developing countries.

Sewerage treatment generally involves three stages: primary, secondary and tertiary treatment. In primary treatment, solids are removed by physical operations. In secondary treatment, biological and chemical processes are used to remove most of the organic matter. In tertiary or advanced treatment, additional processes (e.g. nutrient removal, removal of toxic materials, additional organic and suspended solids removal) are used to remove components. During all these processes, considerable changes occur in the distribution of the bacterial population *(25)*. The general observation in literature is that treatment determines a significant reduction in the bacterial numbers, including the total numbers of resistant bacteria *(26, 27)*. It has also been suggested that STPs concentrate AMR bacteria. Currently, no controlled studies have been undertaken comparing STPs to open defecation in countries where sanitation is pitifully poor. However, reports state that wastewater, or even treated wastewater, contain higher proportions of various resistant bacterial populations in relation to the respective proportions contained in surface water *(27)*.

There is very little doubt that the exchange of genetic information between bacteria does occur in sewerage treatment plants (STPs) and some commentaries have suggested STPs as epicentres of antibiotic resistance exchange *(27)*. According to these studies, the conditions in STPs are favourable for the exchange of resistance genes from AMR bacteria to susceptible bacteria. Several studies

The published information about water and sewage decontamination procedures with respect to antibiotic resistance remains extremely scarce, and it is urgent to design actions to fill this critical gap

indicated that the environmental conditions in wastewater treatment plants may enhance the likelihood of gene transfer *(28)*. However, links are not yet well established between the presence of antibiotics in STPs and the favouring of resistant bacteria as well as the transfer of resistance at concentrations as low as those found for antibiotics in the environment. There is also very little data on whether the mechanics applied in STPs accelerates the exchange of genetic material between bacteria and at what stage of the treatment process if any, would this happen. What is also not well understood is the role of bacteriophages in controlling bacteria populations, and thus AMR bacteria populations, in STPs or the environment per se which is an area that warrants significant attention.

The published information about water and sewage decontamination procedures with respect to antibiotic resistance remains extremely scarce, and it is urgent to design actions to fill this critical gap. Specifically, the activities should provide a meta-analysis of current national and international activities concerning the situation of waste disposal including the availability of suitably clean potable water, and its relation with the spread of antibiotic resistant organism among humans and animals. Related to this meta-analysis, is information on antimicrobial resistance and whether community carried AR/community acquired infections is a key concern.

Decontamination procedures of antibiotic resistant organisms and resistance resistant platforms, as well as antibiotic detoxification in water and soil should be explored. Currently, there are a number of technologies to purify wastewater but do not necessarily address the issue of environmental decontamination with AMR populations. Eventually, a number of these interventions might even contribute to the selection of resistant bacteria. Thus we should explore the merits of these technologies and whether they can contribute to a holistic initiative that will potentially eradicate antibiotic resistant populations and avoid re-colonization. Currently, international studies are on an ad-hoc basis with very little international collaboration.

The overriding issue addressing AMR is a sociopolitical one and sanitation is but one of many factors that contribute to the creation and dissemination of AMR in communities particularly developing communities. Health systems in South and SE Asia are a mixture of public and private and therefore implementing a national system for AMR surveillance and infection control practices will be extremely challenging. Many of these countries do not commit to a national health system and seemingly public expenditure on sanitation is also pitifully inadequate. Regrettably, these countries also have rapidly growing economies (Brazil, China, India and Thailand) and are vying for the global export market in poultry by 2030 and some are, bizarrely, promoting medical tourism as an unmet global medical need. And thus, we are faced with a paradox whereby the environment is carelessly being continually contaminated and yet international trade is being promoted that has direct contacted with that environment. When Indian Prime Minister Modi came into power is mantra was "a clean India" – an admirable notion, but as *Time Magazine* pointed out in 2013 *(29)*, there is still a vast amount to do – not least change the mind set of citizens and plan for the long term. Regrettably, such noble intentions cost money and thus often lack political traction which is the core root of this entire problem. •

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References

1. Poirel L, Kämpfer P, Nordmann P. Chromosome-encoded Ambler class A beta-lactamase of Kluyvera georgiana, a probable progenitor of a subgroup of CTX-M extended-spectrum beta-lactamases. *Antimicrob Agents Chemother.* 2002 Dec;46(12):4038-40.
2. Lartigue MF, Poirel L, Aubert D, Nordmann P. In vitro analysis of ISEcp1B-mediated mobilization of naturally occurring beta-lactamase gene blaCTX-M of Kluyvera ascorbata. *Antimicrob Agents Chemother.* 2006 Apr;50(4):1282-6.
3. Nordmann P, Lartigue MF, Poirel L. Beta-lactam induction of ISEcp1B-mediated mobilization of the naturally occurring bla(CTX-M) beta-lactamase gene of Kluyvera ascorbata. *FEMS Microbiol Lett.* 2008 Nov;288(2):247-9.
4. D'Andrea MM, Arena F, Pallecchi L, Rossolini GM. CTX-M-type β-lactamases: a successful story of antibiotic resistance. *Int J Med Microbiol.* 2013 Aug;303(6-7):305-17.
5. Aminov, R.I., Mackie, R.I., 2007. Evolution and ecology of antibiotic resistance genes. FEMS Microbiol. Lett. 271, 147–161. 6. Thiele-Bruhn, S., Beck, I.C., 2005. Effects of sulfonamide and tetracycline antibiotics on soil microbial activity and microbial biomass. *Chemosphere* 59, 457–465.
7. Kotzerke, A., Sharma, S., Schauss, K., Heuer, H., Thiele-Bruhn, S., Smalla, K., Wilke, B.M., Schloter, M., 2008. Alterations in soil microbial activity and N-transformation processes due to sulfadiazine loads in pig-manure. *Environ. Pollut*. 153, 315–322.
8. Sarmah, A.K., Meyer, M.T., Boxall, A.B.A., 2006. A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. *Chemosphere* 65, 725–759.
9. Wright, G.D., 2007. The antibiotic resistome: the nexus of chemical and genetic diversity. *Nat. Rev. Microbiol.* 5, 175–186.
10. Kemper, N., 2008. Veterinary antibiotics in the aquatic and terrestrial environment. *Ecol. Indic.* 8, 1–13.
11. Batt, A.L., Snow, D.D., Aga, D.S., 2006. Occurrence of sulfonamide antimicrobials in private water wells in Washington County, Idaho, USA. *Chemosphere* 64, 1963–1971.
12. Giger, W., Alder, W.A.C., Golet, E.M., Kohler, H.P.E., McArdell, C.S., Molner, E., Siegrist, H., Suter, M.J.-F., 2003. Occurrence and fate of antibiotics as trace contaminants in wastewater, sewage sludges, and surface waters. *Chimia* 57, 485–491.
13. Al-Ahmad, A., Hai, A., Unger, J., Brunswick-Tietze, A., Wiethan, J., Kummerer, K., 2009. Effects of a realistic mixture of antibiotics on resistant and non-resistant sewage sludge bacteria in laboratory-scale treatment plants. *Arch. Environ. Contam. Toxicol.* 57, 264–273.
14. Wiethan, J., Al-Ahmad, A., Henninger, A., Kmmerer, K., 2000. Simulation of the selection pressure of the antibiotics ciprofloxacin and ceftazidim in surface water with classical methods. Vom Wasser 95, 107–118.
15. Beaber JW, Hochhut B, Waldor MK. SOS response promotes horizontal dissemination of antibiotic resistance genes. *Nature.* 2004 Jan 1;427(6969):72-4.
16. Walsh TR, Weeks J, Livermore DM, Toleman MA. dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infect Dis.* 2011 May;11(5):355-62.
17. Nagulapally, S.R., Ahmad, A., Henry, A., Marchin, G.L., Zurek, L., Bhandari, A., 2009. Occurrence of ciprofloxacin-, trimethoprimesulfamethoxazole-, and vancomycin-resistant bacteria in a municipal wastewater treatment plant. *Water Environ. Res.* 81, 82–90.
18. Zhang, T., Zhang, M., Zhang, X., Fang, H.H., 2009a. Tetracycline resistance genes and tetracycline resistant lactose-fermenting Enterobacteriaceae in activated sludge of sewage treatment plants. *Environ. Sci. Technol.* 43, 3455–3460.
19. Zhang, Y., Marrs, C.F., Simon, C., Xi, C., 2009b. Wastewater treatment contributes to selective increase of antibiotic resistance among Acinetobacter spp. *Sci. Total Environ.* 407, 3702–3706.
20. Selvaraj KK, Sivakumar S, Sampath S, Shanmugam G, Sundaresan U, Ramaswamy BR. Paraben resistance in bacteria from sewage treatment plant effluents in India. *Water Sci Technol.* 2013;68(9):2067-73.
21. Rutgersson C, Fick J, Marathe N, Kristiansson E, Janzon A, Angelin M, Johansson A, Shouche Y, Flach CF, Larsson DG. Fluoroquinolones and qnr genes in sediment, water, soil, and human fecal flora in an environment polluted by manufacturing discharges. *Environ Sci Technol.* 2014 Jul 15;48(14):7825-32.
23. Chakraborty R, Kumar A, Bhowal SS, Mandal AK, Tiwary BK, Mukherjee S. Diverse gene cassettes in class 1 integrons of facultative oligotrophic bacteria of River Mahananda,West Bengal, India. *PLoS One.* 2013 Aug 9;8(8):e71753.
24. WHO-UNICEF (2014) Progress on Drinking Water and Sanitation: 2014 update. Available: http://www.unicef.org/media/files/JMP_2014_Update.pdf. Accessed 21 July 2014.
25. Wagner, M., Loy, A., 2002. Bacterial community composition and function in sewage treatment systems. *Curr. Opin. Biotechnol.* 13, 218–227.
26. Bouki C, Venieri D, Diamadopoulos E. Detection and fate of antibiotic resistant bacteria in wastewater treatment plants: a review. *Ecotoxicol Environ Saf.* 2013 May;91:1-9.
27. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A,Bergstrom R, Wright GD, Brown ED, Cars O. Antibiotic resistance-the need for global solutions. *Lancet Infect Dis.* 2013 Dec;13(12):1057-98.
28. Davies, J., 2012. Sanitation: sewage recycles antibiotic resistance. *Nature* 487, 302.
29. Time Magazine. Reinventing India: can India recover some of its magic? October 2012.
30. Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the globalization of CTX-*M. Clin Microbiol Rev.* 2013 Oct;26(4):744-58.

CONFRONTING ANTIMICROBIAL RESISTANCE

DIAGNOSTIC SOLUTIONS CRITICAL TO LIMIT ANTIMICROBIAL RESISTANCE DEVELOPMENT

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Today, patients with suspected infections receive empirical treatment, unguided by laboratorial bacteriology, resulting in the overuse of antimicrobials, the emergence of drug resistance and a rapidly dwindling inventory of effective antimicrobials. Emerging diagnostic technologies have the potential to ameliorate this situation by fostering rapid and precise diagnosis and the early refinement of antibiotic therapy, making diagnosis central to the battle against antimicrobial resistance. While innovative technology platforms exist that enable the differentiation of pathogen classes and the detection of specific pathogens and their resistance profile with speed, sensitivity and ease of use, there are major challenges to the development, regulatory pathway and clinical integration of diagnostic tests that employ these recent technological advancements. In order to foster the development of appropriate diagnostics necessary to address the AMR crisis, creative solutions are needed. Specifically, we need to make a better case for the economic benefits of diagnostics to induce changes in the funding landscape, attract new funding partners, and enhance funding coordination among donors. Furthermore, we need to create incentives to attract manufacturers to this field. This includes addressing regulatory challenges and improving the diagnostic ecosystem, notably in low-income countries, to accelerate uptake of new tools.

Despite significant advances in diagnostic technologies, many patients with suspected infections receive empiric antimicrobial therapy without prior identification of the causative agent. The result is overuse of a small arsenal of effective antibiotics, and the spread of antimicrobial resistance (AMR) at an alarming pace, with more than 500,000 deaths from resistant infections in the world annually.

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. The actions necessary to deal with the AMR threat have been identified by health authorities and principally come down to the following:

- Create awareness among stakeholders of the AMR threat and align them on the principles of antibiotic stewardship and appropriate use of antibiotics;
- Through regulation, avoid the overuse of antibiotics in humans and farm animals and restrict use to the appropriate infections;
- Improve sanitation, hygiene, infection prevention and control measures to increase the likelihood that infection is prevented, thereby reducing the need for antibiotics;
- Enhance surveillance of resistance and monitoring of antibiotic usage in humans and animals to achieve a better understanding of the magnitude of the AMR problem.

A central component and enabler of all four action points is appropriate diagnosis to clarify the etiology of the illness in order to target treatment and quantify the problem, and create an effective public health surveillance and response mechanism. Today, we do not have the diagnostic tools to effectively address AMR. We need easy-to-use and affordable tests that are rapid enough to have a positive

impact on patient care, can identify a specific pathogen or, at a minimum, distinguish between bacterial, viral and parasitic infections, and also provide information on susceptibility to antimicrobial agents. Connectivity and electronic health aspects are critical to ensuring that the results can be effectively communicated to health-care providers, and are actually used to guide care and control efforts.

Challenges to better diagnostics

The rapid and accurate establishment of a microbial cause is central to providing quality care. However, the process of clinical bacteriology remains antiquated, with timing determined by the speed of bacterial growth. Usually, it takes one day to grow bacteria from the clinical specimen and another to identify and measure antibiotic susceptibility; for diseases like tuberculosis, it takes from two to eight weeks to grow the bacteria and several more weeks to determine the resistance profile. Emerging diagnostic technologies have the potential to ameliorate this situation by fostering rapid and precise diagnosis and the early refinement of antibiotic therapy. For example, new antigen detection methods can improve the accuracy of detecting pneumococcal antigens in urine and thus enable rapid diagnosis of pneumonia. Molecular tools may hold even greater promise to increase the speed and sensitivity of pathogen identification and can be combined with drug resistance detection. In the case of tuberculosis, for example, the time to diagnosis of multidrug resistance has decreased from several months to two hours through the introduction of Xpert MTB/RIF, a game-changing molecular test. The utilization of molecular assays is increasing for the detection of all infectious organisms, in particular for the diagnosis of viral illnesses. Newer automated tests allow for use at the point of care and can detect multiple different causative organisms to provide a comprehensive diagnostic panel for major clinical syndromes (e.g. fever and respiratory symptoms or unspecified fever). In addition, there are alternative methods, such as mass spectrometry, that hold great potential to improve the ability to detect infectious organisms and resistance, and to do so rapidly. While these types of tests are currently confined to high-resource settings miniaturization efforts are underway.

Such tests need to be complemented with triaging tests that can be used by clinical staff to differentiate between causative organism classes (i.e. viral, bacterial or parasitic) and thus guide initial empiric therapy prior to the availability of more comprehensive results. More research and development is urgently required to identify differentiating biomarkers. Inflammatory markers, such as a white blood cell count or acute phase proteins (e.g. C-reactive protein) are not specific enough. Procalcitonin (PCT) is thus far the only potentially more specific marker for bacterial infections. It is released in response to bacterial infections and correlates with their extent and severity. However, all data available to date has evaluated the use of PCT in the context of pneumonia or sepsis in high-resource settings. There are currently no data available from low-resource settings where, for example, malaria or tuberculosis are endemic and co-infections are often present. Therefore, the utility of PCT in these contexts remains to be proven. Other approaches to triaging markers to differentiate viral, bacterial or parasitic diseases have been studied, but no marker besides PCT has penetrated clinical care to date.

Newer automated tests allow for use at the point of care and can detect multiple different causative organisms to provide a comprehensive diagnostic panel for major clinical syndromes (e.g. fever and respiratory symptoms or unspecified fever)

Much progress has been made in enabling the detection and quantification of pathogen burden with speed, sensitivity and ease of use; however, there are major challenges to the development, regulatory pathway and clinical integration of diagnostic tests that employ these recent technological advancements. While diagnostics are significantly less costly to develop compared to drugs or vaccines for infectious diseases, the process required to develop and introduce tests that can be used in diverse settings, including in low-resource countries, is not without its challenges. In order to halt and reverse the trend of spreading drug resistance, new tests would need to be implemented in diverse settings ranging from hospital intensive care units, outpatient clinics, and point-of-care (POC) environments in villages in the developing world and other remote areas without access to reliable power supply or where high temperatures are a major consideration. Diagnostic tests to accommodate these settings should be affordable, sensitive, specific, user-friendly, robust and rapid, equipment-free and deliverable (ASSURED tests). Testing should be feasible using minimally invasive sample types and simple enough to be executed by personnel

Much progress has been made in enabling the detection and quantification of pathogen burden with speed, sensitivity and ease of use; however, there are major challenges to the development, regulatory pathway and clinical integration of diagnostic tests that employ these recent technological advancements

without extensive technical skills and potentially by the patient in the home. Besides these test design challenges in terms of robustness and automation, there are multiple other obstacles for manufacturers to achieving commercialization, notably in developing countries. These include a complex regulatory approval landscape, weak health systems and a chronic lack of funding for procurement. In addition there are numerous phases where development may confront significant hurdles: biomarker selection, prototype development and technical validation; manufacturing validation; performance evaluation and clinical validation; and endorsement and scale-up. The successful introduction of a new diagnostic will require effective collaboration with companies, the health-care sector, the World Health Organization, and health ministries, leaving private firms with numerous impediments when attempting to bring new tests to market in the various settings.

Recommendations to accelerate the development of diagnostics

In order to foster the development of the appropriate diagnostics necessary to address the AMR crisis, creative solutions are needed. These include the following:

- Make the case for the economic benefits of diagnostics. All stakeholders need to be better educated on the importance of diagnostics in the fight against AMR. If they gain a better understanding of the value of diagnostics to world health, they are more likely to increase their investments in diagnostic development, and ensure appropriate levels of reimbursement for diagnostic testing.
- Attract new funding sources. Historically, funding sources for diagnostics development has been concentrated in the public sector, with the philanthropic sector providing limited funding. More funders will need to be brought into the AMR diagnostic initiative in order to bring diagnostics to fruition. While the health world community has articulated the steps for preventing the spread of drug-resistant bacteria, the risk is that the funding for AMR diagnostics, if prior experience is a guide, is likely to turn out to be inadequate to develop the necessary diagnostics for dealing with AMR. Therefore, if the world health community is to seriously address AMR, it will have to provide sufficient funds for the development programmes necessary to create diagnostics. In the past, the focus has been on the development of new antibiotics, and diagnostics are likely to be insufficiently emphasized.
- Enhance funding coordination among donors. As AMR is a global issue, it would behoove governmental bodies and private donors to coordinate funding for diagnostics to establish common priorities and avoid multiple grant applications, underfunding of projects and duplicative research and support. A coordinated network could share information, resulting in better funding decisions.
- Create incentives to attract manufacturers. There is a need to incentivize the development of POC diagnostics that could differentiate between a bacterial and viral infection, and at the same time diagnose specific resistance pattern within hours. While this challenge is a difficult one, if achieved it would be transformational. While diagnostic development costs generally are less expensive than antibiotics or vaccines, price is still a deterrent for manufacturers to enter the marketplace. If manufacturers were provided with scientific and regulatory expertise and funding assistance, they would be incentivized to commercialize diagnostics, and product development would be accelerated. This assistance is of critical importance to smaller or nascent diagnostic manufacturers. Resources for this purpose are already in existence – the diagnostic-focused product development partnerships (PDPs) funded by the Bill and Melinda Gates Foundation and a number of governmental agencies. PDPs, such as the Foundation for Innovative New Diagnostics (FIND) in Geneva, have the requisite experience to assist manufacturers in a) establishing the initial target product profiles; b) conducting clinical trials; c) providing mentoring services; and d) developing other supporting activities to help overcome obstacles to achieve development, adoption and eventual roll-out.
- Address regulatory challenges and accelerate uptake of new tools. There is a need for governmental bodies to clarify and revise conflict of interest policies to allow

collaboration among diagnostic manufacturers, laboratories and opinion leaders in order to meet various regulatory requirements. Other reforms should focus on: better regulatory guidance for development of diagnostics; the harmonization of regulations to enable manufacturers to more rapidly develop and introduce diagnostics worldwide, and strengthen recommendations and training schemes on the use of new tests, with emphasis on changing clinical practices.

Conclusion

Improved diagnostic solutions for the identification of pathogens and resistance patterns are urgently required to limit the spread of AMR in the globalized world and preserve the available drugs to treat infectious diseases. The novel technologies that have emerged in recent years should be leveraged and adapted to develop diagnostic tools that are appropriate for use in developed countries and in low-resource settings to address both direct patient care needs and surveillance. To achieve this, significant funding will be required to integrate diagnostic solutions as a critical tool in a larger AMR control strategy. The world health community has recognized that the need for a solution to AMR has never been greater, but the question remains as to whether there is the political will to limit the unregulated use of antimicrobials in patient care and the nontherapeutic antimicrobial consumption in livestock. Without increased political commitment and funding, the battle against infectious diseases is not likely to be won. •

Dr Catharina Boehme leads FIND, an international non-profit organization based in Geneva, Switzerland that supports the development and delivery of much-needed diagnostic tests for diseases of poverty, including tuberculosis, malaria, hepatitis C, sleeping sickness and other neglected tropical diseases. Since its creation in 2003, FIND has delivered 11 new tests and created an enabling environment for countless more through its specimen banks, reagent development and better market visibility. FIND's achievements have helped increase the global prioritization of diagnostics and in many cases have revolutionized the diagnostics landscape. Dr Boehme holds a Doctor of Medicine in Internal Medicine from Ludwig Maximilians University in Munich, Germany, as well as diplomas in Public Health and in Management & Leadership. Prior to joining FIND in 2005, she worked as programme coordinator for the Department of Infectious and Tropical Diseases in Munich and established a TB research unit at Mbeya Medical Research Program in Tanzania.

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THE ROLE OF IMPROVEMENT SCIENCE IN INFECTION CONTROL





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This chapter discusses the application of the science of improvement (also known as delivery science or implementation science) to infection prevention and control, illustrated through a case study from Namibia. It emphasizes processes and systems that can be targeted to yield reliable and effective results for the prevention of health-care-associated infections. This includes the importance of testing changes and monitoring results as a strategy for continuously improving infection control processes. Collaborative improvement and strengthening the capacity of health workers to produce and sustain results is also emphasized.

Quality care is defined as care that is: safe, effective, patient-centred, timely, efficient and equitable *(1)*. With regards to the dimension of safety, the global burden of disease caused by unsafe medical care presents a significant public health issue. Deaths from medical errors are the third leading cause of death in the United States, following heart disease and cancers *(2)*. Of the 421 million annual global hospitalizations, approximately 42.7 million result in adverse events, resulting in the loss of 23 million disability adjusted-life years (DALYs), two-thirds of which occur in low- and middle-income countries (LMICs) *(3)*. LMICs have five-times the population of high-income countries, and experience 50% more adverse events and related injuries: 25.9 million versus 16.8 million annual injuries *(3)*. A study of seven key adverse events experienced in inpatient hospital settings estimated that unsafe health care is the twentieth leading cause of global morbidity and mortality; this figure is likely to be even higher when accounting for adverse events that occur in ambulatory settings or for which there is poor data *(3, 4)*.

Health-care-associated infections and antimicrobial resistance

The WHO Patient Safety Programme has identified 12 key adverse events which contribute most to the global burden of disease for unsafe medical care. These include:

- adverse drug events (ADEs);
- catheter-related urinary tract infections (CR-UTIs);
- catheter-related blood stream infections (BSIs);
- nosocomial pneumonia;
- venous thromboembolisms (VTEs);
- falls;
- pressure ulcers;
- substandard or counterfeit drugs;
- unsafe blood products;
- unsafe injections;
- medical devices; and
- surgical errors *(4)*.

Health-care-associated infections (HAIs) are linked to many of these adverse events, and are a key source of the global disease burden of unsafe medical care. Furthermore, while HAIs are a key issue across country settings, a 2010 systematic review estimates that HAIs are two- to three-times more prevalent in low-income countries than in high-income countries *(5)*.

HAIs prolongs hospital stays, increase mortality rates and raise health-care costs. A study of over 1,000 intensive care

units (ICUs) in 75 countries found that about half of patients were infected, and that infected patients were two-times more likely to die in the ICU than uninfected patients *(6)*. While HAIs may be caused by a variety of pathogens, including viruses and fungi, approximately 80% of HAIs are caused by eight main bacterial pathogens *(7)*. Antibiotic resistant bacterial infections are a global threat, a 2014 global review by WHO revealed that more than 50% of the common pathogens (*E. coli*, *K. pneumoniae* and *S. aureus*) were resistant to commonly used antibacterial drugs *(8)*. Antibiotic-resistant pathogens are more expensive to treat, and result in longer hospital stays. In the United States alone, compared to antibiotic-susceptible pathogens, antibiotic-resistant infections result in an additional US$ 21–34 billion annual cost to the health system and 8 million additional hospital days *(9–11)*. 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.

Improvement science

Health care is provided through processes in which health-care workers provide clinical interventions to patients that need them *(12)*. Delivery of good quality care requires use of the best evidence available and organizing care so that the best evidence is delivered to each patient every time it is needed. This requires meticulous attention to detail and organizing care to the appropriate context, including organizing who does what at each step, and ensuring they have the competencies, equipment, time and resources to do so *(13)*. The process by which this happens utilizes improvement science (also known as quality improvement, implementation science or delivery science), and includes all actions taken to make health care better *(14)*. The basic principle that underlies improvement is that every system is perfectly designed to achieve the result we see *(15)*. We must change the process if we wish to improve. Furthermore, the only way to see if we are improving is by measuring. The two key types of measurements needed to assess the effectiveness of improvement interventions are: 1) process-level measurement in which we are tracking the steps of the care delivery process and ensuring all the patient care actions are aligned with the best knowledge we have, for example tracking handwashing rates and 2) outcome-level, to confirm whether we are meeting the desired objectives, for example tracking HAI rates *(16)*. The extent we are better at process indicators will allow us to see fewer negative outcomes.

Global experience in improving health care has found that working with multiple teams on common objectives has been more effective in the production of systematic, sustained gains *(17)*. The process by which multiple teams work together to improve the same thing and share their learning has become a mainstay in improving health care, and is called collaborative improvement. Collaborative improvement allows for real-world testing of strategies to implement evidence-based interventions. Each team involved in the collaborative applies small-scale tests of changes to improve care processes. These tests are measured regularly using agreed upon indicators, and results and best practices are shared across teams through periodic experiential learning cycles, from which subsequent changes are informed *(18)*. This cyclic processes of testing and learning are known as "Plan, Do, Study, Act" (PDSA) cycles. The collaborative improvement approach allows teams to conduct multiple PDSA cycles in parallel in different locations, and thus accelerates learning and spread of the most effective change concepts, while building energy and ownership over learning *(19, 20)*.

The application of improvement science to reducing HAIs

About half of adverse hospital events may be preventable *(21-23)*. While there is a large body of evidence-based preventive clinical interventions which can reduce HAIs *(24-27)*, there is limited knowledge of how to implement these interventions to address systems failures, which cause communication breakdowns, uncoordinated and inefficient care. However, there is a growing evidence which demonstrates that improvement science strategies can help bridge the "know-do" gap to increase adoption of evidence-based prevention interventions, and reduce HAI rates. A recent systematic review of 30 studies found improved adherence to evidence-based infection control guidelines and reduced infection rates when improvement science strategies like audit and feedback, and provider reminder systems, were added to organization change and provider education *(28)*.

The application of improvement science will be illustrated through a case study of an injection safety and waste management programme in Namibia which was led by the Namibian MOHSS in collaboration with University Research Co., LLC (URC) and the United States Agency for

International Development (USAID) Health Care Improvement (HCI) Project, and the President's Emergency Plan for AIDS Relief (PEPFAR). Together with USAID, URC has led one of the largest improvement science portfolios in low- and middle-income countries.

Case study: Namibia medical injection safety programme

Background

In 2004, the WHO estimated that the global burden of unsafe injection practices is over 9.2 million DALYs lost per year *(29)*. An estimated 16 billion injections were administered annually in LMICs, for an average of 3.4 injections per person per year *(30)*. Up to 96% of those presenting to a primary health-care provider receive an injection, of which 70% are unnecessary or could be given in an oral formulation. While significant global progress has been made in the reduction of injection-related viral infections in the decade since 2000, at the time this case study began, unsafe injections accounted for 5%, 32% and 40% of new HIV, hepatitis B, and hepatitis C infections, respectively, resulting in 260,000, 21 million and 2 million incident cases annually *(29-31)*. The more injections are given, the more people are exposed to the risk of unsafe injection equipment and practices, including blood borne infections and health-care-acquired drug resistant organisms, and the more waste is generated *(32)*.

In 2004, an average of 11.2 injections was prescribed per person per year in Namibia. Most of these injections were for conditions that could be treated with oral medication. A significant proportion (39%) of patients expressed a preference for injections. In some assessed facilities, injections were not prepared in a designated, clean area, and 62% of facilities reported the presence of sharps in their immediate surroundings, posing a risk of needle-stick injury to HCWs and others. Additionally, injection safety boxes were observed in only a handful of facilities and recapping needles was a common practice in most facilities *(33)*.

Intervention

Under PEPFAR, and with support from USAID, University Research Co., LLC (URC) supported the Namibian Ministry of Health and Social Services (MOHSS) in a nationwide programme to promote rational use of medication, medical injection safety, and safe disposal of medical waste. The aim of this work was to prevent HAIs, including HIV, by promoting targeted infection control measures. This work began with the Making Medical Injections Safer Project (2004–2009) and continued with the USAID Health Care Improvement Project (HCI) (2007–2014) *(33)*.

The project aimed to reduce per capita injection use to less than one per year by the end of the project in 2009. The project also aimed to achieve significant decrease in needle-stick injuries over the life of the project through improved clinical practices. These two goals were to be achieved through the following:

- (a) develop and support national policy for safe injection practices;
- (b) develop and/or identify cost-effective and sustainable "best practices" to change provider prescription practices and community demand to reduce unsafe and unnecessary injections;
- (c) assist in improving the use of disposable/sterilized syringes;
- (d) improve infection prevention practices at facilities;
- (e) improve disposal practices of sharps and implement standards for safe withdrawal of blood for HIV testing.

A modified version of WHO's Safe Injection Global Network (SIGN) toolkit was used to conduct a rapid baseline assessment in July 2004 to identify existing injection and waste management practices, and opportunities for improvement. A National Injection Safety Group (NISG) was convened with the MOHSS, and national, regional and facility injection safety improvement plans were developed.

A collaborative improvement approach was used to improve injection and waste management practices, and inform national and regional policies. This included training 34 facility-based Safe Injection Teams in improvement methods, these teams then carried out regular Plan, Do, Study, Act (PDSA) cycles. During these PDSA cycles, teams reviewed data on a select number of process and outcome indicators. Ideas across teams were shared in regular learning sessions, and led to the development of a safe injection improvement package, which consisted of the following: effective communication of safe injection guidelines to public and private health-care workers (HCWs); ongoing monitoring of injection equipment use and disposal practices; implementation of strategies to improve awareness among medical injection users (community members) about safe injections; and overall capacity-building at national, regional and facility levels in infection prevention and control. Over the life of the project, URC assisted regional- and facility-level staff in adapting the improvement package in their local settings. The impact of these interventions were monitored closely to track changes in injection safety practices and the participating regions conducted quarterly assessments as part of the PDSA cycle.

Improvement plans were adjusted quarterly, based on the results of the quarterly assessments.

Results

Policy-level advocacy

The project covered all 13 regions in Namibia and 327 facilities. The facilities included a number of large private hospitals as well as independent rural private providers.

Over the course of the project several key national policies were developed by the NISG and adopted by the MOHSS, including: National Infection and Prevention and Control Guidelines, which incorporate TB infection prevention; HIV post-exposure prophylaxis (PEP) guidelines and job aids; National Standard Treatment (STG) guidelines; National Waste Management Policy; Integrated Waste Management Plan and guidelines; Revised Hepatitis B Policy; Quality Assurance (QA) Policy.

URC also established infection prevention and control (IPC) committees at the regional, district and facility levels to develop and implement regional and district IPC plans to promote the availability and use of infection control guidelines. This included training of HCWs, conducting quarterly facility audits, procurement of necessary supplies, prescription review, and support supervision of services.

Capacity building

The project trained over 12,000 HCWs on safe injection practices and waste disposal topics, including: data monitoring and paperwork completion, needle-stick reporting, use of PEP, and management of medical waste. The project also worked closely with the MOHSS to procure over 350,000 safety boxes for sharps disposal, personal protective equipment for waste handlers, and color-coded disposal bin liners. URC worked with the Central Medical Stores (CMS) and MOHSS to develop a long-term procurement plan including the development of a tender for the safety boxes. URC trained procurement officers on forecasting and ordering, promoted the use of stock cards, and collected consumption data submitted to the procurement agency.

Another key action that facilities undertook was to appoint an on-site point person to advocate for and supervise safe injection and waste management practices. This point person was responsible for conducting quarterly facility audits, training staff in the guidelines established, and working with the regional, district and facility-level IPC committees to review progress. Facility audits had previously been done by facility supervisors, however, the point person chosen was usually a nurse. Appointing nurses to perform facility audits, and to manage information system data tools, was seen as a more effective alternative, as nurses could notice shortcomings better and work to improve safe practices during trainings of HCWs.

Behaviour change

URC targeted community and provider perceptions in order to reduce the demand for and prescription of unnecessary and potentially unsafe injections. In particular, there was a perception among some community members and provides that injections were more effective than oral medicines. Furthermore, patients who were not offered an injection would simply go to a different clinic to find one.

URC worked with the MOHSS and its Information, Education and Communications (IEC) Office to develop a communication strategy and materials to change the behaviour of clients regarding the demand for injections and of providers on safe injection practices and prescription practices according to national standards. This included the development of communication materials in local languages to improve knowledge about safe injections and reduce the demand for and prescription of unnecessary injections.

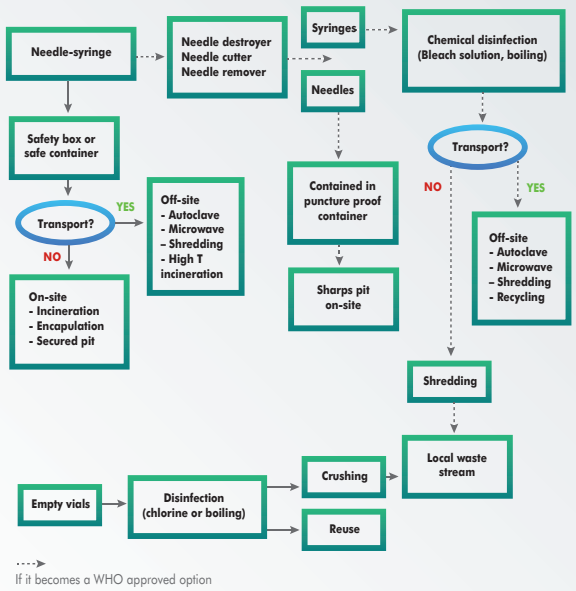
URC also enabled community educators to raise public awareness on the rational use of medication. The objective was to reduce demand for unnecessary injections and ensure proper disposal of infectious waste generated in the community, such as by insulin-dependent diabetics.

To influence provider prescription and injection administration practices, the educators worked with HCWs to communicate injection safety and waste management messages, for example through posters and wall charts along with job aids for HCWs. This included flowcharts on safe disposal of used needles and syringes for a broad arrange of scenarios, including facilities in: urban, peri-urban and rural areas with and without access to modern waste treatment facilities, as well as for primary health centre- and community-based immunization outreach activities (Fig. 1). These flow charts encouraged compliance with approved guidelines, including use of the safety boxes for correct disposal of sharps.

Another key change included training in the use of color-coded bags for correct waste segregation, as well as the development and dissemination of job aid posters (Fig. 2). Additional posters developed included posters on: 1) first do no harm; 2) hand hygiene; 3) prevention of cross-infection; 4) PEP flowcharts, 5) responsibilities of HCWs when injured on duty; g) nature of the workforce.

Additionally, the project conducted regular chart audits as well as observed provider practices in a sample of facilities.

Figure 1: Senario 5: Needle syringes waste management – immunization at PHC



Citation: Namibia Integrated Health Care Waste Management Plan (2011)

Figure 2: Namibia Medical Injection Safety Project and USAID Health Care Improvement Project (2011)

Citation: Namibia Medical Injection Safety Project and USAID Health Care Improvement Project (2011)

The results from audits and observations were shared during the quarterly Plan-Do-Study-Act (PDSA) cycle meetings so that teams could take action based on the data.

Outcomes

Over the life of the project, significant improvements in provider practices were made. The project made PEP kits widely available across facilities, as well as guidelines and job aids. Knowledge of PEP and injury reporting was increase among all staff, including morgue workers, students, laundry workers and waste handlers. For example, knowledge on use of PEP within 72 hours post exposure increased from 47% in 2004 to 100% in 2009. There were also significant reductions in sharps related injuries as well as increases in the use of post-exposure prophylaxis (PEP) among HCWs experiencing needle-stick injuries. For example, no cases of occupationally-acquired HIV infection was reported in Namibia in 2010. Furthermore, the average number of injections administered per patient per quarter declined from 11.2 in the first quarter of 2005 to fewer than 2 in facilities reporting by the last quarter of 2011 (Fig. 3).

The programme also monitored the injection process in supported facilities and adherence to safe practices, like the use of safety boxes. Safety boxes were only seen in 2% of 32 hospitals at baseline, however by the end of June 2011, they were present in 98% of 190 facilities reporting. Additional improvement included a reduction in the practice of leaving needles in multi-dose vials after injection, and proper disposal of needles without recapping, in order to reduce needle-stick injuries. The project also introduced the use of single dose vials to minimize cross-infections that can occur when using multi-dose vials without proper needle sterilization techniques.

Additionally, waste management practices were monitored, including: replacing containers once they were three-quarters full to prevent overfilling, which can cause needles to pierce the sides; ensuring containers meet safety standards; and ensuring facilities had access to a functional incinerator (Fig. 4). In addition to repairing old incinerators, the project procured and installed 17 new incinerators, and included proper use of incinerators in regional waste policies and guidelines. Access to functional incinerators increased from 60% at the beginning of 2009 to 98% among 198 facilities reporting in September 2011. Use of effective waste management strategies was also associated with a reduction in the presence of used needles and sharps on health facility grounds, which decreased from presence at 62% of facilities in 2004 to less than 1% in 2011.

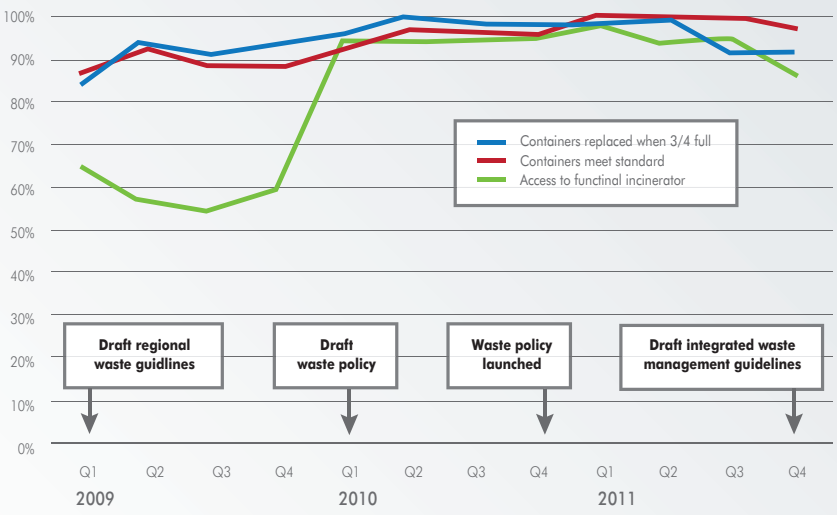
Discussion

There are many established best practices that are known to reduce if not eliminate HAIs. However, as important as the discipline-specific knowledge is for reducing HAIs, it is

Figure 3: Average number of doses administered per patient in Namibia, 2005–2011

Citation: Namibia Medical Injection Safety Project and USAID Health Care Improvement Project (2011)

Figure 4: Improvement in waste management practices in Namibia, 2009–2011



Citation: Namibia Medical Injection Safety Project and USAID Health Care Improvement Project (2011)

invariably on its own insufficient to just "know." What we need to do is address the "know-do" gap *(18)*. To a large extent, we know what needs to be done to reduce HAIs: hand hygiene, safe sharps disposal and rational use of injections. However like this case study in Namibia showed, this knowledge is not consistently implemented in practice. When health-care workers in Namibia learned improvement science and applied its methods, they were able to implement this knowledge and bring down the rate of injections and improve health worker safety. Thus, improvement science became a powerful tool for change.

The work of the Namibian MOHSS, supported by the USAID Health Care Improvement Project demonstrated that a combination of policy-level changes as well as facility-based improvement allowed for significant, sustained implementation of interventions that have a direct link with reductions HAIs and spread of antimicrobial resistance. These changes involved building the capacity of health workers through trainings, and through the use of nurse champions, and involvement in collaborative improvement efforts. The collaborative improvement approach strengthened HCWs ability to collect and use relevant data for decision-making, and to inform an improvement package which was scaled up nationally.

Due to space constraints, we have described only one example, but there are others examples from developing countries in the use of improvement science to improve infection control. In 2012, The USAID Health Care Improvement Project collaborated with Bridge Consultants, Karachi, to improve injection safety and waste management in Karachi, Pakistan. In this project 25 health-care providers worked together to improve compliance with 11 key infection prevention practices (availability of soap and water, hand hygiene, use of sharps boxes, etc.) from 18% at baseline (February 2012) to 54% at endline (December 2012) *(34)*. The USAID Applying Science to Strengthen and Improve Systems (ASSIST) Project is currently implementing similar interventions in 60 sites in Swaziland.

There are more examples in developed country contexts, including many led by the Institute for Healthcare Improvement (IHI). These include studies which led to the development of How-to Guides and change packages to prevent catheter-associated urinary tract infections, surgical site infections and central line-associated bloodstream infections *(35, 36)*. One key example includes the use of improvement science methods to implement evidence-based interventions to reduce ventilator-

associated pneumonias (VAP) under the Scottish Patient Safety Programme, led by Scotland's National Health Service and using IHI methods. PDSA cycles were used to identify an implementation method which maximized compliance, including the use of nurse and medical champions, teaching materials and posters, education sessions, and 24-hour observation charts. Overall, bundle compliance was 70%, and there were significant reductions in VAPs, from 32 cases per 1,000 ventilator days to 12 cases per 1,000 ventilator days ($p<0.001$) *(37)*. In addition to reduced VAP acquisition, patients also had significantly reduced antibiotic use and decreased rates of methicillin-resistant Staphylococcus aureus acquisition *(37)*. These findings have significant implications, as VAPs are the third most common HAI, accounting for approximately 15% of all HAIs *(38)*.

Additionally, a recent systematic review of 30 HAI reduction studies primarily from U.S. hospitals found evidence that use of improvement science strategies provided added benefits over provider-education only interventions, including improved adherence to evidence-based infection control guidelines and reduced HAI rates. *(28)* The improvement strategies included audits and feedback, as well as provider reminder systems. Further studies are needed in resource-limited settings which use strong quasi-experimental designs appropriate to examining the effects of interventions in real-world settings.

Conclusion

Compared to pure content interventions, the use of improvement strategies combined with content-based approaches allows the best results in improving adherence to guidelines, as well as reduced incidence of HAIs. A focus on improving patient safety requires a patient-centred approach, a focus on systems and processes, teamwork, and improved use of data for decision-making to continuously improve processes to deliver reliably safe, high quality care. Patient safety is one dimension of quality care, and improvement involves a focus on structural factors, care processes and care outcomes *(4)*. The use of improvement approaches can serve as a key tool to reduce HAIs, and thus avoiding unnecessary harm to patients and providers, limiting the unnecessary use of antibiotics and limiting the development of antimicrobial resistance. •

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References

1. Institute of Medicine (IOM). Crossing the quality chasm: A new health system for the 21st century. Washington, DC: National Academy Press; 2001.
2. James JT. A new, evidence-based estimate of patient harms associated with hospital care. *J Patient Saf.* 2013 Sep;9(3):122-8.
3. Jha AK, Larizgoitia I, Audera-Lopez C, Prasopa-Plaizier N, Waters H, Bates DW. The global burden of unsafe medical care: Analytic modelling of observational studies. *BMJ Qual Saf.* 2013 Oct;22(10):809-15.
4. The Research Priority Setting Working Group of the WHO World Alliance for Patient Safety, editor. Summary of the evidence on patient safety: Implications for research. Ashish Jha ed. Geneva: World Health Organization; 2008.
5. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: Systematic review and meta-analysis. *Lancet*. 2011 Jan 15;377(9761):228-41.
6. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009 Dec 2;302(21):2323-9.
7. Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: Summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2009-2010. *Infect Control Hosp Epidemiol.* 2013 Jan;34(1):1-14.
8. WHO. Antimicrobial resistance: Global report on surveillance. Geneva: World Health Organization; 2014.
9. Mauldin PD, Salgado CD, Hansen IS, Durup DT, Bosso JA. Attributable hospital cost and length of stay associated with health care-associated infections caused by antibiotic-resistant gram-negative bacteria. *Antimicrob Agents Chemother.* 2010 Jan;54(1):109-15.
10. Filice GA, Nyman JA, Lexau C, Lees CH, Bockstedt LA, Como-Sabetti K, et al. Excess costs and utilization associated with methicillin resistance for patients with staphylococcus aureus infection. *Infect Control Hosp Epidemiol.* 2010 Apr;31(4):365-73.
11. Roberts RR, Hota B, Ahmad I, Scott RD,2nd, Foster SD, Abbasi F, et al. Hospital and societal costs of antimicrobial-resistant infections in a chicago teaching hospital: Implications for antibiotic stewardship. *Clin Infect Dis.* 2009 Oct 15;49(8):1175-84.
12. Massoud MR, Mensah-Abrampah N, Barker P, Leatherman S, Kelley E, Agins B, et al. Improving the delivery of safe and effective healthcare in low and middle income countries. *BMJ*. 2012 Feb 14;344:e981.
13. Massoud, MR. Askov, A. Reinke, J. Franco, LM. Bornstein, T. Knebel, E. MacAulay, C. A modern paradigm for improving healthcare quality. 2001. Report No.: USAID, URC.
14. Massoud MR, Mensah-Abrampah N, Sax S, Leatherman S, Agins B, Barker P, et al. Charting the way forward to better quality health care: How do we get there and what are the next steps? recommendations from the salzburg global seminar on making health care better in low- and middle-income economies. *Int J Qual Health Care*. 2012 Dec;24(6):558-63.
15. Batalden PB, Stoltz PK. A framework for the continual improvement of health care: Building and applying professional and improvement knowledge to test changes in daily work. *Jt Comm J Qual Improv.* 1993 Oct;19(10):424,47; discussion 448-52.
16. Langley G, Moen R, Nolan K, Nolan T, Norman C, Provost L. The improvement guide: A practical approach to enhancing organizational performance. 2nd ed. San Francisco, CA: Jossey-Bass; 2009.
17. Franco LM, Marquez L. Effectiveness of collaborative improvement: Evidence from 27 applications in 12 less-developed and middle-income countries. *BMJ Qual Saf*. 2011 Aug;20(8):658-65.
18. Davidoff F. Improvement interventions are social treatments, not pills. *Ann Intern Med.* 2014 Oct 7;161(7):526-7.
19. OVretveit J, Bate P, Cleary P, Cretin S, Gustafson D, McInnes K, et al. Quality collaboratives: Lessons from research. *Qual Saf Health Care.* 2002 Dec;11(4):345-51.
20. Wilson T, Berwick DM, Cleary PD. What do collaborative improvement projects do? experience from seven countries. *Jt Comm J Qual Saf.* 2003 Feb;29(2):85-93.
21. Hakkarainen KM, Hedna K, Petzold M, Hagg S. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions--a meta-analysis. PLoS One. 2012;7(3):e33236.
22. Gawande AA, Thomas EJ, Zinner MJ, Brennan TA. The incidence and nature of surgical adverse events in colorado and utah in 1992. Surgery. 1999 Jul;126(1):66-75.
23. Kable AK, Gibberd RW, Spigelman AD. Adverse events in surgical patients in Australia. *Int J Qual Health Care*. 2002 Aug;14(4):269-76.
24. Anderson DJ, Podgorny K, Berrios-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol.* 2014 Jun;35(6):605-27.
25. Coffin SE, Klompas M, Classen D, Arias KM, Podgorny K, Anderson DJ, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals. *Infect Control Hosp Epidemiol.* 2008 Oct;29 Suppl 1:S31-40.
26. Lo E, Nicolle L, Classen D, Arias KM, Podgorny K, Anderson DJ, et al. Strategies to prevent catheter-associated urinary tract infections in acute care hospitals. *Infect Control Hosp Epidemiol.* 2008 Oct;29 Suppl 1:S41-50.
27. Marschall J, Mermel LA, Fakih M, Hadaway L, Kallen A, O'Grady NP, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014 Jul;35(7):753-71.
28. Mauger B, Marbella A, Pines E, Chopra R, Black ER, Aronson N. Implementing quality improvement strategies to reduce healthcare-associated infections: A systematic review. *Am J Infect Control*. 2014 Oct;42(10 Suppl):S274-83.
29. Hauri AM, Armstrong GL, Hutin YJ. The global burden of disease attributable to contaminated injections given in health care settings. *Int J STD AIDS*. 2004 Jan;15(1):7-16.
30. Hutin YJ, Hauri AM, Armstrong GL. Use of injections in healthcare settings worldwide, 2000: Literature review and regional estimates. *BMJ*. 2003 Nov 8;327(7423):1075.
31. Pepin J, Abou Chakra CN, Pepin E, Nault V, Valiquette L. Evolution of the global burden of viral infections from unsafe medical injections, 2000-2010. *PLoS One*. 2014 Jun 9;9(6):e99677.
32. Miller MA, Pisani E. The cost of unsafe injections. *Bull World Health Organ.* 1999;77(10):808-11.
33. URC. Medical injection safety program - namibia. end of project report (2004-2009). contract number GHS-I-00-03-00029-00, task order no. 001. Bethesda, Maryland: University Research Co., LLC for USAID; 2011.
34. URC. USAID health care improvement project: Improving injection safety and waste management in peri-urban Karachi, Pakistan. contract no. GHN-I-03-07-00003-00. Bethesda, Maryland: University Research Co., LLC for USAID; 2013.
35. Leape LL, Kabcenell AI, Gandhi TK, Carver P, Nolan TW, Berwick DM. Reducing adverse drug events: Lessons from a breakthrough series collaborative. *Jt Comm J Qual Improv*. 2000 Jun;26(6):321-31.
36. Institute for Healthcare Improvement. Changes to prevent healthcare-associated infections. http://Www.ihi.org/resources/pages/changes/ChangestoPreventHAIs.aspx.; 2014.
37. Morris AC, Hay AW, Swann DG, Everingham K, McCulloch C, McNulty J, et al. Reducing ventilator-associated pneumonia in intensive care: Impact of implementing a care bundle. *Crit Care Med*. 2011 Oct;39(10):2218-24.
38. Klevens RM, Edwards JR, Richards CL,Jr, Horan TC, Gaynes RP, Pollock DA, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep*. 2007 Mar-Apr;122(2):160-6.

ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEILLANCE

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Resistance to anti-tuberculosis drugs has been documented since the 1940s, when the first medicines for tuberculosis were introduced. Systematic monitoring of development of drug resistance was initiated through a global project in 1994 through a network of quality assured supranational reference laboratories. At present nearly 60% of all countries in the world have implemented surveillance activities that are being disseminated at a global level by the World Health Organization through their Global Anti-tuberculosis Drug Resistance Reports. Systematic surveillance for TB drug resistance monitoring is the best way to document its presence and has been very difficult to establish in most of the high-burden countries as the major obstacle to the expansion of routine surveillance activities has been the lack of laboratory capacity needed to detect resistance. In the past 15 years, special surveys have been the most common approach to investigate the frequency and patterns of drug-resistant tuberculosis. The advent of newer more rapid tools to detect drug resistance and with increased laboratory capacity, routine surveillance linked to patient care, which represents the best approach to monitor drug resistance, now has the possibility of becoming a reality even in resource-limited countries. Several countries across the globe have been reporting drug resistance data derived from their country specific survey methods. India has in the past reported drug resistance from sub-national level surveys and has currently commenced its first national level survey. The survey will provide a statistically representative national estimate of the prevalence of anti-tuberculosis drug resistance among new and previously treated patients in India, and will contribute to a more accurate estimate of anti-tuberculosis drug resistance globally. In addition India is moving towards systematic surveillance of drug resistance as it is already offering drug resistance testing to all treatment experienced patients and is moving towards universal DST by 2019.

The story of anti-tuberculosis chemotherapy is a miniature of the history of anti-infective chemotherapy. In the first half of the twentieth century the problem of tuberculosis appeared insolvable due to the lipid-rich cell wall that was believed to make chemotherapy impossible *(1)*. This gloomy view seemed to be confirmed when the first antibiotics developed, sulfonamides and penicillin, had no useful activity against *Mycobacterium tuberculosis*. With this in mind it is easy to understand the early euphoria surrounding Albert Schatz and Selman Waksman's discovery of streptomycin while working at Rutgers University in New Jersey *(2)* and Harold Lehmann's discovery of para-amino salicylic acid (PAS) shortly afterwards *(3)*.

Drug-resistant TB was recognized shortly after the introduction of effective anti-TB chemotherapy, with the description of streptomycin resistance by Pyle in 1947 *(4)*. In 1948, the British Medical Research Council (MRC) published its ground breaking report of streptomycin therapy for pulmonary TB and noted that mortality was similar in treated and untreated patients *(5)*. Among patients who had been treated with streptomycin, however, most who died had experienced a relapse that was the result of streptomycin-resistant strains. The recognition of this phenomenon led to the principle of multi-agent chemotherapy for TB, which was proved effective in a subsequent trial by the MRC *(6)*. Resistance to anti-TB drugs continued to be recognized as a sporadic clinical problem through the 1960s, 1970s and 1980s, but little attention was paid to the problem by researchers or public health officials. The emergence of multi-drug-resistant TB (MDR-TB) in the United States in the early 1990s led to renewed interest in

this topic *(7)*. During that period, a number of MDR-TB cases, defined as disease caused by strains resistant to at least isoniazid and rifampicin, were identified in epidemics in New York, New Jersey and Florida. The majority of these cases were the result of micro-epidemics with direct transmission among persons in hospital, jails, and homeless shelters, particularly among people with HIV infection *(7-9)*. The mortality in MDR-TB has been reported to be high both in HIV-infected and uninfected individuals *(10-14)*. Aggressive public health interventions at a cost of tens of millions of dollars helped to quickly contain these outbreaks, but not before the loss of many lives *(15)*.

In subsequent years, drug resistant TB, especially MDR-TB, has been recognized as a potentially catastrophic challenge to global public health. Major outbreaks of MDR-TB have been reported in the former Soviet Union, and low levels of MDR-TB in countries with high rates of TB, such as Peru, have resulted in large numbers of patients with disease. As a consequence, drug resistant TB now constitutes a global problem *(16)*.

The circumstances in which drug resistance emerges are well known and have been so since shortly after the first clinical trials became available and their lessons were digested *(17)*. In recent years the molecular basis for the mechanism of action of anti-tuberculosis agents and the way in which the organisms become resistant have begun to be unravelled.

Although management of TB has faced many challenges in the past, today there are two monumental threats to global TB control: the HIV epidemic and the increasing prevalence of drug resistance. HIV infection is contributing to large escalations in the incidence of TB in countries most heavily affected by AIDS, notably sub-Saharan Africa *(18)*. Resistance to anti-TB drugs, a problem recognized in the very early days of the chemotherapeutic era has also emerged as a serious problem. TB drug resistance is characterized by both the types of drugs to which the bacteria lack susceptibility and the manner in which resistance was acquired. Resistance to single agents is the most common type; resistance to multiple agents is less frequent but of greater concern. By convention, "multi-drug resistance" is defined as resistance to at least isoniazid and rifampicin.

An understanding of the molecular basis of drug resistance may contribute to the development of new drugs. *M. tuberculosis* is often acquired early in life with acute infection and with developing immunity, granuloma formation, and calcification. This is followed by a long latent period, which continues until reactivation occurs in a proportion of the individuals. This means that individual

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strains of *M. tuberculosis* have little opportunity to interact and exchange genetic information with other strains compared with, for example, organisms that colonize the nasopharynx or the gastrointestinal tract. In these locations, other bacteria may transmit antibiotic resistance determinants through transmissible genetic elements, transposons, integrons and plasmids, by transduction or transformation. This option is not available for *M. tuberculosis*, so resistance can only occur through chromosomal mutation although rarely movement of mobile genetic elements, such as the insertion sequence IS6110, has been associated with new resistance emerging through the inactivation of critical genes *(19, 20)*.

In any prokaryotic genome mutations are constantly occurring due to base changes caused by exogenous agents, DNA polymerase errors, deletions, insertions and duplications. For prokaryotes there is a constant rate of spontaneous mutation of 0.0033 mutations/DNA replication that is uniform for a diverse spectrum of organisms *(21)*. The mutation rate for individual genes varies significantly between and within genes. The antibiotic resistance genes encoding fundamental replication functions of the organism such as *rpoB* and *gyrA* are typically highly conserved *(22, 23)*.

The genetic basis of resistance for some anti-tuberculosis agents is not fully known. For example, streptomycin resistance emerges through mutations in *rrs* and *rpsL* that produce an alteration in the streptomycin binding site, but these changes are identified in just over one-half of the strains studied to date *(24, 25)*. Thus there is a considerable amount of research into the mechanisms of resistance that is still required. It should be noted that in many cases mutations found in association with drug resistant organisms may cause different levels of resistance and also may not be directly related to the mechanism of resistance. Isoniazid-resistance is a case in point. Modification of KatG, partial or total deletions, point mutations, or insertions, leads to the abolition or diminution of catalase activity and

Table 1: Average proportions of cases of tuberculosis, new or previously treated that are multi-drug resistant, in regions of the World Health Organization (WHO) and the world, 1994-2000.

WHO region	New cases	Previously treated cases
African region	1.9	9.4
Region of the Americas	2.1	11.5
Eastern Mediterranean region	3.4	20.6
European region	12.1	36.5
South East Asia region	2.1	17.2
Western Pacific region	4.9	23.2
World	3.4	19.8

Source: Bull World Health Organ 2012

Table 2: Multi-drug resistant tuberculosis (MDR-TB) rate in new and previously treated cases. (India-sub national surveys)

Survey	New Cases	Previously treated cases
Gujarat, 2007–2008 (population – 56 million)	2.4%	17.4%
Maharashtra, 2008 (population – 108 million)	2.7%	14.0%
Andhra Pradesh, 2009 (population – 86 million)	1.8%	11.8%
Tamil Nadu, 2011 (population – 70 million)	1.8 %	11.2%
RNTCP - India routine surveillance data, 2007-13	NA	16%

Source: Protocol for the first Nationwide Anti-Tuberculosis Drug resistance survey, India, 2014-2015

confers high-level resistance to isoniazid *(26, 27)*. Catalase activity is essential in activating isoniazid to the active hydrazine derivative. A deficiency in enzyme activity produces high-level resistance and is found in more than 80% of isoniazid-resistant strains *(28)*. Alternatively, low-level resistance can be caused by point mutations in the regulatory region of *inhA* operon, resulting in over expression of *inhA*. Strains with this mutation have normal mycolic acid synthesis but low-level resistance to isoniazid. Point mutations in the regulatory region of *ahpC* have also been demonstrated; these are a compensation for the effects of absent or reduced catalase (KatG) function and do not directly result in resistance *(29, 30)*. Most pyrazinamide-resistant organisms have mutations in the pyrazinamidase gene, although the gene may also be inactivated through the insertion of IS6110 *(31)*. Pyrazinamide is essential in producing the active pyrazinoic acid derivative, and mutants are unable to produce an active drug. In addition to this, some resistant strains have no defined mutation *(32)*. The rate at which resistance emerges differs for all of the anti-tuberculosis agents, being highest for ethambutol and lowest for rifampicin and quinolones. The risks of mutation for most of the antibiotics used in tuberculosis treatment have been defined previously *(33)*; for rifampicin, isoniazid, streptomycin, and ethambutol, they are 3.32×10^{-9}, 2.56×10^{-8}, 2.29×10^{-8}, and 1.0×10^{-7} mutations per bacterium per cell division, respectively. The mutation rate, rather than the mutation frequency, is the most reliable measure, as it records the risk of mutation per cell division rather than the proportion of mutant cells.

It has been assumed that the risk that an organism will develop resistance to two agents is the product of the risks of developing resistance to each separately. For example the resistance risk for a combination of rifampicin, streptomycin, and isoniazid is10–25/bacterium/generation.

Global anti-Tuberculosis Drug Resistance Surveillance Project

In 1993, Tuberculosis was declared as a global emergency following which, in 1994, the Global Project on Anti-Tuberculosis Drug Resistance Surveillance was initiated by the World Health Organzation (WHO) and International Union against Tuberculosis and Lung Diseases, aiming to measure the magnitude of drug resistant tuberculosis and to monitor trends *(34)*. Since 1994, five global reports on anti-tuberculosis drug resistance surveillance have been published *(35-39)*. Drug resistance data have been systematically collected and analysed from 114 countries (59% of all countries of the world).

Worldwide, approximately 5% of new cases and 20% of previously treated cases had multi-drug resistant TB (MDR-TB), (Table 1). Extensively drug resistant TB (XDR-TB) has been reported by 92 countries, and the average proportion of MDR-TB cases with XDR-TB is 9%.

Since the beginning of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance, two main mechanisms to measure drug resistance have been used: the organization of special surveys (surveys are defined as discrete studies measuring drug resistance among a specially-designed sample of tuberculosis cases representative of an entire population of TB cases) on selected samples of patients, and the establishment of a surveillance system based on routine drug susceptibility testing of all patients.

In the past 15 years, surveys and surveillance have been largely relying on culture and drug susceptibility testing methods based on solid media, which are associated with a very long turn-around times for results (at least 3–4 months) and enormous workload for laboratory personnel. We are

now in a new era for tuberculosis and MDR-TB diagnosis resulting from the advent of technological advances that make it possible to detect tuberculosis and rifampicin resistance much more rapidly.

Types of TB drug resistance surveys:

1. Surveillance system based on routine drug susceptibility testing

A surveillance system based on routine DST of all TB cases is able to provide continuous information on drug resistance patterns among patient groups, and is therefore able to accurately detect trends, as well as localized outbreaks.

2. Periodic surveys

In resource constrained settings where capacity is currently not available for routine DST of all TB cases, surveys can be conducted to measure drug resistance among a sample of patients' representative of the geographically defined population under study. When properly constructed and periodically conducted, such surveys provide a sound estimation of the resistance profile of all TB cases in the population under study and can detect general trends over time.

3. Sentinel surveillance systems

Some countries with well-established laboratory networks have opted for a sentinel system for surveillance. This type of system continuously reports DST results of all TB cases from a selection of laboratory or hospital sites, and therefore can be useful in documenting trends and detecting outbreaks or localized epidemics of drug resistance. For countries where resources, the health-care system structure, or geographical features preclude routine DST of all patients or surveys of sampled patients, the establishment of a sentinel surveillance system may be an option. A sentinel system could be a useful interim approach for countries intending to expand routine DST to all retreatment cases while moving towards this goal.

4. Regimen surveys

"Regimen surveys" measure first-line and /or second-line drug resistance among a group of selected patients that cannot be considered representative of a patient population. These surveys can help determine the predominant patterns of drug resistance, and can be useful in providing guidance on appropriate regimens for MDR-TB treatment for particular patient groups. These include return cases after treatment failure, chronic cases and symptomatic contacts of MDR-TB cases. Regimen surveys should be conducted in the process of developing MDR-TB treatment programmes or within selected centres or diagnostic units that regularly address high-risk cases.

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Indian surveys

India has more new TB cases annually than any country globally. Annually, 2.3 million cases are estimated to occur and thus contributing to 26% of world's TB burden.

Anti-tuberculosis drug resistance among new and previously untreated TB cases, a proxy indicator for primary or initial drug resistance, suggests tuberculosis transmission. Anti-tuberculosis drug resistance among previously treated TB cases, a proxy indicator for acquired drug resistance, suggests failure of effective management in the prior TB episode.

Although the country had conducted several district level surveys in the past, it has also conducted four state level surveys using the WHO guidelines for Drug Resistance Survey, beginning in 2007 (Table 2). However acknowledging that India needs to move towards systematic surveillance, and as part of the scaling up of DR TB services all treatment experienced patients are being tested for drug resistance. India is also planning to move towards universal DST for all TB cases by 2019 as articulated in its National Strategic Plan and the Revised National Laboratory Scale up Plan 2015–2019 in line with post 2015 strategy.

In the interim, in order to plan, strategize and refine the quality of services for DR TB, data on the rates of drug resistance at a National level has been recognized as vital and towards this goal, India has initiated a National TB Drug Resistance Survey. This will be the first such survey that will be conducted in India as there has been no attempt previously as this was an enormous task and fraught with many challenges like the population to be covered, sampling strategy to include all geographical regions, number of patients to be screened, number of drug susceptibility testing to be undertaken to name a few. More than 5,000

patients from 120 clusters representing the country are expected to be enrolled for the survey. The samples collected would be subjected to a 13 drug DST (five first-line drugs and eight second-line drugs) using liquid culture systems. The survey will provide a statistically representative national estimate of the prevalence of anti-tuberculosis drug resistance among new and previously treated patients in India, and will contribute to a more accurate estimate of anti-tuberculosis drug resistance globally.

At a global level, India is the first among both the 22 high-burden TB and first among the 27 high MDR TB burden countries and this survey is considered ground breaking as it will provide a unique data set for both national and global level information on drug resistant TB and management.

Dr Kuldeep Singh Sachdeva is an expert in tuberculosis and chest diseases and health management with more than 30 years of experience. He is currently serving as Additional Deputy Director General, Central TB Division, Ministry of Health and Family Welfare, Government of India. He has extensive experience in programmatic management of drug resistant tuberculosis and is overseeing the implementation of largest ever and nationally representative Drug Resistance Survey in India. He is a core group member of WHOs Global Drug Resistance Initiative (GDI) and also Vice Chair of the Regional Green Light Committee of WHO South East Region.

Dr S Anand, a graduate in Microbiology, obtained his Master's degree in Applied Microbiology with a University rank. He also has a Master's in Environment and Ecology, and M Phil as well as PhD in Biotechnology. He is currently working as a Consultant Microbiologist at the Central TB Division, Ministry of Health and Family Welfare, Government of India. He has served as Unit Head of the National Reference Laboratory at the National TB Institute, Bangalore. He has industrial R&D experience and has also spent over a decade in teaching undergraduate and post graduate students of Microbiology and Biotechnology.

Dr Ranjani Ramachandran is an expert in the field of TB bacteriology with a post-graduate in medical microbiology from Madras Medical College. She also has post-graduate degree in Internal Medicine from National Board of Examinations. She has pursued her doctoral research in the field of TB-HIV opportunistic infections. She started her career as a clinical scientist working in the field of TB research including randomized clinical trials, field surveys in TB-HIV and then moved to laboratory medicine, TB drug resistance surveys and research in evaluation of new diagnostic tools. She has more than two decades of experience of working in the National Institute of Research in Tuberculosis (ICMR) Chennai and then moved to the World Health Organization as Medical Officer TB labs in 2009 and is at present the Technical Officer (Labs) at the WHO India country Office for India since 2012.

References

1. Dormandy T. 1999. The white death: a history of tuberculosis. *Hambledon Press*, London, United Kingdom
2. Schatz A and Waksman SA. 1944. Effect of streptomycin and other antibiotic substances upon Mycobacterium tuberculosis and related organisms. *Proc. Soc. Exp. Biol. Med*. 57:244–248
3. Lehman J. 1946. Para-aminosalacylic acid in the treatment of tuberculosis. *Lancet* i:15
4. Pyle MM. 1947.Relative numbers of resistant tubercle bacilli in sputum of patients before and during treatment of streptomycin. *Proc Staff Meetings Mayo Clinic* ;22:465
5. Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *Br Med J* 1948;2:769-82
6. Medical Research Council. Treatment of pulmonary tuberculosis with para-aminosalicylic acid and streptomycin. *Br Med J* 1949; 2:1521-5
7. Frieden TR, Sterling T, PablosMendez A, Kilburn JO, Cauthen GM, Dooley SW. 1947.The emergence of drug resistance tuberculosis in New York City. *N Engl J Med*; 328:521-6
8. Edlin BR, Tokars JI, Grieco MH, et al. 1992. An outbreak of tuberculosis caused by multiple-drug resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. *N Engl J Med* ;326:1514-21
9. Fischl MA, Uttamchandani RB, Daikos GL, et al. 1992. An outbreak of tuberculosis caused by multiple-drug resistant tubercle bacilli among patients with HIV infection. *Ann Intern Med* ;117:177-83
10. Coninx R, Mathieu C, Debacker M, et al. 1999. First line tuberculosis therapy and drug-resistant Mycobacterium tuberculosis in prisons. *Lancet*;*353:969-73*
11. Espinal MA, Kim SJ, Suarez PG, et al. 2000. Standard short-course chemotherapy for drug resistant tuberculosis: treatment outcome in six countries. *JAMA;283:2537-45*
12. Garcia-Garcia M, Ponce-de-Leon A, Jimenez-Corona ME, et al. 2000. Clinical consequences and transmissibility of drug resistant tuberculosis in Southern Mexico. *Arch Intern Med* ;160:630-6
13. Goble M, Iseman MD, Madsen LA, White D, Ackerson L, Horsburgh C.1993. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* ;328:527-32
14. Park MM, Davis AL, Schluger NW, Cohen H, Rom WN. 1996. Outcome of MDR-TB patients, 1983–1993: prolonged survival with appropriate therapy. *Am J Respir Crit Care Med* ;153:317-24
15. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. 1995. Tuberculosis in New York City: turning the tide. *N Engl J Med* ;333:229-33
16. Schluger NW, 2000. The impact of drug resistance on the global tuberculosis epidemic. *Int J Tuberc Lung Dis* ;4:71-5
17. McDermott, W. 1960. Antimicrobial therapy of pulmonary tuberculosis. *Bull*. W. H. O. 23:427–461
18. Raviglione MC, Harries AD, Msiska R, et al. 1997. Tuberculosis and HIV: current status in Africa. AIDS ;11(B):115-23
19. Dale JW. 1995. Mobile genetic elements in mycobacteria. *Eur. Respir. J. Suppl.* 20:633s–648s
20. Lipsitch M and Levin BR. 1998. Population dynamics of tuberculosis treatment: mathematical models of the roles of non-compliance and bacterial heterogeneity in the evolution of drug resistance. *Int. J. Tuberc. Lung Dis.* 2:187–199
21. Drake JW. 1999. The distribution of rates of spontaneous mutation over viruses, prokaryotes, and eukaryotes. *Ann. N. Y. Acad. Sci.*870:100–107
22. Drlica K and Zhao X. 1997. DNA gyrase, topoisomerase IV, and the 4-quinolones. Microbiol. *Mol. Biol. Rev.* 61:377–392
23. Telenti A, Imboden P, Marchesi F, Lowrie D, Cole S, Colston MJ, Matter L, Schopfer K and Bodmer T. 1993. Detection of rifampicin-resistance mutations in Mycobacterium tuberculosis. *Lancet* 341:647–650
24. Honore N and Cole ST. 1994. Streptomycin resistance in mycobacteria. Antimicrob. *Agents Chemother.* 38:238–242
25. Sreevatsan S, Pan X, Stockbauer KE, Williams DL, Kreiswirth BN and Musser JM. 1996. Characterization of rpsL andrrs mutations in streptomycin-resistant Mycobacterium tuberculosis isolates from diverse geographic localities. *Antimicrob. Agents Chemother.* 40:1024–1026
26. Heym B, Alzari PM, Honore N and Cole ST. 1995. Missense mutations in the catalase-peroxidase gene, katG, are associated with isoniazid resistance in Mycobacterium tuberculosis. *Mol. Microbiol.* 15:235–245
27. Zhang Y, Garbe T and Young D. 1993. Transformation with katG restores isoniazid-sensitivity in Mycobacterium tuberculosisisolates resistant to a range of drug concentrations. *Mol. Microbiol.* 8:521–524
28. Ramaswamy S and Musser JM. 1998. Molecular genetic basis of antimicrobial agent resistance in Mycobacterium tuberculosis: 1998 update. Tuber. Lung Dis. 79:3–29
29. Heym B, Saint-Joanis B and Cole ST. 1999. The molecular basis of isoniazid resistance in Mycobacterium tuberculosis. *Tuber. Lung Dis.* 79:267–271
30. Sreevatsan S, Pan X, Zhang Y, Deretic V and Musser JM. 1997. Analysis of the oxyR-ahpC region in isoniazid-resistant and -susceptible Mycobacterium tuberculosis complex organisms recovered from diseased humans and animals in diverse localities. *Antimicrob. Agents Chemother.* 41:600–606
31. Lemaitre N, Sougakoff W, Truffot-Pernot C and Jarlier V. 1999. Characterization of new mutations in pyrazinamide-resistant strains of Mycobacterium tuberculosis and identification of conserved regions important for the catalytic activity of the pyrazinamidase PncA. *Antimicrob. Agents Chemother.* 43:1761–1763
32. Davies AP, Billington OJ, McHugh TD, Mitchison DA and Gillespie SH. 2000. Comparison of phenotypic and genotypic methods for pyrazinamide susceptibility testing with Mycobacterium tuberculosis. *J. Clin. Microbiol*. 38:3686–3688
33. David HL. 1970. Probability distribution of drug-resistant mutants in unselected populations of Mycobacterium tuberculosis. *Appl. Microbiol*. 20:810–814
34. Cohn DL, Bustreo F and Raviglione MC. 1997. Drug-resistant tuberculosis: review of the worldwide situation and the WHO/IUATLD Global Surveillance Project. International Union Against Tuberculosis and Lung Disease. *Clin Infect Dis* ;24(Suppl 1):S121-30.
35. World Health Organization (WHO). Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response.Geneva, Switzerland: WHO; 2010. (WHO/HTM/TB/2010.3).
36. World Health Organization (WHO); Geneva, Switzerland. Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. WHO; 1997. (WHO/TB/97.229).
37. World Health Organization (WHO). Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Report 2: Prevalence and trends. Geneva, Switzerland: WHO; 2000. (WHO/CDS/TB/2000.278).
38. World Health Organization (WHO). Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Third global report. Geneva, Switzerland: WHO; 2004. (WHO/HTM/TB/2004.343).
39. World Health Organization (WHO). Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Fourth global report. Geneva, Switzerland: WHO; 2008. (WHO/HTM/TB/2008.394).

MONITORING, SURVEILLANCE AND CONTROL OF HIV DRUG RESISTANCE: THE EXPERIENCE OF A HIGH BURDEN COUNTRY




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In 2012, the South African National HIV drug resistance working group (coordinated by the Department of Health and comprising relevant stakeholders from National Department of Health, public, academic and private health clinicians and laboratories) established a strategy for HIV drug resistance prevention, monitoring and control. The strategy aims to address multiple levels of intervention required to establish activities needed to prevent, detect and monitor the emergence of drug resistance.

Antiretroviral therapy (ART) has provided unprecedented gains and benefits, particularly in countries with heavy HIV burdens. South Africa has the largest number of people living with HIV, recently estimated at 6.4 million, of who >2 million are receiving ART *(1)*. The widespread availability of ART has resulted in significant increases in life expectancy from 52 years in 2005 to 61 years in 2014. AIDS-related deaths are estimated to have decreased from 363,910 in 2005 (51% of all deaths) to 171,733 deaths in 2014 (31% of all deaths), and the infant mortality rate has fallen from 58 deaths per 1,000 live births in 2002 to 34 in 2014 *(2)*. The use of ART to prevent mother-to-child transmission (pMTCT) has significantly reduced infection rates in infants to <3% *(3)*.

The scale up of ART is inevitably accompanied by the emergence of HIV drug resistance (HIVDR), which can compromise the success of ART *(4)*. Resistance is caused by mutations within the viral enzymes that result in a significantly reduced susceptibility to antiretroviral agents. Poor adherence or, in rare situations, factors that lower antiretroviral drug concentrations (e.g. malabsorption, drug interactions) favour the selection of resistant variants. HIVDR can be selected for during regimen failure (acquired or ADR), and transmitted to ART-naïve, newly-infected individuals (transmitted or TDR). Studies conducted in South Africa have shown a high prevalence of ADR in patients failing first-line ART regimens, similar to that reported from other low- and middle-income countries and evidence of TDR has also been documented *(5)*. Given the large number of people in South Africa on ART and high HIV incidence rates, the ongoing surveillance of HIVDR is therefore critical for the continued efficacy of the ART programme to reduce HIV-related morbidity and mortality in South Africa.

The South African National Treatment Program

The South African national treatment programme, implemented in 2004, provides ART utilizing a population-based approach with standardized first and second-line regimens as recommended by the World Health Organization (WHO), coupled with regular viral load monitoring. Tenofovir replaced stavudine in 2010 in first line recommendations. In 2013, a fixed dose combination (FDC) of tenofovir, emtricitabine and efavirenz became available for first-line treatment of all adults in the state sector, and is now used in the vast majority of patients. The use of FDCs is encouraged as they are likely to reduce HIVDR selection by avoiding the risks associated with pharmacy stock-outs of one or two drugs in a regimen, and to simplify adherence. Furthermore, viral load

monitoring allows for detection of regimen failure and switch. Protease-inhibitors are used in second-line treatment of adults and in first-line treatment of young children and have been associated with higher levels of viral suppression and lower rates of HIVDR.

Access to third-line ART was implemented in 2013 in the public sector. Empiric switches to third-line ART following virologic failure are not recommended as many of these patients have no PI resistance, and are possibly still failing due to poor adherence. Currently, HIVDR testing is provided for adults and children failing a PI regimen, and access to third-line ART requires demonstration of PI resistance. Selecting individuals who are likely to benefit from third-line ART requires a thorough assessment of adherence and exposure to PIs for a minimum of 12 months. Once PI resistance has been confirmed, a new regimen is constructed based on ritonavir-boosted darunavir together with the most active dual NRTI combination (always including lamivudine/emtricitabine), with the addition of raltegravir and possibly also etravirine for patients with more extensive resistance. The third-line regimen is approved by a small central committee of experts. However, an algorithm based recommendation for selecting third line antiretrovirals has been developed to facilitate regimen selection.

Much of the success of the national programme has been due to a decentralization approach towards ART provision and scale-up, with widespread Nurse Initiated Management of ART (NIMART) and training of nurses at all health facilities, including primary care clinics. Importantly, one programme monitoring system, the Three Interlinked Electronic Register (Tier.net), is implemented at all facilities. This incorporates data from paper-based or electronic registers and allows for minimum data elements and indicators to be reported monthly at district and provincial levels. However, as yet, Tier.net is unable to track patients between facilities, compromising long-term retention and adherence. Patients have been reported to fall out of facility programmes at rates approaching 40% after two years: reasons include defaulting treatment completely, transferring to other government or private sector programmes, or death. A single patient identifier that will allow for differentiation between those who default and those who simply transfer between facilities is needed since tracking of people on ART is critical to containing the spread of HIVDR, and has been agreed to by the national Department of Health.

The South African National Strategy for HIVDR prevention and monitoring

In 2012, the South African National HIV drug resistance working group (coordinated by the Department of Health and comprising relevant stakeholders from public, academic as well as private health-care clinicians and laboratories) developed a strategy for HIVDR prevention, monitoring and control. The strategic objectives of this working group are:

- To prevent HIVDR by identifying associated risk factors and devising new preventive strategies;
- To monitor HIVDR through ongoing national surveillance of selected populations;
- To develop sufficient capacity to address the increasing need for HIVDR testing, clinical interpretation and management;
- To strengthen HIVDR monitoring and evaluation, through central data repositories, regular reporting and epidemiological analysis.

The National HIVDR Working Group has drafted a national strategy for HIVDR prevention and monitoring, and is currently preparing an implementation and budgeting plan. The group meets quarterly, to discuss and provide advice on issues related to HIVDR in the country.

In addition, guidelines on the use of resistance testing have been published by local Southern African experts that encompasses a more patient-focused and research-intensive approach *(6)*. The recommendations include HIVDR testing of all first and second-line failures as well as infants exposed to pMTCT. While these recommendations are being adopted in some centres, at present they are not practical on a national level, given the scale of the ART programme in South Africa and the lack of sufficient laboratory and general infrastructure. In addition, recent major developments, such as the EARNEST study results, have yet to be evaluated and integrated in to more updated guidelines *(7)*. Nevertheless, this is an active group that promotes and supports a role for HIVDR testing and routinely hosts skills building workshops and conferences to promote a better understanding of HIVDR.

Early warning indicators for HIVDR

WHO has recommended a set of five early warning indicators (EWIs) for HIVDR which includes measuring on-time pill pick-up, retention in care, pharmacy stock-outs, appropriate dispensing practices and virological suppression *(8)*. The National Strategy for HIVDR plans to extract EWIs from patient records, ART registers and pharmacy records, in order to provide individual facility-based performance assessments. These indicators are intended to enable targeted interventions aimed at improving daily practices to minimize the risks of HIVDR emergence and optimize HIV care. A plan to phase in EWI reporting through Tier.net is in development,

spanning three phases over a five-year period. The pilot assessment (2014/15) will be carried out in two districts in two provinces and will assess the quality of data in each health facility, the availability of laboratory support to the facility, and the human resources capacity at the facility to implement this analysis. The second and third phases will expand this to at least half of, then all, facilities using Tier.net nationwide. A local collaboration of health and human rights non-governmental organizations, in consultation with the Department of Health, have set up a national monitoring system to assess and address drug stock outs, with a strong focus on ART and TB.

Surveillance of HIVDR in South Africa

To support programmatic data, South Africa has adopted the WHO-recommended approach for national HIVDR surveillance, including estimation of rates of resistance in adult and paediatric patients at the time of initiating ART (pre-treatment HIVDR or PDR surveys) and those receiving ART (ADR surveys), patients infected with resistant HIV strains (TDR surveys surveys) and infants infected with HIV despite possible exposure to PMTCT (pediatric HIVDR surveys) *(8)*. The WHO study protocols are readily available, standardized, and can easily be adapted to become country-specific. The HIVDR Working group is tasked with prioritizing, implementing, and assessing the outcomes from these surveys.

TDR surveys have been conducted in South Africa since 2002 using samples from primagravid young women participating in the national annual antenatal survey. These assessments have shown that transmitted resistance was low prior to and for the first five years of the national ART programme. However, moderate levels (5–15%) of transmitted resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) drug class have been detected in KwaZulu-Natal, the province with the highest HIV burden and largest ART programme. More recently, TDR has been estimated to be at moderate levels to NNRTIs in additional provinces *(9)*. A pilot study to assess ADR in KwaZulu-Natal was conducted in 2013, and a national ADR survey is currently underway in sentinel sites to estimate levels and patterns of HIVDR in treated individuals. These surveys serve to assess the performance of and identify gaps in the ART programme. Surveys among children <18 months of age are also ongoing making use of specimens collected as part of early infant diagnosis (EID) testing, many of who will have been exposed to antiretroviral drugs through PMTCT programmes.

Scaling up resistance testing for individual patient management

Incorporating HIV drug resistance testing into routine clinical management in ART-naïve patients and in patients failing first-line ART is currently unrealistic in low-middle income countries such as South Africa, due to the large numbers of people initiating and failing ART and the technological sophistication and costs of current HIVDR tests. Viral failure rates of 10–20% have previously been reported among first-line ART failures which equates roughly to >200,000 HIVDR tests if routine testing were implemented. Although NRTI resistance mutations are commonly present in patients failing first-line ART *(5)*, a number of observational studies have shown that that the presence of resistance to the dual NRTIs used in second-line PI regimens does not increase the risk of virologic failure, which illustrates that ritonavir-boosted PIs have high genetic barriers to resistance and are potent *(7, 10)*. There is residual activity of NRTI regimens even with "high level resistance", notably with resistance mutations to lamivudine *(11)*/emtricitabine, which is sufficient to achieve virologic suppression when combined with ritonavir-boosted PIs.

Clinical and laboratory support for HIVDR testing

HIVDR testing occurs in specialized centralized provincial facilities that mostly use in-house genotyping assays. The ongoing expansion of the ART programme and the anticipated increased numbers of patients failing PI-based ART is being supported by expansion of clinical and laboratory capacity. The National Health Laboratory Service is currently capacitating additional facilities to provide five specialized antiretroviral resistance testing centres nationally. These, in conjunction with the surveillance testing laboratory at the National Institute for Communicable Diseases, aim to provide capacity for over 15,000 tests per annum for the public sector. To accommodate further increases in capacity and additional testing recommendations, current research focuses on using next-generation sequencing technologies to allow for pooled testing strategies with higher through-put and exploring simpler and cheaper point-of-care testing options. The number of HIV specialists that can facilitate resistance testing interpretation and deal with complex cases will also need to be increased, who will initially operate at a provincial level with gradual decentralization to district level.

Data management

Comprehensive, robust and accurate analysis of HIVDR data is essential. A key component of the HIVDR strategy is to develop a central database that can curate, store, analyze and distribute resistance data, collected through routine testing and surveillance activities. In order to accommodate data from a range of systems currently in use, both from private

and public sectors, a minimum set of standardized information has been devised, to be reported to the national database at quarterly intervals. From this, the HIVDR working group will produce written reports and electronic summaries to the National Department of Health. The South African mirror of the Stanford HIV Drug Resistance database is hosted by the Southern African Treatment and Resistance Network (SATuRN http://www.bioafrica.net/saturn) and provides a platform from which to develop a centralized database system.

Conclusion

Significant progress has been made in improving the quality of care for HIV-positive people in resource-limited settings. However, resistance to ART must be monitored quickly and effectively in order to maintain the efficacy of ART regimens. Continued surveillance of HIVDR levels in persons living with HIV and those receiving ART is needed to prevent the widespread emergence of resistance that may have a public health impact. Whilst these efforts are needed to preserve current regimens, this information should further inform new ART options for high burden countries. Such new regimens should prioritize once daily FDC for easier adherence, with higher resistance barriers, and be affordable. Of note, the integrase inhibitor dolutegravir is considered a viable option to replace efavirenz in first-line regimen, due to superior viral suppression *(12)*, fewer side-effects, low dosage and potential low cost, and should be considered in regions with high levels of NNRTI TDR. To support these efforts, continued research is imperative to provide improved regimens, patient monitoring practices and scientific evidence for alternative approaches. ●

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References

1. UNAIDS: South Africa HIV Estimates and Projections 2012.
2. Statistics South Africa: Mid-year population estimates 2014.
3. Sherman GG et al. *S Afr Med J* 2014; 104(3 Suppl 1): 235-8.
4. Arts EJ and Hazuda DJ. *Perspectives in Med* 2012; 2(4): a007161.
5. WHO HIV Drug Resistance Report 2012.
6. Conradie F et al. *S Afr J HIV Med* 2012; 13: 162-7.
7. Paton NI et al. *New Engl J Med* 2014; 371(3): 234-47.
8. WHO Global Strategy for the Surveillance and Monitoring of HIV Drug Resistance 2012.
9. NICD: Communicable Diseases Surveillance Bulletin, Nov 2013.
10. Sigaloff KC et al. *JID* 2012; 205(11): 1739-44.
11. Castagna A et al. *AIDS* 2006; 20(6): 795-803.
12. Walmsley SL et al. *New Engl J Med* 2013; 369(19): 1807-18.

THE GLOBAL ANTIBIOTIC RESISTANCE PARTNERSHIP

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The Partnership operates to bring a set of new voices to the antibiotic resistance issue and to establish local capacity to develop and help to implement evidence-based policies in eight low- and middle-income countries in Africa and Asia. Awareness of antibiotic resistance and its potential to derail gains against infectious diseases was not on the global health agenda for low- and middle-income countries in 2008, when GARP began. Significant in-country progress supports expansion of the GARP model.

The Global Antibiotic Resistance Partnership (GARP)[1] began in 2008 with funding from the Bill & Melinda Gates Foundation. The aim has been to develop sustained local capacity to formulate and promote locally relevant policy related to antibiotic use and resistance in low- and middle-income countries (LMICs).

For several years prior, CDDEP (then a centre at Resources for the Future, an established United States think tank) had been examining the policy process and analyzing options for the United States in a project called Extending the Cure. That effort, which continues, gave CDDEP entrée into the global discussion about antibiotic resistance, mainly among the high-income countries. The absence of voices from LMICs led us to begin GARP.

Antibiotic resistance has gained prominence in recent years, but in 2008 it had a much lower profile – in LMICs it is not much of an exaggeration to say that it had no public profile, although some researchers everywhere had been active and interested. Importantly, it was not a high priority among the main bilateral health funders, such as the United States Agency for International Development (USAID) and the Department for International Development (DfID). AIDS, malaria and tuberculosis were – and remain – the highest priorities. An exception was the Swedish International Development Cooperation Agency (SIDA), which was active globally on antibiotic resistance, but with a different focus from that of GARP.

Yet it was clear that antibiotic use was growing in LMICs, the bacterial disease burden was high, and the loss of effective treatments for common infections could have even more dire consequences in LMICs than in high-income countries. In the United States, some people die from antibiotic-resistant infections, but a major consequence is economic: later-generation antibiotics are significantly more expensive, and extended stays can double (or more) hospital bills. In low-income countries, however, those newer antibiotics are simply not available at all, and in middle-income countries, availability is limited.

An obvious question is whether the policy prescriptions from the United States and Europe, which focused almost entirely on reducing use, could simply be applied in LMICs. It was clear that the answer was no for at least two main reasons: first, because unlike high-income countries, lack of access is still a significant problem in LMICs. One million children die from pneumonia every year, nearly all of whom could be successfully treated with an inexpensive, simple antibiotic. Second, weak regulatory capacity in LMICs means that controlling access through laws and regulations – such as prescription-only laws – could not be relied upon. It was apparent that policy solutions would have a greater chance of success if local experts customized them to the local context.

The GARP concept was, therefore, to identify local experts in each country, assemble them into a working group, and provide them with the resources to meet, discuss, and analyze the national situation regarding antibiotic use and resistance, identify critical data gaps, and work toward developing locally relevant policy that could be adopted by government and private sector organizations, such as hospitals and professional societies.

GARP was established in 2009–2010 in four countries – Kenya, India, Vietnam and South Africa – chosen because they represented a range of conditions, particularly in type

[1] http://cddep.org/projects/global-antibiotic-resistance-partnership

of government, culture and income level. After promising starts and progress in those countries (phase 1), in 2011, a second grant was awarded, and programmes were established in four additional countries (phase 2): Mozambique, Tanzania, Nepal and Uganda.

CDDEP has provided support in each country for three to five years, after which countries are expected to raise the modest amounts needed to sustain the working group and any activities that it chooses to do.

GARP working groups

CDDEP found no models for the proposed approach, which was to create multidisciplinary, multisectoral groups and empower them to participate in a national policy process. The aim was that they would become trusted advisers to government, professional groups and the public (e.g. through the media). The working group members would be volunteers, but a paid staff person (the coordinator) was essential for the group to be productive.

CDDEP identified potential working group members in each country through literature searches and networking with professional contacts. Chairpersons were selected for their stature in the scientific and/or academic community and for affiliation with a prominent academic or scientific organization. In two cases (Vietnam and Uganda), the secretariat itself is the prominent organization and a principal investigator has assembled the working group, including the chairperson, in consultation with CDDEP.

From the beginning, GARP working groups included experts in both human and veterinary medicine, from the public and private sectors, and represented a range of scientific and health disciplines. Invariably, some group members were acquainted with or knew of other members, but no one knew everyone else; the mix of disciplines (especially animal and human sciences) was unusual – and is one of GARP's hallmarks. Moreover, in no country does the GARP working group duplicate another group, although interests may overlap (e.g. in Kenya, the Infection Prevention Network-Kenya [IPNET–Kenya], started by the GARP–Kenya vice chair, deals with infection and antibiotic use in hospitals). In some countries, the GARP working group is the only entity inside or outside government with the antibiotic resistance mandate.

GARP–Kenya and GARP–South Africa are offered as examples of successful programmes.

GARP–Kenya

Kenya was the first GARP project, beginning work in 2009 with a "situation analysis," which has become standard for newly organized GARP projects. The situation analysis was not focused narrowly on studies of antibiotic resistance but looked at a range of factors impinging on antibiotic use and access in both humans and animals: the burden of infectious disease, which vaccines are in use and the coverage rates, the antibiotic supply chain, antibiotic use patterns and variation in these characteristics around the country. The situation analysis was the foundation document for the working group to define an evidence-based policy agenda for the coming years, including a research agenda aimed at filling important information gaps.

The situation analysis had additional value in Kenya, as elsewhere, as a means of building cohesiveness among the working group with a high-quality collaborative product that was recognized externally as authoritative and novel. It was a calling card that could be used to approach government and others and signaled seriousness of purpose.

Gap-filling research

CDDEP offered to fund small research projects (on the order of US$ 10,000) that would produce information to fill important knowledge gaps identified in the situation analysis. In Kenya, two projects were funded.

1. Antibiotic use in food animals

This was a first-of-its-kind study of antibiotic resistance levels in bacteria cultured from carcasses (of cows, pigs and chickens) in slaughterhouses and in retail meat, coupled with interviews of farmers and herders in the same areas from which the slaughtered animals came. The bacterial sampling, culture and analysis were carried out by Dr Samuel Kariuki, chair of the GARP–Kenya working group, and Patrick Irungu, a young academic agricultural economist who has since become a member of the working group, conducted the fieldwork. The farmers and herders were asked about many things, including their practices related to antibiotics use.

This project was small and limited to the area around Nairobi, but it was used as a pilot to approach FAO for a larger project involving a nationwide sample, which has been completed.

Antibiotic use was widespread among all farmers and herders. Tetracyclines, sulfonamides, penicillins and streptomycins were the most frequently used. Most antibiotics were purchased directly at agro-vet stores, without the intervention of veterinarians (mainly because they are scarce and inaccessible for most animal husbandry men). Antibiotic resistance was equally prevalent in samples from all three types of animals: most bacteria cultured from beef were resistant to most of the commonly used

antibiotics, about half those cultured from chicken were resistant to some antibiotics and a smaller percentage of those cultured from pigs were resistant.

Other findings suggested effective interventions. One, in particular, was that nongovernmental organizations (NGOs) that provided support to farmers and herders often gave them free antibiotics. Not surprisingly, this increased antibiotic use (though it was not necessarily appropriate use). NGOs also provided other types of support – restocking, water provision and animal dips for parasites – that had no effect on antibiotic use.

This study (awaiting publication) provided a baseline and some interesting findings but also opened the conversation about antibiotic use in food animals.

2. Knowledge, attitude, perception and pricing of antibiotics in hospitals in two areas of Kenya

Another small study in and around Nairobi and in western Kenya in Nyanza province, was conducted by the Ecumenical Pharmaceutical Network, led by Donna Kusemererwa, then vice-chair of the working group and current vice-chair of the new GARP–Uganda working group. The study included public, private and mission hospitals in both regions. At least four individuals were interviewed at each hospital: a medical professional and one person each from pharmacy, laboratory and administration.

Not surprisingly, the large majority of professionals interviewed in the study were aware of the seriousness of antimicrobial resistance as a national problem, but many fewer it found a problem at their own hospital. The survey (awaiting publication) points to missing information (e.g. a survey of practices) and indicates what is and is not known by health professionals.

The associated study of antibiotic pricing *(1)* found that cash-flow problems force hospitals to engage in significant purchasing of small lots, even though large-quantity purchases result in lower costs per dose. It also found a wide range of markups – from 50% to 400% – for individual antibiotics, depending on where they were sold.

GARP–Kenya 2014

GARP–Kenya has matured into an independent group, incorporating in 2014 as an autonomous arm of IPNET–Kenya. A sampling of its recent activities includes the following:

- November 2013: two-day workshop on antimicrobial stewardship in Mombasa, with participation from around Africa (and Haiti), following an infection prevention and control meeting;
- November 2013: presentation on antimicrobial stewardship to the National Infection Prevention Control Committee at the invitation of the Infection Prevention and Control Unit of the Ministry of Health;
- February–March 2014: presentations on antimicrobial use, with the Ministry of Health, to the health executive members in each county (formerly states) on antimicrobial use in Kenya;
- November 2014: the second "antibiotic awareness week" in Kenya.

After several years of CDDEP nurturing, GARP–Kenya has become a trusted adviser to government and a recognized source of expertise for the country.

GARP–South Africa

Success in South Africa looks very different. An antimicrobial resistance summit was held in Johannesburg in October 2014, to introduce an "Antimicrobial Resistance National Strategy Framework for South Africa" and secure commitment of stakeholders to its implementation. The framework is the culmination of several years of work, which was set in motion by the publication of the GARP–SA situation analysis in the *South African Medical Journal* in 2011. GARP continues to support this work.

The GARP Network

The first four GARP country projects have evolved in somewhat different directions, but have all succeeded in creating a hub of antibiotic resistance expertise and activity. In Vietnam, for example, the secretariat is the Oxford University Clinical Research Unit (OUCRU) in Hanoi. The working group is chaired by Dr Nguyen Van Kinh, Director of the Infectious Disease Hospital (under the Ministry of Health) in which OUCRU is housed. GARP–Vietnam therefore has close ties to government. The GARP "brand" has been useful in setting policy research apart from purely scientific and clinical work, and gives voice to the policy implications of basic research.

GARP working groups in other countries – for example, Kenya and Nepal (where the secretariat is the Nepal Public Health Foundation) – have found value in being totally independent of their governments because of turnover and even new constitutions. While it is important for governments to take action on antibiotics, the value of authoritative groups outside government has obvious value.

GARP – Uganda is the last of the eight GARP projects started under the Gates Foundation grants; its inaugural meeting was held in February 2014. The secretariat is

lodged in the Uganda National Academy of Sciences, an organization whose main mission is to advise the government.

In addition to country-specific activities, GARP working group members are regular participants in global discussions on antibiotic resistance.

Moving forward

CDDEP is committed to maintaining GARP, expanding it and strengthening the partnership. CDDEP researchers continue to conduct innovative research on antibiotics and antibiotic resistance globally, for example, a study that quantified, for the first time since 1987, antibiotic consumption in 63 countries between 2000 and 2010 *(2)* and a call for global action in *The Lancet Infectious Diseases (3)*.

In a move mirroring the development of GARP after work in the United States, CDDEP has also begun constructing a global version of Resistance Map (http://cddep.org/projects/resistance-map), an interactive tool to explore the evolution of antibiotic resistance in a set of pathogens over time in North America and Europe.

Conclusion

GARP has succeeded in bringing 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. •

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References

1. Kusemererwa D, Kariuki S, Winters C, Braykov N, Megiddo I, Plant S, & Wesangula E. (2013). Survey of antibiotic prices in public, private, and mission district-level hospitals in Kenya. *Pharmaceutical Journal of Kenya*, 21(3), 208.
2. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradi N and Cars O. (2013). Antibiotic resistance-the need for global solutions. *The Lancet Infectious Diseases*, 13(12), 1057–98. doi:10.1016/S1473-3099(13)70318-9
3. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, & Laxminarayan R. (2014). Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *The Lancet Infectious Diseases*, 3099(14), 1–9. doi:10.1016/S1473-3099(14)70780-7

THE CHENNAI DECLARATION AND ANTIBIOTICS STEWARDSHIP IN DEVELOPING COUNTRIES

ABDUL GHAFUR, COORDINATOR, CHENNAI DECLARATION, INDIA

India has the taken the lead in antibiotics stewardship in developing countries through the Chennai Declaration. The coordinator of the declaration explains how it came about, how they took a pragmatic view of what could be achieved in a high-burden/low resource country and the positive progress they made.

Antimicrobial resistance is a global challenge, prompting academicians, politicians and policy-makers across the globe to launch initiatives to control this ever-increasing menace.

South Asia is the major epicentre of Gram-negative bacterial drug resistance and Mediterranean countries hold the status of the minor epicentre *(1, 2)*. Both these regions have reported similar rates of resistance, but the large population and resulting high bacterial biomass makes South Asia the major epicentre *(1, 2)*.

Contributing factors to the high resistance rates in Developing countries

- 1. Lack of functioning antibiotic policies;
- 2. Inadequate infrastructure for infection control;
- 3. Large population and socio economic disparity;
- 4. Sanitation issues;
- 5. Lack of political motivation;
- 6. Influence of the pharmaceutical industry.

The Solution is:

- 1. Mobilise political will;
- 2. Formulation and implementation of national antibiotic policies;
- 3. Regulation of OTC (Over the counter) sale of antibiotics;
- 4. Improving sanitation in the community setting;
- 5. Improving infection control infrastructure and practices in all health-care institutions.

Indian scenario: Resistance crisis and tackling resistance initiatives

Let us take India as an example of a developing country with high antibiotic resistance statistics. India has reported very high resistance rates with no pre-existing serious initiatives to tackle the scenario. Many other developing countries share similar scenarios and contributing factors.

"A Roadmap to Tackle the Challenge of Antimicrobial Resistance – Joint meeting of Medical Societies in India" 2012, was the first ever meeting of medical societies in India. All stakeholders including representatives of medical societies, various Governmental bodies, media, academics and international representatives came under one roof to discuss the antimicrobial (AMR) issue. The aim was to formulate implementable recommendations to tackle AMR in India. The Roadmap meeting led to the creation of the document – "The Chennai Declaration". The declaration is based on the theme of "a practical but not a perfect policy" for a developing country. The document received widespread attention of national and international academic community (3).

Summary of Chennai Declaration recommendations *(3)*

- 1. There is an urgent need to initiate measures to tackle the scenario at national and global level.
- 2. The Indian Ministry of Health (MoH) will need to take urgent initiatives to formulate a national policy to control the rising trend of antimicrobial resistance.
- 3. The Drugs Controller General of India (DCGI) will need to formulate and implement a policy on rationalizing antibiotic usage in the country, both in hospitals and over the counters.
- 4. State Departments of Health will need to take initiatives to improve infection control standards and facilities in hospitals.
- 5. The Medical Council of India will need to make necessary curriculum changes so as to include structured training on antibiotic usage.
- 6. An Infection Control Team (ICT) must be made

mandatory in all hospitals. Regulatory authorities and accreditation agencies (NABH, ISO) must insist on a functioning ICT, during the licensing and accreditation process.

- 7. State Department of Health (DoH) should take initiatives in organizing regional and state infection control committees.
- 8. A National Task Force should be set up to guide and supervise the regional and state infection control committees.
- 9. The National Accreditation Board of Hospitals (NABH) is required to insist on strict implementation of hospital antibiotic and infection control policy.
- 10. The Indian Council of Medical Research should broaden the antimicrobial resistance surveillance network.
- 11. The Indian division of the World Health Organization should step up interaction with the government on issues related to drug resistance.
- 12. There is an urgent need to standardize microbiology laboratories in India.
- 13. Medical societies to take active interest in initiating infection control and antibiotic stewardship awareness activities among the society members.
- 14. Medical journals should make deliberate attempts to educate readers on infection control and national antibiotic policy-related issues.
- 15. Electronic and print mass media should take initiatives on public awareness campaigns on the dangers of misuse of antibiotics.
- 16. Non-governmental organizations (NGOs) have to play a major role in tackling AMR activities.
- 17. There is a need to evaluate the extent and to regulate the usage of antibiotics in veterinary practice.

Chennai declaration strategy *(3)*

"An implementable antibiotic policy" and NOT "A perfect policy" could be the practical strategy in developing countries. Adopting a strict antibiotic policy, with absolute and strict control on antibiotic use in the community and in hospitals, on a background of enforcement of good infection control standards in hospitals may not be feasible in developing world. Introduction of step-by-step regulation of antibiotic usage, concentrating on higher end antibiotics first and then slowly extending the list to second and first line antibiotics will be a more practical option *(8)*.

Progress

- 1. The Chennai declaration document was reviewed in detail in more than a dozen reputed international journals, many international academic and health policy related conferences *(4–12)*.
- 2. Highest officials in Indian Ministry of Health studied the document.
- 3. The Chennai Declaration could convince Indian authorities on seriousness of the resistance scenario in the country and the importance of taking measures to control it.
- 4. The initiative could mobilise medical societies and all the other stakeholders.
- 5. The initiative has also created international awareness regarding the ground reality in developing countries and how a policy has to be tailored as per local requirement.
- 6. Efforts by the Chennai Declaration team through interaction with the ministry, creation of public and professional awareness via media, journals and meetings, and inspiring political leadership to discuss the issue in the Indian parliament, did speed up the publication of the new over-the-counter rule.
- 7. The new rule issued by the ministry of health includes 24 antibiotics and 11 anti-tuberculosis drugs in the schedule H1 category. This rule is meant to regulate over-the counter dispensing of drugs. Pharmacists not only have to insist on a prescription from a registered medical practitioner, but they also need to enter details in a register. Drug inspectors will monitor compliance. First-line antibiotics will not come under the strict monitoring as those are excluded from the list, at least initially. The new H1 list is based on a step-by-step strategy of the Chennai Declaration *(4)*.

In tune with the basic spirit of the Declaration – a "Practical not Prefect" approach – Chennai declaration team proposed a five year strategy to control antibiotic resistance *(13)*. The five year plan recommends nationwide implementation of the over the counter rule in one year and expanding the list to include additional antibiotics by second year and most antibiotics by fifth year. All tertiary care hospitals should have an antibiotic policy by the end of first year and all secondary care and primary care hospitals by second year. Time bound initiative to monitor high-end antibiotics in hospital must be given high priority to rationalize usage of these antibiotics. The practice of getting a second opinion by an antibiotic steward while high-end antibiotics are used must be encouraged. Step-by-step introduction of surgical prophylaxis monitoring sheet in all hospitals will help a long way in reducing unnecessary antibiotic usage. An autonomous antibiotic policy accreditation agency can accredit antibiotic policies of all hospitals. All secondary and tertiary care hospitals to have an infection control committee by the end of first year itself and primary care hospitals by second year. National, district and

state task forces can monitor performance of these committees. All hospitals need to follow isolation precautions to the best of their ability and compliance with the recommendations needs to be ensured in a stepwise manner. The national committee needs to prepare infection control and antibiotics usage guidelines.

Antibiotics used in human treatment to be banned as growth promoters in food animals by the first year itself and by fifth year all veterinary antibiotics should need prescriptions. A national veterinary antibiotics monitoring network with step wise expansion to include more centres is the need of the hour. Multicentre clinical studies on combination therapy against MDR Gram-negative infections need to be initiated on an urgent basis. By end of the second year results of the large multicentre trials could be published. By fifth year India can be making a significant contribution to academic world on treatment of MDR bacterial infections.

Medical Council of India to initiate discussions on necessary curriculum changes to encourage rational antibiotic usage and infection control. By second year new modules must be introduced into all medical schools. National antibiotics resistance monitoring network to include more centres every year to reach at least a 100 centres by the fifth year *(13)*.

Discussion with pharmaceutical industry to identify molecules already in development and encourage the progression of promising leads should be a priority. Fast tracking of promising antibiotics especially those active against MDR Gram-negative bacteria will reduce the antibiotics free period. Public private partnership to develop new molecules needs to be explored. All medical societies need to conduct CMEs (continuing medical education) on antibiotic stewardship and infection control. All medical societies need to participate in antibiotics awareness day activities. Introduction of online modules on antibiotics usage will cover all doctors by fifth year. Medical journals and media will increase their participation in antibiotics awareness activities *(13)*.

In order to improve sanitation across the country, we need to seek advice from experts in relevant areas of public health, and various branches of science. Practical and implementable strategies identified and implemented nationwide. Hospital accreditation agencies have to ensure strict monitoring on the compliance to the infection control and antibiotic policy, during accreditation and reaccreditation process. All tertiary care hospital labs should be able to perform culture from all sample types. Secondary care hospitals should be able to perform culture of all kinds of samples and if unable to process, outsourcing of samples could be an option *(13)*.

Five-year action plan prepared by the Chennai Declaration team can be implemented in hospitals in all developing countries, including India *(7, 8)*.

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References

1. Abdul Ghafur. Can India be the wing commander in the global fight against antimicrobial resistance? JAPI 2012; 60:42-43
2. Abdul Ghafur, An Obituary – on the death of Antibiotics. JAPI, 2010; 58:143-144
3. Ghafur A, Mathai D, Muruganathan A et al. "The Chennai Declaration" Recommendations of "A roadmap- to tackle the challenge of antimicrobial resistance" - A joint meeting of medical societies of India. Indian J Cancer [Epub ahead of print] DOI:10.4103/0019-509X.104065. http://www.indianjcancer.com/preprintarticle.asp?id=104065
4. Abdul Ghafur.Perseverance, persistence, and the Chennai declaration. Lancet Infectious Diseases, Volume 13, Issue 12, Pages 1007 - 1008, December 2013
5. Matlin SA, Clift C, Told M, Kickbusch I, Heymann D. Anti-Microbial Resistance – An Urgent Global Concern. A Brief for Policy-Makers. Global Health Programme, Graduate Institute of International and Development Studies, Geneva and Centre on Global Health Security, Chatham House, London. Published April 2014, Geneva.
6. Goossens H. The Chennai declaration on antimicrobial resistance in India. Lancet Infect Dis 2013; 13: 105–06.
7. Yusuf I, Adam RU. Adopting Chennai declaration strategies in the prevention and control of the spread of multidrug-resistant hospital-acquired bacterial infections in Nigeria: A call to action. J Global Antimicrob Resist (2014), http:// dx.doi.org/10.1016/j.jgar.2014.03.003
8. Ibrahim Yusuf, Rabi'atu Umar Adam, Siti A Ahmad, Phang L Yee. Ebola and compliance with infection prevention measures in Nigeria. Lancet Infect Dis 2014 Published Online October 2, 2014. http://dx.doi.org/10.1016/S1473-3099(14)70954-5
9. Hopkins S. Improving antimicrobial stewardship and surveillance: The Chennai Declaration. BMJ 2013;346:f591. BMJ 2013; 346 doi: http://dx.doi.org/10.1136/bmj.f591
10. Gould IM. 'The Chennai Declaration': India co ordinates action against antimicrobial resistance. J Glob Antimicrob Resist 2013;3. Available from: http://linkinghub.elsevier. com/retrieve/pii/S2213716513000106
11. Holmes AH, Sharland M. The Chennai Declaration: India's landmark national commitment to antibiotic stewardship demonstrates that 'truth alone triumphs'. J Antimicrob Chemother 2013;68:1453 4.
12. Davies SC, Fowler T, Watson J, Livermore DM, Walker D. Annual Report of the Chief Medical Officer: Infection and the rise of antimicrobial resistance. Lancet 2013;381:1606 9. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140 6736 (13) 60604 2/fulltext
13. Team C. "Chennai Declaration": 5-year plan to tackle the challenge of anti-microbial resistance. Indian J Med Microbiol [Epub ahead of print] http://www.ijmm.org/preprintarticle.asp?id=129053

ALTERNATIVES TO ANTIBIOTICS

PHAGE THERAPY BACK TO THE FUTURE!

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Antibiotic resistance is growing steadily; this is currently a worldwide problem. The economic costs are very high and the human impact is real. Environmental viruses called Bacteriophages are natural killers of bacteria. Experts agree that they are one of the strongest alternatives to antibiotics. They have been used empirically for many years in former Russian republics. Phagoburn is the first international multicentric study which aims to assess the safety and efficacy of two cocktails of bacteriophages to treat infected burn wounds either by *Escherichia coli* or by *Pseudomonas aeruginosa*. The 7th Framework Programme for Research and Development (European Community) funds this collaborative project. Henceforth, politicians should consider the future conditions of phage use in medicine. More human, economical and legal resources will be necessary for the next years. New public health rules will have to be written and anti-infection policies would have to be changed.

Antimicrobial resistance is a natural phenomenon in microbes, but the unrestrained use of antibiotics accelerates its occurrence. Treatment options for common infections are running out. All World Health Organization (WHO) regions but one report over 50% of resistant *Escherichia coli* strains to third generation cephalosporin (3GC) antibiotics. 3GC is one of the most potent class of antibiotics within our anti-bacterial arsenal. Worldwide, over 50% of *Klebsiella pneumonia* strains became resistant to 3GC. The risk of mortality is twice as high when patients are infected by an antibiotic resistant *Escherichia coli* strain.

Additional costs such as hospitalization, antibacterial therapy, medical care, etc. are increased by antibiotic resistant infections. In Europe, antibacterial resistance is responsible for 25,000 deaths per year and 2.5 million extra hospital days: the overall societal cost is estimated to reach €1.5 billion per year including €900 million for hospitalization days. In the United States, 23,000 deaths per year and 2 million illnesses are related to antibacterial resistance: direct and indirect societal costs are estimated to €20 and €35 billion, respectively *(1)*.

In January 2014, the executive board of the WHO, urged member states "to encourage and support research and development, including by academia and through new collaborative and financial models, to combat antimicrobial resistance and promote responsible use of antimicrobials, develop practical and feasible approaches for extending the lifespan of antimicrobial drugs and encourage the development of novel diagnostics and antimicrobial drugs".

Phage therapy is currently identified by many world experts as a promising way to fight resistance *(2–6)*.

Phages ecology and physiology

Phages are environmental viruses and natural bacterial parasites. They are the most important biomass on earth (7). Some of them are able to kill their specific targeted bacteria. They have been fighting bacteria for billions of years and help maintain a proper balance between host cells and bacterial populations within all living creatures. They are highly specific and only effective on bacteria. No toxic effects on mammalian (human) cells have been reported.

When a lytic phage finds its receptors on the bacterial wall, it hooks them up strongly. Then, the virus injects its genetic material inside the cytoplasm through the bacterial wall. The phage DNA (or RNA) sequence uses the bacteria to multiply and propagate. Bacteria are quickly destroyed (20 minutes), releasing many new phages able to strike new bacteria. The infection of bacteria by phages spreads very fast. As a consequence, the bacterial population is severely reduced, helping the human immune system get rid of it.

The bacteria destruction process may slow down if a strain

becomes resistant to the phage. To reduce such a risk one uses a "cocktail", i.e. a mix made of several different phages, to quickly decrease the bacterial inoculum, through various modes of action.

Historical clinical uses

Suspected in 1915 by Twort and discovered by d'Hérelle in 1917 at the Pasteur Institute (Paris) phages started to be used without any proper knowledge, leading to amazing but sometimes capricious results *(8)*. The discovery of penicillin in the late 1930s and the rise of antibiotics in the late 1970s led to their oblivion. It is only in the late 1980s, after the methicillin resistant *Staphylococcus aureus* (MRSA) superbug emerged in the United States, followed by the discovery of vials containing phages on Soviet Union soldiers (first Afghanistan war) that phage therapy was reborn in Western European countries.

Phages have been used in Tbilissi (Georgia) at the Georges Eliava's Institute since the 1930s and have been commercialized in Russian pharmacies by Microgen Co.® for decades. In the European Community, The Phage Therapy Centre in Poland offers phage therapy for compassionate treatment under the Declaration of Helsinki. Recently, the Queen Astrid Military Hospital in Brussels obtained approval from the Federal Government to perform such treatments. In France, phage therapy is scarcely used and only once all antibiotic drugs failed, but without any proper regulatory framework. In Washington and Oregon (USA), surgeons led by Dr Betty Kutter used Eliava Institute products on a case by case basis for treating diabetic foot infected ulcers. All these small initiatives show that phage therapy has to become a professionalized therapy, with approved manufacturing and clinical evaluation processes, before it can strengthen our anti-bacterial arsenal.

For years several western academic teams have been working on phage therapy – L Debarbieux (Pasteur Institute, Paris, France), J-P Pirnay (Queen Astrid Military Hospital, Brussels, Belgium), M Clockie (University of Leicester, UK), A Gorski (Institute of Immunology and Experimental Therapy, Wroclaw, Poland) and Betty Kutter at Evergreen State College (WA, USA), to name a few. By the turn of the century, various SME's Intralytix, Ampliphi Biosciences, Novolytics, Technophage, Micreos and Pherecydes Pharma, in collaboration with these public research institutions, started to look at phages with modern techniques - microbiology, electronic microscopy, molecular biology including phage genome sequencing and annotation.

Several phage products targeting various bacterial

Table 1: **Listings of companies**

Name of companies	Country	Web	Notes
AmpliPhi BioSciences Corporation	Australia	http://www.ampliphibio.com	Clinical trials against infections of the group « ESKAPE » on humans and among pets and livestock animals for MRSA and PYO
Biophage Pharma Inc	Canada	http://www.biophagepharma.net/index.php/en/	Biosensor division : dev. & commercialization of simple, accurate, highly sensitive biosensors based on phages / Therapeutic division dev. Phage therapies for human health.
Pherecydes Pharma	France	www.pherecydes-pharma.com	Development of phagetherapies for human health. EU funded PHAGOBURN clinical trial
Gangagen Inc.	India	www.gangagen.com	Developments of products against MRSA and PYO infections
Biotech Laboratories	Israel	www.biotec.com/index.asp	Rapid detection of rifampicine resistance in sputum positive for M.tb / Rapid detection of BK in human sputum
Micreos Food Safety	Netherlands	www.ebifoodsafety.com	Protection against LISTER in food preparation
CheilJedang Corp.	South Korea	www.cjj.co.kr	To protect chicken feed from Salmonella gallinarum et pullorum
Phico Therapeutics	UK	www.phicotherapeutics.co.uk	Bacteriophages for several bacteria : Listeria monocytogenes , M. tuberculosis), MRSA, MSSA
Novolytics	UK	www.novolytics.co.uk	Gels /MRSA / C. Difficile and products to decrease nasal portage of MRSA /gels for skin infections and medical devices
Biocontrol	UK	www.biocontrol-ltd.com	Cinical trials on otitis to treat PYO infections
Omnilytics	USA	www.phage.com	Development and use of lytic bacteriophages against tomato wilt disease
Intralytix	USA	www.intralytix.com	Decontamination and food additive against Escherichia coli O157:H7 in food preparation /Food additive against contamination by LISTER of uncooked food
Viridax Inc.	USA	www.viridax.com	Development of products against staphylococcal infections.
New Horizons Diagnostics Corporation	USA	http://www.nhdiag.com/phage.shtml	Enzybiotics: Phage Associated Enzymes (PAE) that act as antibiotics

infections such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Acinetobacter baumani*, *Clostridium difficile*, are being developed by SMEs, in various therapeutic domains: respiratory tract, intestinal tract, post-surgical, skin infections including burn wounds *(5,9–12)*, etc.

Standardized processes to produce this new class of therapeutic biological products, according to pharmaceutical Good Manufacturing Product (GMP) standards, are being developed. The clinical evaluation of phage cocktails within international, randomized, multicentric trials is ready to start in order to consolidate the historical data that have been developed by Eastern European countries.

Phagoburn

In burn wounds, the Phagoburn study aims at evaluating two phage cocktails, PP0121 and PP1131, for treating burn wound infections caused respectively by *Escherichia coli* or *Pseudomonas aeruginosa* bacteria, according to modern Western standards. The Phagoburn clinical trial is the first of its kind on a world scale.

It is a European collaborative project funded by the 7th Framework Programme for Research and Development (Health Programme). It has been launched on 10 June 2013 with a grant that amounts to €3.8 million for an overall budget of €5 million. Under the coordination of the French Ministry of Defence (Army Health Service in close collaboration with Pherecydes Pharma (French SME), Phagoburn gathers six other international burn treatment centres (France, Belgium, Switzerland). Starting in April 2015, phage therapy efficacy and safety will be evaluated through a phase II clinical multicentre study in accordance to Good Clinical Practices in France, Belgium and Switzerland. Prior to that, a second French SME, Clean Cells (France) has been in charge of adapting the genuine laboratory bioproduction process developed by Pherecydes Pharma into a true GMP (Good Manufacturing Practices) pharmaceutical manufacturing process to produce both clinical phage cocktails.

National drug regulatory agencies, ANSM (France), Swissmedic (Switzerland) and AFMPS (Belgium) are active supporters. Together with the European Medicine Agency (EMA), study on how to adapt the current regulatory framework for developing, testing and commercializing inert antibacterial molecules – antibiotics – for living biological therapies – bacteriophages. Phage diversity is outstanding and offers numerous way to fight anti-bacterial resistance, which needs to be taken in account within our western pharmacopeia guidelines. To make a parallel with flu vaccines: their valence can be adjusted each year to new viral strains. Phages offer a similar potential of adaptation to new form of bacterial resistance. But, our regulatory guidelines should allow phage addition or substitution within a therapeutic drug product, without starting from scratch the full process of clinical evaluation (7 to 10 years) after modifying a phage cocktail.

Phage and bacterial resistance

Our environment is full of phages, which can be associated in cocktails to target specific bacteria infections in specific areas, using various modes of action to reduce resistance occurrence.

Because of their bacterial specificity, phage cocktails are tailored to preserve the normal flora. When the human microbiota is maintained during an anti-bacterial treatment, it is more difficult for a phage resistant bacteria to emerge in such a competitive environment where other bacteria species are growing: this is a significant advantage compared to large spectrum antibiotics that destroy blindly all species of bacteria.

In addition, if a bacteria becomes resistant to phage, there is a fitness cost to acquire resistance: as a consequence the resistant strain becomes less virulent and can be more easily destroyed by the human immune system.

Future perspectives

Controlling phage therapy is necessary to avoid a misuse of a powerful therapy. However, patients without therapeutic options could benefit of this therapy, before market authorization is granted, under the control of specialized clinicians and the surveillance of national medicine agencies. As we learn from Ebola fever *(17)*, such an innovative therapy could be allowed by regulators before all the processes of clinical evaluation are completed, in regard to ethical considerations. Actually that issue may rise up quickly from patients infected by *E. coli* or *P. aeruginosa* resistant strains (they are very common bacteria), once the Phagoburn clinical trial is started.

As with antibiotics, phages could be used in animal farming to limit infectious diseases *(18)* and to boost productivity. However, politicians may have a key role in balancing their use between human and animal applications. A lose control in farming may lead to the same blast of resistance as we observed with antibiotics. Unwillingly selecting bacterial strains that are both resistant to antibiotics and phages could be the worst-case scenario. If a restricted use of phages to dead end patients is chosen, a restriction of phage use in industry/food/farming may be considered too.

From a fixed phage mix product today, to an evolving product where phages are added or substituted by others, one can even expect a product tailored to personalized medicine: phage preparations could be quickly and easily prepared for a local hospital infection or a food bacteria poisoning epidemic. But, the current regulatory framework in western countries is not tailored for that.

The association of phages with antibiotics could increase both product potencies. For instance, some phages are able to digest bacterial slime (biofilm), where most antibiotics are unable to reach the "encysted" pathogenic bacteria. Once the biofilm is loosen up, antibiotics may be able to kill the bacteria. Biofilms are commonly found on prosthesis.

Several actors are currently involved in the challenge of finding the right place for phage therapy in our future medicine arsenal. Patients infected by antibiotic multi-drug resistant strains expect an efficient anti-bacterial treatment to improve their life conditions and expectancy. SMEs are developing the pharmaceutical products. Regulators are ready to support desperately needed new anti-bacterial innovations. Medical teams hope that phages could push away the impact of antibiotic resistance on mortality related to bacterial diseases *(13–16)*. Certain European deputies and senators have started to advocate for phage therapy. However, more support is needed to develop bacteriophage collections, product formulation, high standard clinical trials and to adapt regulations.

Politicians have a key role to play.

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Both authors are coordinating a European Community funded project (FP7) to develop new bioproduction standards for phage drug manufacturing under the European pharmacopeia umbrella.

References

1. Organization WH, others. Antimicrobial resistance: global report on surveillance [Internet]. World Health Organization; 2014 [cited 2014 Dec 1]. Available from: http://apps.who.int/iris/handle/10665/112642
2. Abedon ST, Kuhl SJ, Blasdel BG, Kutter EM. Phage treatment of human infections. *Bacteriophage*. 2011 Mar 1;1(2):66–85.
3. Harper DR, Kutter E. Bacteriophage: Therapeutic Uses. In: John Wiley & Sons, Ltd, editor. Encyclopedia of Life Sciences [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2008 [cited 2013 Sep 26]. Available from: http://doi.wiley.com/10.1002/9780470015902.a0020000
4. Kutter E, Gvasalia G, Alavidze Z, Brewster E. Phage Therapy. In: Grassberger M, Sherman RA, Gileva OS, Kim CMH, Mumcuoglu KY, editors. Biotherapy - History, Principles and Practice [Internet]. Springer Netherlands; 2013. p. 191–231. Available from: http://dx.doi.org/10.1007/978-94-007-6585-6_8
5. Weber-Dąbrowska B, Mulczyk M, Górski A. Bacteriophages as an efficient therapy for antibiotic-resistant septicemia in man. *Transplant Proc*. 2003 Jun;35(4):1385–6.
6. Housby JN, Mann NH. Phage therapy. *Drug Discov Today*. 2009 Jun;14(11-12):536–40.
7. Lodder WJ, van den Berg HHJL, Rutjes SA, de Roda Husman AM. Presence of Enteric Viruses in Source Waters for Drinking Water Production in the Netherlands. *Appl Environ Microbiol*. 2010 Jul 9;76(17):5965–71.
8. Duckworth DH. " Who discovered bacteriophage?". *Bacteriol Rev*. 1976;40(4):793.
9. Harper DR, Morales S. Bacteriophage therapy: practicability and clinical need meet in the multidrug-resistance era. *Future Microbiol*. 2012 Jul;7(7):797–9.
10. Letkiewicz S, Międzybrodzki R, Kłak M, Jończyk E, Weber-Dąbrowska B, Górski A. The perspectives of the application of phage therapy in chronic bacterial prostatitis: Phage therapy in chronic bacterial prostatitis. *FEMS Immunol Med Microbiol*. 2010 Nov;60(2):99–112.
11. Ricard J-D. New therapies for pneumonia: Curr Opin Pulm Med. 2012 May;18(3):181–6.
12. Ryan EM, Gorman SP, Donnelly RF, Gilmore BF. Recent advances in bacteriophage therapy: how delivery routes, formulation, concentration and timing influence the success of phage therapy: Bacteriophage delivery routes review. *J Pharm Pharmacol*. 2011 Oct;63(10):1253–64.
13. Sulakvelidze A. Phage therapy: an attractive option for dealing with antibiotic-resistant bacterial infections. *Drug Discov Today*. 2005;10(12):807–9.
14. Sulakvelidze A, Morris JG. Bacteriophages as therapeutic agents. *Ann Med*. 2001 Jan;33(8):507–9.
15. Veiga-Crespo P, Barros-Velázquez J, Villa TG. What can bacteriophages do for us? Commun Curr Res Educ Top Trends Appl Microbiol Mendez-Vilas-Spain Formatex. 2007;2:885–93.
16. Kutateladze M, Adamia R. Bacteriophages as potential new therapeutics to replace or supplement antibiotics. Trends *Biotechnol*. 2010 Dec;28(12):591–5.
17. Baize S, Pannetier D, Oestereich L, Rieger T, Koivogui L, Magassouba N, et al. Emergence of Zaire Ebola Virus Disease in Guinea. *N Engl J Med*. 2014 Oct 9;371(15):1418–25.
18. Zhang J, Kraft BL, Pan Y, Wall SK, Saez AC, Ebner PD. Development of an anti-Salmonella phage cocktail with increased host range. *Foodborne Pathog Dis*. 2010;7(11):1415–9.

PHAGE THERAPY: COULD VIRUSES HELP RESOLVE THE WORLDWIDE ANTIBIOTIC CRISIS?

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Bacteriophages are bacterio-specific viruses. Involved in the origin of life and evolution, constituting a major part of the biosphere, they are promising as a sustainable, ecological and intrinsically cheap antibacterial. Félix d'Hérelle, one of the discoverers was the first to propose "phage therapy" in the early twentieth century. It was further developed at the Eliava Institute in Tbilisi, Georgia, and used in medical practice in all the previous Soviet Republics until now. The Western world, however, with the advent of antibiotics, forgot about phage therapy.

The antibiotic resistance crisis brought back phage therapy as a potential complementary or alternative treatment. The main problem is a lack of evidence-based studies using modern standards as well as the lack of an adapted regulatory framework. Attracting industrial partners and initiating studies in this context is difficult. Phage therapy is sporadically applied under certain conditions like the Helsinki Declaration or specific national regulations (for example, in Poland). This impedes scientific progress and clinical reimplementation.

Although several groups have set up animal and human studies, and bacteriophages are already used as antibacterials in the food industry, the clinical reimplementation is lacking while the antibiotic crisis is intensifying worldwide.

Antibiotic resistance (ABR), not a newly discovered biological phenomenon, is a fact and impacts negatively our global world society *(1-6)*. Fernando Baquero and colleagues described antimicrobial resistance as a "typical emerging characteristic of a dynamic, highly complex and self-organizing system evolving at the edge of chaos" *(7)*. The antibiotic crisis is obviously multifactorial and consequently not straightforward to resolve.

Although it seems not easy to cope with the global and complex ABR problem there is one approach, bacteriophage therapy, that could be an essential part in the process of resolving this antibiotic crisis (8–10). This is an antibacterial treatment approach that is scientifically proven, sustainable and timely, while intrinsically safe and cheaper than the development of a new antibiotic.

Bacteriophages

Bacteriophages were independently discovered and described almost a century ago by Dr Frederick Twort (1915), a UK microbiologist and Félix d'Hérelle (1917) a French-Canadian microbiologist *(11-12)*. It was d'Hérelle who coined the word bacteriophage and proposed to use these entities as antibacterial agents. An idea he quickly tried out in practice *(12)*.

Bacteriophages are bacterio-specific viruses that interact exclusively with bacterial cells (prokaryotes) *(13)*. The bacterial biochemical machinery that enables the interaction of bacteriophages and bacterial cells does not exisit in the cells that constitute our bodies (eukaryotic cells). This is why bacteriophages are bacterio-specific and non interactive with our body cells and in principle "safe" to use.

Factually bacterio-specific bacteriophages are composed of a nucleic acid genome packed in a protein capsid. In order to multiply itself the viral particle, called a virion, has to anchor itself on a specific bacterium. This happens through a specific bacterial outer membrane receptor that interacts with the virion's specific capsid coat molecular appendages such as the typical spikes. Once physico-chemically anchored on the bacterium's outer membrane, the bacteriophage injects its genomic material (composed of a nucleic acid) into the bacterial cell where it can be amplified and the capsid packed by the bacterial "hijacked" specific biochemical machinery.

Table 1: **The pros and cons of phages and antibiotics**

Phages	Antibiotics
Very specific (species or even strain specific and does not disturb the commensal flora)	Not specific (disturbs the commensal flora/ collateral damage)
Infecting bacteria need to be known (cocktails could solve this; use of rapid diagnostics)	Infecting bacteria don't need to be known (large spectrum antibiotics)
Development of new phage preparations: quick and cheap	Development of new AB: time consuming and costly
No side effects known so far	Multiple side effects
Complementary and synergistic	

This results in the production of tens of newly formed bacteriophages that will spread as virions after the infected bacterium is lysed. Indeed specific bacteriophage genome encoded and produced enzymes (holins) break open the bacterial cell wall after which the virions are released in the environment where they can look to infect again a specific (host) bacterium and restart the cycle through which the host bacterium is killed. It is this bacterial lysis process of natural lytic bacteriophages that is going to be used as a self-amplifying antibacterial in bacteriophage therapy for fighting specific bacterial pathogens. This bacterium killing process is independent of the bacterium's antibiotic resistance status. This means that, as well as a sensitive pathogen, a resistant pathogen will also be killed by the bacteriophage. Biofilms, the bacteria's main lifestyle modus especially in chronic infection, are known to inhibit antibiotic activity by a differential gene expression but not bacteriophage activity *(14–15)*. As such bacteria and antibiotics could even have a specific synergistic effect *(16)*. Here, specifically, research is needed in order to optimize both approaches: bacteriophages with or without antibiotics.

The advantage of phage therapy as a complimentary tool or substitute for antibiotics in the combat of bacterial infections is the existence of scientific evidence at several levels: theoretical, in vitro laboratory experiments and in vivo studies, in animal models and in humans.

The molecular biology that gave rise to the actual biotechnological industry was largely built thanks to the huge amounts of scientific experimental work carried out with the bacterial workhorse *Escherichia coli* and its bacteriophages. This gave a tremendous amount of experimental data enabling the development of a theoretical biological working framework. Furthermore, there exists a huge, and still increasing amount of laboratory experiments and in vivo studies using bacteriophages and their targeted bacterial host cells in animals and humans *(17–20)*.

Bacteriophage therapy

The human experience however is actually almost empirical and from the former Soviet Union republics with the Eliava Institute in Tbilisi (Georgia) as the main centre. In Poland, an actual EU country, phage therapy is in use under specific conditions. The Polish phage research centre (Ludwik Hirszfeld Institute of Immunology and experimental therapy in Wroclaw) is emerging as a very active scientific unit conducting and starting bacteriophage studies in order to help to re-implement phage therapy in routine medicine in accordance with actual scientific and medical care standards (19–20). In recent years, other countries have also conducted some human studies in accordance with modern biomedical standards and detailed clinical case reports are being published showing the potential of phage therapy *(20–26)*. Bacteriophages are in fact self-amplifying anti-bacterial agents that are eliminated naturally from our bodies by our reticulo-endothelial system, urine and faeces, after their targeted host cells disappear from the site of infection.

Safety issues

Are bacteriophages, bacterial viruses, safe for use in human beings? This is one of the first questions people will want to know if viruses are to be used on patients. In fact, we are living in an ocean of viruses which includes bacteriophages. Bacteriophages are apparently the most abundant biological entities in our biosphere *(27–29)*. Wherever there are bacteria there are bacteriophages. We eat, drink and carry in our bodies more bacteriophages than bacteria while the latter already exceed the number of cells in our body.

Bacteriophages co-evolve with their host bacteria and provide the earth's ecological equilibrium in several environmental or ecological niches. In fact, we have to think from the co-evolving couplet phage/bacterium that is continually co-adapting to each other and as such provides a long-term sustainable antibacterial approach.

Indeed for each existing or emerging pathogen there exists a bacteriophage, which makes bacteriophage therapy sustainable. This ecological point of view fits well in the emerging field of evolutionary/Darwinian medicine as well as the increasing societal and political interests in long-term

Figure 1: Large model of a phage. Courtesy, Perron, University Hospital of Geneva

sustainable and green approaches for managing our globalizing world *(30)*.

Bacteriophages, the other facet of a bacterium, have existed since the bacterial cells originated. Recent work from Raoult and Forterre brought viruses, including bacteriophages, into the tree of life and consider them as living biological entities, although a different kind than we are used *(31)*.

It is estimated that half of the bacterial biomass daily is lysed by lytic bacteriophages, while their total number in our biosphere approaches 10^{31}.

A recent study by the group of Rohwer showed that all epithelial mucus layers in multicellular organisms (metazoan), such as our gut mucus layer, is in fact a bacteriophage-based symbiotic defence system against potential invading bacteria *(32)*. This is one of the recent breakthrough studies showing the inherent and basic inoffensiveness and safety, of the use of bacteriophages as an antibacterial.

During the Seventies, the FDA had to set up a review of safety since bacteriophages were found in several vaccine preparations. The study review had to conclude that bacteriophages were not a safety issue and the vaccines containing phages were allowed to be used *(33)*.

Also researchers were allowed to apply phage phiX174 intravenously into HIV positive patients. The FDA concluded that bacteriophages are safe for humans. This knowledge in conjunction with the existing empirical clinical data as well as several animal and a handful of modern human applications show that, from the safety point of view, phage therapy concept is intrinsically safe *(33–35)*.

The advantages of phage therapy versus antibiotics

Phage therapy is bacteriospecific and has no or at least lower collateral damage then the use of antibiotics as far as is known. Even if small spectrum antibiotics are used more than the specifically targeted pathogen is influenced or hampered. The (side) effect of using antibiotics on our natural microbiota is so huge that it seems that a lot of actual diseases are associated with a microbiome disturbance caused by their use. This aspect is recently well-described in its global aspects by Blaser *(36)*.

By using phages we could prevent those side effects or in certain cases (*Clostridium difficile*), infections or other gastrointestinal diseases, could restore or re-equilibrate the situation.

Looking for a specific phage against a specific bacterium should always be possible and in a much shorter timeframe (days to weeks) than searching and developing a new antibiotic *(37–39)*. It should also be cheaper. This specifically makes phage therapy a relatively cheap "online" approach in the fight against specific bacterial infections.

Phage therapy in public health and in developing countries

The problem of antibiotic resistance not only affects individual patients in clinics, but exists in all types of health-care institutes, and affects whole communities. Remember the Enteroaggregative Hemorrhagic *Escherichia coli* (EAHEC) 0104:H4 outbreak in Berlin in 2011. Antibiotic use was even of questionable help *(39)*.

However, different research groups obtained potent lytic phages against this problematic enteroaggregative *E. coli*, either by the isolation of new phages from the environment or by selection and "improvement" of phages from existing collections, and this was often accomplished in a matter of days. As such, phages could probably have been used to help control the O104:H4 *E. coli* outbreak that caused the death of more than 50 patients. Unfortunately, authorized use of phages was not possible in this otherwise feasible phage therapy context, because under the existing medicinal product legislation such an anti-O104:H4 phage preparation would have taken years to develop, produce and approve. It is thus crucial to set up new therapeutic phage collections (including in low-income and emerging countries) and to maintain and continuously update existing phage collections, which can be

used to counter bacterial epidemics in a timely and cost-effective way.

In large parts of the world bacterial diarrhoeal diseases of all kinds are a big burden in public health. Diarrheal disease is one of the major problems in third world countries. Many common causative agents are multi-drug resistant (MDR) bacteria and considering the poor sanitation the control of those epidemics and pandemics such as cholera for example run quickly run out of control. Bacteriophages could play a significant role *(40)*.

The Mekalanos group showed some time ago the effective natural role of bacteriophages as agents at the origin of the natural collapse of the local endemic diarrheal epidemics in Bangladesh *(41–42)*. This observation brings us to the idea that further studying and optimization of this bacterial/phage interaction could bring phage therapy to public health authorities as a way of controlling or at least inhibiting diarrhoeal diseases, which are still a major issue, especially in developing countries.

Why is phage therapy not implemented?

Bacteriophages are natural biological entities that co-evolve with their bacterial host cell. This is in contrast with a chemical stable molecule like an antibiotic. We have to think of bacteriophages and bacteria as a couplet in continuous interaction. Since our actual pharmacoeconomic model, mainly based on stable static chemical molecules as a drug, and its associated highly sophisticated regulatory, quality and safety system it seems difficult in our modern Western countries to (re)introduce phage therapy which, in contrast to classic antibiotics, is based on a self-amplifying and co-evolving viral natural entity *(37–38; 43–44)*. Also intellectual property rights are a thorny issue since it is the basis for private/industrial incentives in the field. With respect to bacteriophages as natural biological entities, patents could be granted and exist, but how robust they are? They seem to be fragile and thus not very attractive for the classical big pharmaceutical companies in the context of today.

However, seeing the impact of ABR on our societies, we think that the phage therapy concept should be taken in consideration as a valuable instrument to resolve our actual antibiotic crisis worldwide.

The current hurdles that SMEs need to overcome to put phage therapeutics on the European Union or United States markets are throttling, and largely undetermined. Therefore, some phage companies decided to circumvent some regulatory obstacles by seeking first to market phage products for agricultural and food applications, where regulations are less stringent. For example, in 2006 the FDA approved a bacteriophage preparation on ready-to-eat meat and poultry products as an antimicrobial agent against *Listeria monocytogenes*.

Conclusions and perspective

Conclusively we can state that the use of bacteriophages as antibacterial agents makes sense, scientifically and empirically. Bacteriophages, bacteriophage therapy, as a tool for resolving the antibiotics resistance crisis, should be re-introduced in regular medicine all over the globe where it could be optimized for specific treatments. It will not only help to treat individual patients at hospitals or in other health-care settings, but it could be a real beneficial tool from the standpoint of public health for inhibiting and/or controlling emerging bacterial epidemics especially gastrointestinal infections or chronic bacterial-related diseases. Especially in developing countries where bacterial diarrheal disease, amongst others, is a major part of the infectious burden and phage therapy could bring a solution.

Phage therapy can also be applied in conjunction with or without antibiotics, depending on the situation, while in general a more judicious use of antibiotics should be promoted.

Further it seems that all future strategies should be integrated and involve different fields: human and veterinary medicine, the agro-bio and food industry.

It would be important today to be open to a more sustainable ecological approach enabling the development, optimization and implementation of phage therapy as a recognized scientifically meaningful bacterial treatment approach. •

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References

1. Fleming, A. Nobel prize Lecture, 1945 (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf).
2. Allen HK, Donato J, Wang HH et al. Call of the wild: antibiotic resistance genes in natural environments. *Nat Rev Microbiol* 2010;8:251-9
3. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat. Med.* 10(12), S122–S129 (2004)
4. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J. Infect. Dis.* 197(8), 1079–1081 (2008)
5. European Centre for Disease Prevention and Control (ECDC) & European Medicines Agency (EMEA). Joint technical report: the bacterial challenge: time to react (ECDC-EMEA, Stockholm, 2009)
6. Antimicrobial resistance: Global report on Surveillance. Geneva, World Health Organization (WHO), 2014. Available from: http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1 (accessed 18/09/14).
7. Baquero F, Coque TM and Canton R. Antibiotics, complexity and evolution. *ASM News*, 2003, 69:547-552
8. Pirnay J-P, De Vos D, Zizi M and Heyman P. (2003). No easy way to exterminate 'superbugs' at the dawn of the third millennium. *Exp. Rev. Anti-Infectiv. Ther.* 1, 523–525
9. Thiel K. Old dogma, new tricks – 21st century phage therapy. *Nat. Biotechnol.* 22(1), 31–36 (2004).
10. Bush K, Courvalin P, Dantas G, Davies J, Eisenstein B, Huovinen P, et al. Tackling antibiotic resistance. *Nat Rev Microbiol.* 2011;9:894-6
11. Twort, F. W. An investigation on the nature of the ultramicroscopic viruses. *Lancet*, 1915, 186, 1241-1243
12. D'Hérelle F. Sur le rôle du microbe bactériophage dans la typhose aviaire. *C. R. Acad. Sci.* 169, 932–934 (1919)
13. Sulakvelidze, A.; Kutter, E. Bacteriophage therapy in humans. In: Bacteriophages: Biology and Application; Kutter, E., Sulakvelidze, A., Eds.; CRC Press: Boca Raton, Florida, 2005, pp. 381-436
14. Whiteley M, Bangera MG, Burngarner RE et al. Gene expression in Pseudomonas aeruginosa biofilms. *Nature* 2001;413:860-4
15. Beloin C, Valle J, Latour-Lambert P et al. Global impact of mature biofilm lifestyle on Escherichia coli K-12 gene expression. *Mol Microbiol* 2004;51:659-74
16. Comeau AM, Tetart F, Trojet SN, Prere MF and Krish HM. Phage-antibiotic synergy (PAS): beta-lactam and quinolone antibiotics stimulate virulent phage growth. *PLoS One* 2007, e799
17. Brussow H. Phage therapy: the Escherichia coli experience. 2005 151, 2133–2140
18. Smith HW and Huggins MB. Successful treatment of experimental Escherichia coli infections in mice using phage: its general superiority over antibiotics. *J Gen. Microbiol.* 1982 128, 307–318
19. Chanishvili N, Sharp R. Eliava Institute of Bacteriophage, Microbiology and Virology, Tbilisi, Georgia. A literature review of the practical application of bacteriophage research. Tbilisi: Eliava Foundation; 2009
20. Górski A, Miedzybrodzki R, Borysowski J, Weber-Dabrowska B, Lobocka M, Fortuna W, et al. Bacteriophage therapy for the treatment of infections. *Curr Opin Investig Drugs.* 2009;10:766–74
21. Kutter E, De Vos D, Gvasalia G, Alavidze Z, Gogokhia L, Kuhl S and Abedon ST. Phage therapy in clinical practice: treatment of human infections. *Curr. Pharm. Biotechnol.* 2010 11, 69–86
22. Merabishvili M, Pirnay JP, Verbeken G, Chanishvili N, Tediashvili M, Lashkhi N, et al. Quality-controlled small-scale production of a well-defined bacteriophage cocktail for use in human clinical trials. *PLoS One.* 2009;4:e4944.
23. Rose T, Verbeken G, De Vos D, Merabishvili M, Vaneechoutte M, Lavigne R, Jennes S, Zizi M, and Pirnay J-P. 2014. Experimental phage therapy: Difficult first steps. *International Journal of Burns and Trauma*. Accepted 140916
24. Phage Therapy, Current Research and Applications. 2014. Edited by Boryzsowski J, Miedzybrodski R and Gorski A. *Caister Academic press*, 2014
25. Rhoads DD, Wolcott RD, Kuskowski MA, Wolcott BM, Ward LS and Sulakvelidze A. Bacteriophage therapy of venous leg ulcers in humans: results of a phase I safety trial. J. *Wound Care* 2009 18, 237–243
26. Khawaldeh A, Morales S, Dillon,B, Alavidze, Z, Ginn AN, Thomas L, Chapman SJ, Dublanchet A, Smithyman A and Iredell JR. Bacteriophage therapy for refractory Pseudomonas aeruginosa urinary tract infection. *J. Med. Microbiol.* 2011 60, 1697–1700
27. Bergh O, Borsheim, KY, Bratbak G and Heldal M. High abundance of viruses found in aquatic environments. *Nature* 1989 340, 476–468
28. Fuhrman JA. (1999). Marine viruses and their biogeochemical and ecological effects. *Nature* 399, 541–548
27. Hendrix RW. Bacteriophages: evolution of the majority. *Theor. Popul. Biol.* 61(4), 471–480 (2002)
29. Bamford DH. (2003). Do viruses form lineages across different domains of life? *Res. Microbiol.* 154, 231–236.
30. Shanks N and Pyles RA. (2007). Evolution and medicine: the long reach of 'Dr. Darwin'. *Philos. Ethics Humanit. Med.* 2, 4
31. Raoult D and Forterre P. (2008). Redefining viruses: lessons from the mimivirus. *Nat. Rev. Microbiol.* 6, 315–319
32. Barr JJ, Auro R, Furlan M, Whiteson KL, Erb ML, Pogliaeno J, Stotland A, Wolkowicz R., Cutting AS, Doran KS, et al. (2013). Bacteriophage adhering to mucus provide a non-host-derived immunity. *Proc. Natl. Acad. Sci.* USA. 110, 10771–10776
33. Sulakvelidze A. The challenges of bacteriophage therapy. Eur. Ind. Pharm. 10, 14-18 (2011)
34. Biswas B, Adhya S, Washart P, et al. Bacteriophage therapy rescues mice bacteremic from a clinical isolate of vancomycin-resistant Enterococcus faecium. *Infect Immun.* 70 (1), 204–210 (2002)
35. Brüttin A and Brüssow H. Human volunteers receiving Escherichia coli phage T4 orally: a safety test of phage therapy. *Antimicrob. Agents Chemother.* 49(7), 2874–2878 (2005)
36. Blaser M. Missing Microbes: How the overuse of antibiotics is fuelling our modern Plagues, 2014, Henry Holt and Company, New York
37. Pirnay J-P, De Vos D, Verbeken G, Merabishvili M., Chanishvili N, Vaneechoutte M, Zizi M, Laire G, Lavigne R, Huys I, et al. (2010). The Phage therapy paradigm: pret-a-porter or sur-mesure? *Pharm. Res.*28, 934–937
38. Pirnay J-P, Verbeken G, Rose T, Jennes S, Zizi M, Huys I, Lavigne R, Merabishvili M, Vaneechoutte M, Buckling A., and De Vos D. (2012). Introducing yesterday's phage therapy in today's medicine. *Future Virol*. 7, 379–390
39. Merabishvili M, De Vos D, Verbeken G, Kropinski AM, Vandenheuvel D, Lavigne R, et al. Selection and characterization of a candidate therapeutic bacteriophage that lyses the Escherichia coli O104:H4 strain from the 2011 outbreak in Germany. *PLoS One.* 2012;7:e52709
40. De J Sosa A, Byarugaba DK, Amabile-Cuevas CF, Hsueh P-R, Kariuki S and Okeke IN. (eds). Antibiotic resistance in developing countries. *Springer*, 2010. (DOI 10.1007/978-0-387-89370-9)
41. Faruque SM, Naser IB, Islam MJ et al. Seasonal epidemics of cholera inversely correlate with the prevalence of environmental cholera phages. *Proc. Natl Acad. Sci.* USA 102(5), 1702–1707 (2005)
42. Faruque SM, Islam MJ, Ahmad QS et al. Self-limiting nature of seasonal cholera epidemics: role of host-mediated amplification of phage. *Proc. Natl Acad. Sci.* USA 102(17), 6119–6124 (2005)
43. Verbeken G, De Vos D, Vaneechoutte M, Merabishvili M, Zizi M and Pirnay J-P. (2007). European regulatory conundrum of phage therapy. *Future Microbiol.* 2, 485–491.
44. Verbeken G, Pirnay JP, De Vos D, Jennes S, Zizi M, Lavigne R, Casteels M, Huys I. Optimizing the European regulatory framework for sustainable bacteriophage therapy in human medicine. *Arch Immunol Ther Exp (Warsz).* 2012;60:161-72.

ANIMAL HUSBANDRY AND ANTIMICROBIAL RESISTANCE

COSTS AND BENEFITS OF ANTIMICROBIAL USE IN LIVESTOCK

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Antimicrobial use in food-animal production is rising rapidly, driven by the increasing demand for animal protein and livestock globally. The volume of antimicrobials used in livestock outstrips that used for disease treatment in humans and creates significant selection pressure for the evolution of antimicrobial resistance. This article overviews the available data on the use of antimicrobials in livestock, the public health questions it raises, and the specific issues of the economic value of antimicrobial growth promoters (AGPs) to producers and consumers.

The discovery of antimicrobials is one of the most significant achievements of modern medicine and has substantially contributed to a reduction in the burden of common infectious diseases of humans and livestock globally. Antimicrobials are used in various applications including human and animal medicine, food production, plant agriculture and industrial applications. In food producing animals they are typically used for three purposes: therapeutic reasons (cure a disease), prophylactic reasons (prevent a disease) and as growth promoters (sub-therapeutic quantities of antimicrobials increase animal growth rates and improve feed efficiency).

Rapid income growth in low- and middle-income countries has increased demand for animal protein *(1–3)*. This increasing demand is being met by a shift toward intensive livestock production systems that depend on antimicrobials to keep animals healthy and operate efficiently *(4)*.

The widespread use of antimicrobials in human medicine and in agriculture comes at a cost: it has created selection pressure and fostered the emergence and spread of antimicrobial resistant pathogens worldwide. Resistant microbes and resistance genes can circulate among humans, animals, food, water and the environment and there is greater awareness of the deep connections between animal and human health. Moreover, trade, travel and migration are carrying resistant organisms globally at an unprecedented pace, and highlight the need for cooperation between countries and sectors for controlling the spread of antimicrobial resistance *(5)*. At the Ministerial Conference on Antimicrobial Resistance that took place in the Netherlands in June 2014, a global call was made to take action on antimicrobial resistance, acknowledging it as a global threat to effective prevention and treatment of infections *(6)*.

Since many antimicrobials commonly used in sub-therapeutic concentrations are the same as or similar to antimicrobials used in human medicine, there is global concern that drug-resistant organisms may pass from animals to humans and present a serious threat to public health *(7)*. This article presents an overview of the available data on the use of antimicrobials in livestock, the public health questions it raises, and the specific issues of the economic value of antimicrobial growth promoters (AGPs) to producers and consumers.

Overview of antimicrobial use in livestock

➤ *There are major knowledge gaps about the extent of antimicrobial use in livestock globally*

Surveillance systems monitoring the quantity of antimicrobials used in food-producing animals exist in relatively few countries (including European Union countries, the United States, Canada, Australia, Japan, South Korea and New Zealand). According to a survey conducted by the World Organisation for Animal Health (OIE) in 2012, only 27% of the OIE member countries had an official system for collecting quantitative data on antimicrobial use in livestock *(8)*. Data on the use of antimicrobials is lacking in areas where the food production is increasing rapidly, such as China, India or Brazil.

In the United States, antimicrobials are used primarily in swine and poultry production, and to a lesser extent in dairy cows, sheep, and companion animals. Antimicrobials are also widely used in feedlot cattle *(9)*. In the rest of the world, most

antimicrobials are used for growth promotion and prophylaxis in intensive pig and poultry operations. The only publicly available information on the quantity of antimicrobials used in food animals in the United States are aggregate data on annual sales and distribution obtained from antimicrobial drug sponsors. These data have been published by the US Food and Drug Administration (FDA) for the years 2009 to 2013. 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 *(10)*. The total quantity of medically important antimicrobials sold or distributed for use in food-producing animals increased by 20% between 2009 and 2013. In comparison, an estimated 3,290 tons of antimicrobials were sold during 2011 for human use *(11)*.

The European Surveillance of Veterinary Antimicrobial Consumption report, which covers 26 EU countries and approximately 95% of the food-producing animal population in the European Economic Area, reported sales of 8,046 tons of veterinary antimicrobials in 2012. The intensity of antimicrobial use in animals (defined as the annual sales divided by the estimated weight of livestock and of slaughtered animals) fell overall by 15% between 2010 and 2012 in Europe *(12)*.

➤ *With no major changes in policy, global consumption of antimicrobials could rise by two-thirds by 2030*

In the absence of data on global antimicrobial use in livestock, a recent study has used indirect means to estimate consumption for cattle, pigs and chickens raised in both extensive and intensive farming systems in 228 countries *(13)*. Global consumption of antimicrobials in food animal production was estimated at 63,151 (±1,560) tons in 2010 in this study, and is projected to rise by 67%, to 105,596 (±3,605) tons by 2030. The biggest increases are likely to be in larger emerging economies, and especially important for poultry, as demand is more important and growing faster than for other livestock products. In hotspots like India for instance, areas of high consumption (30 kg per km^2) for industrial poultry production are expected to grow 312% by 2030. Whereas these projection numbers are highly indicative and should not be considered as a prediction, these results show that excessive antimicrobial consumption will become a more global, if not uniform, problem in the coming years and consequently a concern for all.

The widespread use of antimicrobials in human medicine and in agriculture comes at a cost: it has created selection pressure and fostered the emergence and spread of antimicrobial resistant pathogens worldwide

Antimicrobial use in livestock: The public health question

Numerous studies have demonstrated that food animals on farms using low levels of AGPs harbour a higher percentage of resistant bacteria than farms that do not use AGPs *(14)*. Increased resistance to certain drugs in both animals and humans coincides with their use in food-animal production. For instance, increased resistance to fluoroquinolones in both humans and animals is temporally associated with the introduction of fluoroquinolones in veterinary medicine, primarily for the treatment of respiratory diseases in poultry *(15,16)*. Additionally, studies comparing resistance prevalence in both humans and animals before and after AGP bans have documented significant decreases in resistance, primarily in vancomycin-resistant enterococci isolated from farm animals and healthy ambulatory people following the ban of avoparcin as a growth promoter *(17,18)*.

Increasing levels of resistance in bacteria isolated from food-producing animals and retail meat sources have been reported by the National Antimicrobial Resistance Monitoring System *(19)*. FDA reported that resistance to third-generation cephalosporins rose among isolates from retail ground turkey between 2008 and 2011, and among certain salmonella serotypes in cattle between 2009 and 2011 *(19)*.

Most important from a public health perspective, extensive research has documented the spillover of resistance genes and resistant pathogens from food animals into human populations via three primary pathways:

➤ (1) the release of antimicrobial-resistant bacteria into the environment *(20)*;
➤ (2) resistance transmission through the food chain *(21)*;
➤ (3) the acquisition of resistant strains through direct contact with food animals *(22)*.

How much these processes contribute to resistance of human pathogens to antimicrobials is still unclear. Nevertheless, a report from the Centers for Disease Control

and Prevention (CDC) states, "Because of the link between antimicrobial use in food-producing animals and the occurrence of antimicrobial-resistant infections in humans, antimicrobials should be used in food-producing animals only under veterinary oversight and only to manage and treat infectious diseases, not to promote growth" *(23)*.

The Economic cost of withdrawing antimicrobial growth promoters from the livestock sector

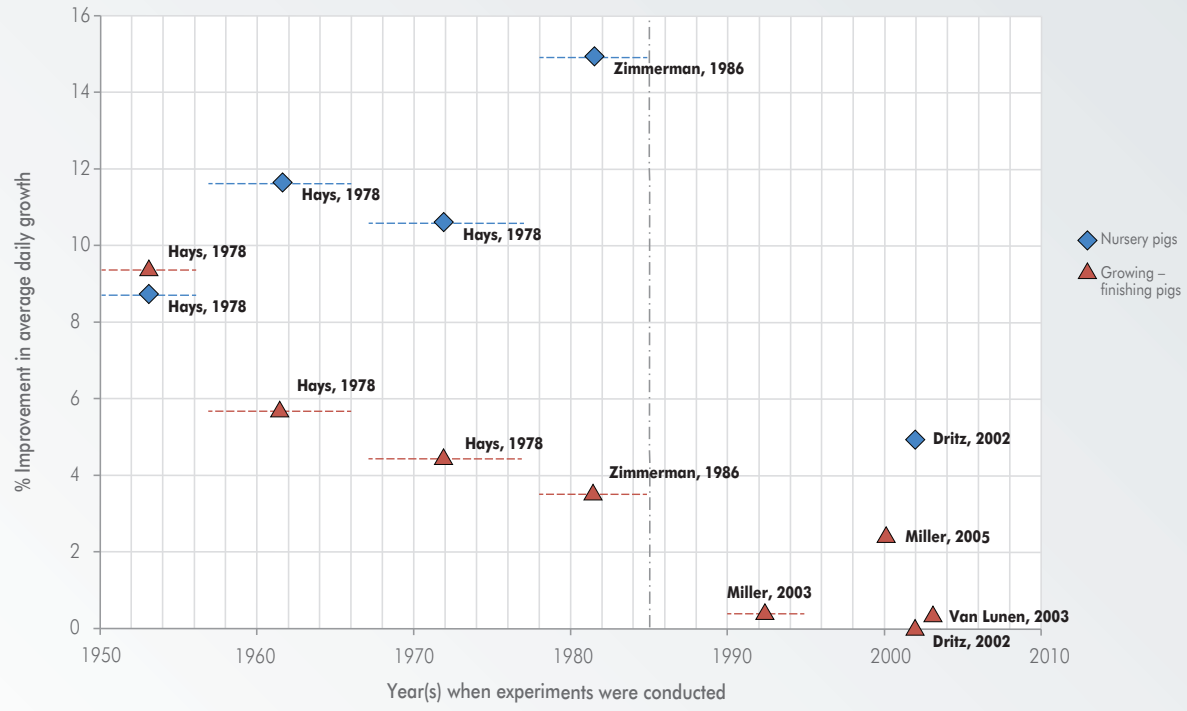
In 1986, Sweden became the first country to ban antimicrobial growth promoters (AGPs) – initially because of consumer's concern about antimicrobial residues in food – and require veterinary prescription of therapeutic doses for treating or preventing disease *(24)*. Concerns about increasing antimicrobial resistance led to bans on AGPs in the European Union in 2006. In the United States, AGPs are not banned, but the FDA recently issued guidelines for the veterinary drug sponsors to voluntarily withdraw medically important antimicrobials from growth promotion *(25)*. In 2014, the Canadian government published a strategy mimicking the voluntary FDA approach on phasing out AGPs.

Some other OECD countries have a ban on AGPs (as for instance Mexico, South Korea and New Zealand). AGPs are not banned in most of the non-OECD countries which are major meat (poultry, pig and cattle) producers, such as China, Brazil, Russia Federation, Argentina, India, Indonesia, Philippines and South Africa *(26)*.

In 1986, Sweden became the first country to ban antimicrobial growth promoters (AGPs) – initially because of consumer's concern about antimicrobial residues in food

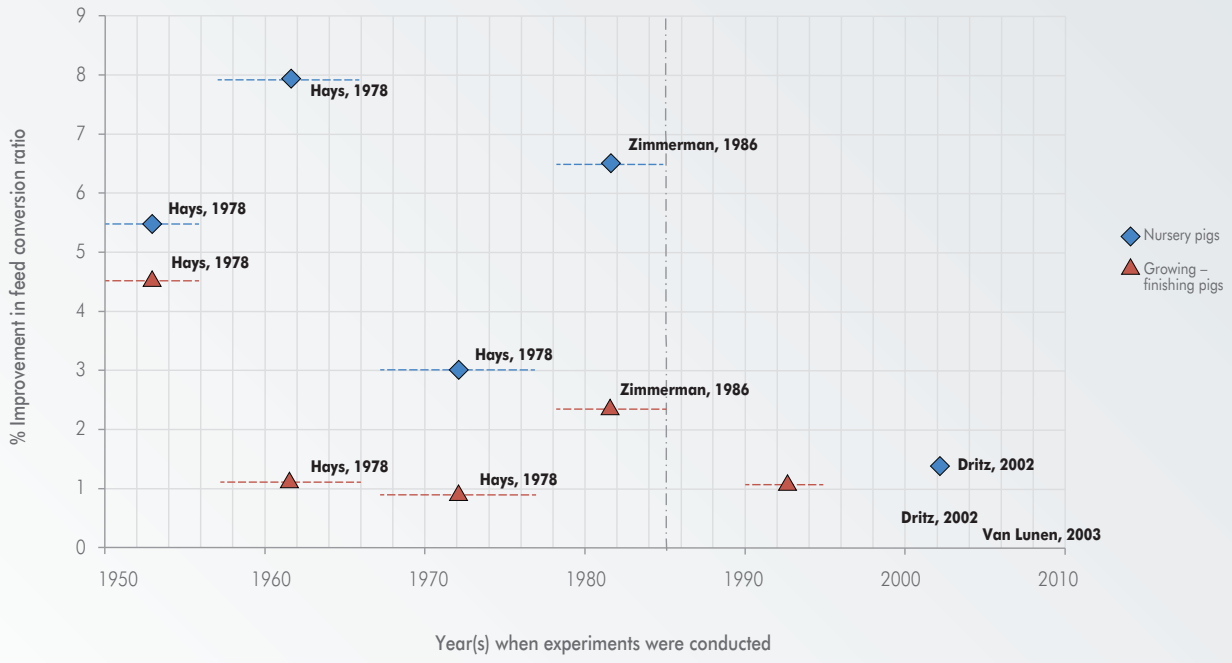
Policy-making on the use of antimicrobials in the livestock sector requires a clear understanding of the benefits and the costs of antimicrobial use in livestock to society. Since the preponderance of antimicrobial use is for growth promotion in livestock, it is important to accurately quantify the economic contribution of this mode of antimicrobial consumption. In the next section, we summarize recent

Figure 1: Percentage improvement in average daily growth of pigs fed antimicrobials over time



Note: The x-axis refers to the year when the experiments were conducted. Hays, 1978 and Zimmerman, 1986 are reviews of studies conducted over a given time period. The horizontal lines represents the period during which the experiments were conducted.
Source: Data compiled from Hays (1978), Zimmerman (1986), Miller (2003), Dritz (2002), Miller (2005), Van Lunen (2003).

Figure 2: Percentage improvement in feed conversion ratio of pigs fed antimicrobials over time



Note: The x-axis refers to the year when the experiments were conducted. Hays, 1978 and Zimmerman, 1986 are reviews of studies conducted over a given time period. The horizontal lines represents the period during which the experiments were conducted.
Source: Data compiled from Hays (1978), Zimmerman (1986), Miller (2003), Dritz (2002), Miller (2005), Van Lunen (2003).

evidence on the economics of AGP use in the livestock industry and the potential economic consequences for producers and consumers of phasing out AGPs.

➤ *The growth response to Antimicrobial Growth Promoters (AGPs) is small in optimized production systems*

The discovery that antimicrobials fed in sub-therapeutic concentrations to livestock can hasten their growth and prevent disease came just as farmers in the United States were struggling to keep pace with demand for food and animal protein *(27,28)*. Antimicrobial use for growth promotion and disease prevention soon became an integral part of a new agricultural production model, despite early warnings about the potential risks of developing resistance *(29)*.

In spite of 50 years of antimicrobial use as growth promoters, recent and reliable data on the effect of AGP use on productivity are lacking. There is considerable variability in the growth response to sub-therapeutic antimicrobials, according to the species, the age of animals, their genetic potential, and the specific hygiene and management conditions. While studies conducted before the 1980s

In spite of 50 years of antimicrobial use as growth promoters, recent and reliable data on the effect of AGP use on productivity are lacking

reported improvement in the growth rate and feed efficiency of pig, poultry and cattle fed sub-therapeutic antimicrobials as high as 5–15%, studies conducted in the United States, Denmark and Sweden after the 2000s point to more limited effects (Figs. 1 and 2). In pigs, less than 1% improvement or not statistically significant improvement have been reported recently, except for nursery pigs in which improvement in growth rate can still reach 5% *(30)*.

Table 1 provides a comparison of three studies on the effects of AGPs on broiler production: one animal-level experimental study of the removal of AGP in two United States broiler farms *(31)*, one farm-level observational study

Table 1: **Comparison of production and economic effects of AGP restrictions in the poultry industry, United States and Denmark**

	US animal-level experimental research (31)	US farm-level observational research (32)	Denmark observational research pre (1994–1997) and post (1998–2000) ban on AGPs (33)
Change in feed conversion ratio, value (percentage change)	Site 1: +0.016 (0.8%*) Site 2: +0.012 (0.6%*)	No HACCP: +0.08 (4%) HACCP: +0.05 (2.6%)	+0.016 (0.9%)
Average weight differential grams (percentage change)	Site 1: –13.6 g (0.6%*) Site 2: –18.1 g (0.8%*)	2–7% production decline without AGPs when controlling for labor, capital and other inputs, not statistically significant	+ 53 g
Mortality rate	Differential: Site 1: –0.2% Site 2: –0.14%	With AGP: 3.95% No AGP, no HACCP: 5.01% No AGP, HACCP: 3.95%	Pre-ban: 4.1% Post-ban: 4.0%
Cost-effectiveness	Cf. Graham et al. study, based on Engster data: Net effect of using AGP = lost value of $0.0093 per chicken (savings in cost of AGPs more than compensate for decrease in production)	Growers using no AGPs and with HACCP receive 2.1% more fees per kg than growers using AGPs, suggesting higher costs of production in absence of AGP Non-AGP premium that would be paid to growers by integrators: $22.5 million	Calculations suggested that savings in cost of APG almost exactly offset cost of decreased feed efficiency Potential substantial costs associated with modifications to production systems (not evaluated)

Source: Emborg et al. (2001), Engster et al. (2002), Graham et al. (2007), MacDonald & Wang (2011)
Abbreviations: HACCP, hazard analysis and critical control points (food safety plan).

** The baseline values of feed conversion ratio and average weight were not provided in (31). We assumed that baseline feed conversion ratio = 1.95 and average market liveweight = 2.27 kg to calculate the percentage change in feed conversion ratio and average weight.*

based on US Department of Agriculture (USDA) poultry national survey *(32)*, and one observational study with data from before and after the ban on AGPs in Denmark *(33)*. Similarly to what is observed in recent studies on the growth response to AGP in hogs, recent results in poultry suggest limited effect of withdrawing AGP on growth performance (Table 1).

A common explanation for these results is that the growth response to antimicrobials is less important when nutrition, hygiene practices, the genetic potential of animals and health status of the animal herd or flock are optimal. With drastic changes in the animal industry over the last 30 years in the OECD countries, all of these key parameters have changed, potentially explaining the decrease in the efficacy of AGPs.

➤ *Projected effects of restricting sub-therapeutic antimicrobial use on livestock production globally vary widely*

In a recent report produced for the OECD, the potential loss of production and meat value following a ban on AGPs was estimated in two scenarios: a scenario where the growth response to AGPs is still high (based on growth response data from the 1980s), and a scenario with a low growth response to AGP (based on data from the 2000s) *(26)*. In this study, it was projected that the cumulative loss of global meat production resulting from a worldwide ban on AGPs would result in a decrease by 1.3% to 3% from its current level (1980s vs 2000s scenarios), corresponding to a global loss in meat production value between US$ 13.5 and US$ 44.1 billion in the two scenarios respectively *(26)*.

➤ *The economic impact of a ban on AGPs could be limited in high-income industrialized countries but higher in lower*

income countries with less optimized production systems

Studies from Denmark and Sweden, as well as recent estimates in the United States, suggest limited economic effects of phasing-out AGPs *(34–36)*. However, such limited economic effects may not be applicable in every country or every operation within a country. It is likely that countries which have modern production systems applying good hygiene and production practices would see limited productivity and economic effect of phasing out AGPs *(32,36,37)*. However, countries with less optimized production systems could observe larger productivity and economic effects. The cost of investing in improved hygiene practices and their indirect benefits are difficult to estimate but potentially significant.

Conclusion

There are major data gaps on the use of antimicrobials in livestock globally. Data on the quantity and patterns of antimicrobial use will be essential to evaluate the efficacy of potential policy options. The most controversial use of antimicrobials in livestock is their use as growth promoters. Our review of the economics of AGPs indicates that the magnitude of the growth response to antimicrobials in the swine and poultry industry appears to have decreased over time, even if recent data are relatively sparse. Based on the Danish and Swedish cases, maintaining production after AGPs are phased out would involve substitution practices such as improved hygiene management and biosecurity measures. However, the cost of investing in improved production systems is unknown and could be significant for some producers. In the long-term, investing in more biosecurity measures could improve the productivity of the industry by reducing the spread of all infectious diseases, including those that cannot be controlled with antimicrobials, and by preserving the efficacy of antimicrobials to prevent and treat animal disease. Restricting antimicrobial use in food animals and decreasing antimicrobial resistance reservoirs in animals could have major public health benefits, even if such benefits are difficult to quantify. •

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References

1. Delgado CL. Rising Consumption of Meat and Milk in Developing Countries Has Created a New Food Revolution. *J Nutr*. 2003 Nov 1;133(11):3907S – 3910S.
2. Popkin BM. Contemporary nutritional transition: determinants of diet and its impact on body composition. *Proc Nutr Soc*. 2011;70(01):82–91.
3. Tilman D, Balzer C, Hill J, Befort BL. Global food demand and the sustainable intensification of agriculture. *Proc Natl Acad Sci*. 2011 Dec 13;108(50):20260–4.
4. Steinfeld H, Wassenaar T, Jutzi S. Livestock production systems in developing countries: status, drivers, trends. *Rev Sci Tech Int Off Epizoot*. 2006 Aug;25(2):505–16.
5. WHO. Draft global action plan on antimicrobial resistance. 2014 Oct.
6. WHO. Ministerial Conference on Antimicrobial Resistance - Joining Forces for Future Health. WHO [Internet]. The Hague, The Netherlands; 2014 [cited 2014 Nov 18]. Available from: http://www.who.int/drugresistance/netherlands_meeting_june_2014/en/
7. Economou V, Gousia P. Agriculture and food animals as a source of antimicrobial-resistant bacteria. *Infect Drug Resist*. 2015 Apr;49.
8. Diaz. Antimicrobial use in animals: Analysis of the OIE survey on monitoring of the quantities of antimicrobial agents used in animals [Internet]. 2013; Paris. Available from: http://www.oie.int/eng/A_AMR2013/Presentations/S2_4_Fran%C3%A7oisDiaz.pdf
9. USDA. Feedlot 2011 - Part III: Trends in Health and Management Practices on U.S. *Feedlots*, 1994–2011. 2013.
10. FDA. FDA Annual Summary Report on Antimicrobials Sold or Distributed in 2013 for Use in Food-Producing Animals [Internet]. 2015 [cited 2015 Apr 13]. Available from: http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm440585.htm
11. FDA. Drug use review [Internet]. 2012 [cited 2014 Jul 29]. Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM319435.pdf
12. ESVAC. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2012. European Medicines Agency; 2014.
13. Boeckel TPV, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, et al. Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci*. 2015 Mar 19;201503141.
14. Marshall BM, Levy SB. Food Animals and Antimicrobials: Impacts on Human Health. *Clin Microbiol Rev*. 2011 Oct 1;24(4):718–33.
15. Endtz HP, Ruijs GJ, van Klingeren B, Jansen WH, van der Reyden T, Mouton RP. Quinolone resistance in campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. *J Antimicrob Chemother*. 1991 Feb;27(2):199–208.
16. Nelson JM, Chiller TM, Powers JH, Angulo FJ. Fluoroquinolone-resistant Campylobacter species and the withdrawal of fluoroquinolones from use in poultry: a public health success story. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2007 Apr 1;44(7):977–80.
17. Bager F, Madsen M, Christensen J, Aarestrup FM. Avoparcin used as a growth promoter is associated with the occurrence of vancomycin-resistant Enterococcus faecium on Danish poultry and pig farms. *Prev Vet Med*. 1997 Jul;31(1-2):95–112.
18. Klare I, Badstübner D, Konstabel C, Böhme G, Claus H, Witte W. Decreased incidence of VanA-type vancomycin-resistant enterococci isolated from poultry meat and from fecal samples of humans in the community after discontinuation of avoparcin usage in animal husbandry. *Microb Drug Resist Larchmt N*. 1999;5(1):45–52.
19. FDA. National Antimicrobial Resistance Monitoring System – Enteric Bacteria (NARMS): 2011 Executive Report [Internet]. 2013 [cited 2014 Nov 24]. Available from: http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm409035.htm
20. Berendonk TU, Manaia CM, Merlin C, Fatta-Kassinos D, Cytryn E, Walsh F, et al. Tackling antimicrobial resistance: the environmental framework. Nat Rev Microbiol [Internet]. 2015 Mar 30 [cited 2015 Apr 13];advance online publication. Available from: http://www.nature.com/nrmicro/journal/vaop/ncurrent/abs/nrmicro3439.html
21. Aarestrup FM, Wegener HC, Collignon P. Resistance in bacteria of the food chain: epidemiology and control strategies. *Expert Rev Anti Infect Ther*. 2008 Oct;6(5):733–50.
22. Van Cleef BAGL, Graveland H, Haenen APJ, van de Giessen AW, Heederik D, Wagenaar JA, et al. Persistence of Livestock-Associated Methicillin-Resistant Staphylococcus aureus in Field Workers after Short-Term Occupational Exposure to Pigs and Veal Calves▿. *J Clin Microbiol*. 2011 Mar;49(3):1030–3.
23. CDC. Antimicrobial resistance threats in the United States, 2013 [Internet]. 2013 [cited 2014 Dec 2]. Available from: http://www.cdc.gov/drugresistance/threat-report-2013/index.html
24. Wierup M. The Swedish experience of the 1986 year ban of antimicrobial growth promoters, with special reference to animal health, disease prevention, productivity, and usage of antimicrobials. *Microb Drug Resist*. 2001;7:183–90.
25. US Food and Drug Administration. Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food - Producing Animals: Recommendations for Drug Sponsors for Voluntar ily Align ing Product Use Conditions with GFI #209. 2013 Dec.
26. Laxminarayan R, Teillant A, Van Boeckel T. The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector [Internet]. 2015 Feb [cited 2015 Apr 13]. Report No.: 78. Available from: http://www.oecd-ilibrary.org/agriculture-and-food/the-economic-costs-of-withdrawing-anti-microbial-use-in-the-livestock-sector_5js64kst5wvl-en
27. Jukes. Growth-promoting effect of aureomycin on pigs. *Arch Biochem*. 1950 Apr;26(2):324–5.
28. Moore PR, Evenson A, Luckey TD, McCoy E, Elvehjem CA, Hart EB. Use of Sulfasuxidine, Streptothricin, and Streptomycin in Nutritional Studies with the Chick. *J Biol Chem*. 1946 Oct 1;165(2):437–41.
29. Starr MP, Reynolds DM. Streptomycin Resistance of Coliform Bacteria from Turkeys Fed Streptomycin. *Am J Public Health Nations Health*. 1951 Nov;41(11 Pt 1):1375–80.
30. Dritz SS, Tokach MD, Goodband RD, Nelssen JL. Effects of administration of antimicrobials in feed on growth rate and feed efficiency of pigs in multisite production systems. *J Am Vet Med Assoc*. 2002 Jun 1;220(11):1690–5.
31. Engster HM, Marvil D, Stewart-Brown B. The Effect of Withdrawing Growth Promoting Antimicrobials from Broiler Chickens: A Long-Term Commercial Industry Study. *J Appl Poult Res*. 2002 Dec 21;11(4):431–6.
32. MacDonald JM, Wang S-L. Foregoing Sub-therapeutic Antimicrobials: the Impact on Broiler Grow-out Operations. *Appl Econ Perspect Policy*. 2011 Mar 1;33(1):79–98.
33. Emborg H, Ersboll AK, Heuer OE, Wegener HC. The effect of discontinuing the use of antimicrobial growth promoters on the productivity in the Danish broiler production. *Prev Vet Med*. 2001;50:53–70.
34. Graham JP, Boland JJ, Silbergeld E. Growth Promoting Antimicrobials in Food Animal Production: An Economic Analysis. *Public Health Rep*. 2007;122(1):79–87.
35. WHO. Impacts of antimicrobial growth promoter termination in Denmark [Internet]. 2002 [cited 2014 Sep 8]. Available from: http://www.who.int/gfn/en/Expertsreportgrowthpromoterdenmark.pdf
36. Sneeringer S. The economics of Sub-therapeutic antimicrobial use in U.S. *livestock agriculture*. 2014.
37. Key N, McBride WD. Sub-therapeutic Antimicrobials and the Efficiency of U.S. Hog Farms. *Am J Agric Econ*. 2014 Apr 1;96(3):831–50.

WORLD ALLIANCE AGAINST ANTIMICROBIAL RESIATNCE

THE WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE (WAAAR): A MAJOR PLAYER IN THE GLOBAL DRIVE TO PROTECT HUMAN HEALTH

"Our Alliance has several important strengths: a multidisciplinary and multiprofessionnal structure including veterinary medicine, strong involvment from consumers, participation from politicians, parliamentarians and deputies, global programmes including antibiotic stewardship, infection control, use of old and recent diagnostic tools, research, and upgrading of vaccination programmes, all with the official support from many professionnal societies, from many different countries and other related bodies. "

www.waaar.org

About WAAAR

The Non-Governmental Organization ACdeBMR (*L'Alliance contre le Développement des Bactéries Multirésistantes aux Antibiotiques*) was constituted on 2 December 2011 in France. Subsequently, as its work became more internationally focused, it adopted the English name it is now known by: "The World Alliance Against Antibiotic Resistance" (WAAAR).

WAAAR is registered in Paris, France. From the start it has had strong bonds with French speaking Africa, with many distinguished African supporters, such as Benin's Minister of Health, Dorothée Kinde Gazard, MD, PhD, who had been very active in the promotion of high quality safe health-care in Africa, and who organized an inter-ministerial conference on that subject *(1)*.

Board members

The Board Members are Dr Céline Pulcini, Vice-President, Jean-Pierre Hermet, Dr Joel Leroy, Garance Upham, and Dr Jean Carlet, President.

Membership

The 730 members of WAAAR are physicians, hospital managers, scientific researchers, hygiene nurses, patients and patients organizations, economists and interested persons, from over 55 countries.

Drawning on the skills and experience of its members WAAAR's expertize ranges widely from antibiotic stewardship for family physicians and hospital managers, for protecting and prevention control, to water and sanitation to protect populations from the spread of drug resistant bacteria, vetenarians, food quality experts, researchers and representatives of patient and consumer groups.

The Paris Declaration

In June 2014, the WAAAR initiated the Paris Declaration (see below) which enlisted the support of over 90 scientific societies, up to 145 societies or institutes including ACCP, ATS, CDC-USA, ESCMID, ESICM, IDSA, SCCM, ISID, ISC and SPILF.

WAAAR is among the largest network along with REACT or APUA, of people actively working to make the world safe for human beings in the "post-antibiotic era", to quote the Director-General of the World Health Organization, Dr Margaret Chan.

Actions: National and International

France

Intenive lobbying and meetings with high level officials, resulting in a national Décret sur les Référents, and the

creation of a National Task Force on Antibiotic Resistance.

In January 2015, Dr Jean Carlet was named Project manager for the French government National Task Force for the Preservation of Antibiotics created by Health Minister Marisol Touraine.

Infection control

WAAAR is very active in the domain of infection control and participates in global efforts in this domain.

Professor Didier Pittet, known for his worldwide work on hand hygiene with the patient section at WHO

initiated the bi-yearly World Conference on Infection Control in Geneva, ICPIC to which we participate.

Dr Pittet was a key scientific collaborator to the Benin conference and has been keen to support IPC /patient safety efforts including those for the French speakers from Africa who have benefited from a special programme in ICPIC *(2)*.

Patient safety

Patient Safety undertakings were also key to WAAAR's work with the association *Le Lien* (founding Member) *(3)*. The NGO Le Lien organizes regular events to highlight errors in health care and the way to counter them.

As well, WAAAR co-founding member, Garance Upham, was on the Steering Committee of Patients for Patient Safety of the World Alliance for Patient Safety for ten years, later renamed WHO Patient Safety Programme (2004–2014).

Communications

Media/Research seminar with the Sorbonne University of Paris to examine various aspects of public communication on AMR for the population, by WAAAR Member Professor Antoine Andremont, Hôpital Bichat, Paris and member AGISAR/WHO.

Interventions in scientific and political conferences

Dr Carlet and other prominent members of WAAAR ave presented scientific papers in conferences around the world including Isqua, JNI, MSF, ESICM, Creirif, Santé et Biodiversité, Le Lien, World Health Assembly, Journées de Pathologies exotiques, ISF, Pathologies émergentes, Madrid MoH, and Davos 2015.

WAAAR is a partner of the World Sepsis Day, a collaborator of COMBACTE *(4,5)*.

Work with the United Nations

Putting antibiotics on the UNESCO list is one of its founding members' objectives.

At the May 2012 World Health Assembly, with the French Ambassador to the UN, and the support of the MoH, the memory of WHO Water and Sanitation Engineer, Yves Chartier, who died in a mountain accident was honoured. Chartier had done outstanding work in infection control and French public health, (Protocol on Natural Ventilation, injection safety, collaboration with USAID on water, guidelines on sanitation). The event and the Journal highlighted the urgency of AMR control with Dr Jean Carlet.

Chairing the 2012 World Healthcare-Associated Infections Forum at the Biomérieux Foundation and follow-up events. Ready for a world without antibiotics? The Pensières Antibiotic Resistance Call to Action (4) and again in 2014.

Participation in Oslo's Diplomacy and Health (Brazil, France, Indonesia, Norway, Senegal and Thailand) meeting in November 2014 sponsored by the Norwegian Institute of Public Health. Outcome document from Oslo meeting "Commitments to Responsible Use of Antimicrobials in Humans" *(5)*.

Participation in COMBACTE, in World Sepsis Day to create guidelines, to support and actions for the Chennai Declaration and European Antibiotic Awareness Day *(6,7)*.

Publications

Dr Jean Carlet has published in scientific journals for more than 20 years, specializing in acute care, on Sepsis, ARDS, issues in infection control and antibiotic resistance. Just in the past few months, Dr Carlet has published in *ICHE (Infection Control Hospital Epidemiology)*, *AJRCCM*, *Indian Journal of Critical Care*, *CID*, *Intensive Care Medicine*, *Réanimation*, *Lettre infectiologue*, *ISID*, as well as in the public press (*Le Monde*, *Huffington Post*) and he has attended many congresses.

References

1. La Conférence Internationale des Ministres de la Santé sur la prévention et le contrôle de l'infection en milieu de soins en Afrique (CIMSEF), in the news bulletin of WHO-OMS AFRO (in French): http://www.afro.who.int/ fr/benin/press-materials/item/5252-la-cimsef s%E2%80% 99est-achev%C3%A9e-%C3%A0-cotonou.html
2. ICPIC's web site : http://www.icpic.com
3. Le Lien: http://lelien-association.fr/asso/index.php.
4. 2012 http://www.ncbi.nlm.nih.gov/pubmed/22958833, and again subsequently: http://www.biomerieux.com/fr/4eme-forum-mondial-sur-la-resistance-bacterienne
5. Norwegian Institute of Public Health Meeting: "Commitments to the responsible use of antimicrobials" http://www.fhi.no/eway/default.aspx?pid=240&trg=MainContent_6898&Main_6664=6898:0:25,8195:1:0:0:::0:0&MainContent_6898=6706:0:25,9026:1:0:0:::0:0 and outcome document: http://www.fhi.no/dokumenter/ 739155c19b.pdf
6. http://www.combacte.com
7. www.world-sepsis-day.or

Appendix 1: The WAAAR declaration against antibiotic resistance: The Paris Declaration: June 2014

The increase in antibiotic resistant bacteria poses a major healthcare threat. In the face of an almost complete absence of new antimicrobial drugs in development, antibiotic resistance (ABR) has become one of the main public health problems of our time. Antibiotics are a unique class of medications because of their potential societal impact; use of an antibiotic in a single patient can select for ABR that can spread to other people, animals, and the environment, making an antibacterial used in one patient ineffective for many others. Bacterial resistance can evolve rapidly. As bacteria acquire resistance mechanisms, the altered bacterial genetic material coding for resistance mechanisms can be transmitted at times readily between bacteria, broadening the reach and extent of resistance. Treatment failures because of multidrug resistant (MDR) bacteria, once rare, notable, and limited to hospitals, now occur very commonly in hospitals and increasingly in the community as well. It is estimated that at a minimum 25,000 patients in Europe and 23,000 in the USA die each year from infections caused by resistant bacteria. The cost of antibiotic resistance is tremendous, whether measured as the personal and societal burden of illness, death rates, or healthcare costs.

Although it is a never-ended phenomenon, antibiotic resistance is directly related to the volume of antibiotics used. We are using increasing amounts of antibiotics in health care and agriculture, and discharging these active drugs into the environment. The impact of widespread antibiotic use is enormous, promoting the development and dissemination of antimicrobial resistance.

Safeguarding antibiotics will require a concerted effort by citizens, patients and prescribers. The primary goal of WAAAR is to raise awareness about the urgency and magnitude of the threat and to promote an international dialogue to assist in effective responses. The Alliance, in particular through this declaration, is dedicated to actively promoting antibiotic preservation and to raising awareness among antibiotic prescribers, politicians and policy-makers, patient safety and advocacy groups, the pharmaceutical industry, international health organizations, and the general population. Individual actions, no matter how well intended, are doomed to failure unless there is an international dialogue, a common sense of purpose, and broad consensus on how best to proceed.

We must change how antibiotics are used and adopt proactive strategies, similar to those used to save endangered species. Preservation of the efficacy of antibiotics and to stabilization of antibiotic-susceptible bacterial ecosystems should be global goals.

We urge all of you to participate in this crusade, in your own field of interest. The medical miracle of antibiotic therapy must be protected – this is a global priority and our duty. Please, help us to act NOW, by supporting this declaration, to promote wiser use of antibiotics in animal and human health, and the necessary accompanying political actions to support better education, integrated surveillance for public health action, and research.

WAAAR advocates for the following 10 actions:

- 1. Promotion of awareness of all the stakeholders - including the general public - of the threat represented by antibiotic resistance
  - Strong cooperation among international political, economic and public health organizations, which, all together, must take the lead of this action against antibiotic resistance.
- 2. Organization, in each country, ideally by Ministries of Health or regulatory bodies, of a financed national plan for the containment of antibiotic resistance, with the participation of all stakeholders, including patient advocacy groups
- 3. Continuous access to antibiotics of assured quality, especially in middle and low income countries
- 4. Integrated Surveillance of antibiotic resistance (ABR) and antibiotic use Standardized monitoring of antibiotic use and resistance at institution, regional, and country (comprehensive national data instead) level (through a Centers for Diseases Control and Prevention model) to allow comparative statistics (benchmarking), to be updated preferably in real-time and at least every 12 months. This will require adequate laboratory capacity using international standardized methods that may be facilitated by a centralized technologic coordinating infrastructure and information technology
- 5. Use of diagnostic tests
  - Appropriate use of existing diagnostic tests and development and implementation of new rapid, cost-effective and accurate diagnostic tests, adapted to the local context, to aid in distinguishing bacterial and nonbacterial etiologies. Rapid diagnostics may help clinicians avoid unnecessary treatments, rapidly select appropriate targeted therapies and inform the duration of treatment
- 6. Antibiotic stewardship (prudent, controlled and monitored approaches to the use of antibiotics)

- In humans (hospitals, long term care facilities and primary care).
- In animals (animal husbandry, agriculture, aquaculture and animal health /veterinary setting), in a "one health" philosophy.
- Progressive elimination of the "over the counter" (i.e. available without a prescription) access to antibiotics (systemic and topicals) for humans or animals.
- Ban of the use of antibiotics as growth promotion in food animals, and exceptional use in prophylaxis.
- Rational use of metaphylaxis (Prophylaxis when some animals in the livestock are sick, or at high risk to be sick), and of animal treatment.
- Limitation of the use of critically important antibiotics in humans and animals (e.g., carbapenems)

➤ 7. Educational efforts for change

- Educational programs directed at children/teenagers on antibiotics, bacterial resistance, and infection control (e-Bug model)
- Development of large coordinated, effective information and awareness campaigns directed at the public on expectations about the rational/appropriate use of antibiotics.
- Continuouseducation and training programs in the curriculum for all health care professionals in all settings (veterinarians, medical, dental, nursing, pharmacy and allied health care schools) and continuing professional education programs, on the rational use of antibiotics, including indications, dosing and duration of therapy. Education of farmers

➤ 8. Containment of bacterial transmission and prevention of infection

- Promotion of universal hand hygiene and all infection control interventions that have been proven to reduce rates of resistance
- Relentless efforts to prevent transmission of MDR organisms in healthcare, food production and animal husbandry
- Programs to limit the contamination of drinking water with MDR bacteria, as well as contamination of the environment
- Promotion of the use of available vaccines, in humans and animals

➤ 9. Basic and applied research, and development of new antibiotics

- Increased support for basic and applied research aiming at curbing bacterial resistance in human and veterinary medicine.
- Use of the principles of orphan drugs for new antibiotics
- Incentives to stimulate research of new drugs (antibiotics and novel compounds) and vaccines via regulatory pathways that allow for fast track development.
- New economic business models to support the cost of innovation while safeguarding public health interests.

➤ 10. Request for UNESCO to include the "concept of antibiotic" in the list of the intangible cultural heritage.

WAAAR is a group of 700 individuals from 55 different countries representing all the key stakeholders (physicians, veterinarians, microbiologists, surgeons, pharmacists, nurses, evolutionary biologists, ecologists, environmentalists, patient advocacy groups). The Alliance receives support from more than 140 learned societies or professional groups throughout the world. WAAAR is a nonprofit organization open to professionals and consumers worldwide. WAAAR receives no funding from the pharmaceutical industry

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Appendix 2: "Commitments to Responsible Use of Antimicrobials in Humans" 13-14 November, 2014 Oslo, Norway

We, the participants[i] of the Oslo meeting[ii] on responsible use of antimicrobials in humans, gathered in Oslo, Norway on the 13–14 of November, 2014 to discuss the urgent need to improve human use of antimicrobials, and to identify clear strategies and actions to increase their appropriate responsible use while assuring their access. We recognize that prompt coordinated and collective action is essential because of the rapidly growing global spread of antimicrobial resistance.

We acknowledge antimicrobial resistance to be a severe threat to global health that could undermine decades of progress in combating infectious diseases and preventing surgical and other health care related infections, and that misuse and overuse of antimicrobials are key drivers. At the same time, we recognize that where use is warranted, the lack of antimicrobial treatment, or inadequate treatment, either through lack of access or inappropriate use, remains an important contributor to death and illness. We applaud the efforts by WHO to place antimicrobial resistance on the

[i] Countries and organizations participating in the Oslo meeting on responsible use of antimicrobials in humans, 13-14 November can be found on the webpage of the Norwegian Institute of Public Health.

[ii] The meeting on responsible use of antimicrobials in humans is hosted by Brazil, France, Indonesia, Norway, Senegal, South Africa and Thailand, organized together with the WHO.

global agenda to assure continued effectiveness of and access to effective antimicrobials for future generations. In reference to the consultation in The Hague, Netherlands on 25-26 June 2014, we agree that antimicrobial resistance needs a "One Health" approach[iii] engaging all stakeholders from the human and animal health, agriculture, aquatic and environmental sectors, both governmental and civil society. We see the ongoing collaboration between the WHO, OIE and FAO as a cornerstone in this work.

We recognize the need to strengthen health systems, noting the importance of interventions to assure infection prevention and control. This should be done through behavioral change, appropriate and timely treatment, immunization coverage and development of new vaccines, access to safe water, hygiene, sanitation, and waste management. Models for supporting research and development into new and novel antimicrobials need to be aligned with global needs. These models should actively explore alternative mechanisms for incentivizing research and development, including delinking research and development costs from product prices, and decoupling reimbursement to manufacturers from the volume of consumption. These models need to include mechanisms to reserve the use and maintain the effectiveness of these new antimicrobials.

This consultation has focused on concrete strategies to shift words into action. We acknowledge the challenges of developing a global action plan which aims to guide efforts to combat antimicrobial resistance in all countries, taking into account the many differences in health systems, culture, ecology, epidemiology and economic status. However, we consider international collective effort, including political commitment at the national level, to be essential for the success of the proposed Global Action Plan in combating antimicrobial resistance. The final Global Action Plan should send a clear and strong message that addressing antimicrobial resistance and responsible use of antimicrobials is a priority for all countries and stakeholders, and the plan should give guidance on how to implement mitigating actions. Political will coupled with concrete steps are the keys to meaningful impact.

Meeting recommendations:

We believe that all stakeholders, including policymakers and regulators, providers and health professionals, patients and the public, producers and distributors, and payers, from the public and private sectors and civil society alike, have a shared responsibility to tackle antimicrobial resistance. Together they should develop mechanisms to work cooperatively and constructively to understand the health systems, societal, and economic drivers of inappropriate antimicrobial use, share good practices, limit harmful practices and achieve the goal of responsible use of antimicrobials in humans. These mechanisms are needed to drive locally appropriate and sustained action.

We also agreed that assuring access to appropriate and effective antimicrobial medicines is an integral part of the universal health coverage agenda, as well as maintaining effectiveness of antimicrobials.

This consultation recommends that the following issues that received support during the meeting should be strongly considered during the final formulation of the Global Action Plan on Antimicrobial Resistance:

1. All nations should develop and implement national action plans, including awareness campaigns based on a good understanding of social and cultural realities, for combating antimicrobial resistance and promoting responsible use of antimicrobials, based on a multi-sectoral One-Health approach.
2. Infection prevention and control is essential for minimizing the development of antimicrobial resistance and needs to be prioritized across health care systems.
3. All nations should commit to improving and ensuring universal access to essential vaccines, rapid diagnostic tools, and effective antimicrobials, and to the further development of these important tools.
4. All nations should implement antibiotic stewardship programs across their health care systems. In support of this, the international community should establish a framework (including standards and metrics) to support stewardship efforts, and countries with established expertise should assist other countries to set up their own stewardship programs. For those countries with limited resources and internal capacities, international assistance with financial, material and technical support should be an important consideration.
5. Evidence-based treatment and stewardship guidelines, adjusted for local resistance patterns, epidemiology and differences in health systems, need to be developed, implemented, monitored and evaluated to guide health professionals and other providers in appropriate and sustainable use of antimicrobials.
6. Regulation and assurance of the efficacy, safety and quality of antimicrobials, addressing the full supply and

[iii] The One Health concept addresses issues of infectious diseases and their control at the interface between human health, animal health, food and agriculture, and the ecosystem, recognizing that infectious organisms often cross species in ways both known and unknown.

distribution chain, needs to be implemented in all countries.

7. International collaborations should be initiated to address the problems of substandard/spurious/falsely-labelled/falsified/counterfeit medical products as part of the efforts to ensure responsible distribution and dispensing of antimicrobials of good quality, particularly in areas with limited access to health care.
8. Local, national, and international monitoring systems on distribution and consumption of antimicrobials and current resistance patterns (including regional and sub-regional approaches to address cross-border dynamics including areas of conflict, high mobility, and refugees) should be developed and implemented.This information needs to be made publicly available to support an understanding of extent, trends and impact of antimicrobial resistance in all countries using common, validated surveillance methodology.
9. Education and continuing professional education of all health workers who dispense or promote the use of antimicrobials, should include strong elements on the threat of antimicrobial resistance, the drivers and dynamics of antimicrobial resistance, and antibiotic stewardship and other measures to avoid, minimize and mitigate the spread of antimicrobial resistance.
10. Healthcare providers and health professionals should take greater responsibility for promoting responsible use within their communities, including engaging in awareness raising and educational activities among their peers and the public to encourage behavioral change to optimize the effective use of antimicrobials.
11. Access to antimicrobials should be by prescription only or by a similar form of authorization appropriate to the local health care system (e.g., dispensing based on regionally appropriate guidelines).
12. National authorities should implement reimbursement schemes that encourage responsible and appropriate use of antimicrobials.
13. Financial incentives and marketing that stimulate inappropriate antimicrobial prescribing and dispensing practices (including use of broad-spectrum agents, inappropriate prescriptions, dosages or pack sizes, or wrong route of administration or duration of treatment) should be eliminated through legislation or other nationally appropriate measures.
14. Direct-to-consumer-marketing of antimicrobials should be prohibited or tightly regulated in all countries. Although some participants expressed the view that all such marketing should be fully prohibited, consensus was not reached on this point.
15. Antimicrobial manufacturers, importers, wholesalers, and distributers should adopt a code of conduct, limiting the marketing of antimicrobials, while promoting their appropriate use as part of antibiotic stewardship.
16. Medically-important classes of antimicrobials should be restricted to clearly defined criteria for the use of selective medical practitioners only, aimed at preserving the effectiveness of these medications while assuring accessibility and affordability to low income populations. Although some participants expressed the view that new classes of antimicrobials should be restricted to humans only, consensus was not reached on this point.
17. Countries should regulate and enforce control measures on manufacturing waste from production of antimicrobials, and other routes by which antimicrobially active substances, their constituents and byproducts are released into wastewater, soil and air, and should monitor possible impact on the environment and the biosphere.
18. The success of the Global Action Plan is dependent upon international and intersectoral collaboration, to support the development of implementation mechanisms. International bodies should explore ways to strengthen intersectoral collaborations and discuss possibilities for international agreements to combat antimicrobial resistance, including full use and applapplication of the core capacities of the International Health Regulations (2005).