AMR CONTROL 2018

OVERCOMING GLOBAL ANTIMICROBIAL RESISTANCE

EDITORS-IN-CHIEF: DR JEAN CARLET, PRESIDENT, WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE
AND GARANCE UPHAM, VICE-PRESIDENT, WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE

GLOBAL AND NATIONAL GOVERNANCE • IPC AND SURVEILLANCE
ONE HEALTH • NGO ENABLERS • RESEARCH & DEVELOPMENT
ALTERNATIVES • INVESTMENT AND SOCIETY

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INTRODUCTION: AMR AND UNIVERSAL HEALTH COVERAGE

DR TEDROS ADHANOM GHEBREYESUS, DIRECTOR-GENERAL, WORLD HEALTH ORGANIZATION

Left unchecked, antimicrobial resistance (AMR) will roll back a century of medical progress, damage the environment, interrupt food production, cause more people to fall into extreme poverty and imperil global health security. Furthermore, the World Bank estimates that its impact on economic growth will be greater than that of the 2009 financial crisis, putting at risk up to US$ 100 trillion of economic output by 2050. In recognition of this threat, countries came together at the World Health Assembly in 2015 to adopt the Global Action Plan on AMR and since then, over 100 countries have developed and are implementing their own national action plans. A further 67 plans are in progress.

At the same time, the nations of the world have expressly committed to achieving universal health coverage (UHC) as part of the Sustainable Development Goals. The vision of UHC is that all people should have access to the services they need without facing financial hardship. Ensuring equitable access to appropriate and affordable antimicrobial medicines is a fundamental part of that vision. Tackling antimicrobial resistance must therefore be seen in the broader of context of efforts to strengthen health systems and achieve UHC.

UHC is a long-term vision for low- and high-income countries alike. It is built on the conviction that precious financial resources should be put to work for the benefit of all, and that no one should be forced to suffer financially through ill health. Tackling antimicrobial resistance and UHC require that all health systems have access to the resources needed, both financial and technical, to ensure that infections are prevented and treated. Everyone must have equal access to vaccines that prevent infections, as well as quality antimicrobials that can deliver effective treatment when they become sick. Poverty should not be a barrier to that access, nor force people towards substandard or unregulated medicines. Clinicians must have access to affordable diagnostics as well as data on local and regional resistance trends to ensure they are able to prescribe the right treatment for their patients. And guiding how we all use, develop and preserve existing and new antimicrobials, not just within the human health sector, but also in our farming and animal husbandry practices and in the environment, requires global commitment to an overarching stewardship framework that will help to ensure that equitable access to antimicrobials remains an integral and achievable part of UHC.

Progress towards UHC is vital for tackling the threat of AMR. Strong health systems built on the foundation of people-centred primary care are vital not only for ensuring access to precious medicines and treating infections, but for preventing the wastage of precious resources that can be invested to address other health threats and make progress towards better health for everyone, everywhere. ■

Dr Tedros Adhanom Ghebreyesus was elected as WHO Director-General for a five-year term by WHO Member States at the 70th World Health Assembly in May 2017, the first person from the WHO African Region to become WHO Director-General. Dr Tedros served as Ethiopia's Minister of Foreign Affairs, 2012–2016, and Minister of Health, 2005–2012. Born in Asmara, Eritrea, Dr Tedros holds a PhD in Community Health from the University of Nottingham and a Master of Science in the Immunology of Infectious Diseases from the University of London, He has published numerous articles in prominent scientific journals, and received awards and recognition from across the globe.

ANTIMICROBIAL RESISTANCE IS EVERYONE'S BUSINESS!

DR JEAN CARLET, PRESIDENT, THE WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE AND **GARANCE UPHAM,** VICE-PRESIDENT, THE WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE - EDITORS-IN-CHIEF, *AMR CONTROL*

"Tackling antimicrobial resistance must be seen in the broader of context of efforts to strengthen health systems and achieve UHC" wrote WHO Director General Dr Tedros Adhanom Ghebreyesus, in the introduction to this edition of *AMR Control*.

The coming of a new team to head the World Health Organization could bode well for the necessary effort against antimicrobial resistance. Throughout the developing sector, the essential element of success would demand building up health systems' capacities.

If the campaign for Universal Health Coverage (UHC) combined with a revival of the Alma Ata goal of Health for All and primary healthcare everywhere, advocated by WHO leaders – the Director General Dr Tedros, Dr Soumya Swaminathan, the Assistant Director General in Charge of Programmes, and AMR Secretariat Coordinator Dr Marc Sprenger – are given substance, then 2018 could be a turn-around year.

But, for that to succeed, we need to mobilize

Dr Soumya Swaminathan: We need all parties for UHC!

"As Dr Tedros often says, you need basically all parties for UHC and similarly you need UHC to make progress in any of the other SDG goals, so it's basically to help countries to strengthen their health systems in all their different aspects. WHO's role is going to be focused on the countries and what the countries need.

And we see that as a change in the way we operate, so we will no longer be content just to do the normative work or the guidelines work or recommendations but we will be going a step further and actually providing and handling any other kind of support countries could ask for.

And this is to be done by insuring that the HQ here in Geneva and country offices are working as one.

So, for example, if a country doesn't have the technical expertise, it will be our responsibility to arrange that either from HQ or from a country office.

And this to be done on top of the normative work.

Yet there is a need for civil society to get involved because health has never been high on political agenda for any country, unlike infrastructure or education, unlike energy or electricity. Healthcare infrastructure is never on the list of demands."

Dr Soumya Swaminathan, to AMR Control editor-in-Chief, Garance Upham (January 2018).

Public awareness is key in the OECD as in the LMICs

Understanding that among the most dangerous drug-resistant bacteria - those at the source of enteric diseases and urinary tract infections - don't even need evolution to transmit their capacity for resistance to antibiotics, is really needed for governments to assume their responsibility in making sure that all public and private entities act responsibly: which means enough health staff, well trained, to ensure the highest hygiene levels in health centres and highest level of waste disposal and water sanitation systems for the environment.

The catch word is investment: decreasing budgets for health may put millions of lives in danger in the immediate future.

The United States Centers for Disease Control lead team on Healthcare Quality advocates strongly for investments in IPC.

It is the same team of Dr Denise Cardo which recently reported on the incredibly massive savings achieved by containment of drug-resistant outbreaks in healthcare facilities over the past five years.

Now it is important for this fact to enter into the consciousness of policy-makers.

US CDC: Investing in infection prevention and control to contain antibiotic resistance can be achieved and should be prioritized

"In many low- and middle-income countries, infection prevention and control (IPC) is an often overlooked, but critical, capacity for safe clinical care, including the reduction and containment of antimicrobial-resistant (AR) pathogens. Around the world, there remain fundamental gaps in IPC capacity and implementation, with many efforts limited to temporary stop-gap measures, e.g., during emergencies. However, it is critical to identify and implement sustainable solutions to address those gaps in all healthcare settings. Progress can be achieved and should be prioritized. All countries have a stake."

No one should be ignorant of the faecal threat!

And it ought to mean, in many if not most of our wealthy but "dirty" countries, a public targeted effort to improve understanding and respect for basic hygiene.

Were any gastro-intestinal severe epidemics to arise with drug-resistant microbes, it could be as devastating as the "Spanish flu" according to experts, and there is really insufficient consciousness of the risks; in France as in Southern Europe, for example, even basic school hygiene is terrible.

The rise and campaign on preparation against HIV risks, sadly, is in part linked to an explosion of severely drug-resistant "super-gonorrhea".

WAAAR Vice-President Dr Vincent Jarlier and Sandra Founier, Central IPC team, APHP, France

We have emphasized above that the "classical" measures successfully used for controlling MRSA cross-transmission (contact isolation procedures) were not effective enough to control CPE/GRE outbreaks.

Only the reinforced procedures, implemented in 2006 (in France), finally allowed such control. The reasons for this apparently striking fact are actually obvious. CPE/GRE (and ESBLs as well) share several critical features concerning their dissemination potential: (a) they are hosts of the digestive tract and consequently are easily disseminated by faecal route (or urines in case of urinary infection) whereas MRSAs are hosts of nasopharynx, a more remote site, (b) their resistant traits are harboured on mobile elements, increasing the risk of bacteria to bacteria dissemination whereas methicillin resistance is chromosomal and (c) the bacterial loads are far higher for CPE/GRE (108/gr of faeces, i.e. ~1010 excreted per day by a carrier) than for MRSA (maximum ~108 bacteria in nose).

It is a good example of the need to adapt infection control policy to the characteristics of the targeted organism.

We should raise the point that limitations in nursing staff may be an obstacle to dedicating healthcare workers to a single index CPE/GRE case

CPE: carbapenemase-producing enterobacteria

GRE: glycopeptide-resistant enterococci

Preserve antibiotics!

"Antibiotic prescription is still considered everywhere like a trivial act!"

We have proposed to UNESCO to list antibiotics in their World Heritage Programme! Dr Jean Carlet

The gut is the silent epicentre of antibiotic resistance, because the antibiotics modify profoundly the gut microbiome, and allow resistant microorganisms to grow and to colonize this organ for prolonged periods of time. Those resistant strains can then be transferred to other patients in the hospitals, or to relatives in the community.

Antibiotics and resistant microorganisms present in the effluents can contaminate the environment. Microorganisms carried by animals can contaminate humans via either the environment or the food chain.

Antibiotics are overused nearly everywhere.

Those are the main reasons why we have proposed to UNESCO to list antibiotics in their World Heritage Programme.

(UWH) , Jean Carlet, President WAAAR

Phages can help: Time to act in the European Union

In the United States, the decision to create, for the first time, an R&D centre on phage therapy. The Center for Innovative Phage Applications and Therapeutics (IPATH) at the University of California San Diego (UCSD) – highlights the importance of "older" and yet futuristic modes of ecological control to face antibiotic resistance.

We at WAAAR have always supported phage research and we are glad to present two important authors in this edition: Dr Nagel with her United States-Africa team developing R&D know-how in sub-Saharan countries and, in France, a lead team with Professor Tristan Ferry, on drug-resistant bone and joint infection; a "first" success using a phage cocktail. This shows the urgency of reform in the legislation for the European Union to permit development of use of phagotherapy.

R&D

Lots of action on R&D with the launch of a new AMR R&D Hub, an idea that emerged from Germany (which will be investing 500 million euros) and the past two G20s when AMR was coming on the agenda, while CARB-X, featured in this edition of *AMR Control* can boast of increased funding, notably from the United Kingdom, while the DHDi-WHO initiative on AMR is gaining more support as well.

One Health interest is growing, Chatham House in the United Kingdom with Professor David Heymann's group is advocating and meeting on vaccines to improve prevention for AMR infections both in the animal and human health sectors.

As always, the incredible news and trends in AMR are such that a yearly publication such as *AMR Control* finds it hard to cover all tracks.

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GLOBAL AND NATIONAL GOVERNANCE

AMR CONTROL IN DISCUSSION WITH...

DR MARC SPRENGER, DIRECTOR, ANTIMICROBIAL RESISTANCE SECRETARIAT, WORLD HEALTH ORGANIZATION

Q: When you came to WHO, you stated that you wanted to improve and facilitate cooperation across teams working on AMR, such as Infection Prevention and Control (IPC), the platform for diagnostics at point-of-care, water and waste management and R&D for new antibiotics, surveillance with advocacy... Where do we stand today?

Marc Sprenger: When the global action plan was approved, it was clear to the senior management that there should be a mechanism in place for the coordination of all the different parts. And that went quite well. We were able to develop a comprehensive programme. I began by setting up an informal coordination structure with workstreams and that has resulted in a comprehensive programme area (now numbered 1.6) and you can now find a WHO programme with a budget, so that is a big win compared to the past. And now there is very good cooperation here among the teams inhouse.

Q: Indeed groundbreaking. Are you finding that some agenda items are progressing quickly and others are less advanced in implementation?

Marc Sprenger: Of course, WHO is a norm standard-setting organization. But I am also interested in seeing real change come about at the country level. But what is real change, that's the question? Certainly, it is important to have rigorous standards on the core requirements for IPC, for example, on how antibiotics should be used in human or animal health sectors. These are the basics, but just as important is the question of how these can be implemented.

What I have learned recently is that the practice in many developing countries is that they are not prescribing the right antibiotics. The question is: do they have access to the right antibiotics and if they do, do they use them prudently and not in irrational or expensive combinations when cheaper and equally effective alternatives are available? Are these being prescribed for the correct duration and not for the two-week course which is commonly seen but not necessary? So, from that perspective I am not satisfied.

But I was very pleased when I visited the Kenyatta Hospital in Nairobi and was able to meet the main nurse who was in charge of IPC, and I thought, "Great!" that is good. And then in another hospital I could see that they were adhering very closely to good practice on handwashing.

Q: It's good news that most countries have set up a national action plan (NAP), not so good news (to quote Dr Mirfin Mpundu, chair of the Ecumenical Pharmaceutical Network) is that not many have started implementation. Do you agree that this is the case?

Marc Sprenger: Yes, most countries have one or are in the final stages, all good news, but is that enough? No! We need to see implementation of these plans. There are targets, for example, of a decrease of about 25% in the use of antibiotics, and that's all fantastic, but of course that needs to be matched with a programme and with money, so that you can train people and make a real difference.

We have to be realistic and I should be happy and pleased that we have already reached that level of awareness. But in the end, what counts is where there is a real difference? And that's for the next five years.

Regarding the guidelines for medically important antimicrobials in food-producing animals, it's a big step forward, but again it is about the implementation. We know that some countries like the Scandinavian countries, the United Kingdom and the Netherlands, have done that; they implemented restricting antibiotic use in husbandry and they even increased productivity at the same time. But the question is: are all countries willing to change? To go along with the guidelines? Together with the reduction in human use, this will really make a difference.

Q: Access to old medicines is in danger. Even in wealthy countries, like France, there is an increasingly shortage of older generic antibiotics (as well as of old vaccines).

Marc Sprenger: We are aware of that and it should be high on

the political agenda. But it's not a sexy topic, it's more sexy to talk about new R&D, new innovative drugs, no one wants to talk about the old generics. Yet it's important to remember that most infections do not need the most advanced antibiotics. We can still treat them with simple antibiotics.

This is a challenge for communication, because we talk about superbugs and then people with a common pneumonia assume that it is always caused by a superbug, and assume therefore, that they always need a super antibiotic, which is not the case. It's all about prudent use and appropriate diagnostics.

Q: And the right duration. For example, if you look at recent scientific studies on antibiotic prescribing and HAI in surgery, you see that in LMICs they use a lot more antibiotics over longer periods of time, before, during and after surgery, while having higher rates of surgical site infections (probably because their health structure is weak in terms of hygiene and IPC standards – and these weak standards may be the cause of higher dosage and duration in antibiotics, a vicious circle)...Your thoughts? Dosage has decreased by perhaps 30% over the past 15 years and duration as well.

Marc Sprenger: From a global public health perspective, a much shorter course is better. It would be good if the guidelines would reflect this. WHO has been asked to take the lead in developing new guidelines, but this is a costly and lengthy exercise.

We also need tailor-made packages, so you don't buy 20 pills for a five- or seven-day course. It would be good if countries would pay more attention to this in order to reduce the use of antimicrobials.

Q: At Thailand's Prince Mahidol Conference, the incoming head of the GFATM, Peter Sands gave a tremendous speech; he said that to be efficient we need to focus on existing infectious disease and build healthcare systems. That, he said, is true of AMR and global health security. To think not only of infectious threats of the future, but to treat the existing ones was the best and only path and that was true also in the face of AMR. Do you agree?

Marc Sprenger: I fully agree with that. In fact, it goes back to my own ideals, which is the Alma Ata declaration, which will be renewed. Alma Ata was about primary healthcare, and I think we should pay more attention to this, because doctors, vets, nurses, or midwives can play an important role and could have the knowledge about prescribing and IPC (infection, prevention and control). And even further back, it's about WASH; it's about having basic facilities like safe drinking water, like well-managed sewage. How can we be seriously talking of AMR if we don't pay attention to these basic elements?

Q: At the WHO Executive Board meeting last November, the new head of Dr Tedros' cabinet, Dr Bernhard Schwartländer deplored the lack of interest from health ministries in countries, and the lack of power and funding for these MoH, and he called for empowering them. I thought that very important to achieve the GPW (Global Program of Work) of the WHO which includes AMR. Your thoughts?

Marc Sprenger: It's a very political issue, and it varies from one country to the next. In some countries the ministry of health plays a very important role, while in other countries, like India, health governance is decentralized to federal states. But it is, nevertheless, important that they all take on their responsibility for AMR. On the other hand we need to recognize the power of NGOs, of FBOs (faith-based organizations) and of professional associations (such as nurses and midwives). In that respect, I am very pleased that the Director General of WHO has appointed a chief nurse officer. Working with her, we hope to empower the nurses and midwifes.

Regarding the FBO, it is important to recognize that in some countries they play a very important role in healthcare delivery. For example, FBOs in some countries run 70% of healthcare facilities, as in Nigeria. I have seen impressive work being conducted by the Ecumenical Pharmaceutical Network.

The challenge is to find out how NGOs and FBOs can help achieve the AMR objectives in countries.

I think we are still examining the narrative of AMR; it is hard to explain. We need to reflect and discuss that with others: how to get the narrative right.

Q: The role of the environment as a source and conveyor belt for bacterial genes conferring resistance is now coming up in the news: notably the dumping of antibiotic-containing waste in lakes, rivers, soil and from factories, or the waste from the meat industry to hospital systems. It was also presented to the STAG meeting for the first time this winter.

Marc Sprenger: The UNEP programme, Frontiers, has come up with a great document on the environment as a source of AMR.

We try to keep WASH (Water-Sanitation-Hygiene) on the political agenda. But it has also been noted that there is a relation between environment and AMR. I think we don't have a clear insight on the environment's contribution to the problem because there are different aspects: waste water facilities, antibiotics in manure and many more. We need to get a clearer understanding in order to develop recommendations. This is something to work on.

Q: There is a lot of emphasis on getting new antibiotics, but are countries doing enough on infection control?

Marc Sprenger: In my talks, I always stress the importance of IPC. I don't believe we will get a lot of new antibiotics, the pipeline doesn't look promising. Only one, maybe two new products are expected in the next seven years, so we need to pay a lot more

attention to prevention in all its forms, including better waste management and sewage systems.

Q: How do you see the interlink between AMR and the Global Health Security Agenda (GHSA)? It's a subject of debate as we go towards the first international conference on GHS in Sydney?

Marc Sprenger: There is a clear link with the Health Security Agenda, but also a strong link with Universal Health Coverage. Both are priorities for WHO.

Q: In the outcomes of the STAG, it says there is "increasing awareness on IPC, however, improved communication with policy-makers who do not think IPC is important as a key next step".

Ebola expert, Professor Nasidi, who built the Nigerian CDC, told me in an interview that we could save millions of lives if ministers understood the key role of hygiene, of prevention. Today, IPC is seen as secondary, and not viewed as the main conveyor belt for solving the AMR epidemic.

To quote ECDC's Dr Dominique Monnet: "If we just put new antibiotics on the market without better IPC, it will be pouring oil on the fire".

Marc Sprenger: We should first go for the basics: sewage and a safe water supply, because you cannot advocate handwashing when there is no water. And the reality is that there is a real lack of safe water and proper sewage management in health structures. From a political perspective, this should be number one. Then more attention to IPC is needed.

If you look at the priority pathogen list, at the top are the Gram negatives that are spread, in particular in hospitals, in healthcare settings.

It's not very sexy to say that cleaning the beds and the floors is of real importance. And this has often been outsourced because it's not seen an important work. But, in fact, all these things are very important in order to prevent HAI. So I think we should invest a lot more in that. It goes without saying that we also need new innovative antimicrobials or treatments. But let's make sure that first of all the basics are well done.

Q: We can remember the WHO EU event with Suzanna Jacob on the 200th anniversary of Simmelweiss, an early pioneer of handwashing. Two centuries ago, advice on handwashing was not always followed and as a result patients' lives were put at risk. In 2015, health staff put on the web a video of a most filthy hospital in West Africa. But the lack of cleaning personnel and training, in the era of the return of the "faecal threat" is a gaping hole, globally.

The right to clean care is the right not to kill, the right to health, part of Alma Ata.

Lack of understanding of AMR, all the emphasis on new drugs and new diagnostics as in the framework meeting at WHO, but leaders don't see how IPC is the only barrier for outbreaks of AMR infections, and it's not costly. IPC can mean tremendous savings for national budgets and for societies, and most importantly, it saves lives. Yet, IPC is seen as an aside.

Marc Sprenger: It's difficult because if you look at hospitals in the western world, they would like to make a profit. In order to make a profit you need to reduce costs, so you outsource food, outsource cleaning... Some are inclined to reduce the costs of hiring infection control nurses and question whether they contribute to the wellbeing of the patients? In fact, yes, they do. Because a hospital-acquired infection will always result in a prolonged stay and increased costs. In other words, it is a good investment to spend money on IPC.

I think we should have norms about IPC and pay more attention to accountability. In my own country, the Netherlands, there was a huge outbreak of nosocomial pneumonia, over 30 people died and the question was: who was responsible? Everyone was evading responsibility, although in the end the hospital's executive management team was held accountable and had to step down. So the lesson we can learn here is that the management of a hospital is accountable. Of course, I realize that this is more difficult in low-resource settings. Nevertheless, the executives should take responsibility by paying attention to infection prevention. The STAG recommended that IPC should be implemented at different minimum levels, because the WHO guideline may be too ambitious for LMICs. Therefore, a grading system should be considered. I really hope that this gets the highest attention from the healthcare management. ■

Marc Sprenger spoke to AMR Control's co-Editor-in-Chief, Garance Upham

Dr Marc Sprenger is Director of the Antimicrobial Resistance Secretariat at the World Health Organization and is responsible for the coordination and implementation of the Global Action Plan on AMR. Formerly, Dr Sprenger served as Director of the European Centre for Disease Prevention and Control (ECDC) and Director General of the Dutch National Institute for Public Health and the Environment (RIVM). Dr Sprenger studied General Medicine at University of Maastricht, specializing as a medical microbiologist at Erasmus Medical Center (Rotterdam) and obtained a PhD in Epidemiology at Erasmus University.

THE SWISS RECIPE FOR CONTAINING ANTIMICROBIAL RESISTANCE

MIRKO SAAM (TOP LEFT), CO-FOUNDER AND ASSOCIATE, COMMUNICATION IN SCIENCE LTD, GENEVA, SWITZERLAND;
ALEXANDRE VON KESSEL (TOP RIGHT), SENIOR ADVISOR, INTERNATIONAL AFFAIRS DIVISION, FEDERAL OFFICE OF PUBLIC HEALTH, BERN, SWITZERLAND AND **KARIN WÄFLER** (BOTTOM), STAR PROJECT LEADER, FEDERAL OFFICE OF PUBLIC HEALTH, BERN, SWITZERLAND



In 2015, the Swiss Federal Council adopted a national strategy to ensure the long-term efficacy of antibiotics, while preserving human and animal health. Developed through a consultation process involving all interested stakeholders (across public health, animal health, agriculture and the environment), this strategy is well matched with the WHO Global Action Plan on Antimicrobial Resistance. A range of measures are currently being implemented to monitor and contain antimicrobial resistance, appropriately use antibiotics, develop new drugs and diagnostic tools, and foster cooperation and education across the public and private sectors.

The Strategy on Antibiotic Resistance *(1)* was established jointly by the Federal Office of Public Health (FOPH), the Federal Food Safety and Veterinary Office (FSVO), the Federal Office for Agriculture (FOAG), the Federal Office for the Environment (FOEN), the regional authorities (cantons), and a wide array of stakeholders. Its content is therefore comprehensive and broadly supported, and grounded on a One Health approach.

Switzerland being a federal state, duties and responsibilities in the healthcare system are decentralized and divided among the federal, cantonal, and municipal levels, the cantons playing a vital role. Each of the 26 cantons has its own constitution and is responsible for licensing healthcare providers, coordinating hospital services, and subsidizing institutions. There are also multiple scientific institutions, which are active either at the federal or cantonal levels. These include universities, professional societies, associations and expert groups.

All these stakeholders and interest groups were involved in the preparation of the national strategy, with the aim of achieving a coordinated, cross-sectoral implementation. They all had the opportunity to express their viewpoints and experience in three workshops for devising the strategy. This process also took into account national AMR strategies of other countries and lessons learned in implementing them. Eventually, a public consultation was held before the strategy was adopted; the feedback from this process was summarized in a report and incorporated into the implementation.

Many of these stakeholders – in particular at cantonal level – are currently in charge of implementing the strategy. Four federal offices (FOPH, FSVO, FOAG and FOEN) are in charge of coordinating the activities, while the FOPH has the overall lead. In addition, two new permanent coordinating bodies based on the revised Law on Epidemics have been created to facilitate the cooperation between the Confederation and the cantons. In particular, a cross-sectoral One Health Coordination Body created in 2016 facilitates the adoption of any complementary laws or amendments *(2)*.

The measures of the Strategy on Antibiotic Resistance are divided into eight fields, which are depicted in Figure 1. The following sections of this article briefly provide examples of activities currently being implemented, following the structure of WHO's Global Action Plan on AMR.

National public awareness campaign

Switzerland's inaugural National Antibiotic Awareness Week took place in November 2017. It aimed to inform stakeholders and the public about the dangers of antibiotic resistance and provide the latest information on regional and national projects *(3)*. Universities, consumer associations and multiple stakeholder groups held their own events across the country.

During this week, pharmaSuisse (the umbrella organization of pharmacists), the Swiss Medical Association (FMH) and the FOPH jointly launched the first nation-wide initiative to improve awareness about appropriate antibiotic use.

After several focus groups, representatives of these three institutions prepared an information leaflet to be distributed to patients affected by an infectious disease, whether or not they are prescribed antibiotics. In 2018, general practitioners, specialists and a network of 1,500 pharmacies will distribute nearly a million of these leaflets, which are available in four languages. A short animated movie will provide complementary information on a dedicated website, where printed leaflets can be ordered free of charge *(4)*. An evaluation of this information campaign is planned for the end of 2018.

Surveillance of AMR epidemiology and antibiotic use

From 2001 to 2006, a national research programme (NRP 49) mapped antibiotic resistance in Switzerland for the first time, in humans, animals and the environment. As a product of this research programme, the Swiss Centre for Antibiotic

Figure 1: The structure of the Swiss Strategy on Antibiotic Resistance

8 fields of activity – 35 measures

The measures of the Strategy on Antibiotic Resistance concern human medicine, veterinary medicine, agriculture and the environment and are divided into eight fields of activity. The strategy follows the One Health approach.

MONITORING
The antibiotic resistance situation and consumption must be monitored systematically in all sectors. This is the only way that correlations between usage, the nature of the antibiotics and the development of resistance can be identified, so that the success of the measures taken can be assessed.

PREVENTION
Lower antibiotic use contributes the most to fighting resistance. The time-honoured saying "prevention is better than cure" applies: the fewer people and animals that suffer from infections, the fewer antibiotics need to be used. Preventive measures such as better hygiene, targeted diagnostics, vaccination and optimized animal husbandry can reduce the use of antibiotics to what is strictly necessary.

APPROPRIATE USE OF ANTIBIOTICS
The excessive and inappropriate use of antibiotics is primarily responsible for the increase in resistance. Clear guidelines on prescription, dispensing and use in human and veterinary medicine are needed, especially for newly developed antibiotics or those classified as critical.

RESISTANCE CONTROL
Resistance must be identified quickly and its further spread prevented. In human medicine, the risk of bringing resistance into hospitals or nursing homes when patients are admitted needs to be reduced – notably by preventive screening. The focus in veterinary medicine is on limiting the spread of resistant pathogens between herds.

RESEARCH AND DEVELOPMENT
An understanding of causes and correlations is the basis for effective measures. Targeted and interdisciplinary research fills gaps in our knowledge. New findings will lay the foundations for product development, for example in diagnostics or in the field of antimicrobial substances.

COOPERATION
Cooperation is needed to tackle the problem successfully. This is why multidisciplinary and cross-sector coordination is essential. A coordinating and expert body is supervising the implementation of the strategy. International networking and knowledge exchange will also continue to be encouraged.

INFORMATION AND EDUCATION
The general public also has an important role to play. Information at all levels aims to raise the awareness of individuals so that they realise their own responsibility in dealing with antibiotics. The aim among professionals is to increase their specific knowledge about resistance, preventive measures, diagnostics and the correct use of antibiotics.

GENERAL CONDITIONS
The general conditions have to be right for antibiotics to remain effective in the future. Appropriate measures, e.g. at the political or legislative level, should support the development of new antibiotics and their sensible use. The question of finding incentives in animal husbandry which will lead to better animal health and less antibiotic use is also being examined.

Resistance (anresis.ch) was established in 2004 to monitor AMR in the human population. Anresis.ch brings together a representative network of 22 microbiology laboratories covering more than 60% of inpatients and about 30% of outpatients. It maintains an open online database with updated resistance data, and publishes surveillance results monthly for the FOPH Bulletin and through a dedicated website for specialists *(5)*.

Figure 2 below illustrates the evolution in Switzerland of various forms of resistance in pathogenic bacteria responsible for invasive infections of the brain or bloodstream.

The declaration of cases of resistance to last-resort antibiotics (carbapenems) is mandatory since 2016. *A National Reference Centre for Emerging Antibiotic Resistance* was created in 2016 to help any laboratory – free of charge – in the identification of new or emerging forms of antibiotic resistance *(6)*. The Swiss cantons have also set up a nationwide network of laboratories, which closely collaborate with the Federal authorities and the National Reference Centres on bacterial pathogens.

In the veterinary sector, a system aligned with European provisions *(7)* was established in 2006 to enable continuous monitoring of antimicrobial resistance in livestock animals and meat. Since 2009, data on sales of veterinary antimicrobials and results of resistance monitoring have been published yearly. More recently, a pilot project has been launched to further analyse resistant pathogens causing infections in livestock and pets.

Since 2013, data on the use of antibiotics in livestock and on resistance in animals and meat has been published every other year in a joint report, together with data from the human sector (*8)*. The next Swiss Antibiotic Resistance Report (to be published in November 2018) will feature new surveillance results from 1) pilot projects to enhance surveillance of infections caused by resistant bacteria (e.g., in long-term healthcare facilities), 2) pathogens causing infections in livestock and pets, and 3) resistant microorganisms in rivers and lakes. The analysis of all these data in a One Health perspective will be strengthened.

Finally, in 2016 a five-year *National Research Programme on Antimicrobial Resistance* (NRP72) was launched; it aims at enhancing our knowledge of antibiotic resistance development and transmission *(9)*.

Infection prevention and control

The NOSO Strategy for the monitoring, prevention and control of healthcare-associated infections was adopted in 2016 *(10)*. Long before the adoption of this strategy, national guidelines were already published in this field, for instance for reprocessing medical devices and for antimicrobial prophylaxis in surgery. And more than half of all hospitals (164 at the latest count) already take part in a National Surgical Site Infection Surveillance Programme.

Currently, infection prevention and control policies and operational plans are available at all health facilities. They include hand hygiene measures and recommendations regarding isolation of colonized or infected patients. A network of public health and academic partners is in place to develop and evaluate these prevention interventions.

As for the *Strategy on Antibiotic Resistance*, one of the goals of the NOSO Strategy is to enhance the adoption of common practices across the country, and to fill in the gaps. For instance, there is no healthcare-associated infections prevention & control plan available for residential healthcare facilities. And it is still unclear whether (and how) such facilities may screen for multidrug-resistant organisms, or if they have specific plans to prevent and combat outbreaks caused by these pathogens.

These two closely related strategies will allow for the development of screening and outbreak management guidelines for multidrug-resistant organisms, and for the monitoring of adherence to those guidelines.

In the veterinary sector, there are officially endorsed animal health schemes for cattle and pigs. There are programmes in place, designed and delivered by stakeholders, which identify and promote good practice in livestock production and healthy animals as a way to reduce the use of antimicrobials. Animal health services have also stepped up their advisory services and activities to encourage infection prevention; as a result, a number of infectious diseases have been eradicated (e.g., enzootic pneumonia and actinobacillosis in pigs, and *Salmonella enteritidis* in chickens).

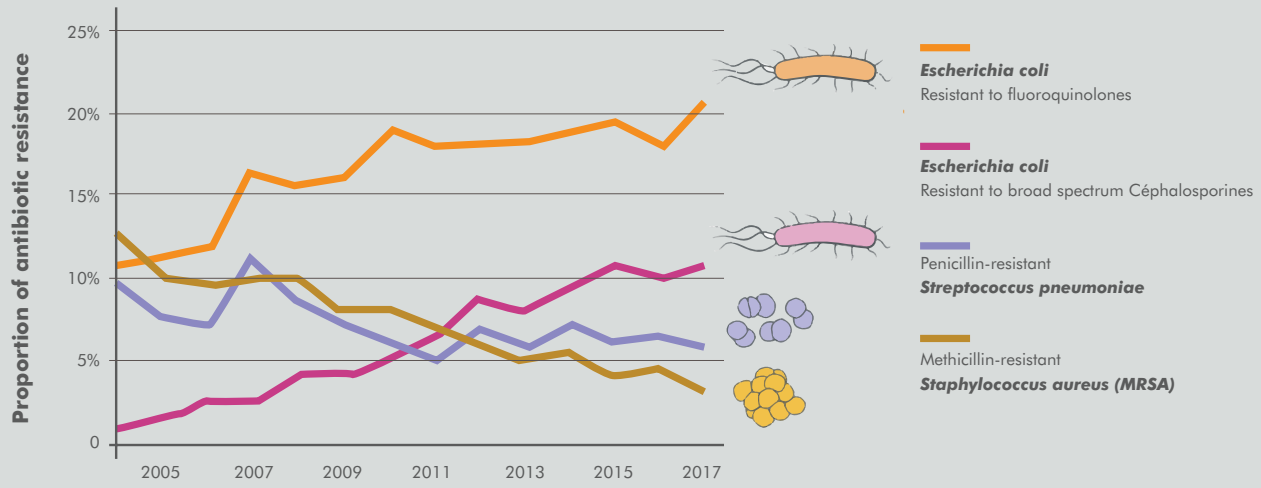
Finally, antibiotic residues in rivers and lakes are also monitored across the country. To curb the entry of these residues into the environment, wastewater treatment plants will be upgraded with additional treatment steps. With this upgrade, Switzerland is assuming a pioneering role, which has attracted considerable international interest.

Regulation to limit antibiotics use in agriculture

Back in 1999, Switzerland banned the addition of antibiotics to animal feed as growth promoters. Other legal requirements were introduced in 2004, such as a prohibition on the administration of antibiotics to livestock without a prescription by a veterinarian. A regulation on the use of antibiotics in veterinary medicine was adopted to curb the use of antibiotics for prophylactic treatment. Since 2016, the sale of critically important antimicrobials for human medicine has also been restricted in veterinary medicine.

Antibiotic pescription guidelines are available online for the most frequent infections affecting pigs and cattle *(12)*. Currently, only “sales data” on antibiotics for veterinary use

Figure 2: **Evolution of some resistant bacterial strains in Switzerland** *Source: anresis.ch*



are available; a system to collect "veterinary prescription data" at species level is under construction.

Antibiotic stewardship programmes in hospitals and in the community

The Swiss Centre for Antibiotic Resistance also monitors antibiotic use. For inpatients, consumption has been monitored since 2006 through a sentinel network of hospital pharmacies. Yearly data from 65 hospitals (or hospital networks) are collected on a voluntary basis, representing 56% of acute care hospitals (excluding psychiatric and rehabilitation centres). The participating hospitals receive a yearly benchmarking report, allowing them to compare their results with those of similar-sized institutions. From 2018, this qualitative and quantitative feedback will be provided on a monthly basis.

Swiss hospitals are at very different stages of antibiotic stewardship implementation. Comprehensive programmes are only implemented in about one third of acute-care hospitals, which may be related to a lack of funding or personnel. Whereas prescription guidelines are available in the majority of them, levels of adherence to those guidelines are not systematically measured.

The roll-out of modular national antimicrobial stewardship guidelines is planned to improve the current situation and generalize stewardship programmes in Swiss hospitals, while offering flexibility to account for local healthcare structure and resources. Swissnoso is in charge of preparing these guidelines, in collaboration with hospital pharmacists, insurance representatives, the Swiss Medical Association (FMH), and the Swiss Hospital Association *(13)*. The stewardship guidelines will be prepared in accordance with the Global Framework for Development & Stewardship to Combat Antimicrobial Resistance currently being developed by FAO, OIE and WHO.

Box 1: International commitment

In May 2018, Switzerland joined the G20's Global Collaboration Hub on AMR Research and Development, a new high-level global partnership aimed at maximizing the impact of existing and new initiatives in antimicrobial research and product development.

With a view to promoting the R&D of new antibiotics and diagnostic tools at the international level, Switzerland extended in 2017 its financial support to the Global Antibiotic Research and Development Partnership GARDP, launched by the Drugs for Neglected Diseases initiative DNDi.

Switzerland supported, with the international community, the adoption in 2015 of the Global Plan of Action to Combat AMR - developed by WHO in collaboration with FAO and OIE - and of the 2016 Political Declaration of the UN high-level meeting on AMR.

Switzerland is participating in other international initiatives such as WHO's Global Antimicrobial Resistance Surveillance System (GLASS), the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) and the EU Joint Programming Initiative on Antimicrobial Resistance (JPIAMR).

In a bid to strengthen international cooperation against AMR, Switzerland also joined the Global Health Security Agenda initiative, launched by the United States of America to combat communicable diseases. In this context it published in 2015 a comparative study of various national AMR strategies, with the aim to define best practices *(14)*.

Finally, to enhance the implementation of the national strategy, a Swiss interministerial delegation greatly appreciated the opportunity to visit the Netherlands (2016) and Norway (2017) to learn from the practical experiences of these countries in AMR control.

In the outpatient setting, a comprehensive set of prescription guidelines for the most common infections in ambulatory care was issued in early 2018. Physicians' adherence to

these guidelines should now be promoted and monitored. These guidelines will hopefully have an impact on outpatient consumption, which is being monitored since 2013 and is based on information provided by 65% of all privately run pharmacies in Switzerland.

Financial support for the development of new antibiotics

The NRP 72, with a budget of 20 million Swiss Francs, also aims at discovering novel antimicrobial molecules and developing rapid diagnostic techniques.

Conclusion

Despite all these positive efforts, there is still a great need for action; the global situation shows that isolated measures focusing on individual fields cannot provide a lasting solution to the problem of antibiotic resistance. The Joint External Evaluation of the capacity of Switzerland to prevent, detect and rapidly respond to public health threats, performed in 2017, identified several priority actions *(15)*: 1) Develop screening and outbreak management guidelines for multidrug resistant organisms, and monitor adherence to those guidelines; 2) Enhance surveillance of antimicrobial resistant infections through pilot projects, and implement a national monitoring programme for animal pathogens; 3) Expand and consolidate monitoring of healthcare-associated infections; 4) Foster adherence to outpatient antibiotic prescription guidelines and to the Swiss national plan for stewardship in hospitals (to be released in 2018/19). ■

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ANTIMICROBIAL RESISTANCE (AMR): STRESSING THE ROLE OF THE HEALTH INDUSTRY

MARTIN BERNHARDT, HEAD OF PUBLIC AFFAIRS GLOBAL HEALTH, SANOFI

"By 2050, the death toll could be a staggering one person every three seconds if AMR is not tackled now" *(1)* .

AMR, one of the most pressing global health issues, has to be tackled globally and through multi-sectoral actions, as the AMR fight spans across human and animal health, welfare, economics and policy *(2)*. The pharmaceutical industry, among the other stakeholders, is strongly engaged through the Industry Declaration *(3)* and the Roadmap *(4)*, both signed in 2016. In 2017, the *AMR Industry Alliance* was created to monitor the progress made on these two initiatives and tracks the engagement of life sciences companies, while enhancing coordination and unifying the industry voice.

The signatories have committed to work on reducing AMR by improving access to high-quality antimicrobials, diagnostics and prevention tools; to invest in research and development (R&D) in order to reinvigorate the AMR-related health products pipeline; and to reduce its manufacturing environmental impact, with development of cross-industry initiatives for required technical standards.

As a health journey partner, Sanofi has an established history in the fight against infectious diseases and remains committed to addressing this global health challenge.

Over the last few years Sanofi has been actively supporting the initiative to promote the use of rapid diagnostics and preventive measures to reduce inappropriate prescription and preserve the medical value of current antimicrobials. The company develops new solutions, especially in the alignment of its promotional activities with the appropriate use and through the creation of public awareness campaigns. With the *Bact'Attack* application, an interactive game developed with the scientific support of the francophone infectious diseases academic society, it sensitizes the youngest to the appropriate use of antibiotics.

To reinforce and accelerate the anti-infectives' R&D, Sanofi has entered into exclusive negotiations with Evotec AG in March 2018 to create a new open innovation platform. This joint initiative will bring together more than 150 scientists. For antibiotic manufacturing, a strict management programme to reduce the environmental impact of production sites worldwide has been put in place.

Sanofi is also committed to a key long-term strategy for prevention that reduces the use of antibiotics and the spread of resistant strains. Vaccination is an important part of this approach by preventing bacterial infections (such as *Pneumococcal pneumonia*) or viral infections (such as influenza for at-risk patients), which reduces inappropriate antibiotic prescriptions. Vaccination, and more broadly, prevention policies should constitute a central pillar to combat resistance as complementary tools to the responsible use of antimicrobials.

These actions stress the commitment and the critical role of the health industry in the fight against AMR. *The AMR Industry Alliance* calls for "a greater involvement of the private sector in the international debate" to build a concrete global plan of action *(5)* to face these challenges at the scientific, regulatory, and economic levels. ■

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THE ANTIMICROBIAL RESISTANCE SITUATION IN IRAN: THE NATIONAL INITIATIVE AND R&D TO FACE AMR

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Antimicrobial resistance (AMR) in Iran, as it is elsewhere, is one of the foremost important health issues today. Public and private sectors are exploring different ways to address the problem. Knowledge of accurate prescription and optimal use of antibiotics for different groups of patients is poor. Actually, AMR has been a topic for discussion in Iran for several years. On the other hand, antibiotic susceptibility testing is rarely asked for by clinicians. Therefore, the widespread use of antimicrobial agents in primary care clinics and animal husbandry has allowed for the rapid emergence of resistant bacteria. The increasing antimicrobial resistance rate in Iran, requires a rational drug administration effort in collaboration with infection control committees, as well as the establishment of a national surveillance system.

In Iran, methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-non-susceptible *Streptococcus pneumoniae*, vancomycin-resistant enterococci (VRE), and extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae have emerged and spread into communities and hospitals. During the last two decades, many antimicrobial agents – such as extended-spectrum cephalosporins, carbapenems, fluoroquinolones, and aminoglycosides – have been introduced and empirically used as first-line drugs to treat these resistant bacteria. This has further accelerated the development and dissemination of drug-resistant bacteria. In 2014, the World Health Organization (WHO) reported extensive antibiotic resistance in *S. aureus*, *S. pneumoniae*, *E. coli*, *K. pneumoniae*, *Salmonella*, *Shigella species*, *Neisseria gonorrhoeae* and others *(1)*. It was reported that *E. coli* resistance to fluoroquinolones and *K. pneumoniae* resistance to carbapenems were most frequent with 54% among all microorganisms tested in Iran (Table 1). A systematic review and meta-analysis about epidemiology of multidrug-resistant (MDR) *A. baumannii* strains in Iran showed that the pooled prevalence of MDR- *A. baumannii* was 72% annually *(2)*. In addition, relative frequency of MDR-*A. baumannii* in several studies varied from 22.8 to 100%. Therefore, since the prevalence of MDR- *A. baumannii* is higher than several different countries, measures should be taken to keep the emergence and transmission of these strains to a minimum.

Iran, like many other parts of the world, has experienced a significant increase in the number of ESBLs in the hospitals and communities. In the community setting, ESBL-producing Gram-negative bacteria (GNB) mostly have a lower prevalence than in the hospital. However, it should be considered that the prevalence of ESBL genes varies in several geographical areas. The present rates in some parts of the country are very high, particularly in the central part of Iran, like Tehran Province. Therefore, the highest rate of ESBL-producing *A. baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* has been reported in the hospitals of Tehran in the recent years. Other parts of the country even have high prevalence of ESBL-producing GNB in both hospitals and communities. It is clear that ESBL-producing organisms are widely distributed globally; however, this rate is lower in different parts of the world than Iran. Most frequent types

Table 1: **Major antibiotic resistance in Iran between 2013–2014 (WHO, 2014)**

Microorganisms	Resistance (%)	No. tested isolates	Type of surveillance, population or samples	Period for national data collection	Year of publication or report
Escherichia coli: Resistance to third-generation cephalosporins	41	885	Invasive isolates	2012	2013
Escherichia coli: Resistance to fluoroquinolones	54	885	Invasive isolates	2012	2013
Klebsiella pneumoniae: Resistance to third-generation cephalosporins	48	110	Invasive isolates	2012	2013
Klebsiella pneumoniae: Resistance to carbapenems	54	35	Invasive isolates	2013	2013
Staphylococcus aureus: Resistance to methicillin (MRSA)	53	2,690	Invasive isolates	2012	2013
Streptococcus pneumoniae: Resistance, or non-susceptibility, to penicillin	33.9	115	Invasive	2007	2013
Nontyphoidal Salmonella (NTS): Resistance to fluoroquinolones	6.3	125	Invasive isolates	-	2013
Shigella species: Resistance to fluoroquinolones	2.7	260	Targeted	2012	2013
Neisseria gonorrhoeae: Decreased susceptibility to third-generation cephalosporins	-	-	-	-	2013

of ESBL enzymes in Iran include TEM, CTX-M, SHV, and OXA; however, there are other ESBL enzymes with different frequencies among GNB such as PER, GES and VEB. In most reports, TEM, CTX-M, and SHV are the predominant and OXA-type ESBLs have been found mainly in *P. aeruginosa* and *A. baumannii* isolates in this region. Therefore, the presence of ESBLs genes is a risk factor for the future use of antimicrobial treatment in Iran. ESBLs distribution and the facilitation of their spread in different regions may be caused by factors such as "mobility" of ESBL genes, strong selective pressure of antibiotic use, purchase antibiotics without prescriptions, lack of observing hand hygiene, use of antibiotics in animals, travel, and different weather conditions. Also, the areas with less prevalence of ESBL-producing GNBs and ESBL genes must be considered in order to take specific measures and increase supervision in the hospitals and the community in case any changes or increase occur in terms of prevalence *(3)*.

Increasing resistance to carbapenems by carbapenemase-producing organisms, significantly *Acinetobacter spp.* and *Pseudomonas spp.*, is another concern in this country *(4)*. Carbapenem resistance has been increasingly common issue among *A. baumannii* isolates in Iranian hospitals in recent years with the majority of isolates showing multidrug resistance. Considerably high prevalence (99%) of the isolates were MBL-producing which can be a main cause of high carbapenem resistance among *A. baumanni* isolates. Recent studies have shown the existence of multiple MBLs producing clones of *A. baumannii* in Iran.

The use of colistin and polymyxin B as a therapeutic agent has been prompted by increasing resistance to antimicrobials including the carbapenems, which it had been used with increasing frequency to treat patients infected with MDR-GNB such as *A. baumannii* in the last several years. Iranian data showed that the rate of colistin-resistant *A. baumannii* was 11.6%. So, as the frequency of resistance to colistin is low, it can be used as an easily available drug for treatment of MDR *A. baumannii* strains, which are susceptible to colistin *(5)*.

In April 2015, WHO reported 3–5.9% of all new tuberculosis (TB) cases being MDR *(6)*. Even more serious, the percentage of previously treated TB cases that developed MDR-TB in Iran was 30–49.9%. A meta-analyses regarding the prevalence of drug-resistant tuberculosis in Iran revealed that 23% of new cases and 65.6% of previously treated cases were resistant to at least one drug *(7)*. The highest rate of resistance in new and previously treated cases was seen against streptomycin (19%) and isoniazid (47%), respectively *(7)*.

According to the data, clindamycin and rifampin are good choices for empiric treatment of patients who acquire *S. aureus* or MRSA infections until the results of culture and antibiotic susceptibility pattern become available. However, because of high prevalence of TB infection in this country and rifampin being one of the most important drugs in anti-TB therapy, care

should be exercised in using this drug for non-tuberculous infections, and to prevent occurrence of rifampin-resistant *M. tuberculosis*, physicians should list rifampin as the last choice in treatment of hospital-associated MRSA infections. As a study found linezolid resistance among MRSA and methicillin-susceptible *S. aureus* strains, it was suggested that an antibiotic sensitivity test for all isolates was carried out before using this new and expensive antibiotic *(8)*.

In Iran, several studies targeted various populations, including healthy populations and patients of different ages, and showed lower antimicrobial resistance rates of *Streptococcus pneumoniae* in comparison with other Middle East countries. Since 2007, among healthy Iranian children, penicillin, erythromycin, cotrimoxazole and tetracycline resistance fluctuated between different surveys *(9-11)*. However, Iran was the only Middle Eastern country that reported tolerance or resistance to vancomycin among healthy and sick populations *(10, 11)*. Within clinical isolates from sterile body sites, a variable percentage of resistance to penicillin, erythromycin, FQ and cotrimoxazole was also reported *(12-14)*.

New Iranian data on other microorganisms showed multi-resistant strains in *Campylobacter jejuni*, *Arcobacter* species, *Helicobacter pylori*, *Bordetella pertussis*, *Enterococcus spp.*, *Acinetobacter spp.*, *Candida spp.*, and others. Also, for viral infections including human influenza virus, Hepatitis B virus and HIV, the numbers of isolates resistant towards key antiviral agents are also on the rise. Most notable is the increase in so-called MDR nosocomial pathogens, including VRE. Further research is ongoing to reduce the risk for increasing resistance in human pathogens caused by antibiotic use in animal husbandry. The two main tasks are to restrict use of antibiotics for trivial upper respiratory tract infections and to avoid inappropriate use of antibiotics for surgical prophylaxis.

Iran veterinary organization (IVO) has seriously investigated AMR over the past years. AMR data has been gathered by IVO from various public and private laboratories across the country. The following findings were obtained:

- AMR in *E. coli* from poultry to "old" antimicrobial drugs such as Oxytetracycline and Flumequine was high, up to 80%.
- AMR to "old" antimicrobials was high (up to 70%) in regions with low density of breeding (vs "finishing") farms.
- There is direct relation between use of antibiotics and appearance of resistance.
- For "new" antimicrobial drugs, such as Florfenicol and Fosfomycin Calcium, susceptibility is high and resistance low compared to "old" antimicrobial drugs.
- AMR in *E. coli* was most common against Enrofloxacin (up to 60%), Oxytetracycline (up to 80%) and Flumequine (up to 70%).
- In young chicken, AMR was mainly found against "old" antimicrobial drugs while with increasing age, AMR was also found against "new" antimicrobials like Doxy-tetracycline- Danofloxacin -Florfenicol.
- Highest resistance levels were observed in animals in which antibiotics were used in the feed for disease prevention.

Policies

In order to control hospital-acquired infections and AMR, effective programmes are needed; however, without information about the prevalence of nosocomial infections the burden of estimation and effective programming for such infections is almost impossible. There were limited studies about nosocomial infections in Iran, which supposed 8%–10% prevalence rate, however, additional information is needed to determine the countrywide presence of nosocomial infections. According to regulations proposed by the Ministry of Health and Medical Education, each hospital must have an active hospital infection control committee. In this regard the Nosocomial Infection Surveillance System (NISS) was initiated in March 2007, which based itself on a guideline prepared by the Iranian Center for Disease Control (ICDC).

Every year since its inception, the Food and Drug Administration's National Committee on Rational Use of Medicine in Iran has used public education activities and projects to improve the rational use of antibiotics. As access to effective antibiotics is necessary for all aspects of modern healthcare, an informational campaign was developed targeted at the general public. In 1999, the National Committee on Rational Use of Medicine started a campaign focusing mainly on women and children with only 20% of the educational programmes targeted specifically at men. This was decided as women and children were seen to be more accessible and also in Iran, women are responsible for the family. By educating the women, they could continue spreading the messages within the family. The work in Iran is still ongoing and furthermore, an evaluation for women to measure knowledge after this type of intervention is currently under development. Continued educational programmes for the public are needed to change behaviour, increase knowledge, and enable the public to make good decisions regarding the use of antibiotics.

Summary

In summary, it is very obvious that the prevalence of such isolates is currently high and on the rise in Iran, particularly for the antibiotics of choice. AMR highlights the critical need for a comprehensive Iranian national antimicrobial drug resistance survey to monitor MDR isolates from all parts of country. Considering the increasing antimicrobial resistance

rate in Iran, a committee for rational drug administration is needed to collaborate with infection control committees. The establishment of a surveillance system is also required for registering and reporting antimicrobial resistance of laboratory isolates in hospitals for the purpose of effective and well-timed antimicrobial therapy. Such a surveillance system should continuously report the prevalence of microorganisms and their resistance pattern to hospital wards and the committee for infection control; such information will be used in making decisions at management levels. ■

Acknowledgment

In Iran, the Ministry of Health and Education has been developing national surveillance according to WHONET guideline and all universities were instructed to improve public knowledge and apply antibiotic stewardship in hospitals. We thank all university hospitals for their collaborations and improvements.

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IN ORDER TO PROTECT ANTIBIOTICS, WHICH ARE A REAL TREASURE, WE SHOULD LIST THEM AS UNESCO WORLD HERITAGE!

DR JEAN CARLET, FOUNDER AND PRESIDENT, WAAAR, ARCHITECT OF THE NATIONAL PLAN TO PRESERVE ANTIBIOTICS, FRANCE AND **GARANCE UPHAM,** VICE-PRESIDENT, WAAAR

Antibiotics are in great danger *(1)*. Antibiotic resistance has increased dramatically in the last few years, and very few new compounds have been marketed in the recent years or will be made available in the next few years. Therefore, antibiotic resistance represents one of the most important public health issues of our time *(2,3)*. Resistance to antibiotics is due to many factors, in particular the overuse of antibiotics in both humans and animals, and the cross-transmission of resistant microorganisms in both the community, the hospitals and livestock. The presence of antibiotics and resistant microorganisms in the environment is also a key mechanism.

Antibiotics are very special drugs because their target is a living one, able to adapt and become resistant to the drug. This is unique! In addition, the effect of antibiotics is not only visible in the treated patient, but also in other patients, since antibiotics act not only on the microorganism(s) responsible for the treated infection, but also on the commensal flora, in particular the digestive microbiota. The gut is the silent epicentre of antibiotic resistance, because the antibiotics modify profoundly the gut microbiome, and allow resistant microorganisms to grow and to colonize this organ for prolonged periods of time *(4)*. Those resistant strains can then be transferred to other patients in the hospitals, or to relatives in the community. Antibiotics, and resistant microorganisms present in the effluents can contaminate the environment *(5,6)*. Microorganisms carried by animals can contaminate humans via either the environment or the food chain.

Antibiotics are overused nearly everywhere. There are huge differences in their usage between countries. For example, Scandinavian countries use one third of the amount used by countries like France and Greece. There is a clear relationship between the consumption of antibiotics and the resistance level. It is more than unlikely that Scandinavian patients are less well treated than patients in France or Greece! It is known that between one third and half of the antibiotic therapies are either unnecessary or inappropriate, both in the inpatient and in the outpatient settings. Patients are very often treated with antibiotics for viral diseases, in particular for upper tract respiratory infections, or for simple colonization, in particular for asymptomatic bacteriuria. Even when the treatment is indicated, patients are often treated for too long a period of time.

It is really time to act vigorously in order to save antibiotics through an active protection of available compounds, including the old ones and the acceleration of the innovation to bring new drugs to the clinicians in the near future. The action must be global and worldwide.

Antibiotics need to be actively protected like a precious resource *(7)* and must be considered in the context of sustainable development *(8)*. Antibiotic prescription is still considered everywhere like a trivial act. In many countries antibiotics are available over the counter. This must be combated, as well as the use of counterfeit or outdated antibiotics. Antibiotics are widely available and wasted in developed countries, but the access to those drugs is limited in many developing countries *(9)*. This is not acceptable! In drafting the French national plan, we purposefully placed our objective as "preserving antibiotics" *(10)*.

Those are the main reasons why we have proposed to UNESCO to list antibiotics in their World Heritage programme (UWH). WAAAR is a large international non-governmental organization, with regular contacts with WHO, FAO, OIE, United Nations, European and International agencies (CDC, ECDC…), to cite a few. The members of the association come from many different sectors, in particular, but not only, healthcare professionals, researchers, patients and

consumers. Reading the press, citizens are more and more concerned and afraid of this new worldwide danger.

We perfectly realize that antibiotics are a very different topic than the one usually selected by UWH, which are specific and located geographical sites. However, we do think that it would be very appropriate to have them on board, since they must be actively protected like precious gifts provided by mother Nature to treat severe infections and sepsis. Antibiotic resistance will br perfectly be able, if we remain inactive, to destroy totally our anti-infectious armoury, and bring us to the pre-antibiotic area. We hope that UNESCO will consider that this huge danger for the human community should fall in their range of missions. ■

Dr Jean Carlet, is the President and Founder of ACdeBMR/ WAAAR (the World Alliance Against Antibiotic Resistance). Trained in internal medicine, head of the ICU in Hospital St Joseph, Paris, for 25 years, he has published in medical journals on the issue of antibiotic resistance for over 30 years. WAAAR gained international recognition with the launch of the Paris Declaration which gathered over 700 signatories from 55 countries, or which over a 100 scientific societies. In 2015 Dr Carlet was nominated by France's Ministry of Health to head the Special Task Force for Antibiotic Preservation. He is a steering committee member of several coalitions such as CARA and lately ANTARTICA (ANTimicrobiAl Resistance CriTIcal Care).

Garance Upham, journalist and economist has a long-term involvement in global health issues. In the late 1980s and 1990s she was involved in training healthcare systems in French speaking Africa on the prevention of bloodborne and airborne pathogens transmission in health systems.

She has worked as a consultant on injection safety, tuberculosis, macroeconomics and health, as well as recently mapping civil society globally for the SDGs' health goals.

Between 2004 and 2014, she was on the Steering committee of Patients for Patient Safety, PSP, WHO. A member of WAAAR from the start, she is based in the Geneva suburbs.

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AMR: A KEY FOCUS OF THE UPCOMING 2019 GLOBAL HEALTH SECURITY CONFERENCE

ADAM KAMRADT-SCOTT, ASSOCIATE PROFESSOR, UNIVERSITY OF SYDNEY, AUSTRALIA AND
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Antimicrobial resistance (AMR) necessitates a comprehensive approach that brings together stakeholders across multiple sectors from public health and medicine, to veterinary science and the social and behavioural sciences. Developing strategies to tackle the problem of AMR will be a key theme of an upcoming conference on Global Health Security, to be held in June 2019, Sydney, Australia (GHS 2019). GHS 2019 aims to bring together 1,000 delegates from government, academia, NGOs and the private sector to consider the critical health issues confronting the world and develop new evidence-informed policies. AMR will be one of the top agenda items.

The complex, slow-burn challenge arising from antimicrobial resistance (AMR) necessitates a comprehensive, multi-sectoral approach. Regrettably, the international community has a poor track record with dealing effectively with such menacingly slow-onset issues, as challenges in collaboration on dealing with the threat of global climate change highlights. Even so, if AMR is not successfully addressed, it is estimated that the current 700,000 annual AMR-related deaths will increase to 10 million by the year 2050 *(1)*. The onus of responsibility thus falls to our generation to tackle this problem.

Lord Jim O'Neill, former chair of the United Kingdom's Independent Review on AMR, recently noted there has thankfully been considerable progress in some AMR areas *(2)*. They include the number of researchers now focusing on AMR, investment in early research and development, and the G20's commitment to eliminating the inappropriate use of antibiotics as growth promoters in food animals. Efforts undertaken by multiple international organizations ranging from the World Health Organization (WHO), Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE), even the United Nations General Assembly, have also sought to raise global awareness of AMR, and in so doing, generate new commitments to tackling the problem *(3)*.

Even so, significant challenges remain. A recent report produced by the WHO's new Global Antimicrobial Surveillance System (GLASS) has documented widespread prevalence of antibiotic resistance in some 500,000 people across 22 high and low-income countries *(4)*. Importantly, however, only 52 countries – just one quarter of WHO's 194 member states – have agreed to participate in the GLASS network to date. Further compounding the lack of surveillance has also been significant under-investment in the development of new drugs, diagnostic tools, and local government-led strategies aimed at increasing public awareness about AMR *(3)*. Without concerted, multi-sector wide action in these areas, it is estimated that AMR will result in up to US$ 3.4 trillion in lost GDP by the year 2030 *(5)*. AMR thus not only has a tremendous human cost, but also a significant economic one if left unaddressed.

Creating a new global conversation – GHS 2019

In June 2019, the first ever international scientific conference on Global Health Security will be held in Sydney, Australia. This event aims to bring together 1,000 delegates from across government, academia, the NGO and private sectors to measure progress, determine gaps, and identify new opportunities to enhance national, regional and global health security. AMR, as one of the most critical health issues confronting the international community, will be a key theme of the conference. By bringing together at least 200 representatives from low-income countries (supported by travel bursaries generously provided by our conference partners) GHS 2019 also seeks to provide a platform to enable a truly global conversation – one that will lead to new commitments from government, the academy, non-government and private sectors aimed at tackling the challenge of AMR.

To that end, GHS 2019 aims to do things differently. From the outset, we – as the conference co-convenors – have actively sought to create an alternative to the standard conference format. Ensuring equitable gender and regional representation, not only in approaching a number of global leaders to serve on the conference steering committee but also in those delegates

attending the event, will be a hallmark of the forum. Similarly, the conference seeks to ensure diverse representation from across government, academia, the NGO and private sectors in order to expose decision-makers to the latest evidence and stimulate new thinking. We also endeavour to provide a forum for emerging researchers from around the world to share their work, create a network of collaborators, and push our collective thinking about best approaches to improving global health security.

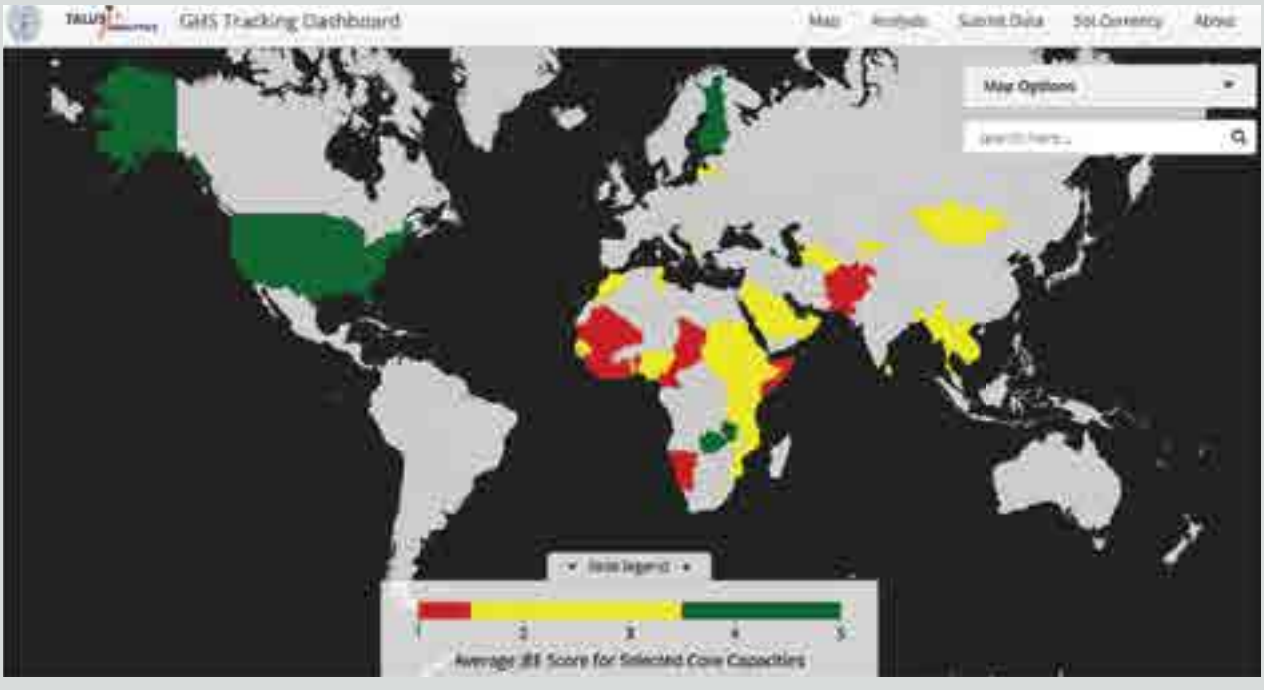
In addition to AMR, the conference will also address themes around contemporary health emergencies, planetary health, the International Health Regulations, pandemic preparedness, the animal-human health interface, deliberate biological events, dual use research of concern, and the intersections between universal health coverage and global health security. We anticipate a series of side meetings dedicated to Joint External Evaluations, innovative financing, and norms for biological sample sharing. These issues, along with AMR, challenge all populations, and we hope GHS 2019 provides a forum for solutions.

Why a conference on global health security and why now?

To date, there has already been strong interest expressed in the event. In part, this is because there appears to be a genuine desire amongst the international community to prevent a repeat of the 2014–2016 West African Ebola outbreak that resulted in over 28,600 cases and 11,315 deaths *(6)*. There is also now seemingly widespread acceptance that health issues can and do, in a highly interconnected world, cause widespread health, social, economic, and political impacts if not efficiently addressed. The Australian Government's new Indo-Pacific Centre for Health Security has, for instance, recently come on board as a Conference Partner for GHS 2019 as part of the Australian Government's commitment to enhancing health security within the Indo-Pacific region and its assumption of the role of co-chair for the Joint External Evaluation (JEE) Alliance *(7, 8)*. Other entities have similarly expressed a willingness to support GHS 2019, and it is anticipated that further announcements will be forthcoming soon.

Critically, however, it must also be acknowledged there continues to remain much confusion about global health security and what precisely it refers to. For while the WHO's new director-General, Dr Tedros Adhanom Ghebreyesus, recently reinforced his organization's commitment to global health security, arguing strongly that universal health coverage is critical to achieving security for all *(9)*, fault-lines remain amongst his member states, the policy and academic communities as to the alleged benefits of framing health issues within security language and concepts *(10)*. One of the core objectives of the GHS 2019 conference, therefore, is to develop a consensus statement that will establish a series of guiding principles for actors working in this field, thereby building on the Oslo Ministerial Declaration on global health *(11)*. To ensure global participation in the development of any set of guiding principles, submissions to inform the consensus

Figure 1: Joint External Evaluation Scores on AMR, as of February 2018. Only countries in green have sufficient capacity for AMR. Available at tracking.ghscosting.org



statement will be invited from any interested parties from September 2018 onwards via the conference website (www.ghs2019.com).

The global health challenges such as AMR that now confront us are profound. Initiatives like the US-led Global Health Security Agenda (GHSA) and the JEE Alliance have helped to generate renewed interest in the need for investing in health systems. Yet despite decades of work led by organizations like the WHO, the World Bank and others, multiple reports and thousands of recommendations on what health issues require priority funding, divisions remain on the best way forward. Recent announcements by the US Centers for Disease Control and Prevention (CDC) that it is reducing funding to its global outbreak alert and response efforts by 80% also should give the wider international community pause *(12)*, and highlights that the need for obtaining political consensus on what health issues deserve priority.

GHS 2019 will not be the panacea for the world's ills. By itself, it will not solve the problem of AMR nor the raft of pressing health issues that daily cause widespread human suffering and death. Having said this, bringing stakeholders together from across not only the diversity of society but the globe to measure the progress made to date, engage in new conversations, and identify priorities and principles to inform new investment, presents an opportunity for contributing to making a healthier and safer world. We hope you will join us in Sydney in this endeavour.

For regular updates about GHS 2019, follow the conference Twitter handle: @GHS2019conf To lodge an expression of interest to attend the event, please go to the conference website: www.ghs2019.com, ■

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IPC AND SURVEILLANCE

INVESTING IN INFECTION PREVENTION AND CONTROL TO CONTAIN ANTIBIOTIC RESISTANCE: PROGRESS IS ACHIEVABLE

DR BENJAMIN J PARK (TOP LEFT), CHIEF, INTERNATIONAL INFECTION CONTROL PROGRAM, OFFICE OF THE DIRECTOR, DIVISION OF HEALTHCARE QUALITY PROMOTION, CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC), USA; **DR DENISE CARDO** (TOP RIGHT), DIRECTOR, DIVISION OF HEALTHCARE QUALITY PROMOTION (DHQP), NATIONAL CENTER FOR EMERGING AND ZOONOTIC INFECTIOUS DISEASES, (CDC), USA AND **DR MICHAEL BELL** (BOTTOM LEFT), DEPUTY DIRECTOR, DIVISION OF HEALTHCARE QUALITY PROMOTION, NATIONAL CENTER FOR EMERGING AND ZOONOTIC INFECTIOUS DISEASES (CDC), USA



In many low- and middle-income countries, infection prevention and control (IPC) is an often overlooked, but critical, capacity for safe clinical care, including the reduction and containment of antimicrobial resistant (AR) pathogens. Around the world, there remain fundamental gaps in IPC capacity and implementation, with many efforts limited to temporary stop-gap measures, e.g., during emergencies. However, it is critical to identify and implement sustainable solutions to address those gaps in all healthcare settings. Progress can be achieved and should be prioritized. All countries have a stake in fixing this problem.

In past decades, healthcare settings have been recognized as amplifiers of transmission of emerging infections such as SARS and Ebola. Today, antibiotic resistance (AR) is a globally acknowledged threat to healthcare and public safety that is likewise amplified in healthcare. In these settings, the combination of high antimicrobial medication exposure, prevalent invasive procedures and devices, and close contact required for patient care create an environment where AR pathogen transmission can be rapidly amplified. Many healthcare-associated AR threat pathogens have been listed by national and international groups, including US CDC and WHO *(1, 2)*, and many nations and regions have chosen to aggressively target those pathogens for tracking and control *(3, 4)*. Infection prevention and control (IPC) is critical to combat these pathogens and can only be accomplished where robust investments in healthcare personnel, training, supplies and hygienic infrastructure are sustained.

IPC is crucial to delivering and maintaining effective medical care, with direct impacts on the safety of patients and healthcare personnel. It is an ongoing set of activities that take place in the background of clinical settings and is usually only noticed during a crisis (e.g., Ebola epidemic) or when an IPC lapse has occurred leading to patient or healthcare personnel harm (e.g., transmission of hepatitis virus due to incorrect injection practices). IPC activities include ensuring sufficient and sustained hygienic infrastructure (clean water for healthcare facilities, effective sewerage removal, clean and safe removal and containment of medical waste, access to electricity) that is at least sufficient for the nature of care being provided; staffing and material support to implement environmental cleaning and disinfection; adequate supplies of single-use equipment; correct reprocessing of reusable equipment; monitoring and record-keeping for healthcare-associated infection (HAI) surveillance; oversight to ensure consistent adherence to correct injection practices; appropriate use of triage, isolation precautions and personal protective equipment; and staff training to correct any unsafe practices identified in the clinical care setting.

Achieving the broad mission of IPC requires national policies that support human and hygienic infrastructure and resources that are reliably sustained and tailored to intended healthcare delivery needs. Interventions to slow the advance of AR must be safe for patients, appropriate for local conditions and consistently implemented by facilities, clinicians and governments. Short-term options include strong and consistent public and clinician information campaigns to highlight the

negative consequences of antibiotic misuse and change the underlying demand for unnecessary antibiotics. Appropriate attention to individual and environmental hygiene, and standard infection control practices, should be applied by personnel in all facilities to prevent cross-transmission and amplification of pathogens, including resistant organisms, in healthcare settings. In addition, facilities can assess the quality of their microbiology laboratory resources and personnel to identify gaps and areas of need; even limited diagnostic microbiology capacity could be applied to perform periodic prevalence surveys to produce antibiograms to guide clinical staff.

The global challenge of AR continues to grow, particularly in countries with developing economies where healthcare utilization is expanding rapidly. Antibiotics are now widely delivered and basic care, including childbirth in hospitals, is increasingly available thanks to concerted efforts of donors, NGOs, public health and governments. Advanced care, e.g., for cancer and many chronic illnesses, has become more accessible, too; yet, IPC capacities that are critical for patient safety have not grown to adequately support those growing clinical capabilities. As a result, the problem of AR in LMICs is substantial and will likely grow as healthcare expands. Reports from Asia have described the increasing prevalence of Enterobacteriaceae resistant to carbapenems *(5, 6)*. A 2014 WHO report describe AR prevalences as high as 20% in some countries *(7)*, and in Latin America, PAHO's ReLAVRA system reports a 20%–30% prevalence of carbapenem resistance among Klebsiella in some countries *(8)*. Reports of outbreaks of healthcare-associated infections caused by pathogens with emerging resistant genotypes are documented in many countries, along with global spread attributed to travel and migration *(9-11)*.

All countries are stakeholders in containment and therefore need to be part of the solution. High-income countries with robust approaches to antimicrobial stewardship and IPC can still suffer rapid loss of treatment capability for common infections when AR pathogens are imported from abroad. Recent travel is a recognized risk factor for colonization of concerning AR pathogens *(12, 13)*. Receipt of healthcare in other countries has been associated with colonization with locally acquired AR strains and has required public health measures to rapidly identify and isolate colonized patients before spread in the facility occurs *(14)*. The growing practice of medical tourism has also been described as leading to the spread of AR pathogens *(15)*. In addition to risking harm to their own populations, high-income countries also risk economic hazards related to international epidemics (e.g., the 2014 MERS outbreak in the Republic of Korea stemming primarily from IPC gaps that allowed transmission within the healthcare facilities. As community fear led to self-isolation, economic output dropped by 2% and led to intervention by the Central Bank *(16)*); and globally, health investments by donor organizations are threatened by the rapid advance of AMR and its undermining of basic medical care delivery. Finally, despite urgent efforts to identify new antibiotics, pharmaceutical investments will be rapidly washed away if current patterns of healthcare delivery without IPC and optimal use of existing antibiotics are maintained.

Although initial investments in sustainable IPC and hygienic infrastructure for healthcare might seem high, they can and should be tailored to match the specific types of care intended to be provided at each healthcare facility. Implemented thoughtfully, those investments will have the potential for large and lasting impacts. Examples of successful implementation include Vietnam, where a national programme to strengthen IPC to target AR pathogens is now being implemented in phases, starting in selected healthcare facilities and expanding throughout the country over several years. In Kenya, the national AR action plan calls for a phased implementation of surveillance and prevention programmes for AR pathogens, starting at two sites with a plan for gradual expansion. In Sierra Leone, after the Ebola outbreak highlighted the critical role of IPC in public health outbreaks, the Ministry of Health has created a new national office to direct facility level quality improvement programmes.

The success of these programmes hinges on sustained implementation supported by national policies that include a long-term commitment to maintaining IPC wherever patient care is delivered. Policies should specify and prioritize resource allocation to ensure that human resources, training, medical and cleaning supplies, clinical laboratory capacity, water, sewerage, waste management and electricity allow each healthcare facility to operate in accordance with recognized IPC standards to protect patients and healthcare staff. National IPC focal points should be designating and/or strengthening within governments to oversee implementation of IPC capabilities and track progress. The latter requires a meaningful way to measure both AMR outcomes such as HAI incidence or prevalence, antimicrobial use, and processes related to IPC (e.g., adherence to safe injection practices, availability of necessary supplies). By using data for action, governments can determine where to focus national efforts and plan for each successive step in implementing appropriate IPC, addressing AR pathogens and improving the safety for all patients receiving care.

Many LMIC settings work with external support from donors. It is imperative that donor organizations make commitments that are not only responsive to urgent, short-term needs, but also include sustainable, locally suited development of capacity that can sustain improved practices for many years. This should

be a routine consideration for all response activities, which despite being well-intentioned, can have lasting unintended impacts long after the acute crisis has passed.

AR is a threat that encompasses the entire planet without regard to geographic or political borders. It is time for a shared vision and concerted approach that addresses long-term needs of LMIC and high-income nations and moves away from stop-gap or uncoordinated actions that reduce the net impact of precious investments. There is no quick fix for AR, but with consistent, sustained investments in public health measures, in particular IPC and hygienic infrastructure in healthcare settings, we can and must achieve progress. ■

Disclaimers: 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 (CDC). Use of trade names, commercial sources or private organizations is for identification only and does not imply endorsement by the US Department of Health and Human Service and/or CDC.

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What can be done by medtech to fight AMR?

1

Before admission to the hospital / in the community

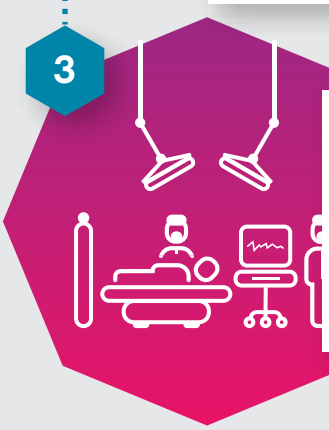
- Innovative multiplex Polymerase Chain Reaction (PCR) diagnostics
- Point of Care C-Reactive Protein (CRP) test
- Step A pharyngitis rapid test

2

Arrival at the ward

- Cleaning & disinfection procedures
- Catheters and closed IV systems
- Antimicrobial dressings

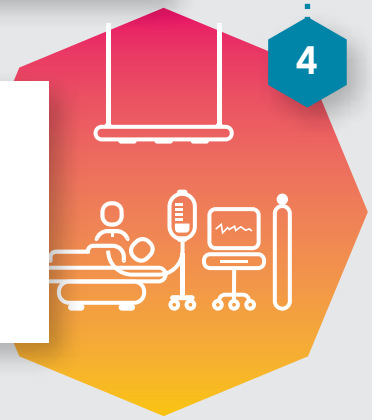
3



In the operating room

- Antibacterial sutures
- Active patient warming
- Reprocessing of reusable instruments

4



During hospital stay & recovery

- Antibiotic susceptibility testing
- Subglottic Secretion Drainage
- Clinical Surveillance Software

5

Discharged and back at home

- Wound care management
- Medication monitoring

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CONTAINING CROSS-TRANSMISSION OF MULTI-RESISTANT BACTERIA: A PRIORITY FOR CONTROLLING RESISTANCE IN HEALTHCARE CENTRES

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Assistance Publique - Hôpitaux de Paris (APHP), is the largest public healthcare institution in France (38 hospitals, 21,000 beds), and since 1993, it has implemented, step-by-step, a long-term programme for controlling the spread of multi-resistant bacteria, targeting successively methicillin-resistant *Staphylococcus aureus* (MRSA) and then emerging extensively resistant bacteria (carbapenemase-producing enterobacteria (CPE), glycopeptide-resistant enterococci (GRE)). Campaigns promoting the use of alcohol-based hand rub solution for hand hygiene as well as excreta management and antibiotics policy were added to these specific programmes. Local infection control teams in each hospital were supported by a strong commitment of APHP central and local administrations. The prevalence and incidence of MRSA decreased by 75% between 1993 and 2016. Despite an increase in CPE and GRE index cases between 2004 and 2016, mainly due (~70%) to patients with a known history of recent hospitalization or trip abroad, the proportion of these leading to secondary cases decreased from 50 to <10%, due to reinforced procedures. APHP's 20 years of experience shows that the spread by cross-transmission of MRBs such as MRSA, CPE and GRE can be strongly limited in healthcare centres, even at the scale of a large multi-hospital institution.

Increased bacterial resistance is nowadays one of the most important public health issues. Multi-resistant bacteria (MRBs) that spread in healthcare centres and are common causes of hospital-acquired infections, such as methicillin-resistant *Staphylococcus aureus* (MRSA), enterobacteria producing extended-spectrum β-lactamases (ESBL) or carbapemenases (CPE), and glycopeptide-resistant enterococci (GRE) are of particular concern, since antibiotics for treating patients infected by such bacteria are limited, raising a fear of a therapeutic dead end. Controlling the spread of MRBs is therefore a challenge for medical institutions. Overuse of antibiotics, a major factor driving bacterial resistance, usually comes to the forefront of control programmes and sometimes overshadows the other factors favouring resistance. Indeed, cross-transmission, which constitutes the central pillar of communicable diseases due to pathogenic bacteria, such as salmonella, pyogenic streptococci, meningococci, etc., also plays a major role in hospital-acquired infections caused by opportunistic commensal bacteria (staphylococci, enterobacteria, etc.), particularly in the case of MRBs. Indeed, the complexity of the multiple genomic events that led to MRSA, ESBL or CPE preclude the possibility to engineer "de novo" these MDRs in each new patient case: exchange of chromosomal genes between closely related species (e.g., the genes constituting the different types of SCCmec cassette in MRSA) or imbrication of chromosomal mutations and acquisition of composite mobile elements (plasmids, transposons, integrons, etc.), in which are inserted genes captured from saprophytic bacteria (e.g., for ESBL and CPE). The only way to ensure the success of such genetic "masterpieces" is to transmit them among humans or animals, directly or through intermediate reservoirs, such as the environment. Indeed, antibiotic pressure plays an important role in maintaining the MRBs in the contaminated hosts. For this reason, all MRBs control guidelines include bundled measures aiming at controlling cross-transmission (e.g., identification

and isolation of carriers, hand hygiene, organization of care) in addition to antibiotic policy.

Assistance Publique – Hôpitaux de Paris, the largest public healthcare institution in France, has implemented from 1993 onwards a long-term programme for MRBs surveillance and control. The objective of the present report is to present the main lines of this programme and share some results obtained during the last twenty years.

Assistance Publique – Hôpitaux de Paris (APHP)

APHP is a public health institution administering 38 teaching hospitals (22 acute care and 16 rehabilitation/long-term care (RLTC) hospitals, spread over Paris, suburbs and surrounding counties), with a total of 21,000 beds (10% of all public hospital beds in France) and serving 12 million of inhabitants. APHP admits approximately one million inpatients per year, employs 22,000 physicians, 20,000 nurses and 30,000 assistant nurses. Administrators and medical committees manage APHP hospitals locally, but decisions on large investments and general medical policy are taken by the central administration. Local infection control teams (LICT) are in charge of prevention and surveillance of healthcare-associated infections in each hospital. Strategic decisions for the whole institution are coordinated by a multidisciplinary central infection control team (CICT: infectious disease physician, bacteriologist, epidemiologist and nurse). The institutional MRBs programme that started in 1993 has progressively included different actions such as promotion of contact precautions, alcohol-based hand rub solutions for hand hygiene, reinforced measures for containing emerging extensively resistant bacteria (CPE and GRE), excreta management policy and campaigns to decrease antibiotics consumption.

The institutional APHP MRBs programme

Each step of the programme was implemented gradually in all APHP hospitals. Actions implemented by all local LICT were supported by a strong commitment of APHP central and local administration.

The first step, in 1993, was to set up bundle measures to control cross-transmission of MRSA whose incidence was at this time higher in France compared to other European countries. The measures called "contact isolation procedures" included identification of MRSA carriers with passive and active surveillance, barrier precautions, training and feedback.

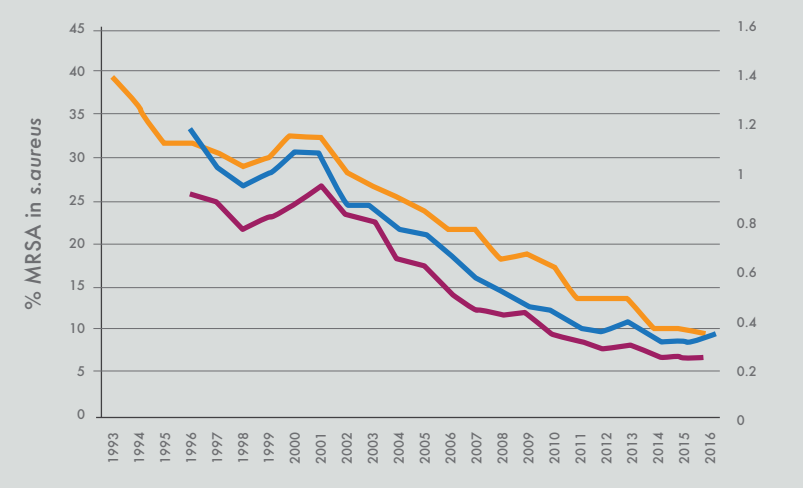
The second step was a large campaign launched in 2001–2002 to promote the use of alcohol-based hand rub solution (ABHRS). This campaign provided pedagogical material to the LICTs; in addition, formal letters from the general director asked all administrators, head of departments and chief nurses to support the campaign.

The third step, in 2006, was to set up a specific strategy for containing emerging extensively resistant bacteria (CPE and GRE), in response to an increase number of cases in APHP hospitals that occurred in 2004/05 though applying the contact isolation procedures as for MRSA. This strategy ("reinforced procedures") emphasized rapid and stringent application of organizational measures as soon as a first CPE/GRE case was identified: (a) reporting quickly every new case to the APHP central infection control team and alerting the hospital administrator, (b) stopping transfers of cases and contact patients (defined as any patient hospitalized in the same unit during the same period of time as cases) to other units of the hospital or to other hospitals, (c) screening for CPE/GRE contact patients extended to those already transferred from the involved unit to other units at the time of index case identification (screening of contact patients had to be pursued once weekly), (d) reinforce hand hygiene with ABHRs, and cleaning patient cases environments with detergent-disinfectant product, (e) if at least one secondary case is identified, cohorting patients in three distinct areas with dedicated nursing staff: "CPE/GRE patients" section, "contact patients" section and "new patients" section for newly admitted patients with no previous contact with carriers patients and (f) identifying discharged case and contact patients if readmitted. These measures were to be maintained until the outbreak was considered as controlled, i.e., after all CPE/GRE cases have been discharged and after a period of at least three months without new case. To stimulate the efforts made by the LICTs and local administrators, the central infection control team followed the number of new cases, and new outbreaks, and the difficulties in programme implementation and regularly disseminated results within hospitals and central administration. The central infection control team visited regularly the hospitals to help the local teams in applying the programme.

The fourth step, in 2008, was to recommend identification and screening for CPE/GRE of any patient repatriated from foreign hospitals or with recent hospitalization abroad.

Recently, a fifth step has been added in response to a 2012 cross-sectional survey that evaluated the equipment for excreta management and healthcare workers' practices about excreta elimination in 536 units of APHP hospitals. The survey revealed that the excreta management was mostly a neglected subject, a point that favours cross-transmission of MRBs that are carried in digestive tract (CPE, GRE). The main results were as follows: half of the patients present the day of the survey were wearing diapers or using a bedpan; >1/3 of the toilets were equipped with hand sprayers, a device favouring the spread of faecal material in the environment; half of the bedpans washer-disinfectors were located in room where ABHRs were not available; bedpans were usually rinsed before

Figure 1: Evolution 1993–2016 of the MRSA rates in the hospitals of Assistance Publique - Hôpitaux de Paris: % MRSA in *S. aureus* (orange triangle), MRSA rate per 1,000 days of hospitalisation (blue diamond) and MRSA rate per 100 admissions (purple Square)



(Figure 1) *(1)*. The decrease in incidence was more marked in ICU (2.9 to 0.5 / 1,000 HDs) and in surgery (1.5 to 0.4) than in medicine (0.7 to 0.2) and in rehabilitation and long-term care facilities (0.5 to 0.15). Interestingly, we note that the decrease was sharper after the launching of ABHRs campaign in 2001 (see Figure 1).

Increase in alcohol-based hand rub solutions use

ABHRs are the major tools for enforcing hand hygiene in a hospital setting. Following the campaign's launch in 2001, the consumption of ABHRs progressively increased from 2 ml per hospital days in 1997 up to 44 ml in 2017 in APHP hospitals (Figure 2).

disinfection, mostly in the patient's bathroom; and only a small number of the healthcare workers said they followed an educational programme about excreta elimination. Following this survey, recommendations for the management of excreta have been set up: appropriate outfit, use of disposable excreta collection bag for patient needing a bedpan, removing hand sprayers, regular maintenance of bedpans washer-disinfectors. An educational programme for healthcare workers was also launched. The implementation of some of these recommendations was included as an incentive in evaluation process within APHP institution (quality indicator).

From the antibiotic policy side, a long-lasting campaign was launched in 2006 to decrease, or at least to stabilize, antibiotics consumption and, consequently, the selection pressure on MRBs. This campaign disseminated several messages during a period of 12 years, for example, treat only infection and not colonization, treat only bacterial infections, prevent infections, prevent cross-transmission, re-evaluate antibiotics prescription after 48 hours, and antibiotic treatment to last no longer than seven days.

Impact of the programmes on MRBs rates and hygiene indicators

Decrease in MRSA prevalence and incidence

Between 1993 and 2016, the percentage of MRSA in *S. aureus* decreased in acute care from 39.4% to 9.6% and the incidence rate of MRSA cases decreased from 1.16 to 0.33 per 1,000 hospitalization days (HDs)

Control of glycopeptide-resistant enterococci (GRE) oubreaks

The mean number of GRE cases increased by 0.8 cases per month in 2004 and 2005 despite the measures previously used for efficiently controlling cross-transmission of endemic MRSA, but began to decrease when the reinforced procedures (mentioned above) have been implemented, resulting in a decrease by 0.7 cases per month (Figure 3) *(2)*. Moreover, the number of cases per outbreak was significantly lower after implementation of the programme.

Control of carbapemenase-producing enterobacteria (CPE) outbreaks

From 2004 to 2017, the number of index cases of CPE sharply increased from less than 10/year 2009, up to near 400 in 2017 (Figure 4). However, despite this increase, which was mainly due (~70%) to patients with a known history of abroad

Figure 2: Evolution 1997-2017 of the consumption of alcohol-based hand rub solutions (in ml per hospital days (i.e., patient day) in the hospitals of Assistance Publique - Hôpitaux de Paris (the sudden increase in consumption that occurred in 2009 was due to H1N1 epidemic)

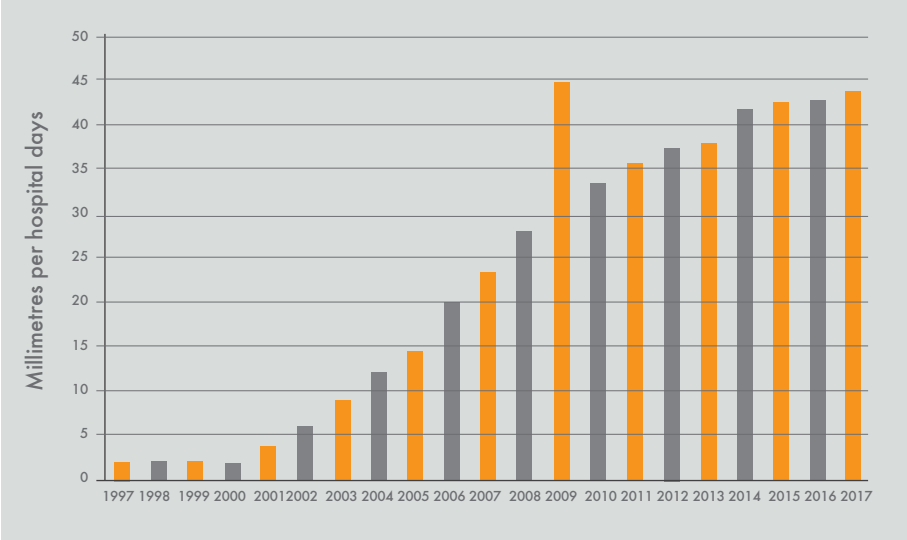


Figure 3: Evolution 2004–10 of the monthly number of glycopeptide-resistant enterococci in the hospitals of Assistance Publique - Hôpitaux de Paris. In 2004–05, classical measures used for controlling MRSA cross-transmission (contact isolation procedures) were applied. Reinforced procedures were implemented in 2006

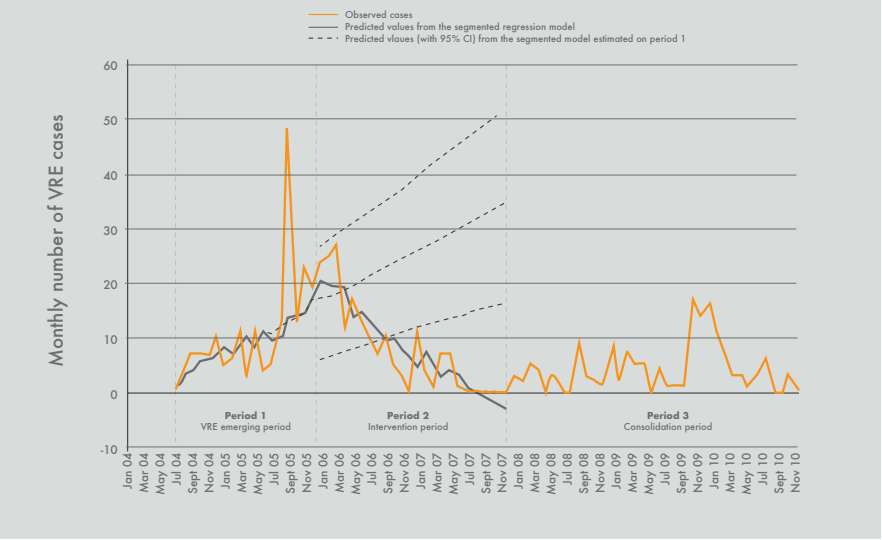


Figure 4: Evolution of the number of CPE index cases (blue columns) and of the proportion of them that led to secondary cases (i.e., outbreaks)(orange line with diamonds), in the hospitals of Assistance Publique - Hôpitaux de Paris, 2004–2017

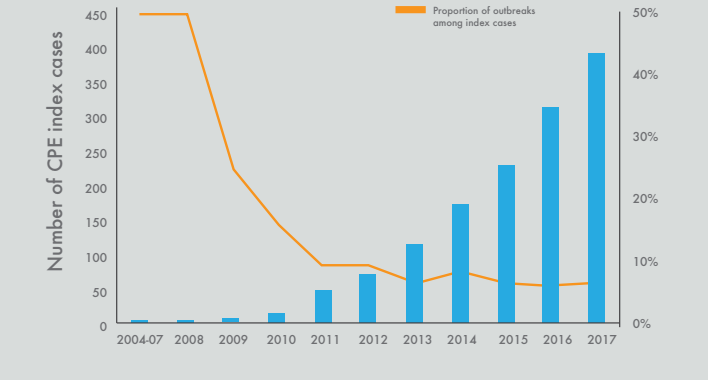
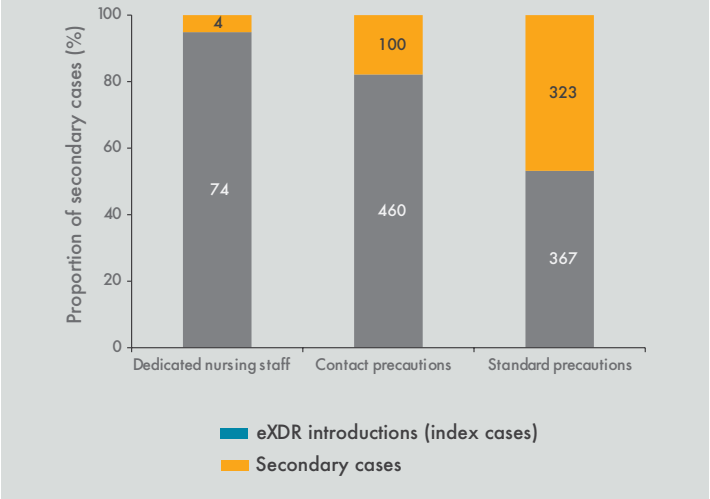


Figure 5: Proportion of secondary cases among CPE cases, according to measures implemented within the first two days around CPE index cases in the 38 hospitals of Assistance Publique - Hôpitaux de Paris, period 2010–2017



hospitalization (or stay) within the past year, the proportion of index cases that led to secondary cases (i.e., to an outbreak) decreased from 50% to 8%, as a result of the reinforced procedures introduced in 2006 (see above) *(3)*. Importantly, the types of measures implemented around index cases was clearly crucial and the proportion of secondary cases was lower when dedicated nursing staff were set up, rather than contact precautions (i.e., MRSA procedures) and even far than standard procedure (i.e., hygiene "as usual") (Figure 5) *(5)*.

Discussion

The institutional programme for controlling MBRs in the 38 hospitals of Assistance Publique - Hôpitaux de Paris progressively included measures targeting successively: (a) MRSA (isolation procedures), MRBs that were considered in 1993 as the priority due to incidence in France markedly higher than in other European countries (EARS-net), and (b) since 2006, reinforced procedures aiming at controlling the spread of emerging extensively resistant bacteria (CPE and GRE). In parallel, specific campaigns have been launched to increase the use of alcohol-based hand rub solutions and decrease antibiotic consumption.

These bundle measures, mainly comparable with those largely described in the literature, succeeded in markedly decreasing MRSA and containing CPE and GRE.

The APHP experience clearly shows that the most aggressive measures (reinforced procedures) are more efficient in controlling CPE/GRE than contact precautions (isolation procedures), which however were sufficient to decrease MRSA spread. Indeed, the rate of CPE/GRE outbreaks was lower when cohorting separately CPE/GRE cases, contact patients and new patients, with dedicated nursing staff for each cohort. Not only occurrence of outbreaks differed according to measures implemented around index cases, but also the size of outbreaks and the number of secondary cases were higher when only isolation procedures or standard precautions were used. We should note that quickly applying isolation procedures around index patients was not always sufficient to avoid secondary CPE/GRE cases, a fact justifying regular screening of contact patients in such situations in order to rapidly detect secondary cases.

In addition, the sharp increase in alcohol-based hand

rub solutions use starting in 2001, as well as excreta policy *(4)*, undoubtedly helped to improve the general level of hand hygiene at APHP. Whereas antibiotics consumption was on a continuous raise in the 1990s and beginning of 2000s (up to 570 defined daily doses per 1,000 hospitalization days in 2005), the campaigns on antibiotic policy launched in 2006 stabilized the figures and even led to a slight downward trend (data not shown), a point that at least eased the selective pressure on MRBs.

We have emphasized above that the classical measures successfully used for controlling MRSA cross-transmission (contact isolation procedures) were not effective enough to control CPE/GRE outbreaks. Only the reinforced procedures, implemented in 2006, finally allowed such control. The reasons for this apparently striking fact are actually obvious. CPE/GRE (and ESBLs as well) share several critical features concerning their dissemination potential: (a) they are hosts of the digestive tract and consequently are easily disseminated by fecal route (or urines in case of urinary infection) whereas MRSAs are hosts of nasopharynx, a more remote site, (b) their resistant traits are harboured on mobile element, increasing the risk of bacteria to bacteria dissemination whereas methicillin resistance is chromosomal,(c) the bacterial loads are far higher for CPE/GRE (108/gr of feces, i.e. ~10^{10} excreted per day by a carrier) than for MRSA (maximum ~10^{8} bacteria in nose). It is a good example of the need to adapt infection control policy to the characteristics of the targeted organism.

We should raise the point that limitations in nursing staff may be an obstacle to dedicating healthcare workers to a single index CPE/GRE case. In this situation, control measures could be adapted, e.g., by organizing "moving forward cases" beginning with MRB-free patients and ending with cases patients. In all settings, it is of foremost importance to promote the use of alcohol-based hand rub solutions, which are the most efficient and convenient tools for hand hygiene in hospital settings. Consumption of ABHRs represents an easy to obtain and self-speaking indicator of hygiene quality that is nowadays used at European level. Management of excreta (stools and urines) is another point of major importance to control the spread of faecal bacteria in hospitals. Healthcare workers should be asked to be especially vigilant about hand hygiene during excreta management and encouraged to use disposable excreta collection bags for the CPE/GRE carriers requiring the use of a bedpan.

In conclusion, the long-lasting experience (more than 20 years) in the APHP hospitals shows that the spread by cross-transmission of MRBs, such as MRSA, CPE and GRE, can be strongly limited in healthcare centres by specific control programmes, even at the scale of a large multi-hospital institution, providing that all stakeholders, infection control teams, medical and nursing staff, microbiologists and hospital administrators, are convinced, stimulated and involved *(6, 7)*. Controlling other types of MRBs that have already spread worldwide in hospitals, and also in the community, animal setting and environment, such as ESBLs, would require far more ambitious and multifaceted programmes that should include increased hygiene in the general population (sanitation in schools and other closed communities, family hygiene, etc.), strong environmental policies (e.g., processes in sewage treatment plants, clean water supply, food control), as well as organization of farming and husbandry in order to cut the intricate chains of transmission. If we fail in setting up such programmes, the antibiotics that are efficient to treat ESBL infections (carbapenems) will be overused and will favour in response the emergence of CPEs, the ultimate step of multi-resistance in Gram negative bacilli. ■

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EU-JAMRAI: EUROPE FOSTERING SYNERGIES TO REDUCE THE BURDEN OF AMR

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The European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI) brings European Union member countries together to foster synergies and contribute to the global movement against microbial resistance to antibiotics. Coordinated by the French National Institute of Health and Medical Research (Inserm), with the support of the French Ministry of Health, EU-JAMRAI started in September 2017 and its implementation will last for 36 months. Being the first European Joint Action in the field, it will capitalize on existing initiatives and propose concrete steps to lessen the burden of antimicrobial resistance (AMR) and reduce healthcare-associated infections (HCAI).

On the edge of a post-antimicrobial era

Life-saving antibiotics revolutionized our society and economy curing previously deadly diseases and making surgeries, cancer treatments, neonatal care and organ transplants increasingly viable. This major achievement is now at risk, mainly due to the excessive and often inappropriate use of antibiotics. Today, antimicrobial resistance (AMR) is a worldwide public health threat. The increase of bacteria resistant to multiple antibiotics, even to last resort drugs, in combination with the lack of new antibiotics is increasingly resulting in cases where doctors are facing major difficulties to treat infections. AMR is responsible for thousands of deaths each year *(1)*. In 2007 alone, multi-resistant bacteria infections caused 25,000 deaths and 2.5 million extra hospital days across Europe *(2)*. AMR does not recognize geographic borders and is currently present in every country of the world.

A global challenge requires a coordinated global response

AMR is a major health threat that decision-makers are well aware of and which has gained a high priority among public health challenges. The multiplication of national, European and international initiatives against AMR over the last decade reflects a shared commitment to actively tackle this issue. To this end, the World Health Organization (WHO) – in collaboration with the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE) – has elaborated a Global Action Plan (GAP) *(3)*. The GAP sets five major objectives and emphasizes the One Health approach, a holistic and multisectoral perspective which recognizes that human health, animal health and the environment are interconnected. Pathogens are transmitted from humans to animals and vice versa and must therefore be tackled in both sectors. Endorsing the WHO initiative, countries committed themselves to draft and implement national strategies aligned with the GAP by mid-2017. In June 2016, the European Union adopted ambitious Council Conclusions on the next steps under a One Health approach to combat antimicrobial resistance committing to set up a One Health network across Member States *(4)*. In June 2017, the European Union published the European One Health Action Plan on Antimicrobial Resistance *(5)*, which comprises three pillars: i) making the EU a best practice region; ii) boosting research, development and innovation, and iii) intensifying EU

efforts to shape the global agenda on AMR. The EU-JAMRAI clearly belongs to the first pillar of the European action plan.

EU-JAMRAI objectives and added value

The overarching objective of EU-JAMRAI is to support European Union Member States to develop and implement effective One Health policies to combat antimicrobial resistance and reduce healthcare-associated infections (HCAI). Through appropriate involvement of each group within the different planned actions, the Joint Action will strengthen the existing public health policies both at national and European level and contribute to achieve the objectives of the WHO Global Action Plan on AMR, the Council Conclusions on AMR and the EU Action Plan on AMR (Table 1).

Strengthening national and international health security initiatives against the AMR challenge mandates a common European approach taking into account local features and existing initiatives. The Joint Action EU-JAMRAI provides the opportunity to strengthen and coordinate efforts directed to both AMR and HCAI issues, following a One Health approach. It is important to recognize that AMR and infection control are tightly linked, so that the fight against AMR will not be efficient without tackling infection control issues. EU-JAMRAI thus addresses both AMR and HCAI and emphasizes that infection prevention and control strategies should go hand in hand with prudent use of antibiotics, appropriate tools for monitoring and surveillance and accurate diagnostic tests to decide on the most appropriate therapy.

This Joint Action will enhance cooperation between Member States, the European Commission and its agencies and other international organizations and will enable each target group to contribute to address the issue of AMR and HCAI.

Think global, act local

The efficiency of any action addressing AMR and HCAI relies on involving policy-makers of different sectors and other relevant stakeholders and on understanding the different contexts. The rationale underpinning the international action on AMR has to be "Think global, act local". This means that for each group, one has to consider its social, cultural, economic and political environment and identify the driving forces.

In this sense, the Joint Action will capitalize on national best practices and current European projects while acknowledging the specificities of various countries and target audiences:

- The different countries: although there are important differences in the epidemiology of AMR and organization of infection control activities across European countries, the principles underlying strategies to control AMR and prevent HCAI are shared *(6)*. However, these national specificities and various approaches to infection prevention and control and antibiotic stewardship must be taken into account within the Joint Action's work and conclusions.
- The target audiences: EU-JAMRAI will develop campaigns to raise awareness targeted to different audiences through various channels. These communication efforts should be tailored to the needs of the different groups taking into consideration their level of health literacy. Through cooperation with and involvement of professional organisations of the animal and human health sectors and of patient groups, the Joint Action will identify the appropriate means to reach the different categories of public, patients and healthcare professionals. The Joint Action has to identify achievable and realistic actions to confront the challenges on the ground.

Bridging the gap between declarations and actions

EU-JAMRAI aims to go beyond declarations. Therefore, it will propose concrete steps to implement best practices to tackle AMR and HCAI, so that good intentions lead to practical actions shared by the Member States. To efficiently implement concrete actions, the participation and commitment of policy-makers and competent authorities of all the European Union countries in the different project working areas is crucial to ensure that the national political contexts of AMR and HCAI status are taken into account in all the planned activities.

By involving policy-makers and competent authorities, EU-JAMRAI will also contribute to the implementation of the EU Action Plan on AMR and of the Council Conclusions and ensure convergence of Member States programmes and actions. By setting up a country-to-country peer review/assessment system, the EU-JAMRAI will evaluate the strengths and weaknesses of NAPs (national action plans) for AMR and HCAI.

In line with the EU Action Plan, this Joint Action will support the establishment of efficient and feasible national infection control programmes. It will be possible through the effective implementation of guidelines and other tools at national, regional and local level to prevent infections and thereby limit the use of antibiotics and prevent the spread of resistant bacteria in healthcare settings.

Acknowledging the differences between Member States, pilot studies will be conducted to identify gaps and barriers in the implementation of best practices in order to provide tailored recommendations and guidelines.

The Joint Action will contribute to a coordinated European response in regards to prioritizing and assisting the implementation of research and innovation related to AMR and HCAI. Identifying gaps in knowledge and contributing to ensure linkage between research on AMR, HCAI and public health policies, as well as encouraging that research is used consistently through evidence-based policy-making.

Table 1: **EU-JAMRAI Objectives**

General Objectives	Specific Objectives
1. Identify and test evidence-based measures to address AMR and HCAI in different contexts and provide recommendations to policy-makers.	1. Facilitate and optimize implementation of national strategies for HCAI prevention at national and local levels. 2. Develop efficient tools and guidelines for antimicrobial stewardship and surveillance of resistance in humans and in animals.
2. Bring together different networks of policy-makers, experts and organizations on AMR and HCAI.	3. Identify the challenges to implement AMR and HCAI national action plans. 4. Ensure discussion among policy-makers on national action plans and strategies, measures taken and actions for improvement. 5. Ensure consistency between research programmes, identify gaps in knowledge and ensure linkage between research on AMR/HCAI and public health policies.
3. Promote: ➔ One Health approach. ➔ One Health in all policies concept. ➔ Health in all policies concept.	6. Ensure that all Member States have developed and implement a One Health objective-driven national strategy.
4. Produce concrete recommendations and promote awareness and commitment by governments and stakeholders for a European contribution to international initiatives.	7. Raise awareness on AMR and HCAI. 8. Disseminate the Joint Action activities and outcomes efficiently to ensure sustainability beyond the project end.

The elaboration of dynamic and diversified awareness campaigns directed to different target audiences will promote a responsible use of antibiotics by highlighting the importance of appropriate prescribing and use, as well as informing about the risks associated with overuse and misuse. Thus, this working area intends to promote healthy habits and to change harmful behaviours regarding antibiotics. Effective communication and dissemination of the Joint Action's main activities and results will be essential to keep the actors informed and aligned with the main objectives to reach other international initiatives. As the sustainability of EU-JAMRAI initiatives beyond the project end is a critical point, a sustainability plan will be formalized to maintain the motivation and the efforts of each stakeholder.

The Joint Action aims to pave the way from declaration to action through proposing concrete deliverables:

- Tools to implement guidelines on proper use of antimicrobials and real-time surveillance of AMR;
- Efficient infection control programmes;
- Evaluation of the national action plans using a country-to-country peer review/assessment system; based on the WHO Joint External Evaluation approach;
- Ensure linkage between research on AMR/HCAI and public health policies;
- Use of social media and communication tools to better understand the underlying sociocultural drivers of antibiotic misuse and resistance; and
- Develop and involve the One Health Network (OHN) in monitoring Member States' policies.

EU-JAMRAI impact beyond EU borders

This Joint Action strives to be an example of an initiative focused on achieving concrete results and testing innovative approaches at the European level. The burden of AMR varies across the European Union and even more so in neighbouring countries outside the EU. Since AMR is a cross border health threat, measures taken within one Member State influence other States. Also, there are common issues and the recommended measures of EU-JAMRAI to a specific group of countries will also be applicable to non-EU countries.

Additionally, thanks to the involvement of international organisations, the geographical coverage and impact of the Joint Action will go beyond the borders of the European Union. Being also members of several multinational initiatives (such as G7, G20, or the GHSA), the coordinator France and other work package leaders (the Netherlands, Norway, Spain, Sweden) together with other Member States involved in the Joint Action, will ensure consistency between the outputs of EU-JAMRAI and discussions or initiatives at the international institutions level (UN, WHO, etc.).

Inclusive governance and commitment

Coordinated by the French National Institute of Health and Medical Research (Inserm), with the support of the French Ministry of Health, EU-JAMRAI brings together 44 European associate partners from 28 countries and more than 30 stakeholders to ensure that the Joint Action is strategically connected to the global challenges and developments in the AMR field. As previously mentioned, key international

organizations such as WHO, OECD, OIE and FAO are part of the stakeholder forum of this Joint Action, driving the debate with their expertise and ensuring consistency with ongoing initiatives. Additionally, representatives from healthcare professionals, patients, students and industry will play an important role as EU-JAMRAI is founded on the principle of inclusiveness and the belief that AMR cannot be tackled by only policy-makers.

This Joint Action is co-funded by the Health Programme of the European Union and by the participating countries. All the partners are already involved in the field of AMR and HCAI and have the capacity to run the activities foreseen in this Joint Action. The partners are not only ministries but also research institutes, clinical centres, public health agencies and universities. EU-JAMRAI will cover all the national specificities of AMR and HCAI as it gathers all European countries as beneficiaries or collaborating partners. Moreover, most of the participants have already successfully collaborated in former or ongoing projects on AMR, in the human and animal areas, proving the excellence of the consortium.

The challenge is still ahead but the good news is that AMR is at the heart of the global political agenda. By joining EU-JAMRAI, the participating Member States have demonstrated their commitment to tackle AMR and reduce HCAI. EU-JAMRAI is an important step to ensure that all European initiatives work in the same direction. Jointly, we will act to lessen and control AMR, reduce antibiotic misuse and make sure that we leave a safer place for future generations. ■

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ESCMID: A SCIENTIFIC SOCIETY WITH A VISION AND A MISSION ON ANTIMICROBIAL RESISTANCE

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A few weeks ago, a young man who had recently undergone a lung transplantation was admitted to my hospital because of a severe pneumonia. My hospital has a very low rate of multidrug-resistant bacteria so we were very surprised to find that all cultures performed yielded a pandrug-resistant *Burkholderia cepacia*. Our microbiologists performed some non-standardised synergistic tests that helped us treat the patient with a combination of antibiotics – which fortunately worked. After more than four weeks in the hospital, thanks to the excellent care of our ICU doctors first and the infectious diseases colleagues afterwards, we were able to discharge our patient. "My life changed after the transplantation. I could never have imagined that an infection with a multidrug-resistant bacteria could ruin all that," he told me when leaving the hospital.

Recently, I visited another hospital, invited by some colleagues to give a talk. They had been struggling with carbapenemase-producing Enterobacteriaceae for a while, finding a 45% mortality rate in patients developing bacteraemia due to these organisms; the bacteria causing the outbreak is highly resistant to carbapenems and colistin and to most other antimicrobials. I participated in a ward round where I could see several of these patients. My colleagues explained that empirical treatment of nosocomial infection in that environment is really challenging: many patients with severe infections are receiving empirically two, three and even four drugs. They have formed a multidisciplinary team comprising infectious disease and intensive care specialists, clinical microbiologists and pharmacists to try to improve the outcome of these patients. The infection control team is also fighting hard to reduce the transmission of the deadly bacteria. "We do need more resources and training to perform better infection control, but we also desperately need new antibiotics to treat our patients," was the conclusion of the head of the infectious diseases division after our discussion.

This is real life, in many hospitals in the world. There are no simple, easy solutions to the problem. Politicians, public health managers, investigators, healthcare workers, journalists and scientific influencers must include the problem of antimicrobial resistance on their agendas. Scientific societies also have an important role to play. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) is committed to the fight against antimicrobial resistance and tackling this problem is one of its top priorities. Of course, ESCMID is also actively involved in finding solutions for other challenges we are facing in infectious diseases nowadays, such as emerging pathogens, neglected infections, tuberculosis, HIV, viral hepatitis, antivaccine movements or fungal infections, just to name a few.

ESCMID's initiatives against antimicrobial resistance are huge and varied. They include organizational and operational aspects, educational activities, scientific activities, promotion and communication efforts.

From an organizational and operational perspective, the two ESCMID committees are very much related in dealing with antimicrobial resistance. The European Committee on Antimicrobial Susceptibility Testing (EUCAST), jointly organized by ESCMID, the European Centre for Disease Control and Prevention (ECDC) and the national breakpoints committees, is a world reference institution harmonising susceptibility breakpoints and methods for susceptibility testing of antimicrobial drugs. EUCAST's recommendations have a major impact on surveillance of resistance and in individual clinical decisions for the treatment of infections. Its independence, scientific reliability and public health involvement has made EUCAST a prestigious, well-respected institution around the world, which ESCMID is very proud of. The other, younger, ESCMID committee is the European Committee on Infection Control (EUCIC). EUCIC aims to strengthen infection control and preventive measures to reduce the burden of healthcare-associated infections (HAIs), including those caused by antimicrobial-resistant pathogens. This is achieved through a network offering resources and know-how, as well as the organization of training programmes and support structures. Despite its youth, national committees

have already been formed in 21 countries. Beyond these and other important activities, EUCIC has launched a certification on infection prevention and control, with the contribution of the ECDC (see below).

ESCMID has more than 30 active study groups which develop educational and scientific activities, and research projects in specific areas. Many of them conduct research related to antimicrobial resistance and are instrumental to building the One Health ESCMID force against resistance, including ESGARS (Antimicrobial Resistance Surveillance), ESGAP (Antimicrobial Stewardship), ESGBIS (Bloodstream Infections and Sepsis), ESGCIP (Critically Ill Patients), ESGIE (Infections in the Elderly), ESGEM (Epidemiological Markers), ESFWISG (Food and Water-borne Infections), ESGICH (Immunocompromised Hosts), ESGNI (Nosocomial Infections), EPASG (PK-PD of Anti-Infectives) and ESGVM (Veterinary Microbiology), among others.

Education and training have traditionally been ESCMID's strengths. Having well-trained specialists in the fight against antimicrobial resistance, from diagnostic, therapeutic and prevention perspectives, is crucial in this endeavour. Our educational programme includes some 20–25 face-to-face stand-alone postgraduate courses and workshops, some 15–20 workshops at our congress (ECCMID), a yearly summer school, and more recently, eLearning activities. Every year, a large share of these activities deal with topics related to antimicrobial resistance. Additionally, the infection prevention and control certification developed by EUCIC with the contribution of the ECDC is a new, ambitious initiative. This is a two-year programme aiming to provide a unique European perspective on infection prevention and control (IPC) by sharing the expertise and competencies within training centres from different countries and professions. This collaborative effort will result in the training of a new generation of IPC specialists capable of fighting against the spread of resistant pathogens, as well as healthcare infections.

ESCMID's observership and mentorship programmes have both educational and career-building objectives. The Observership Programme funds young professionals' short visits (up to one month) to highly-reputed sites (ESCMID collaborative centres) to learn about specific techniques, programmes or activities, and to establish networks and prepare research projects. Many of the observership visits are related to antimicrobial resistance aspects both in microbiology and infectious diseases. As an example, one observer is, at the time of writing, spending one month in my hospital visiting our antimicrobial stewardship programme. The mentorship programmes provide young investigators starting their careers in environments with lower possibilities of a high-level mentorship, access to top researchers who volunteer to help them carry out a research project for two years. Again, some mentees are developing projects related to antimicrobial resistance.

ESCMID is a scientific society and therefore science is a pillar in all our activities. ESCMID has published an evidence-based guideline with recommendations for the control of multidrug-resistant Gram-negative bacteria, and is preparing others for the clinical management of these bacteria and decolonization. ESCMID members collaborate with the ECDC and WHO in guidance documents, including the ECDC document on prevention of trans-border transmission of carbapenemase-producing Enterobacteriaceae, and the World Health Organization (WHO) priority list of pathogens for which research in new drugs are required. ESCMID is a key partner of WHO in the CAESAR project, which is developing an antimicrobial resistance surveillance system for European countries not participating in EARS-Net, and for which data were lacking; ESCMID is also partner in some European research projects related to resistance, including the TROCAR and GRACE projects, among others. ESCMID co-organizes with ASM a yearly conference in October dealing with drug development to meet the challenge of antimicrobial resistance, held alternately in locations in Europe and the United States. This conference has become a landmark for academic researchers and industry. Of course, ECCMID, the largest congress covering infectious diseases and clinical microbiology and attracting more than 12,000 attendants, devotes an important part of its programme to antimicrobial resistance, including educational workshops, symposia, poster sessions and oral presentations. Finally, ESCMID provides in its webpage links to all its activities and to other valuable initiatives on antimicrobial resistance. Our eLibrary, freely accessible to all our members, provides all presentations given at ECCMID and all our conferences and courses for their use as study and teaching material.

With the work and commitment of our members, ESCMID is developing an intense activity to better prevent, diagnose and manage infections that are difficult to treat due to antimicrobial resistance, for the benefit of the society as a whole, the policy-makers and the professionals implicated in this public health problem. ■

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POLITICAL OPPORTUNITIES AND R&D TO COMBAT MDR-TB

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In 2015, TB overtook HIV as the number one infectious disease killer with 1.6 million people dying from this curable disease in 2016. 2018 is a pivotal year for TB, representing an opportunity to build on the commitments from the first high-level ministerial summit on TB in 2017. New funding and political commitments, particularly for TB R&D, must be secured at the upcoming UN high-level meeting on TB and the AMR R&D discussions at the G20. Drug-resistant forms of TB has been highlighted as a cornerstone in the response to AMR and it is vital that the importance that drug-resistant TB will play in future morbidity and mortality for AMR is recognized.

In April 1993, WHO declared a global tuberculosis (TB) emergency, and in 2015 TB overtook HIV to become the number one infectious disease killer. In 2016, 10.4 million new cases of tuberculosis were reported with 1.6 million people dying from this curable infectious disease *(1)*. In addition, the emergence of drug-resistant forms of TB since 1993 means that over 600,000 people were diagnosed with TB that is resistant to the two most effective drugs (Rifampicin and Isoniazid) in 2016 *(1)*. With the increased political attention on antimicrobial resistance (AMR), the importance that drug-resistant TB will play in future morbidity and mortality for AMR cannot be under estimated. The 2014 AMR review commissioned by United Kingdom Prime Minister David Cameron stated that if nothing changes, TB could represent a quarter of the 10 million deaths expected from drug-resistant infections by 2050 *(2)*.

The Global Burden of Disease Study shows that deaths caused by tuberculosis in 2016 were down by nearly 21%, since 2006, and the incidence of tuberculosis was down by 1.7% *(3)*. However, this rate of decline is not nearly sufficient enough to meet the target set in SDG 3 *(4)* or the WHO END TB strategy *(5)*, which aims to end the epidemic by 2030. For these targets to be achieved the annual decline in global TB incidence rates must reach 10% per year by 2025.

The strong link between TB and achieving the SDG goals has been recognized at the highest political level with the first WHO Global Ministerial Conference on TB entitled "Ending TB in the Sustainable Development Era: A Multisectoral Response". The call for a multisectoral response is due to the fact that the impact of TB does not only affect SDG 3 but has an impact for a number of other SDGs (see Figure 1).

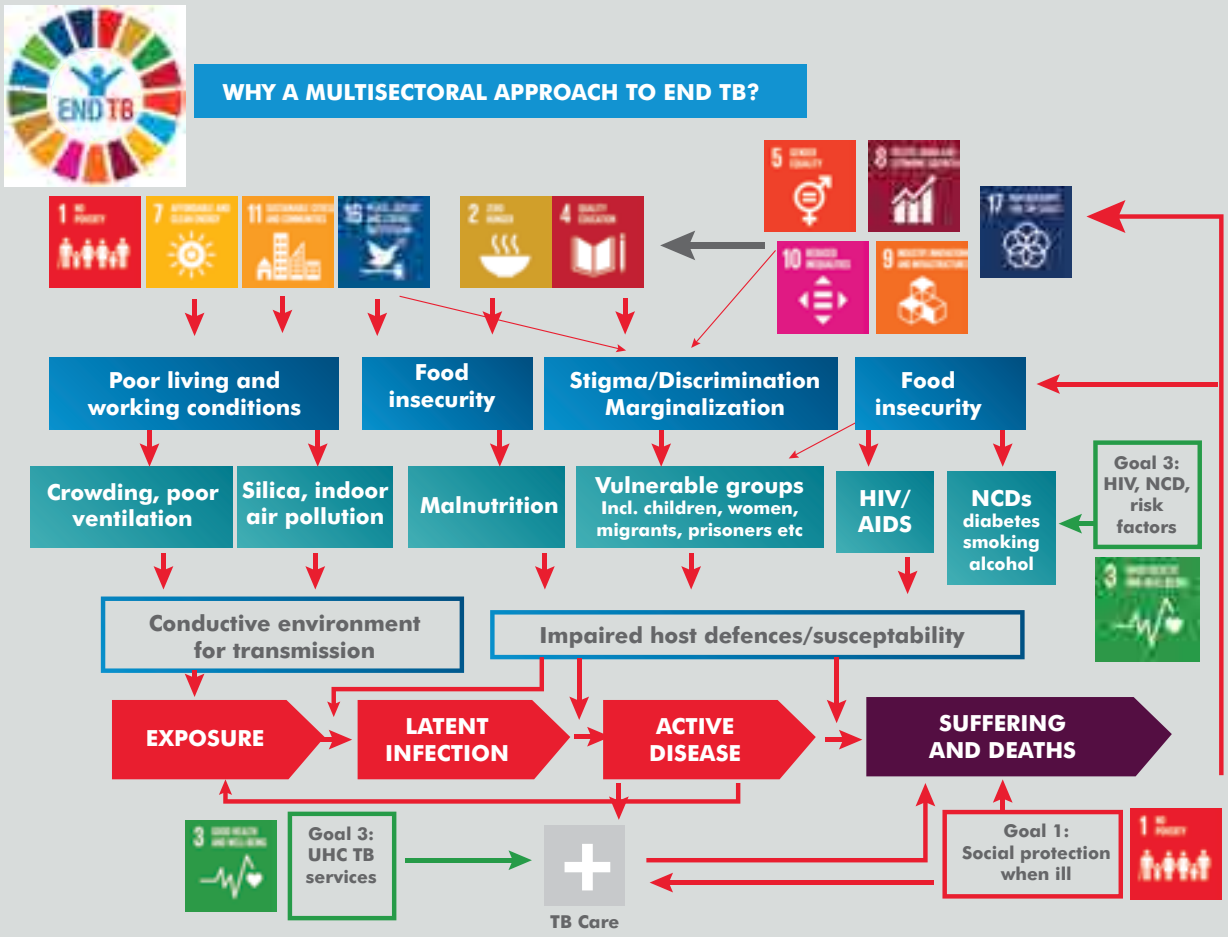
The Moscow Declaration *(6)* reaffirmed the commitment to end the TB epidemic by 2030 as envisaged in the Agenda 2030 for Sustainable Development and the SDGs, the WHO End TB Strategy, and the Stop TB Partnership Global Plan to End TB 2016–2020 *(7)*. The Declaration broke the multisectoral response for TB into four broad areas:

- Advancing the TB response within the SDG agenda;
- Ensuring sufficient and sustainable financing;
- Pursuing science, research and innovation;
- Developing a multisectoral accountability framework.

As part of advancing the TB response within the SDG agenda, the importance of MDR-TB as a priority within the AMR context was highlighted. The declaration had countries commit to implement measures aimed at minimizing the risk of the development and spread of drug resistance taking into account global efforts to combat AMR and to address MDR-TB as a global public health crisis including through a national emergency response in at least all high MDR-TB burden countries, while ensuring that robust systems are sustained in all countries to prevent emergence and spread of drug resistance. The declaration called for WHO, other UN agencies, funding agencies and technical partners to address MDR-TB as a major threat to public health security by supporting implementation of the Global Action Plan on AMR in all countries, and referenced the political declaration of the high-level meeting of the UN General Assembly on antimicrobial resistance.

The importance of MDR-TB as a priority AMR pathogen

Figure 1: **TB and the SDGs**



Source: Knut Lönnroth and Mario Raviglione, WHO Global TB Department. Source: Knut Lönnroth and Mario Raviglione, WHO Global TB Department.

was again highlighted in the declaration's commitment focused on science, research and innovation. The declaration called for WHO, in collaboration with global health and research partners and countries, to make further progress in enhancing cooperation and coordination of TB research and development, considering where possible drawing on existing research networks to integrate TB research, such as the new AMR Research and Development Collaboration Hub proposed in the 2017 G20 Leaders' Declaration *(8)*.

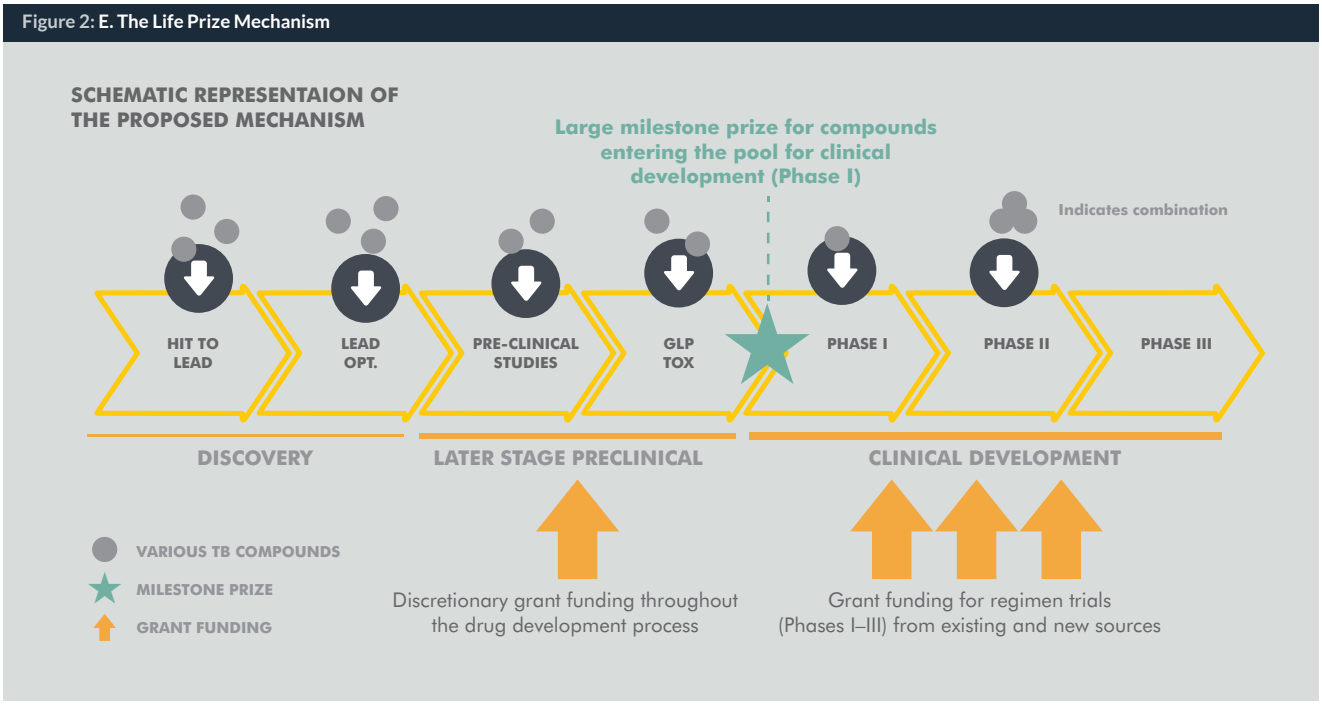
Leaders from more than 120 countries have endorsed the Moscow Declaration, which also called for countries to prepare for and follow-up on the first UN General Assembly High-Level Meeting on TB in 2018 where the link to the SDGs and AMR will be continued.

The SDG and WHO END strategy targets rely on the development of new tools for TB, and the WHO END TB strategy has a whole pillar focused on research and development. TB suffers from the market failure that has been well articulated for AMR. This lack of perceived market to recoup R&D investment has meant that TB R&D funding has never been more than a third of what is required, and in 2016 investment in R&D from the pharmaceutical industry was the lowest since 2009 *(9)*. This sustained lack of investment has resulted in a lack of innovation in all areas of R&D from diagnostic, treatment and vaccine development and without new innovations in these areas, the ambitious SDG and END TB goals will remain unmet.

There have been a number of reports looking at ways that the market failure that exists for antibiotic development (including antibiotics that are used to treat TB) can be overcome and it has been discussed at a number of high level political fora such as a United Nations General Assembly High Level meeting on AMR in 2016 and in recent G7 and G20 meetings. In all the declarations from these meetings, TB was included as a priority pathogen to be included in the resulting commitments.

The declarations included discussions around delinking the costs of research and development from the end product as a path forward. These de-linkage models promote the development of affordable medicines based on the needs of

Figure 2: **E. The Life Prize Mechanism**



patients rather than profits.

One delinkage model for R&D for TB drug and regimen development is The Life Prize *(10)* – a new and innovative funding mechanism, being developed incorporating the de-linkage principle as outlined in the UN declaration on AMR *(11)*. The Life Prize innovates, not just at the level of the traditional WHO definition of innovation (namely, new chemical classes) but also looks to change the current incentives to ensure that not only are the right incentives in place to promote innovation but that new treatments for TB developed within this framework are affordable and accessible to all who need them. The Life Prize consists of three elements: prize funding for drugs entering clinical trials that fulfil predefined criteria, additional grant funding to finance the development of a pan-TB regimen in line with target regimen profiles with all funding to require sharing of intellectual property and pre-clinical and clinical data. This enables open collaborative research and fair licensing for the competitive production of the final treatments. (Figure 2)

The recently launched "G20 Global R&D Collaboration Hub" *(12)* on AMR is intended to pinpoint important gaps in the development of tools to combat AMR, such as antibiotics, diagnostics and vaccines. The Global R&D Collaboration Hub on AMR referenced in the Moscow Declaration could be considered as one possible approach to achieving high-level coordination for new financing mechanisms like The Life Prize and although it is not clear yet how this hub will incorporate TB R&D, it is clear that TB should be a key pathogen for the hub.

Achieving decline rates required by 2020 requires increased political and financial commitments to strengthen member states' TB policies and practices and to close funding gaps, including for research and development for new TB tools appropriate for all ages. A recent report from the Global TB Caucus showed that closing the research and development funding gap could have a transformative impact on TB, and cost less than 1% of the total economic cost of the disease *(13)*.

With all the attention on AMR and TB, 2018 is a pivotal year for TB. The attendance and focus at the Moscow Ministerial Summit and the inclusion in G20 and BRICS declarations shows that TB is rising up the political agenda. It is vital that all member states and relevant stakeholders support the implementation of the Moscow Declaration to End TB and ensure that the political focus of this global killer is raised to the head of state level at the upcoming United Nations General Assembly high-level meeting on TB in 2018. It is vital that the highest level of political participation is secured for the HLM and that the required new funding and political commitments for ending TB are achieved. As the experience from 1993 shows, declaring TB a global emergency was not enough to stop the deaths from a curable infectious disease. It requires concrete actions. ■

Dr José Luis Castro is Executive Director of The International Union against Tuberculosis and Lung Disease and responsible for building today's worldwide network of country offices, experts and programmes serving more than 100 countries.

Prior to this, JL. Castro advised WHO and the Government of India on the implementation of the Revised National TB Control Programme and was Director of Operations for New York City's

Bureau of TB Control during the 1990s MDR-TB crisis. The programme he helped build is still used for tuberculosis control in the city.

JL. Castro currently serves as President of the NCD Alliance and is President & CEO of Vital Strategies, a Union affiliate.

Paul Jensen is The Union's Director of Policy and Strategy. His analysis of tuberculosis, global health and international development policy has earned news coverage from over 100 media outlets worldwide, including the New York Times, the Financial Times, the Washington Post, BBC, CNN, Al Jazeera, Reuters and others. He has conducted field research in over 20 countries across Africa, Asia, Europe and Latin America and has provided strategic consulting services for leaders of global organisations across the public, private and non-profit sectors. He lives in Washington, DC.

Grania Brigden is The Deputy Director of the Department of TB and HIV at the International Union Against TB and Lung disease (The Union). Previously she was the Life Prize Project lead at The Union. The Life Prize aims to rapidly accelerate the delivery of affordable, effective new regimens for TB through an open collaborative approach and novel approaches to financing and coordinating R&D.

Grania studied medicine at the University of Aberdeen, Scotland and continues to work in an ad hoc basis for the NHS as an honorary consultant at the Royal Free Hospital, London. She is based in Geneva, Switzerland.

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ADDRESSING AMR IN MADAGASCAR: THE EXPERIENCE OF ESTABLISHING A MEDICAL BACTERIOLOGY LABORATORY AT THE BEFELATANANA UNIVERSITY HOSPITAL IN ANTANANARIVO

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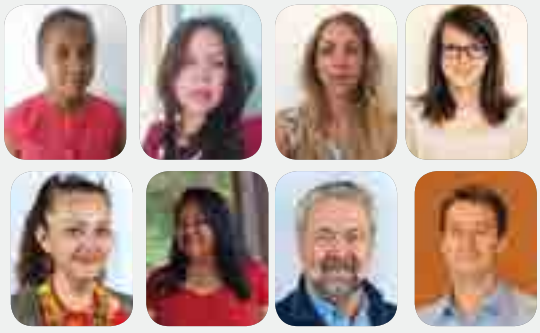

In 2016, the Mérieux Foundation launched a project with the Ministry of Public Health to create a bacteriology laboratory at Befelatanana hospital in Antananarivo (Madagascar).

The objective was to create and ensure the continued viability of operations for an essential package of analyses, to improve diagnosis and produce reliable data on antimicrobial resistance.

The laboratory results have improved patient care and enabled antibiotic stewardship and hospital acquired infection control. Preliminary data show 45% of the *E. coli* and 67% of the *K. pneumoniae* produced extended-spectrum beta-lactamase (ESBL). It provides a baseline for antimicrobial resistance (AMR) surveillance that's being expanded countrywide.

The World Health Organization (WHO) views antimicrobial resistance as one of the greatest threats to global health, responsible for 700,000 deaths per year, mostly in developing countries such as Madagascar *(1)*. WHO therefore recommends that countries develop and implement national strategies to fight against antimicrobial resistance. The Global Antimicrobial Resistance Surveillance System (GLASS), launched by WHO, is starting to be implemented in Madagascar as part of its national strategy.

The Mérieux Foundation has been working in Madagascar since 2007 to strengthen the capacity of its network of clinical biology laboratories, in partnership with the Ministry of Public Health's laboratories department. In particular, the Foundation has renovated and equipped laboratories, trained personnel, and set up a management system using direct cost recovery.

The national laboratory network currently comprises nineteen laboratories in six University Hospitals, eleven Regional Reference Hospitals, and two District Hospitals.

In 2016, we focused on bacteriology by launching a pilot project to establish an essential package of bacteriological analyses at Joseph Raseta Befelatanana University Hospital (HJRB) in Antananarivo. Beyond the technical aspects, we also addressed administrative and financial management to enable the laboratory to become autonomous and thus ensure its sustainability.

The objectives of this pilot project were: i) establish a medical bacteriology laboratory at Befelatanana University Hospital in Antananarivo to improve the diagnosis of bacterial infections

and produce more reliable data on antimicrobial resistance; and ii) ensure its long-term viability.

Material and methods

The medical bacteriology laboratory was established in the following stages:

- **Stage one:** project definition, and collaboration between hospital management and the Ministry of Public Health and their partners: the Mérieux Foundation and the Agence Française de Développement.
- **Stage two:** as soon as the terms of cooperation were defined, the laboratory was renovated to accommodate a fully functional bacteriology laboratory. This required bringing installations up to standard (electricity, laboratory benches, wastewater disposal) and installing equipment (microscopes, autoclaves, incubator, biosafety cabinet, centrifuges) and the supplies needed for bacteriological analyses. The Mérieux Foundation wrote the technical requirements, oversaw the renovation and construction project, and ordered the material and equipment. All this was made possible thanks to the financial support of the partners (the Mérieux Foundation and the Agence Française de Développement).
- **Stage three:** the training of personnel began with a Malagasy doctor who trained for a year at Lariboisière Hospital in Paris (France) to specialize in medical microbiology. Upon his return to Madagascar, he took the civil service exam and was named Clinical Biologist at the HJRB laboratory. In turn, he was able to train the HJRB laboratory personnel, with the help of a young French medical biologist for six months, under the leadership of the Mérieux Foundation. This training made it possible to set up an essential package of bacteriological analyses (direct microscopy, culture - including blood culture, identification using API strips, biochemical tests according to the REMIC 2015 medical microbiology guidelines, antimicrobial susceptibility testing according to CA-SFM / EUCAST guidelines, strain conservation). As a result, three trained technicians were able to begin their work. In parallel, a quality management system started to be put in place with the drafting of standard operating procedures.
- **Stage four:** launch of routine bacteriological analyses, including the production of diagnostic test results, after a phase of technical validation, quality control, and change management. The change management consisted of promoting the medical bacteriology laboratory among clinicians and raising awareness about prescribing bacteriological analyses and compliance with pre-analytic steps.
- **Stage five:** lastly, we trained clinicians on interpreting results and on antibiotic stewardship and raised awareness of hospital hygiene and how to prevent the transmission of multi-resistant bacteria through workshops and clinical case studies.

In addition to the laboratory renovation, we also addressed administrative and financial management. A cost recovery system was created specifically for this new activity. Negotiations took place between the hospital, the Ministry of Public Health, and the partners to provide the medical bacteriology laboratory with budgetary autonomy. As a result of these negotiations, it was agreed that 20% of the laboratory revenues would go to the hospital to contribute to various costs, and 80% would be re-injected into the laboratory to pay for new reagents and supplies and ensure preventive and curative equipment maintenance. The remaining costs (energy, personnel, etc.) would be covered by the hospital. We also set up a joint management committee comprised of representatives from the administration, hospital doctors, and laboratory staff. Its role is to ensure the laboratory runs smoothly.

Results

From December 2015 to March 2018, 4,773 samples were processed by the laboratory. (Figure 1).

Initial data on resistance was established using the diagnostic samples. It shows that for Enterobacteria, 45% of the *Escherichia coli* and 67% of the *Klebsiella pneumoniae* produced extended-spectrum beta-lactamase (ESBL), and 57.6% and 38.8% were resistant to fluoroquinolones. Furthermore, 45% of the *Staphylococcus aureus* strains were resistant to methicillin (MRSA), and 65% of *Acinetobacter baumannii* were resistant to imipenem (IRAB) (Figure 2).

Figure 1: **Total number of bacteriological samples received by the Befelatanana University Hospital laboratory**

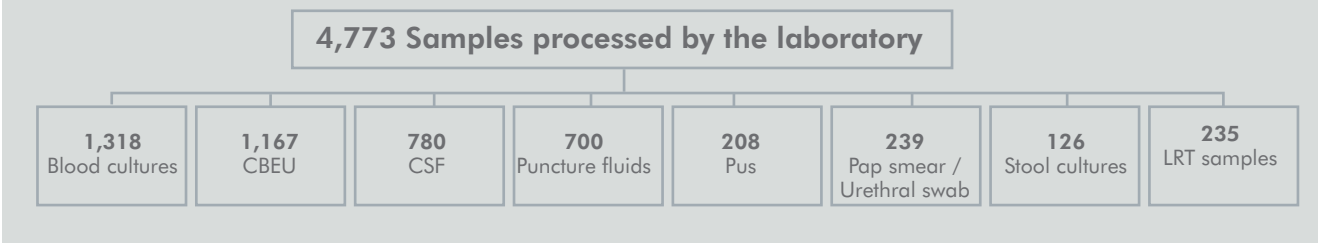

Figure 2: **Comparison of the percentage of bacterial resistance in 2016-2017 at Befelatanana University Hospital and in France, according to InVS in 2016. The key figures are from the 2016 EARS-Net report *(2)***

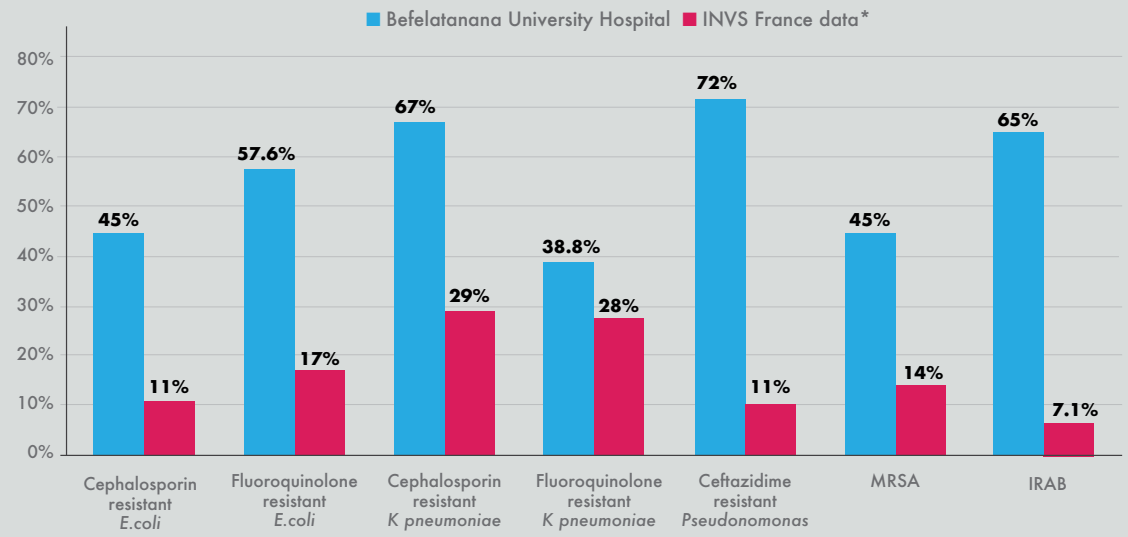

Figure 3: **Financial report for the laboratory's activities in 2016-2017**

	TOTAL	80 % (for the laboratory)	20 % (for the hospital)
Revenues (in euros)	40,590,66	32,472,52	8,118,13
Total expenses (in euros)	29,790,47	24,804,26	4,986,21
Available funds (in euros)	10,800,18	7,668,26	3,131,91

(Oanda exchange rate: 1 euro = 3,960 ariary)

The laboratory generated a total of 40,590.66 euros in revenues for 2016 and 2017. There was a positive balance of revenues (price of the analyses) / expenses (cost of reagents and supplies) for these two years (Figure 3).

The revenues are used to buy new reagents and supplies, and for the preventive and curative equipment maintenance. Since this management system was adopted, the laboratory's activity has thus been continuous, with no shortage of reagents and consumables, all while remaining affordable for patients. Ensuring that the laboratory has budgetary autonomy is key to its long-term viability, since the laboratory is then able to manage its stock and supplies.

Discussion

First, it is important to understand the project's key success factors: i) support from the health authorities, who were involved from the beginning; ii) financial support from the partners for the renovation of the laboratory and the initial contribution of equipment, reagents, and supplies; iii) the competence and motivation of the medical bacteriology laboratory personnel, thanks to the high-level training of the biologist responsible for the laboratory, the organization of the technicians' work, the daily technical support for six months, and coaching and support from the Mérieux Foundation; iv) the value to the hospital, which receives 20% of the laboratory's revenues, has noticed an improvement in patient care, and has access to one of the rare functioning bacteriology laboratories in Madagascar; v) communication and collaboration established between the biologists and clinicians, resulting in increased awareness and understanding of the results obtained, the laboratory's role in patient care, making accurate prescriptions for analyses, the rational use of antibiotics, and basic rules for hospital hygiene; vi) the satisfying performance of the management committee in its monitoring and control of the laboratory's activities and finances, as well as its approval of major decisions, particularly purchases. The laboratory's successful performance is due to all of these factors, so none should be neglected.

The activity and quality of the results produced by the laboratory have led to noticeable improvements in patient care due to the identification of infections and the prescription of appropriate treatment based on the laboratory test results. Looking forward, it would be worth measuring the hospital laboratory's impact on morbidity, mortality, and the duration of hospital stays. For now, such a study has yet to be conducted.

Beyond improving patient care, the laboratory also makes it possible to document hospital-acquired infections and raise awareness about hospital hygiene. As a result, a number of practices have improved, particularly those impacting hand borne transmission in areas at high risk, such as intensive care. Lastly, this work has generated data on antimicrobial resistance

Figure 4: **Laboratories setting up bacteriology testing**

that is useful as an indicator of the country's situation and as a temporal indicator of the impact of all public health measures taken in the country.

The results of this pilot advocate for an extension of bacteriology testing to other laboratories in Madagascar. Six laboratories, in Antananarivo and in the provinces, have expressed interest in replicating this experience by establishing a medical bacteriology laboratory with budgetary autonomy. This interest, expressed both by clinicians, biologists, and their management, is extremely encouraging and motivating, for it shows that there is a real local need. The expansion of this activity will help strengthen the network of clinical biology laboratories.

The project is being conducted in collaboration with and under the authority of the Ministry of Public Health's laboratories department. Future prospects for the laboratory network's development include technical advances, with the establishment of a Laboratory Information Management System (LIMS), such as LabBook *(3)*, to improve monitoring of the laboratory's work, quality, and operations. Implementing an automated and digital data reporting system such as DHIS 2 *(4)* will also further improve and increase the reliability of information sent to the Ministry of Health. The implementation of an External Quality Assessment (EQA) for participating laboratories will also be needed to compare data and increase reliability over time.

Lastly, building this network of medical bacteriology laboratories could lead to the creation of a resistance observatory in Madagascar, through a functional sentinel network. This would be useful to the Ministry of Public Health as well as to projects related to GLASS. The data generated would make it possible to provide recommendations for treatment protocols based on national Malagasy data, inform public health decisions, and initiate studies on research questions this data might raise. A surveillance project including human, animal, and environmental aspects is expected to be launched soon (Tricycle - WHO) *(5)*.

Conclusion

The creation of a medical bacteriology laboratory at Joseph Raseta Befelatanana University Hospital now makes it possible to provide both clinical and laboratory diagnosis. This represents a major progress for hospitalized patients.

Having a functioning bacteriology laboratory in the hospital makes it possible to offer rapid results, reduce hospital stays, optimize antibiotic treatment, and document the hospital's level of hygiene, raising awareness of its importance among medical personnel.

Thanks to this pilot project, we show that the cost recovery system, combined with good revenue management, allows a medical testing lab to cover the preventive maintenance of its equipment and purchase the reagents and supplies it needs to conduct high-quality analyses. This budgetary autonomy means that it can schedule orders, and consequently anticipate stock-outs. Ultimately, treatment of hospitalized patients is improved, which has a direct effect on the hospital's image and reputation. The hospital also receives part of the laboratory's revenues. It therefore has a two-fold reason for supporting the laboratory, creating a virtuous circle between the laboratory-patient-hospital.

Beyond the direct benefit for patients, a bacteriology laboratory makes it possible to assess antimicrobial resistance in Antananarivo, monitor the evolution of resistance over time, and measure the potential impact of various public health recommendations and decisions.

The encouraging results of this pilot project lead us to believe that the Befelatanana University Hospital bacteriology laboratory in Antananarivo will play a central role in antimicrobial resistance surveillance in Madagascar. It is also clear that this experience is worth replicating elsewhere. ■

Dr Saïda Rasoanandrasana, MD, has been the head of microbiology at the Befelatanana University Hospital laboratory since 2016. Her role involves setting up a cost recovery system for laboratory management, improving the diagnosis of bacterial infections and producing reliable data on antimicrobial resistance. She has coordinated the RESAMAD laboratory network in Madagascar, which aims to strengthen the capacity of bacteriology laboratories. During her residency, she completed internships

in several national hospitals as well as at Assistance Publique - Hôpitaux de Paris (APHP). An MD and Head of Research (Clinic Director) in microbiology, her research focuses on the resistance of germs to antimicrobials.

A clinical pathologist at the Tsaralalàna Mother-Child University Hospital laboratory since 2012, Dr Lalaina Rahajamanana , MD, is currently head of the bacteriology laboratory and is the focal point for monitoring rotavirus and other enteropathogenic diarrhea. She has worked with the Charles Mérieux Center for Infectious Disease in Madagascar since 2013 and is one of the technical advisors within the Madagascar laboratory network (RESAMAD) with the Mérieux Foundation.

Dr Camille Boussioux, PharmD, is a Paris hospital resident in medical biology, specializing in the field of microbiology. She currently works for the Mérieux Foundation in Madagascar as part of the RESAMAD Madagascar laboratory network project. She has a Doctorate in Pharmacy and studied at the Faculté de Pharmacie in Marseille. Her thesis work focused on the analytical and workflow assessment of the establishment of an automated nested multiplex PCR system for multi-pathogen detection in CSF.

Dr Marion Dudez , PharmD, is a medical biologist at the hospital center in Bourg-en-Bresse. After her pharmacy studies, she completed her residency in medical biology at Hospices Civils in Lyon. In 2015, she spent a semester as a resident for the Mérieux Foundation in Madagascar during which she was responsible for developing a bacteriology laboratory in one of the university hospitals in Antananarivo. Her tasks included training the team and setting up analysis and a management system to ensure the laboratory's financial autonomy.

She has a Doctorate in Pharmacy and her thesis work focused on this project.

Dr Odile Ouwe Missi Oukem-Boyer, PhD, has been working in health research institutions in West and Central Africa, for the past 20 years. Her main research interests are tropical infectious diseases, clinical trials, bioinformatics and health research ethics. Since 2016, she is working for the Mérieux Foundation where she holds a position of country manager for Mali and Niger. Since 2018, she is simultaneously the acting Director General of the Charles Mérieux Center for Infectious Disease in Mali.

Luciana Rakotoarisoa is the Mérieux Foundation's Madagascar country manager. She graduated as an industrial engineer from Athénée Saint Joseph Antsirabe University and has a master's degree in local development and project management from the University of Antananarivo. She joined the Mérieux Foundation in 2011 after working in the banking sector.

She is responsible for coordinating the foundation's projects in the Malagasy region and managing the local team and expatriate volunteers. She works with technical experts to draft projects and fundraise. As part of her role, she works with the Charles Mérieux Center for Infectious Disease, a center for training and research.

Dr Laurent Raskine, MD, has been the head of specialized biology at the Mérieux Foundation since January 2017. His role is to oversee the microbiology aspect of laboratory capacity building projects by contributing to coordinating and overseeing laboratory network activities, particularly in terms of antimicrobial resistance.

He worked for many years as a hospital practitioner in the Bacteriology Virology Hygiene department at Lariboisière Hospital in Paris, focusing on clinical microbiology.

He works as a specialist at the National Reference Center for Mycobacteria and the Resistance of Mycobacteria to Antituberculosis Drugs and works internationally.

Dr François-Xavier Babin, PharmD, is Diagnostics and Health Systems Director at the Mérieux Foundation since March 2018. A member of the foundation's Management Committee, he is in charge of increasing vulnerable populations' access to diagnostics, by establishing infrastructure, reinforcing skills and processes, improving the management and efficiency of clinical biology laboratories, and assisting health authorities in their governance.

Previously he held roles at the Mérieux Foundation as Director of International Development and Asia Regional Manager based in Cambodia. He started his international work at Institut Pasteur in Cambodia. He did his PharmD residency in biomedical and industrial pharmacy at Hospices Civils in Lyon.

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THE EVIDENCE BASE IN ANTIMICROBIAL RESISTANCE TO INFORM DECISION-MAKING – THE NEED FOR EPIDEMIOLOGY AND SURVEILLANCE

DR GHADA ZOUBIANE (TOP LEFT), SCIENCE LEAD, DRUG-RESISTANT INFECTIONS PRIORITY PROGRAMME, WELLCOME, UK; **PROFESSOR SHARON PEACOCK** (TOP RIGHT), CLINICAL MICROBIOLOGIST, LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE, UK AND **DR TIMOTHY JINKS** (BOTTOM), HEAD, DRUG-RESISTANT INFECTIONS PRIORITY PROGRAMME, WELLCOME, UK

Building global intelligence on superbugs and increasing capacity to gather surveillance data on the rise and rapid spread of these deadly pathogens, is vital if we are to succeed in addressing antimicrobial resistance (AMR).

Resistance to the drugs we have today is rapidly undermining modern medicine. This has been a long-running warning from doctors and scientists, but is now being clearly heard worldwide.

However, to protect progress made against infectious disease and ensure doctors can safely carry out routine and complex medical procedures – such as childbirth, organ transplant and diabetes care – new treatments alone will not be enough.

Understanding the emergence and transmission of drug-resistant infections and having data to clearly determine the effective and appropriate use of these precious medicines, in human and animal health, are critical gaps in the current global response.

In May 2016, the final report of the independent AMR Review – led by Lord Jim O'Neill and funded by Wellcome and the UK government – showed that without effective action the global death toll from drug-resistant infections, already at 700,000 a year, could rise to 10 million within a generation *(1)* . Current data shows AMR is present in every country, but a lack of co-ordinated, comprehensive surveillance needed for effective action.

The World Health Organisation (WHO) has outlined 12 antibiotic-resistant bacteria, the ESKAPE pathogens as research priorities *(2)* - ranking them in three tiers: critical, high and medium. Many strains of these bacteria in many countries worldwide are increasingly untreatable not only with combinations of commonly used antibiotics but also last-resort drugs.

The case of a 70-year-old woman from Nevada dying in September 2016 from systemic inflammatory response syndrome (SIRS) caused by one of the critical ESKAPE pathogens, *Klebsiella pneumoniae*, is now well reported. The woman had been repeatedly hospitalized in India for a hip injury before returning to the United States. Isolates from the patient showed that the strain was resistant to 26 antibiotics. The case was alarming, but not isolated. *K. pneumoniae* is a major cause of hospital-acquired infections such as pneumonia, bloodstream infections, and infections in newborns and intensive-care unit patients. Resistance in the pathogen to the last-resort treatment of carbapenem antibiotics has spread to all regions of the world.

Resistance in *Escherichia coli*, another critical-listed ESKAPE pathogen, to one of the most widely used medicines for the treatment of urinary tract infections, fluoroquinolone antibiotics, is also widespread, with WHO reporting that in many parts of the world this treatment is now ineffective in more than half of patients. And failure of the last-resort medicine for high-priority listed *Neisseria gonorrhoeae*, third generation cephalosporin antibiotics, has been confirmed in at least 10 countries (Australia, Austria, Canada, France, Japan, Norway, Slovenia, South Africa, Sweden and the United Kingdom). These are just a handful of examples of the rise and spread of resistance.

Global recognition and action

Global recognition of the scale and urgency of the problem has, in the past few years, increased. A series of important high-level

political commitments have been made, including the 2015 World Health Assembly endorsement of a global action plan, by leaders at the G20 summit and the United Nations General Assembly declaration in September 2016. And with recognition, action is also increasing. Many countries are progressing action plans, to raise awareness, improve infection control and reduce inappropriate antibiotic use – in human and animal health.

Much-needed investment into the early discovery and development of new treatments and diagnostic tools has also started to increase. The latest WHO analysis shows 51 antibiotics in clinical development – and around a third target the 12 priority pathogens *(3)*. Wellcome is among those providing support, including over US$ 150 million for the development partnerships CARB-X *(4)* and GARDP *(5)*. CARB-X, a partnership with the United States government, is now supporting more than 30 product developers in seven countries, all targeting the most serious drug-resistant bacteria.

For lasting, effective change, however, transformation is vital in the way countries track, share and analyse information about the rise and spread of these potentially deadly infections. Only with better information can policy-makers achieve change at national and international levels.

Surveillance and policy

Which pathogens are developing resistance to which drugs and where? Where are patients getting infections from – are they acquiring them from other patients, from healthcare settings, water or food, or the general environment? Which borders are the drug-resistant infections crossing and how quickly? What interventions are effective?

Detailed and up-to-date information, collated and shared in the most effective, co-ordinated way, is needed to determine effective intervention, from direct patient care to national and international policy development. Monitoring the effectiveness of policies is essential.

Such information is fundamental to ensuring patients get the best treatment against the ever-evolving resistance of pathogens. It is vital for national action plans, which ensure appropriate use of antibiotics existing and new, and improve infection prevention and control.

Antibiotics, old and new, must be treated as a precious resource. To minimise the spread of resistance they must not be over or misused. To know which drugs, in which doses, are needed to treat patients effectively, doctors and prescribers need accurate information on how bugs and drugs interact. Without this, they have to rely on best-guess, empirical prescribing. Surveillance and stewardship go hand-in-hand.

Knowledge of how bacteria spread is also critical to improving infection prevention and reducing the overall need for antibiotics, in human and animal health. With better information, policy-makers at the national and international level will have the evidence needed to initiate change. For example, evidence of the spread of *E. coli* resistance from pigs to humans resulted in the recent ban in China of use the powerful antibiotic of last resort, colistin, as a growth promoter in farming.

Global burden in context

The first step to confronting the problem is determining its extent – both the impact in individual countries and in the context of the burden of all mortality. While the severity of AMR is clear, there is currently a poor level of detail on its geographical distribution and prevalence. Without this information, our ability to tackle it is limited.

Work is now underway to map the burden of AMR on human health through a new collaboration between the University of Washington's Institute for Health Metrics and Evaluation (IHME) and the University of Oxford's Big Data Institute (BDI). The IHME-BDI *Global Burden of Disease* AMR study, launched in October 2017, supported by the UK Department of Health Fleming Fund, Wellcome and the Bill & Melinda Gates Foundation. It aims to:

- gather and assemble global data on selected bacteria-antibacterial drug combinations;
- generate globally comparable AMR burden estimates for those "bug-drug" combinations from 1990 to the present for the 195 countries and territories included in The Global Burden of Disease study;
- produce maps of AMR burden that will allow policy-makers and researchers to tailor future studies and interventions to the local level;
- provide free, public access to study results through interactive data visualizations.

Accurate data on the burden and distribution of AMR will provide a baseline and enable researchers, policy-makers, and health officials to study past approaches and replicate successful techniques; better allocate resources – including treatments – to areas of need and improve targeted prescribing; and improve drug development planning.

Global surveillance capacity

Global surveillance efforts are increasing but there are major gaps and differing levels of capacity between countries. The first report from the WHO's Global Antimicrobial Surveillance System (GLASS), showed that 52 countries have enrolled in it so far – with 40 providing information about national surveillance systems and 22 data on levels of antibiotic resistance (6).

Key challenges are highlighted in the recent inventory report of supranational surveillance networks since involving low- and middle-income countries (LMICs), which is where the impact of drug-resistant infections is greatest *(7)*. The study, led by Dr

Elizabeth Ashley, a clinical researcher at the Myanmar-Oxford Clinical Research Unit at the University of Oxford, found that since 2000, 72 supranational networks for AMR surveillance in bacteria, fungi, HIV, TB and malaria have been created that have involved LMICs. Of these, only around half are ongoing. Lack of laboratory resources, training and un-standardized surveillance activities are some of the key barriers.

Industry-generated surveillance

The pharmaceutical industry routinely collects surveillance data that could be hugely valuable to collective global efforts to curb AMR. These industry programmes monitor susceptibility of clinical isolates to marketed treatments and record pre-launch surveillance of new products as part of regulatory approval requirements. External sharing of this data would help inform and define new drug discovery and development strategies, reveal unmet medical needs and allow the modelling of future resistance trends.

In January 2017, more than 100 pharmaceutical companies committed to sharing surveillance data and making it accessible to public health bodies and healthcare professionals, through the "Davos Declaration", now hosted by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) *(8)*.

Public health officials need data on local antibiotic susceptibility to understand and respond to resistance trends. A project supported by Wellcome and led by the Open Data Institute (ODI) is currently underway to understand what data industry holds, develop an open-access platform to host individual studies, and set-up a wider engagement framework with pharmaceutical companies and other interested organizations.

Surveillance and Epidemiology of Drug-resistant Infections Consortium (SEDRIC)

In recognition of the critical importance of surveillance and epidemiology and the need to build and co-ordinate global capacity Wellcome has also brought together a new international expert group, called the Surveillance and Epidemiology of Drug-resistant Infections Consortium (SEDRIC) *(9)*.

The SEDRIC board, which met for the first time in January 2018, brings together expertise in infectious disease from across the human and animal health and the environment fields. SEDRIC will build on work by GLASS and others, including the United Kingdom's Fleming Fund, to improve global coordination on tackling AMR, identify critical gaps and barriers, and help countries adopt sustainable best practices and strategies.

It will provide technical expertise and knowledge, but will also look at how technology might be better employed to strengthen existing surveillance networks and activities.

Genomic technology and bacterial sequencing, for example, offer huge potential to help understand the mechanism of resistance and how it spreads. How can this knowledge be better used?

Conclusion

Only through better information can we speed up action and improve public health interventions to get ahead – and stay ahead – of superbugs, and save countless lives. ■

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Wellcome exists to improve health for everyone by helping great ideas to thrive. It is a global charitable foundation, both politically and financially independent that supports scientists and researchers, take on big problems, fuel imaginations and spark debate.

Dr Ghada Zoubiane is the science lead of Wellcome's Drug-resistant Infections priority programme. In her role, she is shaping and delivering Wellcome's AMR strategy, bridging the gap between science and policy and providing the evidence base to inform decision-making.

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ONE HEALTH

ESTABLISHING THE IMPORTANCE OF HUMAN AND ANIMAL VACCINES IN PREVENTING ANTIMICROBIAL RESISTANCE (AMR)

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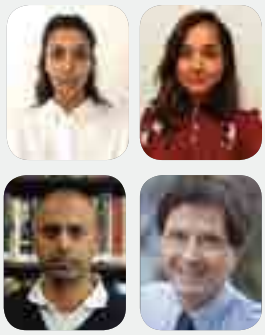

There is an urgent need to consider and develop long-term, sustainable solutions that take into account the complex drivers of AMR cross-cutting the human, animal and environmental sectors. Vaccines represent one of these solutions, but remain largely under-explored in terms of the potential health and economic benefits.

In 2017, the Centre on Global Health Security at Chatham House convened a meeting to review current knowledge and action on the role of vaccines in combating AMR, and to consider the issues involved in modelling how their value for this purpose could be established. A second meeting is planned in 2018 to explore the potential role and impact of veterinary vaccines, specifically, in reducing the global burden of AMR.

Antimicrobial resistance (AMR) – whereby a pathogen adapts in ways that render a drug used against it ineffective – is a natural process that has existed for as long as antimicrobials have been in use. A pathogen's ability to develop resistance evolved as a mechanism to survive environmental assaults, and is triggered in response to antimicrobial use and action *(1)*. The accelerated rate at which AMR has emerged and spread can be attributed to the inappropriate use of antimicrobial agents across the human, animal and environmental sectors *(2)*. The complexity of this global health issue, bridging disciplines, sectors and populations worldwide, has necessitated multi-pronged approaches and recommendations for combating AMR that have been increasingly at the fore of international policy discussions and global health agendas over the past decade *(3,4)*.

Although vaccines have been recognized as part of the solution – in the 2015 World Health Organization (WHO) Global Action Plan on AMR and the European Commission's 2017 One Health Action Plan against AMR for example – the extent to which vaccines can prevent AMR and have an impact on its global burden has been largely under-explored *(5,6)*.

There has been a strong focus, at the policy level, on optimizing the conditions for continued antibiotic use by enhancing awareness and surveillance measures, improving hygiene and sanitation practices, encouraging development of novel diagnostic tools and antibiotics, and shifting antimicrobial prescription and consumption behaviour in both the human and animal health sectors *(7,8)*. Maintaining this focus is of great importance, but should not frame the problem and the solution around antimicrobials such that the potential of alternative options for further research and development (R&D) are neglected. In 2016, around US$ 500 million in new funding was allocated to AMR from 13 existing or new initiatives whose primary purpose is to accelerate the development of new antibiotics *(9)*. New drugs face the same evolutionary process that led to resistance in current drugs, and the majority of those in the pipeline currently are simply modifications of existing drug classes and thus, "insufficient to mitigate the threat of AMR" *(10,11)*. There is a need to be innovative, not only in establishing best practice in antimicrobial use in human and animal health sectors, but in considering the breadth of practical, cost-effective R&D solutions that can reduce the reliance on antibiotics in both sectors. Vaccines are one of those potentially cost-effective solutions.

Vaccines in AMR control

The potential of vaccines in tackling AMR in humans is threefold: firstly, existing vaccines can prevent infections that would otherwise require antimicrobial medicines; secondly, existing vaccines can reduce the prevalence of primary viral infections often inappropriately treated with antibiotics and which can also give rise to secondary infections that require treatment with antimicrobials; and thirdly, the development and use of new or improved vaccines can prevent diseases that are becoming increasingly difficult to treat, or are in fact untreatable, owing to AMR *(7,12)*. Similarly in animals, antibacterial vaccines prevent infections that would otherwise require antimicrobial treatment; for antiviral vaccines, the positive effect on antimicrobial use is mediated through prevention of viral diseases and the associated risk of secondary bacterial infections. There are a number of mechanisms by which vaccines can reduce the burden of AMR in humans and animals, but all are based on the premise that an infection prevented by vaccination is "a case for which, by definition, the burden of AMR disease is reduced, the need for antibiotic therapy is eliminated, and the risk of poor outcomes is avoided" *(7)*.

The human vaccine landscape

The 2016 O'Neill Report made three recommendations pertaining to the development and use of vaccines: (i) to use existing products more widely in both human and animal populations, (ii) to renew impetus for early research and (iii) to sustain a viable market for needed products.

There are human vaccines currently in use against a number of microbial diseases commonly acquired in the general population, including diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae*, which are referred to as community-acquired infections (CAIs) *(7,8)*. Conjugate vaccines targeting these diseases, particularly Hib and *S. pneumoniae*, have dramatically reduced the global prevalence of invasive bacterial diseases most associated with mortality and in doing so, have removed the need for their antimicrobial treatment *(13)*. If the pneumococcal vaccine is universally rolled out, it has been estimated that approximately 11.4 million days of antimicrobial use in children under five years of age would be eliminated in 75 low- and middle-income countries (LMICs), in addition to the prevention of unnecessary childhood mortality *(6,14)*. Universal coverage of these vaccines, however, remains a challenge and varies from low-income to high-income countries. At present, the pneumococcal vaccine is included in 128 national immunization programmes, however global coverage for the three doses reached just 42% in 2016 with significant disparities across the economic spectrum; in low-income countries (LICs), coverage is 68% while in middle-income countries (MICs), it is 24%.

Global coverage of the diphtheria-tetanus-pertussis (DTP) vaccine, defined as children who have received a full three doses of DTP, was 86% in 2016. However, a number of low-income countries, such as the Congo, Guatemala and Iraq, have fallen short of their vaccination targets for several reasons, ranging from under-investment and conflict and civil unrest, to disease outbreaks and generally weakened health systems (World Health Organization, 2016). The DTP and Hib vaccines are typically used in combination, which helps to achieve similar levels of coverage in countries with routine national immunization programmes, although global coverage of the Hib vaccine still lags at 64%.

In the case of higher-income countries such as Romania, Italy and France, there has been a recent drop in immunization rates of vaccine-preventable diseases due to "anti-vaccination" lobbying, which has caused a surge in measles and tetanus cases and led to mandatory vaccination laws for upwards of ten diseases *(15)*.

The 2016 Review identifies three other categories of vaccines with the potential to prevent AMR: vaccines to prevent hospital-acquired infections, which frequently result in fatalities and for which there is a current lack of licensed vaccines, vaccines to prevent viral infections and associated secondary infections, and vaccines to prevent infections in animals. There is a recognized need to develop an evidence-based vaccine priority list for humans that weighs the value of vaccines against the burden and cost of AMR in different geographic and socioeconomic contexts (Heymann & Omaar, 2016) *(14)*. There are several challenges to this task. Firstly, how to define and accurately measure such an impact from a health and economic perspective, taking into consideration the direct and indirect mechanisms by which vaccination can have an effect on AMR *(9)*. A number of key principles were adopted to facilitate prioritization of vaccine R&D for animals based on identifying the most prevalent and important bacterial and non-bacterial infections associated with antibiotic use, patterns of antibiotic use in response to syndromic indication or diagnosed disease, the availability of vaccines (and their effectiveness), and the potential for new or improved vaccines to reduce the need for antimicrobial treatment. These principles, and the process of arriving at a priority vaccine list, provide a model and opportunity for the human health sector to adopt.

An additional challenge to developing new vaccines is the heterogeneity of pathogen interactions with the human body, as well as in response to actual and potential vaccines and antimicrobials. The introduction of the conjugate pneumococcal vaccine, PCV7, in 2000 in the United States

brought the incidence of invasive pneumococcal disease in vaccinated children and elderly populations down significantly, however, it simultaneously contributed to the emergence of new serotypes that PCV7 did not protected against *(14)*. These interactions need to be understood and appropriately targeted, for example by considering all pneumococcal serotypes in novel vaccine R&D, in order to make a sustainable impact on AMR *(14)*. Using vaccines more routinely would benefit from reliable, fast and inexpensive point-of-care diagnostic tools that permit rapid identification of population groups at risk *(9)*. Additionally, there are a number of stakeholders involved across multiple sectors of the health system who need to be engaged and committed to vaccine R&D. These complexities necessitate greater evidence-based research to inform policy makers and engage key stakeholders in a discussion on the value of vaccines for AMR.

The animal vaccine landscape

AMR is a cross-sectoral threat with severe implications for the health and welfare of animal populations, as well as the safety and security of global food systems. In the United States, for example, "70% of antimicrobials that are medically important are used in agriculture" *(8,16)*. There is sufficient evidence linking the consumption of antibiotics in animals to AMR in humans to recommend the immediate "curtailing the quantities of antimicrobials used in agriculture" *(8)*.

It is well understood that veterinary vaccines play an important role in protecting animal health, public health, animal welfare and food production *(17)*. The World Organization for Animal Health (OIE) is strongly aligned with the strategic goals and objectives of the WHO's Global Action Plan on AMR, and has argued that veterinary vaccines represent the single most cost-effective medical countermeasure that can be used to confront the threat of AMR *(18)*. The OIE ad hoc Group on Prioritization of Diseases for which Vaccines Could Reduce Antimicrobial Use in Animals has prioritized diseases in chickens, swine and fish where a new or improved vaccine could have the maximum effect on reducing antibiotic use (Table 1) *(18)*.

Commercial veterinary vaccines exist for the majority of pathogens listed in Table 1, albeit with major challenges to their widespread adoption and use; the most common identified by the OIE ad hoc Group across animal populations is the limited pathogen strain coverage and degree of cross-protection. Additionally, there are vaccine-specific and animal-specific issues, for example the limited efficacy of the Swine Influenza Virus (SIV) vaccine in piglets and the practical challenges of vaccinating some of the major fish species in mass due to the complications of bringing fish out of the water, which requires handling and in some instances, anesthesia, skilled staff, dedicated equipment and application costs. The vaccination strategies in the Norwegian salmon and Japanese yellowtail industries are examples of the effective reduction of antibiotic use due to increased uptake of vaccines in fish production (World Health Organization, 2015). In cattle, the highest antimicrobial use is in treating mastitis and viral diseases in veal production, although new (or re-emerging) pathogens such as *Mycoplasma bovis* demand further vaccine research *(17)*. A second convening of the OIE *ad hoc* Group is planned in late 2018 to discuss high priority vaccines for large livestock. The Group noted a number of data gaps when prioritizing areas for further vaccine research, for example the lack of a current list of all market-authorized available vaccines, the quantities of antibiotics used for different infections and the relative incidence of different infections worldwide. Thus, the Group relied mainly on available expert opinion and not on an evidence base supported by epidemiological modelling of the cost-benefit and cost-effectiveness of vaccine strategies.

The joint European Medicines Agency (EMA) and European Food Safety Authority (EFSA) review of measures taken in the EU to reduce the need for and use of antibiotics outlined more general challenges with existing, commercially available veterinary vaccines. Major limitations of the live and modified live vaccines relate to the risk of potential reversion to virulence, which can be overcome using DNA technology to add more than one attenuating modification, for example the most recent modified live virus vaccine for BVD virus II that has two separate modifications. Autogenous vaccines, primarily used in swine, poultry and fish, are derived from the specific pathogens that infect an individual herd or flock and are used when no registered vaccines for the pathogen (or serotype) exists, or existing ones are deemed ineffective. Despite their widespread use in the European Union, Member States differ considerably on the regulatory terms of production and use of autogenous vaccines; conflicts arise between good manufacturing practice requirements, which specify only one batch of vaccines can be produced at any one time in a facility, and the individual production of herd-specific vaccines. If regulations cannot be harmonized across the EU, there is an increased risk of uncontrolled (and illegal) feeding of faeces and/or intestines from infected to healthy animals in the same herd, so-called "back feeding", a practice that is widely and controversially used in the United States to control enteric infections in swine *(17)*. On the other hand, DIVA vaccines – vaccines that differentiate infected from vaccinated animals (DIVA) – provide an example of innovative vaccine development that meet regulatory standards without impairing the sanitary status of the infected herd and have been key to eradication strategies, for example Aujeszky's disease in Germany, the Netherlands, Italy, Spain, Portugal and Ireland *(17)*.

Table 1: **A list of primary pathogens for which new or improved vaccines would significantly reduce the need for antibiotic use, as identified by the OIE *ad hoc* Group**

Animal	Key syndrome	Pathogen
Chicken	Systemic (broilers)	*Escherichia coli* (yolk sac infection, airsacculitis, cellulitis)
	Systemic (breeders, layers)	*Escherichia coli* (airsacculitis, cellulitis, salpingitis and peritonitis)
	Enteric (broilers, breeders, layers)	Coccidiosis *Clostridium perfringens*
Swine	Systemic (respiratory) Respiratory	*Streptococcus suis* *Pasteurella multocida* (for pneumonic disease) *Actinobacillus pleuropneumoniae* Porcine Reproductive and Respiratory Syndrome virus (secondary bacterial infections) Swine Influenza Virus (secondary bacterial infections)
	Enteric (weaners / finishers)	*Escherichia coli* *Lawsonia intracellularis* Rotaviruses (secondary bacterial infections)
Fish	Systemic bacterioses Dermal bacterioses / red spot disease	*Aeromonas hydrophila* and other species *Pseudomonas spp.*

Conclusion

Despite the number of existing veterinary vaccines, rigorous studies to assess and document the effect of vaccination on antimicrobial use have rarely been conducted, let alone what measurable impact this could potentially have on the global burden of AMR *(17)*. A similar gap in the literature exists in the human health sector, in addition to persisting challenges to the universal coverage of vaccines against CAIs. Demonstrating the cost-benefit of human and veterinary vaccines remains one of the most critical parameters for achieving successful uptake in human health and agricultural systems. This is a particularly crucial element that guides the uptake of vaccines in LMICs where a strong regulatory system is often not in place to support controls over the use and sales of antibiotics, which often makes them less costly, and therefore more favourable than vaccines.

Technological advances can be inconsequential given the expense, time and difficulty of authorizing and registering a new or improved vaccine. This inevitably allows many of the "old" vaccines, with their limitations, to remain on the market for many years. Due to these costs (financial or otherwise), maintaining an economic perspective in the argument for increased vaccine use can help assign values to the contribution of human and veterinary vaccines in AMR avoidance and is critical in providing policy incentives for their R&D and support for their use. Gavi, the Vaccine Alliance's, innovative financing mechanism – Advance Market Commitment (AMC) – has accelerated the global roll out of pneumococcal vaccine and provides an example of alternative approaches to incentivizing vaccine development and production. Global and regional collaborations, such as the EMA and its partners in the European Medicines Regulatory Network who are currently implementing a joint action plan that aims to increase the availability of veterinary vaccines in the European Union, and partnerships with the private sector are needed more and more to address challenges that are exacerbated by sectoral silos and contextual differences.

Tackling AMR will require a concerted global effort to fill gaps in the current knowledge and evidence base, maximize existing resources and identify the most appropriate areas for further investment. A key step towards these goals is realizing the full potential of human and veterinary vaccines in reducing the global burden of AMR. ■

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INTERVENTIONS TO REDUCE ANTIBIOTIC PRESCRIBING FOR UPPER RESPIRATORY TRACT INFECTIONS IN PRIMARY CARE SETTINGS, A MAJOR DRIVER FOR ANTIMICROBIAL RESISTANCE

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We conducted a systematic review of interventions to reduce antibiotic prescribing for upper respiratory infections in primary care. We searched PubMed, Cochrane, Embase, and Google Scholar from 1 January 1980 to 28 February 2018 for published studies, using the following keywords: "antibiotics", "antibiotic prescribing", "primary care", "respiratory infectious", "respiratory diseases", "education", "training", "RCT" and "randomized control trial". Out of 133 studies, we identified 16 trials reporting results relating to interventions for reducing antibiotic prescription rates (APR) in primary care settings. Of these, 12 were conducted in high-income countries (five in the United States, five in Europe, one in Canada and one in Israel), and four in low- and middle-income countries (LMICs) (two in China, one in Vietnam and one in Iran, but only two were properly designed and implemented). Interventions ranged from 14 days to 18 months, targeting either clinicians (11), patients/caregivers (one) or both (four). We reported the intervention strategies, their effects and the gaps in these studies. We called for more studies in developing countries, and studies examining the long-term effects of interventions, to guide international AMR strategies in primary care settings.

Antimicrobial resistance has become one of the most important global health threats with adverse effects on patient health outcomes and health expenditure. The attributable costs per patient with infections of antimicrobial-resistant organisms were US$ 6,000 to US$ 30,000 more than patients with antimicrobial-susceptible organisms *(1)*. Taking societal cost into consideration, a reduction of 0.4% to 1.6% of gross domestic product (GDP) due to antimicrobial resistance was projected in 2004, which is equivalent to many billions of today's dollars globally *(2)*.

Upper respiratory tract infections (URIs) are the most common reasons for children to come to primary care facilities and they are mostly viral infections and self-limiting, and thus don't require antibiotics. However, URIs are frequently associated with high numbers of antibiotic use, ranging from 20% to 90%, with the highest rates being reported in Africa and Asia *(3)*. This is problematic because misuse of antibiotics contributes to the global issue of antimicrobial resistance. Given that primary care settings are usually associated with poor diagnostic tools and less-qualified doctors in developing countries, URIs could be a good starting point to reduce antibiotics use, as they are easier to be diagnosed and treated without antibiotics compared to other diseases, such as pneumonia, which are relatively more complicated.

There have been a number of randomized, controlled trials investigating the impact of interventions to reduce antibiotic prescription rates in clinical cases of URIs. Interventions can be categorized based on whom the intervention was targeted towards: clinicians, patients or both. Including trials that investigated URI patients of all ages, ten interventions targeted clinicians only *(4-14)*, one intervention targeted patients only *(15)*, and three interventions targeted both

patients and clinicians *(16,17,18)*. Intervention strategies on clinicians included clinical guidelines, peer leader training and regular feedback on antibiotic prescription rate. Intervention strategies on patients was focused on patient education with brochures, videos and posters. Ten out of 15 of the included studies were successful in creating a drop of antibiotic prescription rate in the intervention group compared to control group. The relative reduction ranged from 3% to 29% in terms of absolute antibiotic prescribing rate reduction. A study investigating a clinician-only intervention *(12)* and a study investigating a patient-only intervention *(15)* saw no impact. This indicates that the interventions targeting both patients and clinicians are more effective.

A meta-analysis of studies investigating interventions specifically towards antibiotic prescription rates in patients aged 18 and under presenting with URI showed a similar trend *(19)*. The papers selected for analysis included seven cluster RCTs, two individual RCTs, and three non-RCTs. While in general, interventions in these papers were associated with lower antibiotic prescription rates, it was specifically interventions that targeted clinicians and parents that showed a significant effect.

Investigating quasi-experimental trials targeted at both pediatric and general populations had less strong evidence, but they gave insights into effective interventions. Most studies employed a similar strategy of interventions on providers or patients. In addition, one used the tool of universal health insurance to stop reimbursement of antimicrobials for acute upper respiratory infections unless evidence of bacterial involvement was provided *(20)*; the other improved patients' access to point-of-care tests: Strep A and C-Reactive Protein *(21)*. Seven out of eight studies saw a reduction in antimicrobial use. In the four studies that antibiotics prescription rate was used as the indicator, the reduction ranged from 9%–32% *(21-24)*.

Intervention strategies

Peer leader training

Active peer leader training is the most common and effective way to reduce antibiotics use in primary care settings. The training could be conducted through online or onsite tutorial followed by interactive seminar. Training content covers a variety of issues, including principles of prescribing, diagnosis, antibiotic therapy, therapy with anti-inflammatory agents, adverse reactions to drugs, drug interactions, determinants for antibiotic prescription and clinician-patient communication skills. The main purpose of the training is to persuade doctors to reduce unnecessary antibiotic use. However, when antibiotics are indeed necessary, training needs to be moved to teaching appropriate use of antibiotic categories, such as penicillin instead of macrolides and cephalosporin that may potentially promote antibiotic resistance.

Communication skills are as important as, if not more than, other medical-related contents for the training, especially in the countries where the clinician-patient relationship is poor or patients show less trust in doctors. In some cases, it is not the medical knowledge that prevents a doctor from not prescribing antibiotics, but the doctor's concern that patients/caregivers may complain if their symptoms cannot be relieved in a short time. This usually happens when patients/caregivers actively request for antibiotics. Thus, doctors need to be trained to explore patients'/caregivers' main concerns, ask about their expectations and discuss prognosis, treatment options and reasons that should be referred to hospitals of higher level when applicable, and involve patients/caregivers in the decision-making process.

Changing doctors' behaviour is not an easy job and it is hard to sustain. When doctors really wish to improve their professional standards and provide better healthcare, it will be more likely to change their behaviours. Thus, physician engagement and commitment to the educational process is essential for successful training. This could be accomplished by guiding the physicians to play an active role in the training, e.g., role play and group discussion, with the help of a training facilitator, as well as involving local leaders in leading and supervising the training.

Operational guideline

A refined operational clinical guideline, usually less than 20 pages, is essential for primary care physicians, both in the training and the routine consultations. Unfortunately, most international and national AMR guidelines are written by specialists and are too comprehensive, often as thick as a textbook which is not very user-friendly. Clinical pathways or algorithms are effective tools that could be used in the guideline to change antibiotic-prescribing behaviour. They could be designed as a one-page decision support algorithm for each infection, assisting physicians on whether an antibiotic should be prescribed, the optimal antibiotic choice when indicated and the shortest appropriate duration of therapy. Involving patients in decision-making is also a proven way to reduce antibiotics in developed countries *(25)*. It's also important to include referral to respiratory specialists for severe conditions.

Peer reviews or feedback on antibiotics prescription rate

Conducting peer reviews regarding antibiotic prescribing has proven effective. Feedback on antibiotics prescription rate, serving as a stewardship tool, can be conducted in several ways, e.g., calculating prescribing indicators using data extracted from a hospital information system on a monthly or quarterly

basis, ranking healthcare providers at both individual and institution levels using the prescribing indicators and displaying the reports in a public space, submitting performance reports to local health authorities or mailing peer comparison to individual clinicians. Personalized and institution-based prescription audits are essential in this intervention strategy, which could easily be done where electronic prescription data are available. However, it becomes a challenge in some primary health care settings where only paper-based prescription records are used. Alternatively, they can randomly select a sample of prescriptions to review on a regular basis.

How the peer-review is conducted matters to its effectiveness. A trial in China has shown that primary care facilities having senior physicians leading the reviews, having clearly set prescription targets and sanctions for over-prescribing achieved much greater level of antibiotic reduction *(18, 26)*.

The antibiotics prescription rate feedback could be used together with other antibiotics stewardship strategies to achieve better effectiveness. Firstly, it could be linked with performance evaluation for an individual physician or healthcare facility, with relevant reward or sanction. Medical insurance authorities, local health authorities and health organization managers can use the feedback data for decisions in payment or reimbursement, health planning and other performance management. Secondly, the feedback data could be transparent to their patients, displayed in the public area of a healthcare facility, together with key health education messages on how it is linked with quality of care. This effect may be limited where health literacy of local population is poor. In conclusion, antibiotics prescription feedback may impose "pressures" on health providers arising from government, managers, colleagues and patients. However, the level of pressure depends on access to feedback, how the population understand it and whether reward and sanction is involved.

New diagnostic tools

C-reactive protein (CRP) has been proved as a reliable test in primary care settings to predict pneumonia. Studies have shown that training physicians in CRP testing lowered antibiotic prescription rates by between 10–20% *(6, 14, 27)*. Training of physicians on antibiotic prescribing is normally the first step of these trials. The European trial employed internet-based training and showed a 15% reduction in antibiotic prescribing rates *(6)*. Another recent trial introduced CRP in Vietnam and achieved a 20% reduction of antibiotic prescribing in two weeks *(14)*. CRP should be used to address lower respiratory tract infections, not URIs to maximize its cost-effectiveness. CRP has two major limitations: 1) it is relatively costly for developing countries; and 2) it has a blur area in cutoff values where no indication of viral or bacterial infections can be drawn. The effect of using CRP, both for economic and clinical reasons, seems to be diminishing quickly over time. In the IMPACT study, a three and a half-year follow-up found that physician training on antibiotic use and communication skills, not the use of CPR, were likely to be the major reason to maintain the intervention effect in the long-term *(28)*.

Patient/caregiver education

Patient/caregiver education included face-to-face health education during the consultation delivered by doctors (which is more efficient), and education materials handed out, such as leaflets and posters, and videos displayed in waiting rooms. The content of health education materials should be designed to be eye-catching and acceptable by the local population. Electronic versions could be kept by healthcare facilities, so that they can print by themselves after the interventions have ended. Alternately, in the areas that mobile devices are available, health education materials could be designed into these devices and updated via a communication network.

Interventions in developing countries

Most of above evidence derives from trials conducted in developed countries. Evidence from developing countries is rare where the problems are enormous. Up until now, there have been two well-designed and conducted trials in developing countries. One was conducted in rural Guangxi China, which is a relatively poor province bordering Vietnam and has an antibiotic prescribing rate for URIs as high as 70%–90% *(29)*, while another was conducted in northern Vietnam, close to Guangxi, with a similar high antibiotic prescribing rate of 80% *(14)*. The trial in China was to investigate the impact of an antimicrobial stewardship programme *(18)* in township hospitals that targeted both healthcare providers and caregivers of patients aged two to 14 years-old with a clinical diagnosis of URIs. The intervention package included evidence-based clinical guidelines, refresher training, monthly peer review meetings and health education information on appropriate antibiotic use during consultation. In the Vietnam trial, CRP, a diagnostic tool to distinguish either viral or bacterial infection was introduced. Both trials were successful. The trial in China lasted for six months and achieved a fall of 29% in antibiotic prescription rate compared with usual care; while the trial in Vietnam, followed up after two weeks, achieved a 20% reduction in antibiotic prescribing and a 14% reduction in antibiotic use, compared with usual care. Both studies are promising to developing countries. Interventions in China were designed to be embedded within routine primary care and that could easily be scaled up at country level: e.g., to make the best use of routine refresher training and monthly meeting opportunities. The Vietnam trial showed CRP would benefit

developing country settings, if proved cost-effective. However, long-term follow-up studies are badly needed to observe if these interventions, and their effects, are sustainable in a resource-constrained settings.

Conclusion

Effective antimicrobial resistance stewardship strategies in primary care settings have targeted both clinicians and patients/caregivers, which included user-friendly guidelines, training, peer-reviews/feedback to clinicians, use of new diagnostic tools such as CRP, and education for patients/caregivers. More evidence in developing countries, and the long-term effects of these interventions, are urgently needed. ■

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TO REDUCE THE USE OF ANTIBIOTICS FOLLOW A SIMPLE RULE: USE THEM APPROPRIATELY

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Antibiotics are a unique category of therapeutic agents developed to treat bacterial infections. They inhibit and/or kill the bacterial pathogens. Almost 70 years of largely successful antibiotic usage all over the world have changed not only the face of infectious diseases, but also the bacterial world itself.

Sixty years ago a first warning from history came in the form of a spread of difficult to treat staphylococci - methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals which was followed by alternating waves of emergence and the spread of new difficult to treat organisms and the development of new antibiotics designed to tackle emerging resistance. As the result of the initial treatment success, 35 years of slowdown regretfully happened in the research and launching of new antibiotics. Fortunately, serious warnings and even alarming messages have come from many authorities over the last two decades: a bleak picture of a possible post-antibiotic era was publicized and generated important political activity. Lord O'Neill's report released in July 2014 suggested ten key actions to address the potential global consequences of antimicrobial resistance (AMR). A United Nations high-level meeting on AMR was organized in September 2016 to discuss the coordinated global action in order to keep the benefits of antimicrobials in the near and distant future. The strategies to control AMR have been an important subject addressed by several countries following recommendations issued by the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE).

Although AMR is clearly related to the use and misuse of antibiotics in humans, animals and plants, we have to keep on using antibiotics, both old and new, but only when appropriate. There is no way to stop using antibiotics and there is no way to avoid either intrinsic or acquired resistance in bacteria. There are several approaches how to tackle AMR, the most frequent being systemic, routine surveillance of resistant bacteria and antimicrobial consumption, the use of antibiotics only when needed and appropriate antibiotic prescribing (the antibiotic prescribed only against susceptible bacteria in an appropriate dose, by way of administration and duration). Unfortunately, since antibiotics have been historically used without strict rules in most countries, development of a strategy for appropriate and judicious use of antimicrobials to preserve their future effectiveness is the only ethically acceptable way being able to reduce the amount of total antibiotics used and to curb the expansion of AMR. As a prerequisite, all patients in need around the globe should have access to the high-quality antibiotics.

Numerous studies published over the past seven decades, frequently supported by the drug industry, generated sometimes useful, sometimes less useful, solutions on how to tackle the important questions concerning the appropriate use of antibiotics; however more studies are needed with designs adapted to respond to emerging questions. In addition, many guidelines and guidance documents have been produced and may need to be reviewed and updated to integrate new knowledge like age category of the patient, specific care required, infection type/site of infection, comorbidities, epidemiologic and geographic data, etc.

It is impossible to deny enormous efforts made during the last two decades to improve and broaden the view of the need for appropriate use of antibiotics in a wide variety of settings including communitys, hospitals, long-term care facilities, day-care centres, food animals, companion animals, etc. Now a considerable challenge lies ahead of us and requires a high-level political involvement and support, specific approaches tailored to each and every group of stakeholders and substantial

financial support. Among the many approaches recommended to improve and reduce the antibiotic use, we have selected a few for a brief discussion.

The abuse and generous use of antibiotics has been constantly referenced to be a main cause of AMR. Abuse of antibiotics in humans involves mainly the unnecessary prescriptions of antibiotics. When promoting concept of "the appropriate use" of antibiotics, the most difficult real life situation to face is to identify with high probability the cases where the prescription of antibiotics is absolutely useless. The general answer to this dilemma is relatively simple and straightforward: non-bacterial infections should not be treated with antibiotics. Patients with acute viral infections receiving antibiotics represent the major group of individuals where the unnecessary prescription of antibiotics should be avoided. Am informed decision not to treat a patient (child or adult) with an upper respiratory tract infection with antibiotics in reality means that the physician should have 24/7 support of rapid diagnostic testing being able to reliably rule out bacterial infection, or to delay the treatment decision until receiving information generated by a more traditional (and slower) microbiological approach. At present, only limited number of point-of-care or near-the-bed tests with very narrow pathogen spectrum are available; however, more solutions (especially rapid point-of-care molecular tests) are entering the diagnostic market. For molecular point-of-care tests we wish to have self-contained, fully integrated sample-to-report devices that accept raw, untreated specimens, perform all of the molecular steps, and provide interpreted test results in less than an hour. The point-of-care test to diagnose group *A streptococcus* in a classical immunochromatographic or innovative molecular format is a good example of very useful point-of-care test, although other bacteria not targeted by the test may cause pharyngitis requiring antibiotic treatment. To overcome single test-single target concept, new molecular syndromic testing paradigm using highly multiplexed PCR platforms for analysing comprehensive panels of most probable pathogens, which can cause a particular clinical syndrome has been developed recently. This approach allows generation of multiple results from a single sample. At least some of the current platforms are designed to directly probe specimens (respiratory, stool, CSF, blood, urogenital) and positive blood culture bottles for an array of microorganisms and even provide some resistance/susceptibility information. Such an approach may have significant impact on patient care and management and redefine the diagnosis of infectious disease, but there are many obstacles to surmount and many challenges to tackle. Namely, although new diagnostic technologies enable expedited and more accurate microbiological diagnoses, diagnostic stewardship would be necessary to ensure that these technologies conserve, rather than consume, additional healthcare resources and optimally affect patient care. In addition, antimicrobial stewardship is needed to ensure prompt appropriate clinical action to translate faster diagnostic test results in the laboratory into improved outcomes at the bedside.

The next intervention to reduce the use of antibiotics is to optimize the duration of antimicrobial treatment. Ideally, we should stop antibiotic treatment when the patient is objectively cured. The main problems lies in the fact that a substantial amount of evidence concerning optimal duration of treatment of many infectious diseases is relatively old and consequently founded on an old-fashioned approach that longer is better. We should design more clinical studies, which will challenge traditional treatment duration with shorter ones, although keeping in mind that the financial support from industry for such studies will be difficult to obtain. A potential innovative approach would be to identify reliable (host) markers to distinguish early responders from those requiring prolonged treatment. Useless prolonged antimicrobial treatment is also often reported in hospitalized patients. It is usually due to lack of oversight, thus strict compliance with recommendation to regularly review patient's antimicrobial therapy protocol is mandatory. Similar problem is noncompliance with existing guidelines and protocols concerning indications and duration of surgical and nonsurgical antimicrobial prophylaxis.

Another important and unresolved issue which needs to be addressed is excessive use of antibiotics in animals as growth-promoters. Antibiotics have been used as growth promoters in animal agriculture for more than 60 years. The ability of low doses antibiotics to promote growth of animals was discovered serendipitously in the 1940s and the addition of antibiotics to animal feed to stimulate growth has gradually turned into a global practice. The mechanisms of growth promotion are still not clearly understood, but the attributable risk for development and propagation of AMR in humans is apparent. In Europe concerns about AMR led to European Union-wide ban on the use of antibiotics as growth promoters in animal feed as of 1 January 2006. This ban is the final step in the phasing out of antibiotics used for non-medicinal purposes in European Union and is part of the European Commission overall strategy to tackle the AMR, due to antibiotic overexploitation or misuse. We hope that this action will be followed also in other countries.

In conclusion, we strongly believe that appropriate use of antibiotics is possible and the way forward to reduce the use of antibiotics. Due to its high complexity it requires a step by step approach involving large numbers of stakeholders. New studies with innovative and provocative designs are needed as well as continuous life-long education of all healthcare

professionals. All interventions aiming to promote appropriate use of antibiotics must be country-, region-, and hospital-tailored. The high-level political support, a generous budget, dedicated, enthusiastic and well-educated personnel are essential components of every programme aiming to control AMR by promotion of appropriate use of antibiotics. ■

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NGO ENABLERS

STATE-LEVEL AMR ACTION PLANS IN INDIA: PROGRESS AT A SNAIL'S PACE!

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Sincere efforts by the Indian Health Ministry, international organizations such as World Health Organization (WHO) and initiatives like the Chennai Declaration of medical societies have created significant awareness of the AMR issue and inspired national-level action to tackle this enormous challenge. India is a federal country with 29 states and seven union territories. Healthcare is predominantly under the purview of individual states. Coordinated and sincere efforts by the Union Health Ministry and various Indian states is required to ensure the success of National AMR Action plan. Unfortunately, state level AMR action plan implementation is at moving at a snail's pace. This article analyses the possible reasons behind this delay and explores potential solutions.

Sincere efforts by the Indian Health Ministry, international organizations, such as WHO, and perseverance and persistence in initiatives like the Chennai Declaration of Indian medical societies, have created significant awareness of the AMR issue and inspired national-level action to tackle this enormous challenge *(1-5)*. India has a national antibiotics policy, national antibiotics guideline, and H1 rule to regulate the over-the-counter (OTC) sale of antibiotics *(6-8)*. The national infection control guidelines are in their final stages of preparation and will be published soon. The Indian public is being informed about AMR through almost daily newspaper articles and detailed discussions on the topic are a standard agenda item in the annual conferences and regional meetings of all medical societies. The Honourable Prime Minister of India, Narendra Modi, has made public radio announcements on the importance of tackling AMR. Medical professionals and hospitals managers are now well versed in the issue and are not only very comfortable in discussing it, but convinced that patient lives are genuinely being affected by the global and regional challenge of AMR as well. Yes, there is a sincere and serious attitude change among the medical community, the public and the political and bureaucratic leadership.

Then why is the national antibiotic policy not yet implemented in India? Why couldn't we translate the momentum into grass roots-level implementation?

Let us analyse the scenario from a global perspective. Various international initiatives by non-governmental organizations, dedicated efforts by activists, encouragement by the already well-functioning national action plans, such as the United Kingdom AMR action plan and CDC action plan, inspired high-level initiatives such as the UN resolution on AMR and the WHO AMR global action plan. The momentum at the global level and the formal involvement of UN agencies further stimulated action at national level, including in India. In tune with the WHO global action plan, the Indian Ministry of Health prepared a national AMR action plan with the help of Indian experts and the active collaboration of WHO. Five Indian states were selected as the nodal states to prepare state action plans and initiate implementation. The rest of the country will then learn from the challenges the nodal states face and their experiences during the implementation process.

So far, so good…

Has any Indian state implemented an antibiotic policy yet? Well… No.

So what's happening? India has one of the highest rates of antimicrobial resistance in the world. Now that India has realized the seriousness of the issue, we should ideally be mounting our efforts on a war footing. By now, the whole country could have implemented the national policy. The very fact that India has not yet implemented the policy is a proof for the argument that AMR is a sociopolitical issue and not just a scientific conundrum.

India has a population of 1.3 billion, 75,000 hospitals of varying standards, significant sanitation issues, socioeconomic disparity, a one million-strong medical community and half a million pharmacies where you can buy any antibiotic without a prescription. All these factors contribute to the highly complex AMR scenario in India.

India is a federal country with 29 states and seven union territories. Healthcare is predominantly under the purview of individual states, with the union ministry executing the role of

a policy-maker and coordinator of national programmes, such as immunization. The Indian Government and experts having realized that most components of the AMR national action plan cannot be implemented on the ground without the active, wholehearted and sincere involvement of all individual states; rightly and strategically sought collaboration of all the states. We identified five nodal states – Kerala, Andhra Pradesh, Uttar Pradesh, Himachal Pradesh and Orissa to lead the implementation process.

Let us analyse the progress made so far.

- Take the example of Kerala, the nodal state that has the maximum potential for proper implementation of the action plan. The state government, along with National Centre for Disease Control (NCDC, a Union Health Ministry agency) and the Indian division of WHO, coordinated a meeting to formulate the state AMR action plan. The draft action plan is ready for public consultation.
- The Chennai Declaration initiative provided a significant contribution by convincing the highest political leadership of the Kerala state about the importance of the AMR issue and ensured political commitment.
- Unfortunately, the political commitment has not yet been translated into an implementation process. Undue hurry to get international NGOs involved in the state action plan has stirred up controversies in political circles in the state and New Delhi. AMR is a global crisis and no country or state can tackle the issue in isolation. But each country or state should explore its internal strength and expertise to tackle a sociopolitical challenge. International NGOs should respect the individuality and dignity of developing countries. Any wrong strategy or undue political controversies will delay the implementation process. Such a delay will have catastrophic consequences by worsening the already distressing AMR scenario of the country.
- Once the states'/developing countries' action plans find their own feet, international NGOs and developed countries should offer collaboration with mutual respect and exchange of ideas and expertise.
- The state of Kerala has one of the most vibrant, politically active publics in India. Unfortunately, even after the formal announcement of the state action plan and the political commitment from the highest authority, there was no sincere effort to get the public involved or speed-track the implementation process.
- Kerala state's AMR action plan, once anticipated to be the guiding lamp for the whole country, hasn't yet lived up to the expectation.
- The situation is far worse in other nodal states. No other state has succeeded in publishing their state action plan so far. I am writing this document in March 2018, more than a year since the country finalized the national action plan and more than six months since the Union Ministry (NCDC) and Indian division of WHO coordinated the meeting of the representative of various states.

What has gone wrong?

NCDC (on behalf of Union Health Ministry), with the collaboration of Indian Division of WHO, coordinated a meeting of member states to discuss state-level implementation in early 2017. Unfortunately, less than half of the member states participated in the meeting. How can the country implement the action plan when states are not yet convinced of the sociopolitical significance of the AMR issue?

Another important drawback was the assignment of responsibility for coordinating the state representatives meeting to WHO. As we all know, WHO has predominantly an advisory role with no authority in the health issues of individual countries or states. It may be true that WHO provided funds for the meeting (and NCDC was an equal partner in the meeting coordination), but the soft image of WHO as an advisory body made many states literally neglect the meeting and shy away from the initiative. The soft image of WHO, rather than the strong and authoritative face of the Indian Health Ministry was projected as the face of the Centre-State AMR collaboration. The same erroneous strategy was repeated at the state-level AMR action plan meetings.

Strategies for effective implementation at state level

- There is no doubt that Union and state health ministries should involve WHO and that WHO should provide technical advice and expertise when requested. But the union ministry and health ministries of the respective states, with their accountability and authoritativeness, should directly coordinate the action plans, ensuring progress and cooperation from all stakeholders.
- Direct communication and coordination by the Union health secretary (as the chair of the inter-ministerial committee on AMR) and the state health secretaries, with regular updates on the progress of implementation of all components of the AMR action plan.
- Strategy, Strategy and Strategy! Strategy is the key to success!!

AMR implementation is a mammoth task, especially in a developing economy of immense proportions. Effective strategy-making is essential to ensure the success of national and state action plans.

The principal opposition to the implementation of the national and state action plans will be from the pharmaceutical industry. At the same time, support (undue) will also come from

another section of the same pharmaceutical and healthcare industry. A balanced approach will be the key.

Opposition from the industry:

- Implementing over-the-counter sale of antibiotics without prescription (OTC) rule (H1 rule):
  Challenge: from pharmaceutical distributors and pharmacists. They have a genuine concern over the drop in profit margins, once the H1 rule is implemented.
  Solution: The modified H1 rule on OTC sales in India includes only 24 antibiotics. Most of these are injectable drugs and so not sold OTC anyway. Most first-line antibiotics are not included in the list and so do not come under the rule. We should have a discussion with pharmaceutical distributors and allay their financial concerns. If we fail to do this, the OTC component will fail, resulting in the overall failure of the action plan.
- Rationalizing in-hospital antibiotic usage:
  Challenge: Two thirds of healthcare delivery in India is contributed by the private sector. Drug sales, including that of antibiotics, constitute a significant part of the income of the private hospitals. Private hospital managements may be worried about the possible drop in antibiotic sales and income when an antibiotic stewardship programme is implemented.
  Solution: The aim of antibiotic stewardship is not to reduce antibiotic usage, but to rationalize it. Underuse is as dangerous as overuse. Our aim is to ensure usage of the right antibiotic at the right time and for the right duration. Antibiotic stewardship programmes in the developing world are unlikely to produce any significant drop in pharmacy sales and income.

Undue support (push) from the industry:

- Pressure to fast-track licensing of newer antibiotics on the pretext of the AMR issue: This is a minor concern, as there are very few new antibiotics in the pipeline and licensing of new antibiotics is predominantly under the purview of DCGI (Drugs Controller General of India) so the state action plan will have limited involvement in this.
- New vaccines: It is true that there is a serious push from the vaccine industry to introduce new vaccines in developing countries through AMR action plans. Though the role of vaccines in preventing infections is undeniable, due consideration should be given to local epidemiology and cost-effectiveness of new vaccines.
- Veterinary vaccines: There is no doubt that usage of antibiotics as a growth promoter in veterinary practice must be stopped. At the same time, introducing a series of new veterinary vaccines through the AMR action plan may not be appropriate. As mentioned earlier, cost-effectiveness and local epidemiology should be kept in mind. A balanced approach will be the key.
- Manufacturers of microbiology diagnostic equipment: Improving microbiology laboratory facilities in government and private hospitals is a very essential component of AMR action plan implementation. But we should be careful not to spend valuable resources on expensive equipment. Standardization of conventional methodology is more cost-effective than investing in costly equipment. That said, if newer technology can help us provide more cost-effective medical care, we should not be hesitant to consider these options.
- Infection control products: We should exercise diligence not to spend all the precious resources on expensive infection control products. Instead, we should concentrate on improving the basic infrastructure, suitable for the practice of infection control. Improvement in hospital cleanliness and reinforcementing in hand hygiene measures across the healthcare sector should be our priority.

Improving the sanitation scenario in the community: This is the most important component to alleviate the AMR crisis in India. Unless we tackle this issue, all the other components will be futile. Unfortunately, this is a no man's land and we will experience neither support nor opposition from stakeholders.

Tackling AMR needs a multi-pronged approach. The difficulty for developing countries is that we are not able to implement strategies due to the paucity of resources and, in many instances, due to a lack of political will to effectively convince stakeholders of the importance of the AMR issue and the negative impact that it can produce on the healthcare field and economy as a whole.

Rational use of antibiotics and infection control precautions are often neglected. Needless to say, improving the sanitation scenario and broadening vaccination coverage should be the pillars of our strategy. Vaccination, to the best possible extent, should be a responsibility of all governments as this will help save the lives of millions of innocent children. In the developed world, all these components will go hand in hand, but in developing countries the scenario may be entirely different with serious implications.

It is very interesting to observe that both the undue support and the opposition to the AMR action plan implementation will be from industry (two sides of the same coin). There is a possibility that authorities in developing countries may choose the easier path of making both sides of the industry happy by not sincerely implementing the antibiotic policy and merely supporting introduction of new antibiotics, vaccines, and diagnostic and infection control products. If that is the

scenario, then the AMR action plans in developing countries are bound to fail with catastrophic consequences to the healthcare system.

The seeds for the failure or the success of the AMR action plan is within the plan itself. It is for us to choose the right one. ■

Disclaimer: The views and opinions expressed in this article are those of the author and do not necessarily reflect the official policy or position of any governmental or Nongovernmental organizations the author is associated with.

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FACING THE CHALLENGES OF AND PROVIDING SOLUTIONS FOR ANTIMICROBIAL RESISTANCE IN THE INTENSIVE CARE UNIT: A CALL FOR ACTION FROM THE ANTARCTICA (**ANT**IMICROBI**A**L **R**ESISTANCE **C**RI**TI**CAL **CA**RE) COALITION

DR JEAN CARLET (LEFT), PRESIDENT, WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE AND
PROFESSOR JAN DE WAELE (RIGHT), INTENSIVIST, GHENT UNIVERSITY HOSPITAL, BELGIUM

The coalition has identified four key areas for improvement: risk stratification, diagnosis, therapy and prevention. Under each area, there are priorities which will need addressing if the management of AMR is to improve.

Brussels, 15 November 2017. Intensive care and infectious disease specialists from the European Society of Intensive Care Medicine (ESICM), European Society of Microbiology and Infectious Diseases (ESCMID) and World Alliance Against Antibiotic Resistance (WAAAR), united in the ANTARCTICA (ANTimicrobiAl Resistance CriTIcal CAre) – coalition, to call for increased awareness and action among intensive care and infectious diseases health care professionals to reduce AMR development in critically ill patients, to improve treatment of AMR infections and to coordinate scientific research in this high-risk patient population.

AMR is a clear and present danger to patients in any intensive care unit (ICU) around the world. It is associated with increased mortality, prolonged length of stay, increased costs and paradoxically, increased antibiotic use. Studies indicate that at least 25,000 patients die each year of AMR in the hospital, many of them in the ICU. The number of patients affected by and dying from AMR infections in Europe is expected to increase significantly in the next years; by 2050 an estimated 390,000 patients will die from AMR in European countries.

Whereas AMR may affect any patient in the hospital, patients in the ICU are particularly at risk of acquiring AMR infections due to the intensity of the treatment, use of invasive devices, increased risk of transmission and exposure to antibiotics. AMR is present in every ICU, although prevalence is geographically different and AMR pathogens encountered are variable. In Southern and Eastern Europe, the Middle East, and many countries in Asia, AMR is a daily challenge, with often limited options for antibiotic therapy.

Despite this threat, we are confident that we can turn the tide on AMR in our ICUs for a number of reasons:

- Knowledge about the mechanisms involved in the development and spread of AMR are increasing.
- Technologies to rapidly diagnose infections and document the involvement of AMR pathogens are becoming available.
- New antibiotics particularly aimed at AMR pathogens are becoming available and many are under investigation. In parallel, non-antibiotic strategies to treat severe infections are under development.
- The importance of infection control in hospitals is now recognized and infection control programmes are increasingly effective in controlling the spread of AMR infections.

In order to consolidate this knowledge, the Coalition against

Figure 1: ANTARTICA's four prority areas for imprroving AMR management in ICUs

1. Risk stratification
- Identify pathogen-specific risk factors for MDR involvement
- Study impact of different antibiotics on MDR development

2. Diagnosis
- Develop and evaluate tools for:
  - Early diagnosis of sepsis
  - Early differentiation between infection and inflammation, and between infection and colonization
  - Rapid detection and identification of pathogens and resistant patterns
- Improve methods for rapid phenotypic susceptibility testing

3. Therapy
- Obtain pharmaco-kinetic data from ICU patients for all available antibiotics
- Elucidate the role of combination therapy in MDR infections
- Role of alternative route of antibiotic administration (i.e. nebulized antibiotics)
- Improve therapeutic drug monitoring (TDM)

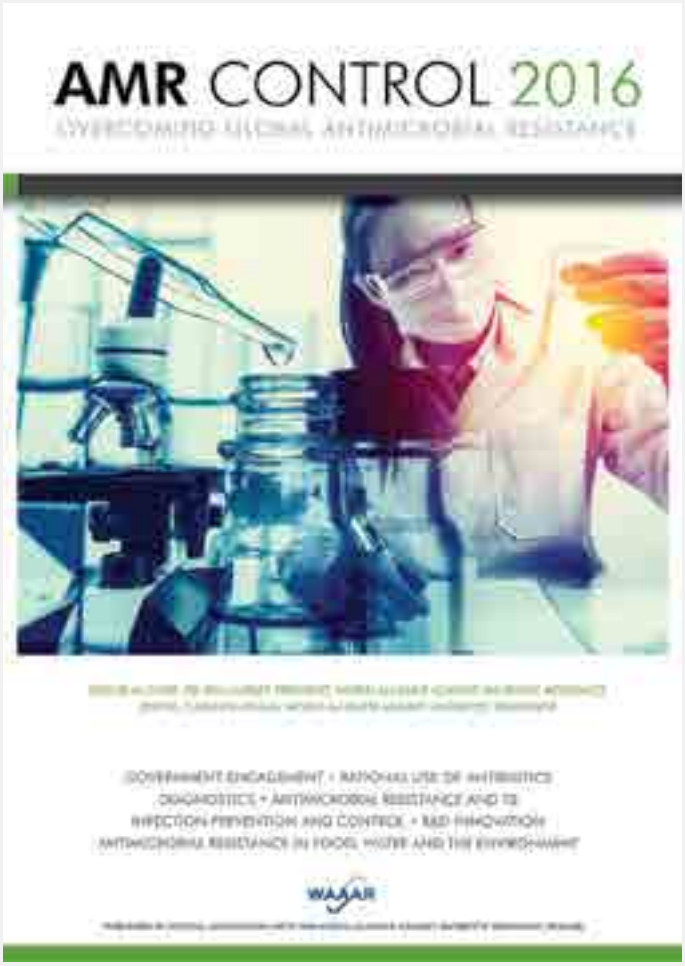
4. Prevention
- Clarify the role of decontamination strategies

antimicrobial resistance in critical care has identified priorities in four areas to improve AMR infection management in the ICU (Figure 1) and urges healthcare professionals, scientific societies and industry to take action.

This will require concerted, multifaceted and continued action from healthcare professionals as well as all stakeholders involved including patient organizations, scientific societies, pharmaceutical industry, healthcare policy-makers and politicians. We are aware that the same threat applies to low-income countries where unfortunately some of the high-technological options may not be available. Nevertheless, we are confident that the other low-cost components also apply and may help to reduce the burden of MDR in these countries. In the ICU, tackling AMR remains a responsibility shared by all healthcare workers, from physicians to maintenance personnel, from nurses to physiotherapists, from consultants to medical students. Together, we can reduce AMR in the ICU, and continue to treat our patients effectively. ■

Dr Jean Carlet, is the President and Founder of ACdeBMR, in English WAAAR (the World Alliance Against Antibiotic Resistance). Trained in internal medicine, head of the ICU in Hospital St Joseph, Paris, for 25 years, he has published in medical journals on the issue of antibiotic resistance for over 30 years. WAAAR gained international recognition with the launch of the Paris Declaration which gathered over 700 signatories from 55 countries, or which over a 100 scientific societies. In 2015 Dr Carlet was nominated by France's Ministry of Health to head the Special Task Force for Antibiotic Preservation. He is a steering committee member of several coalitions such as CARA.

Professor Jan De Waele, MD, PhD, is a surgery-trained intensivist with a specific interest in severe infections in critically ill patients. He works at the surgical ICU of the Ghent University Hospital in Belgium. His clinical interests include AMR and antimicrobial stewardship in ICUs. His research activities currently focus on optimizing antibiotic therapy in severely ill infected patients to improve outcomes and combat resistance development. He is active in several societies; he is currently chairing the Infection Section of the European Society of Intensive Care Medicine (ESICM) and is President of the Belgian Society of Intensive Care Medicine.



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RESEARCH & DEVELOPMENT

CARB-X IS A NEW APPROACH TO ACCELERATING PROMISING RESEARCH INTO NEW ANTIBIOTICS, THERAPEUTICS, DIAGNOSTICS, VACCINES AND DEVICES … AND IT IS MAKING PROGRESS

PROFESSOR KEVIN OUTTERSON, EXECUTIVE DIRECTOR AND PRINCIPAL INVESTIGATOR, CARB-X, BOSTON UNIVERSITY, BOSTON, USA

CARB-X stands for Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator. It is funded by the United States government (through BARDA and NIAID, within the United States Department of Health and Human Services), the United Kingdom government (through the Global AMR Innovation Fund, GAMRIF, in the Department of Health and Social Care), the Wellcome Trust, and the Bill and Melinda Gates Foundation. CARB-X has as its mission to invest more than US$ 500 million in 2016–2021 to support the pre-clinical development of antibiotics and other therapeutics, rapid diagnostics, vaccines and devices to address the rise of drug resistance.

Since Alexander Fleming's discovery of penicillin 90 years ago this year, antibiotics have been the miracle drugs that revolutionized healthcare and helped produce today's era of modern medicine. No other drug class in human history has been more important in curing disease and extending life expectancy.

Fleming himself warned that we are in a perpetual race against bacteria that develop resistance to antibiotics. Yet today, the world is facing a crisis. Superbugs are developing resistance faster than we can come up with new weapons. We are depleting our supply of antibiotics, according to a recent World Health Organization (WHO) study, and there are only a handful of antibiotics in clinical development to treat the most deadly drug-resistant superbugs. The WHO estimates that 700,000 people die each year from infections and that number is growing. In the United States alone, drug-resistant infections kill 23,000 Americans each year and 14,000 more die from infections triggered by antibiotics that upset the normal microbiome of the human gut.

Imagine the potential toll that drug-resistant bacteria could take in a natural or man-made disaster where there is widespread injury.

The danger isn't only to our health. In 2016, the World Bank projected the economic impact: the "optimistic" scenario was a 1.1% reduction in global GDP by 2050; the "high-impact" scenario was more than three times worse.

The reasons are well known. Overuse and misuse of existing antibiotics have contributed to the rapid rise of resistance. Limited access to antibiotics in parts of the world where they are most needed also contributes to the spread of deadly bacteria. At the same time, the antibacterial pipeline is very thin. There have been no new classes discovered for antibiotics approved by the FDA for the most serious bacteria – Gram-negative superbugs – since 1962. Drug developers are reluctant to invest in developing new antibiotics to treat Gram-negative bacteria because the science is difficult and returns are low. Unlike other therapy areas where breakthrough medicines can generate billions in sales, the most powerful antibiotics are reserved as "last-resort" treatments for the hardest-to-treat patients. Companies cannot make money on drugs they do not sell.

The economic model for antimicrobials is broken. We can no longer count on private industry to deliver the antibiotics we need.

We need to think differently about how to drive innovation, and we need bold action at the global level to win the war against the rise of superbugs.

Finding long-term solutions for a complex global problem

It is encouraging that world leaders are looking for meaningful solutions. For several years, the WHO has been sounding alarm bells and urging nations to develop action plans to address the crisis. In 2016, the UN general assembly recognised drug-resistant infections as one of the greatest threats facing humanity. And in May 2017, G20 leaders called for national action plans by the end of 2018.

Sweden and the United Kingdom were pioneers in this area. Professor Otto Cars at Uppsala University had long championed the issue, which was taken up when Sweden chaired the Presidency of the EU in 2009. The Chief Medical Officer of England, Dame Sally Davies, also raised the profile of this issue in the United Kingdom and abroad. The United Kingdom government and the Wellcome Trust commissioned an independent review of the issue, chaired by Lord Jim O'Neill. The Independent Review on AMR called for new business models to provide predictable financial incentives to encourage innovation. After an exchange between the United Kingdom's Prime Minister, David Cameron, and President Barak Obama, the United States government accelerated action. In 2015, the United States government launched its National Action Plan on Combating Antibiotic Resistant Bacteria, a multi-pronged effort to slow the spread of drug-resistant bacteria, improve national surveillance, reduce misuse and overuse of antibiotics in animals, crops and humans, and to accelerate research and develop of new products including antibiotics, diagnostics and vaccines.

The United States, the Wellcome Trust and Boston University came together to create CARB-X in July 2016, a non-profit global partnership to provide funding and support to early development research projects. CARB-X stands for Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator. It is funded by the United States government (through BARDA and NIAID, within the United States Department of Health and Human Services), the United Kingdom government (through the Global AMR Innovation Fund, GAMRIF, in the Department of Health and Social Care, the Wellcome Trust and the Bill and Melinda Gates Foundation. CARB-X and has as its mission to invest more than US$ 500 million in 2016–2021 to support the pre-clinical development of antibiotics and other therapeutics, rapid diagnostics, vaccines and devices to address the rise of drug-resistant bacteria.

Initially, the goal was to support 20 research projects by the end of Year 5, but that goal was exceeded quickly in CARB-X's first year of operation.

CARB-X is making a difference

By June 2018, CARB-X had 33 innovative projects in seven countries in its portfolio and had announced more than US$ 87 million in non-dilutive funding awards to the product developers, plus an additional US$ 118 million for those projects if milestones are met. Among the projects are nine projects that are new classes of antibiotics, many non-traditional therapeutics, projects to boost the body's microbiome, a vaccine, and six rapid diagnostics that will enable doctors to treat patients more quickly. All these projects target antibiotic-resistant bacteria on the Bacterial Pathogen Threat List prepared by the US Centers for Disease Control and Prevention (CDC) or on the Priority Pathogens list published by the WHO. Planning for responsible use of existing antibiotics and equitable access, particularly in low-income countries where need is greatest, are also a condition of CARB-X funding.

With CARB-X support, the companies in the portfolio have made solid progress in just a year: five projects have advanced into clinical Phase 1 trials, several have achieved major milestones on the path to clinical development and the rest of the projects in the pipeline are moving forward on schedule. In the Powered by CARB-X portfolio, one project has been stopped due to negative toxicity studies and another has been parked while the company restructures. The goal is to support projects through the early development phases and Phase 1 clinical trials so that they will attract additional private or public support for further clinical development. This is a vital mission because pre-clinical research is often where projects are abandoned because of lack of funds or expertise.

CARB-X launched two new funding rounds for 2018, inviting applications from around the world. The new rounds are focused on increasing the number of new classes of antibiotics in the portfolio and increasing the numbers of novel therapeutics, rapid diagnostics and other approaches to address the rising threat of drug-resistant bacteria. Hundreds of product developers have applied for CARB-X funding.

CARB-X is also expanding its global network of accelerators – companies and organizations that partner with CARB-X to provide scientific and business support to the projects in the Powered by CARB-X portfolio. It plans to add accelerators in several locations to improve the global footprint, bringing CARB-X closer to the companies it partners with to support innovative projects. A global RFP was conducted in 1Q 2018. New accelerators will be announced in 3Q 2018.

In addition to creating the world's largest early development antibacterial pipeline, one of CARB-X's main distinguishing features is that it is highly entrepreneurial in its approach, lean and effective. It has a small team based at Boston University; 94% of CARB-X's annual budget is invested directly into support for projects. Since it was established, CARB-X has averaged 1.5 funding announcements every month.

Research is a high-risk endeavour and some of the projects in the portfolio are likely to fail. But if only a handful of these innovative projects go on to be approved and to reach patients, that will represent a major victory in the battle against drug-resistant bacteria.

The CARB-X advantage

In addition to providing valuable funding and support to promising research projects around the world, the CARB-X experiment is producing other benefits that can help in the fight against drug-resistant bacteria. It is strengthening the global network of antibacterial product developers, providing expertise, communication channels and access to funding opportunities that may not have existed before.

For governments and funding organizations, CARB-X is a turn-key opportunity to invest in the best science and antibacterial innovation in a meaningful and impactful way at a global level. CARB-X is actively seeking support from other governments, industry and civil society to expand its ability to fund the best science around the world to get the new life-saving treatments so urgently needed. While the funding provided by CARB-X is important, companies are also offered a host of business, technical and regulatory support services from CARB-X and its accelerator network.

But much more is needed. Urgently.

The recent DRIVE-AB report, published earlier last year by 16 public-private partners supported by the European Innovative Medicines Initiative (IMI) and seven major pharmaceutical companies, called for almost doubling the amount of money invested in funding organizations like CARB-X and GARDP, which is supported by DNDi and the WHO. Increased funding would produce increased numbers of new antibiotics and other approaches to address drug resistance.

Grant funding, known as 'push' funding, is not enough. DRIVE-AB also recommended 'pull' funding – a big US$ 1 billion market-entry reward for companies for each new antibiotic approved to attract more private investment antibacterial research. This prize would be in addition to any sales revenues. Others, including the O'Neill Review, has also urged 'pull' incentives to achieve a significant acceleration in the speed of drug development.

Long-term commitment from governments is also needed. It takes years to develop new medicines and so long-term financial commitments from government is also part of the solution. The study suggests that the G20, through its member countries, would be ideally positioned to take the lead globally on public funding of R&D and coordinating efforts to ensure a predictable supply of antibiotics over the next 30 years. The measures proposed by DRIVE-AB would cost an estimated US$ 36 billion and produce some 20 new antibiotics over the next 30 years, which would go a long way to saving lives and battling the rise of superbugs.

The challenge for world leaders is how to make this a reality at a global level. One country acting on its own, or one initiative like CARB-X no matter how impressive the achievements, cannot solve this problem on its own – any meaningful solution must involve concerted, sustainable long-term global action.

CARB-X is making solid progress and is demonstrating that it is essential to stimulating innovation to address the superbug threat. Much more is needed. With so much at stake, and so many lives in the balance, we must act together to find sustainable and meaningful solutions. ■

Professor Kevin Outterson, JD, LLM, is Executive Director and Principal Investigator for CARB-X, a US$ 502 million international public-private partnership to accelerate global antibacterial innovation. He also teaches healthcare law at Boston University, where he co-directs the Health Law Program.

A NOT-FOR-PROFIT ANTIBIOTIC DEVELOPER – THE GLOBAL ANTIBIOTIC RESEARCH AND DEVELOPMENT PARTNERSHIP

DR MANICA BALASEGARAM (TOP LEFT), DIRECTOR, GARDP, GENEVA, SWITZERLAND; **PETER BEYER**[1] (TOP RIGHT), SENIOR ADVISER, WORLD HEALTH ORGANIZATION, GENEVA, SWITZERLAND AND **JEAN-PIERRE PACCAUD** (BOTTOM LEFT), BUSINESS DEVELOPMENT AND CORPORATE STRATEGY DIRECTOR, GARDP, GENEVA, SWITZERLAND

The Global Antibiotic Research and Development Partnership (GARDP) – a not-for-profit drug developer – addresses global public health needs by developing affordable new or improved antibiotic treatments. Initiated by the World Health Organization (WHO) and the Drugs for Neglected Diseases *initiative* (DNDi) in 2016, GARDP is an important element of WHO's Global Action Plan on antimicrobial resistance that calls for new public-private partnerships to encourage research and development (R&D) of new antimicrobial agents and diagnostics. GARDP capitalizes on DNDi's track record of developing, delivering and implementing seven new treatments since 2003 for neglected diseases, and a pipeline of new chemical entities, as well as from WHO's technical expertise and leadership.

The increasing resistance of bacteria is outpacing antibiotic drug discovery at an alarming rate. The current pipeline for new antibiotics and biological treatments fails to address the biggest threats posed by increasingly drug-resistant Gram-negative bacteria, as well as tuberculosis *(1)*, identified by the World Health Organization (WHO) as global public health priorities *(2)*. The pharmaceutical industry has largely left the field of antibiotic development and new and remaining players struggle to mobilize financial resources due to the limited return on investment and the scientific challenges. This calls for coordinated support for basic research and early stage discovery, as well as for bringing new drugs through clinical trials *(4)*. There is also insufficient investment to improve access and optimize the use of existing antibiotics.

The Global Antibiotic Research and Development Partnership (GARDP) – a not-for-profit drug developer – addresses global public health needs by developing affordable new or improved antibiotic treatments. Initiated by WHO and the Drugs for Neglected Disease initiative (DNDi) in 2016, GARDP is an important element of WHO's Global Action Plan on antimicrobial resistance that calls for new public-private partnerships to encourage research and development (R&D) of new antimicrobial agents and diagnostics *(7)*. GARDP capitalizes on DNDi's track record of developing, delivering, and implementing seven new treatments since 2003 for neglected diseases, and a pipeline of new chemical entities, as well as from WHO's technical expertise and leadership.

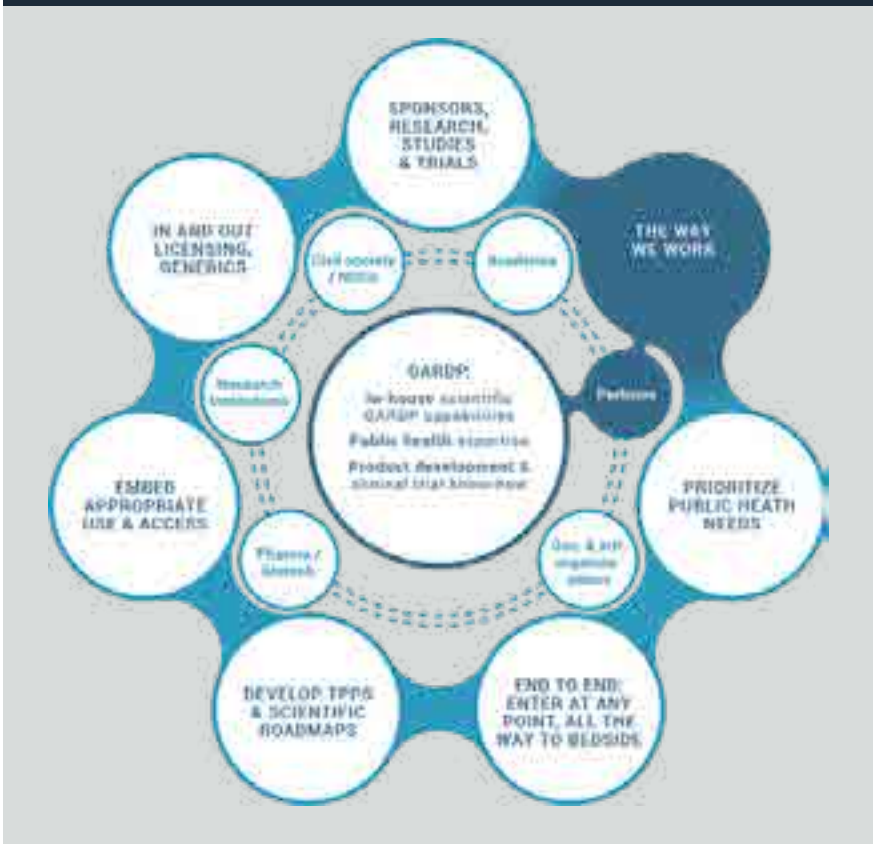
The Berlin Declaration of the G20 Health Ministers in 2017 *(5)*, as well as other UN declarations *(6)* and WHO strategic plans *(7)*, cautioned that success in the fight against antimicrobial resistance cannot be achieved with existing health tools and technologies. The Berlin Declaration welcomed new initiatives, including GARDP, which can "reinvigorate research and development in science and industry for antimicrobials." It recognized the importance of reactivating the R&D pipeline through incentive mechanisms that do not rely on high price/volume combinations and that promote appropriate use of antibiotics. Finally, the Declaration also called for "broadening the voluntary financial support" for such initiatives.

Any new approach must address the complex issues of stewardship, as well as sustainable, equitable and affordable access to existing and new antibiotic drugs. These must meet patients' needs globally and take into account the diversity of national health systems' challenges and levels of economic development.

[1] This contribution has been prepared strictly in a personal capacity and reflects the view of the author. The views expressed must not be attributed to the WHO, its Secretariat, or its Member States.

It is vital that all new tools are designed from inception to meet health priority needs, reflect the realities of clinical practice, and ensure access but not excess. GARDP has committed to explore concrete ways to address this challenge both through its business model and programmes.

Figure 1: **GARDP's business model and operating principles**



GARDP's model

GARDP is a not-for-profit drug developer that focuses on filling R&D gaps identified by WHO. GARDP's business model is different as its ultimate objective – to facilitate access to new treatments and their appropriate use – is built into the R&D process from the beginning. GARDP's programmes not only support public health needs but have the flexibility and capacity to enter at any point from early exploratory to preclinical and clinical studies all the way through to patient access. Its R&D strategies are based on global health priorities, clear target product profiles (TPPs) and R&D roadmaps. This approach creates a favourable environment for equitable access by developing a sustainable and fair pricing system. Partnerships are key to GARDP programmes and include contractual arrangements with pharmaceutical companies, research institutions, and academic partners.

Since its formation, GARDP has built up a skilled team with expertise from a range of sectors and backgrounds, notably public health, clinical infectious disease, industry, academia and working in developing country experience. Furthermore, GARDP has benefited from its unique WHO and DNDi parentage. The incubation period hosted by DNDi gives GARDP access to an international network as well as DNDi's R&D expertise, while WHO's technical departments provide expertise in the different disease areas as well as guidance on priority setting.

GARDP's business model and operating principles

Prioritization process

Prioritization is crucial and should take into consideration the intersection between priority pathogens; specific populations' health needs; and individual diseases and broader syndromes. It is essential that recommendations are evidence-based, and that data also supports access and appropriate use. This ensures any new health tools are designed from the start to address priority needs. GARDP's choice of initial programmes follows these principles and has been supported by expert reviews and input from WHO (including priority pathogens, pipeline *(8)* and landscape analyses). GARDP's work is global in focus, while paying particular attention to the needs of developing countries.

R&D programmes launched

Three programmes have been launched by GARDP in 2017:

- The antimicrobial memory recovery and exploratory programme recovers the knowledge, data, and assets of forgotten, abandoned, or withdrawn antibiotics as well as seeking new treatments. Through REVIVE – an online platform (http://revive.gardp.org) for the antimicrobial R&D community to learn, connect and share good practice on conducting antimicrobial drug R&D *(8)*. This will help improve, accelerate, and streamline antimicrobial drug discovery, and R&D. So far, more than 100 experts have engaged with REVIVE. An exploratory strategy is being developed to support early stage research. This will include building a long-term portfolio of therapeutic interventions necessary to address the unavoidable development of resistance to any novel compound that will be brought to patients.
- The sexually-transmitted infections programme aims to develop treatment for gonorrhoea patients with drug-resistant infections by accelerating the development of

at least one new drug *(9)*. In July 2017, GARDP entered its first partnership agreement with biotech company Entasis Therapeutics *(10)* to co-develop the antibiotic zoliflodacin *(11)* for gonorrhoea. GARDP and Entasis are collaborating to develop the product globally. Phase III clinical trials are being planned in Europe, South Africa, Thailand, and the United States. Should zoliflodacin receive regulatory approval, Entasis will grant GARDP an exclusive license with sublicensing rights in 168 low- and middle-income countries, while retaining commercial rights in high-income markets. The licence also contains provisions on affordability and sustainable access. In addition to zoliflodacin, a review of back-up candidates is underway via, but not limited to, GARDP's memory recovery programme. The investigation of combinations of existing antibiotics, as well as exploring the development of fixed-dose combinations, is also underway.

- The neonatal sepsis programme will provide an evidence base for the use of antibiotics, both old and new, in neonates with serious bacterial infections. A feasibility survey conducted in 2017 has already confirmed high levels of drug resistance in some settings with significant variation in treatment protocols in different countries. Two TPPs have been developed to guide the development of an alternative first-line treatment for clinically diagnosed neonatal sepsis and a new treatment for new-borns with confirmed multidrug-resistant infection. GARDP currently evaluates potential treatment candidates, including through pharmacokinetic trials, to inform on appropriate dosing regimen. Clinical trials are to follow these studies.

GARDP is also exploring ways to optimize current paediatric treatments and accelerate the development of new antibiotics for children through improvements in dosing, treatment duration, drug formulation, or new drug combinations.

Access, innovation, and incentives

One of the key components of GARDP's model is a tailored approach to ensuring sustainable access – embedding stewardship and conservation within an access approach. Sustainable access is an integral element throughout all of GARDP's programmes. This includes building in access and appropriate use considerations in the TPPs; optimizing use of existing antibiotics; ensuring affordability of new antibiotics; and improving formulations and drug profiles. GARDP also includes clauses that ensure affordability and appropriate use of any new products developed by GARDP in any partnership agreement.

With this approach, not-for-profit antibiotic developers such as GARDP can strongly stimulate innovation while promoting global access and appropriate use. While developers can and should play a part in sustainable access, there remains a crucial role for governments, WHO and other agencies to set the appropriate polices and standards at the national, regional and global level.

Antimicrobial resistance R&D in the global landscape

As the current global R&D pipeline is very weak, three key areas are in need of targeted support: basic research and discovery, clinical development of new drugs, and optimization of existing drugs. But any support to R&D and to sustainable access should take an integrated approach, focusing on an intersection of pathogens, diseases and syndromes, and specific populations. Given the scarce data following registration of future antibiotics, post licensing monitoring to further support public health is extremely important.

It is also important that all stages of antimicrobial R&D can be supported, so it is crucial that any new incentives are appropriately designed to reflect the reality of the research landscape *(12)*. To ensure a public return on public investment, any such incentive should include a contractual relationship between payer(s) and recipient(s) with strong governance, definitions around what constitutes innovation (based on public health priorities), and a clear agreement on sustainable access and appropriate use provisions. It is important to remember that access to quality antibiotics remains critical *(11)*. Surveillance activities not only serve epidemiological purposes, but should link to R&D efforts in a mutually reinforcing way – country- or regional-specific R&D programmes should address the resistance profiles and can feed back into surveillance efforts.

While discussions around R&D today often revolve around possible new financial incentives, it is important to prepare the necessary ground for effective use of public money through existing and possible future R&D mechanisms. The R&D pipeline cannot be seen in segmented parts but must be considered as a continuum that flows from beginning to end. If public money is invested, it is important to ensure that it focuses on priority areas. Undertaking the following activities is key, as is strong public leadership:

- Setting public health priorities includes understanding needs and gaps, identifying priorities and how they evolve. WHO has provided leadership by developing and publishing the Priority Pathogens List in 2017 which is already widely used. Priorities, however, include not just pathogens, but also specific population needs and specific medical indications (e.g., populations disproportionally affected where treatments are last line or not evidence based, such as the case with antibiotic use in neonatal sepsis).
- Landscaping analyses also need to take place in order to collect data for evidence-based decisions. WHO has

already provided an analysis of the clinical antibacterial pipeline. This exercise needs to be done on an annual basis to monitor further developments and should be expanded into the pre-clinical area and include alternative approaches. Importantly, surveillance data on antimicrobial resistance (e.g., WHO GLASS and GASP) must be taken into account, as well as monitoring antibiotic consumption and use, to have a better understanding of how to improve use of antibiotics. A first WHO global report on antibiotic consumption data is anticipated for end 2018. Based on this data and identified priorities, WHO has a role to play in developing general target product profiles reflecting the most urgent public health needs, as well as reviewing the funding landscape via the WHO Global Observatory.

- Directing investment into public health-driven R&D can support optimizing the use of existing antibiotics and the R&D of new antibiotics. Risk-taking can be greater where the gaps have been identified. Such investment should stipulate embedment of stewardship and access provisions and, appropriately, support all relevant sectors. Ensuring public return for such investments is crucial. Regulatory strengthening is also required to clarify and streamline processes for new (relevant) drug development, as well as ensuring appropriate quality and use.

Considering these steps ensures a focus based on public health needs and gaps. Ultimately GARDP and other initiatives will rely on broader political will and public leadership for success. Collaboration between all existing and new AMR R&D-related initiatives is also essential to maximise the effort directed towards stimulating R&D for new antimicrobials in the fight against multi-drug resistance. ■

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EVOLUTIONARY BIOLOGY AS A TOOL TO COMBAT ANTIMICROBIAL RESISTANCE

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Fundamental scientific investigations into how bacteria grow, and how they adapt to the development of resistance could have far reaching, translational applications in our attempts to combat antimicrobial resistance. Acquired resistance is usually the result of a mutation in the bacterial genome or the acquisition of DNA containing resistance genes from outside the cell; both of which can affect the fitness of the now resistant bacteria. Here we outline how this knowledge, and that of the related phenomena of epistasis and collateral sensitivity, can be used to preserve the efficacy of existing antibiotics by optimising treatment regimens and stewardship programmes to prevent the emergence and persistence of resistance within bacteria populations.

Why study fundamental cellular and evolutionary processes?

Basic science has a lot to offer in terms of combating AMR and as we scramble to come up with new and inventive solutions and fight for the limited funding available to implement them, it is worth carefully analysing the therapeutic possibilities, and opportunities, presented by increased understanding of the biology of the microbial pathogens themselves. Investigations into the fundamental nature of bacterial growth and evolution are central to our understanding of AMR mechanisms at the molecular level. This understanding is also central to drug design and target identification. There has been, excitingly, an increasing awareness over the last few years that knowledge of evolutionary relationships between resistance acquisition, and how "fit" resistant bacteria are, can be utilized in rationally designed antimicrobial stewardship programmes and treatment options which we will explore below.

Emergence of resistance; mutation and acquisition

Bacteria are remarkably adaptive, which is why they are so successful and have colonised every conceivable environment on earth. It is this adaptive nature that has resulted in bacteria being extremely proficient at evolving mechanisms of resistance to every antibiotic we have ever found, developed or invented.

The adaptation and subsequent resistance occurs at the DNA level within the bacterial cell and is selected for by the enormous quantities of antibiotics used annually for medical, veterinary and agricultural use. Rapid adaptation to stress, such as the emergence of resistance to an antibiotic, is a result of short generation times and two fundamental properties of DNA; mutation and horizontal gene transfer (HGT).

Mutations occur when mistakes are made during the replication of the DNA molecule. Most of these errors are corrected by the cellular replication machinery, but some are not. Of these, most will either not affect the survivability of the cell or will be detrimental, therefore the cell and its descendants will be uncompetitive and its lineage will die out. There are times, however, where a single base-pair mutation in the DNA leads to an amino acid difference in the protein product of the gene which gives that cell an advantage as that protein (or sometimes the RNA) may no longer be a suitable target for a specific antibiotic. An example is a mutation in the dihydrofolate reductase (DHFR) gene in *Staphylococcus aureus* which confers trimethoprim resistance. The DHFR protein plays an essential role in DNA synthesis, however, if the trimethoprim antibiotic molecule is bound to it, DHFR will no longer work and the cell will be unable to produce DNA and will therefore be unable to grow. The mutation in this gene changes a single amino acid in the DHFR protein which means a hydrogen bond which normally locks the DHFR and trimethoprim molecules together will not form, so the antibiotic can no longer bind to its target, resulting in resistance to trimethoprim *(1)*. Similarly, a mutation in a regulatory region of DNA such as a promoter, which drives gene expression, can alter the cellular biology enough to resist antibiotics. A good

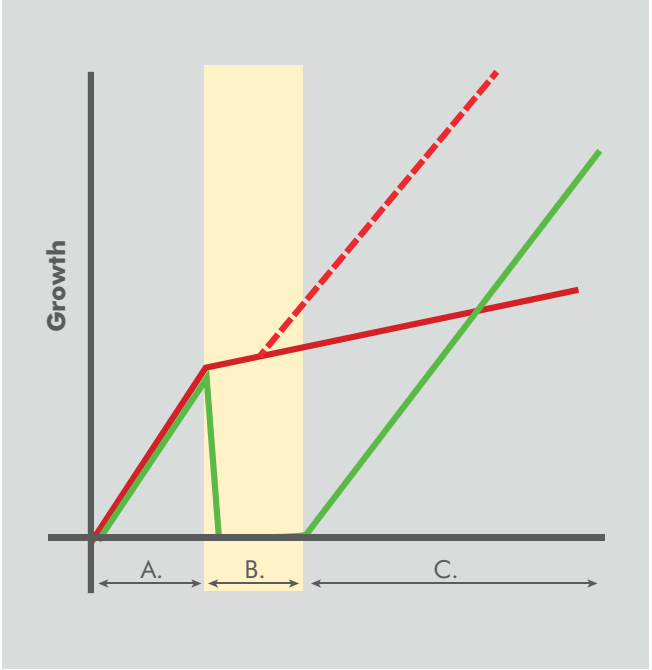
example of this is a single base-pair mutation in the promoter of the *ampC* gene in *Escherichia coli*, which confers resistance to a range of β-lactams, including ampicillin and penicillin. One base-pair change can result in a six-fold increase in expression because the mutation makes it more efficient *(2)*.

Horizontal gene transfer is the second major mechanism of adaptation to antibiotics and is the process whereby bacteria can acquire genes, by one or more of three main mechanisms. These processes are the acquisition of free DNA from their environment, usually originating from dead cells (a process known as transformation), being the recipient in a DNA transfer process directly from a live donor cell (called conjugation), or being infected with a bacterial virus (a bacteriophage) containing its previous host's DNA (a process known as transduction). Each of these, not mutually exclusive, mechanisms of HGT enable bacteria to acquire large sections of DNA containing many genes, often on discrete sections of DNA capable of catalysing their own movement and called mobile genetic elements (e.g., plasmids and transposons). As large regions of DNA containing many genes can be acquired in a single event, HGT can lead to the acquisition of more complex resistance genotypes which require multiple proteins to work such as the eight membered *vanG* gene cluster conferring vancomycin resistance in *Enterococcus* species *(3)*.

Fitness, compensatory mutation and collateral sensitivity

The ability of a bacterium to grow in any environment is referred to as its fitness. Fit bacteria grow well and replicate faster relative to unfit bacteria. When a bacterium becomes resistant to an antibiotic by one or more of the above mechanisms there is usually a fitness cost (also known as a biological cost). This refers to the phenomenon where the bacterium in which the mutation has happened, or which has acquired DNA from an exogenous source, is no longer as fit as it was before the mutation, compared to the ancestral, precursor strain (Figure 1, A). This can be measured by comparing their growth rates in the laboratory. The reasons for these fitness costs vary and may be due to, for example, the bacterial protein responsible for resistance being slightly changed and no longer working as efficiently as it did before, or newly produced, or differentially expressed, proteins being metabolically expensive to produce and/or interacting negatively with other cellular proteins or processes. In the presence of a selection pressure as strong as antibiotics this biological cost is not significant as without the resistance mechanism the cells do not grow or they die (Figure 1, B). However, in the absence of antibiotics, for example when treatment finishes, the impact of fitness on bacteria is fundamental to its survival and persistence within an environment because without the selective pressure of antibiotics, unfit resistant strains will be outcompeted by sensitive, more fit bacterial strains (Figure 1, C).

Figure 1: The growth of two identical bacterial populations are represented by the red and green lines. A: In the absence of antibiotic selection both populations display identical growth. B: Under the selective pressure of antibiotic (shaded region) the "red" bacterial population develop resistance quickly, which also has a fitness cost, indicated by a lower rate of growth. The susceptible green population are rapidly killed. The red dotted line represents a sub-population of the red population which, having undergone compensatory mutations expands rapidly. C: After removal of the antibiotic selective pressure, as would happen once therapy has finished, any remaining susceptible green population rapidly expands and soon exceeds that of the less-fit resistant red population. Note the population which have undergone compensatory mutations are now resistant and able to compete with the susceptible green population as they are of similar fitness. This means that this resistant population will be very difficult to displace



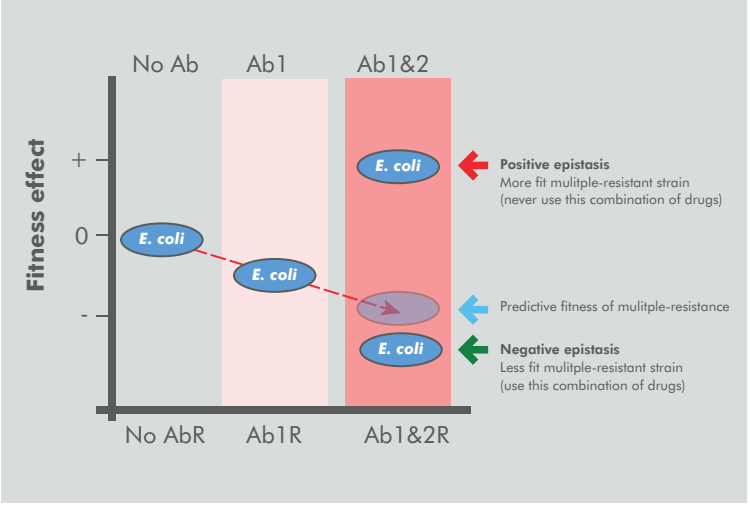
Examples of fitness costs associated with antibiotic resistance acquisition, either by mutation or HGT, are many and include the varied relative change in fitness of *Enterococcus faecium* following acquisition of one of several different plasmids conferring vancomycin resistance compared to the ancestral, plasmid-free strain. The fitness costs determined in these experiments ranged from a fitness cost of 27% to an actual fitness benefit of 10% (meaning the strain with the plasmid grew 10% faster than the ancestral strain) depending on the plasmid that was acquired *(4)*. Fitness costs also arise following mutation, for example mutations resulting in the overexpression of efflux pumps in antibiotic resistant *Pseudomonas aeruginosa (5)*.

Bacteria can often overcome the fitness cost of resistance development by a process known as compensatory mutation. This happens when one or more, often unrelated, mutations occur within the bacterial genome which restores fitness to the cell following acquisition of resistance by mutation or HGT. A globally important and clinically relevant example of this is compensation for the costs associated with rifampicin

resistance in *Mycobacterium tuberculosis*. Following mutations in the gene encoding the RNA polymerase that lead to rifampicin resistance, further mutations elsewhere within the genome have the effect of bringing to the fitness of the rifampicin-resistant strain back up to the levels of the ancestral strain (6). There are also specific instances where compensatory mutations result in a resistant strain which is more fit than the ancestral strain, for example, following acquisition of vancomycin resistance encoding plasmids in *Enterococcus faecium (4)*.

The acquisition of resistance, and indeed these compensatory mutations which can follow, can lead to another phenomenon known as collateral sensitivity. Collateral sensitivity can be defined as a change in susceptibility to one antibiotic upon becoming resistant to another. Collateral sensitivity is a translational phenomenon in that it could be used to design rationale combinatorial therapy where the emergence of resistance to one antibiotic will sensitise the cell to the other, leading to less chance of multiple-resistant strains emerging. An interesting example of collateral sensitivity networks being used to recommend combinatorial therapy is demonstrated with the experimentally determined synergy of a meropenem-piperacillin-tazobactam combination which supresses the evolution of resistance during the treatment of MRSA *(7)*.

Figure 2: Representation of epistasis with a susceptible *Escherichia coli* (No AbR) under no antibiotic selective pressure (No Ab) with a fitness starting point at zero. When the *E. coli* has evolved resistance (Ab1R) to the first antibiotic (Ab1) there is a fitness cost of minus one. This is predicted to change to minus two when resistance to the second antibiotic (Ab2) develops (Ab1&2R). However, sometimes the actual fitness cost is more (negative epistasis) or less than predicted (positive epistasis).



Epistasis and the management of AMR

Another layer of complexity which is being increasingly investigated with respect to AMR is the relationship between mutation or acquisition of resistance, and the genetic background of the host cell. These interactions are known as epistasis and occur when the same mutation, which is responsible for resistance, can have different effects on the fitness of the host cell depending on previous mutations and other differences in the genome (reviewed in *(8)*).

The hypothesis of translatable epistatic control of resistance is that if resistance emerges, or is acquired, by a cell which already has a pre-existing resistance genotype the effect on fitness of the second resistance may be different than if it would have emerged or been acquired in a susceptible cell (Figure 2). This has implications for the choice of antibiotics clinicians use as first, second and even third-line therapy. If resistance is taken as an inevitable consequence of treatment then we should aim for maximising the fitness cost of these resistances to the pathogens.

Predictable epistatic interactions give us an intriguing possibility to force pathogens down an evolutionary route which will maximise the fitness costs associated with multiple antibiotic resistances. If combinations and/or the order in which antibiotics are used give rise to multiple resistance phenotypes which have a greater than predicted fitness cost (negative epistasis) then it is possible that the use of these combinations in the clinic would prevent the emergence of fit multiple-resistant strains. Likewise, if combinations and/or the order of antibiotics is found to lead to multiple resistance phenotypes with less of a predicted fitness cost than the sum of the individual fitness costs then these combinations should not be used in the clinic as they may promote the emergence of fit multiple-resistant strains. Examples of both types of interactions have been previously reported in a wide range of different bacteria demonstrating that this is a common evolutionary phenomenon *(8)*. If a pathogen emerges with multiple resistances and is fitter than the ancestral strains from which it derived there is very little chance of it disappearing from the environment following the removal of the selective pressures of antibiotics. This problem is exacerbated in LMICs where there is less choice of available antibiotics and the access to and quality of antibiotics are less stringently controlled.

Conclusions

Understanding the evolutionary trajectories of AMR in clinically relevant bacteria will present us with a unique opportunity to be able to tailor antibiotic therapy to bacterial isolates with certain resistant profiles. The strategy of harnessing natural selection to suit our clinical requirements has the potential to prevent the emergence of resistant lineages in the population by specifically selecting for fitter, antibiotic-sensitive ones. This will extend the useful lifetime of antibiotics, both old and

new, concomitantly increasing the window of opportunity to discover new antibiotics and therapies. ■

Dr Alasdair Hubbard graduated with a BSc (Hons) in Microbiology from the University of Leeds in 2007 and a PhD from St George's, University of London in 2015. Post PhD, he worked as a Post-Doctoral Scientist at a molecular diagnostic company, Micropathology Ltd, and as a Research Assistant at the University of Oxford. He is currently a Post-Doctoral Research Associate at the Liverpool School of Tropical Medicine with research interests based around AMR, including the evolution of resistance in clinically relevant bacteria, the emergence and spread of AMR in different environments and identifying novel antimicrobials with activity to clinically relevant bacteria.

Dr Adam P Roberts has a BSc (Hons) in Applied Biology from Coventry University (1995) and a PhD from the University of London (2002). He worked as a Post-Doctoral Research Fellow, Lecturer and Senior Lecturer at University College London until joining the Liverpool School of Tropical Medicine as head of AMR research in 2017. His research focuses on the molecular biology of transferable antibiotic resistance in a variety of bacteria and the use of evolutionary biology to combat it. He also leads a citizen science drug discovery programme called Swab and Send; founded and runs the International Transposon Registry; and is an adviser to the Longitude Prize.

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ALTERNATIVES

BASIC NEGLECTED RESEARCH AGAINST AMR: WHAT IF PLANTS PROVIDED A SOLUTION?

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With the continued spread of antimicrobial resistance, new anti-infectives are needed with novel mechanisms of action and the potential to slow or circumvent resistance. The vast and diverse library of chemicals contained in plants, termed phytochemicals, represents a promising and largely untapped source of anti-infectives. This article discusses the highly favourable attributes of plants and their chemicals for drug discovery as well as their advantages over other natural products. In decades past, phytochemicals have not been comprehensively utilized in drug discovery efforts due to a combination of both real and perceived challenges. These challenges and their solutions are also discussed along with new technologies and recent discoveries that have revealed some of plants' tremendous potential as sources of anti-infectives. In recent years, attention has begun to increasingly fall on plants and phytochemicals for drug discovery efforts. It is clear that a re-emergence of phytochemicals in anti-infective drug discovery is inevitable and holds great promise for the development of new therapies against antimicrobial resistance.

Throughout history, plants have been the main resource for medicine for peoples across the world. Even today, it is estimated that in some regions, 80% of the population relies on traditional medicine for their medical needs *(1)*. A decoction of certain fruits may be drunk to relieve stomach ulcers, or a cataplasm of certain leaves may be used to dress infected skin to cure the infection. Countless specific examples of such treatment strategies exist in the traditional medical practices of communities across the world. For over a century, due to improvements in our understanding of biology and chemistry and in the instrumentation to study the two, evidence-based medicine has revolutionized the way in which diseases are treated. Indeed, disease pathology and drug mechanisms of action can be deduced to the molecular level, opening many doors to the discovery of new medicines. Now, instead of medicating a patient with a preparation of fruits or leaves which have been observed to work somehow, we can medicate with a pill or injection of an isolated chemical experimentally known to exert certain biochemical changes in the body. While there are many obstacles scientists face in developing new drugs, a foundational problem is the selection of sets or libraries of chemicals to explore in the effort to find chemical hits that favourably perturb a certain pathological biochemical process. This is where plants and the chemicals they produce become of immense value.

Plants as a source of chemical diversity

Plants are sessile, and as such are incapable of movement to protect themselves from predators. Unlike animals, a plant cannot bark to scare a predator, scratch to defend itself, or run away to protect its life. Instead, for the purpose of self-protection and communication with other organisms in the environment, plants produce a large array of diverse chemicals called secondary metabolites. Some plant secondary metabolites are used for attracting pollinators, while others are used for repelling insects, killing infecting fungi, and countless other functions. As such, any single plant in fact represents a library of hundreds to thousands of architecturally and stereochemically complex chemicals, termed phytochemicals *(2)*. What is more, many of these phytochemicals intrinsically act as anti-infectives: the fact that a cataplasm of certain leaves is capable of curing a skin infection indicates that anti-infective chemicals are indeed produced by and present in those leaves. As it turns out, evidence-based medicine has still barely scratched the surface of this botanical chemical space, even with the many clinical successes of phytochemical-based drugs *(3)*.

Natural products comprise all chemicals produced by living

organisms, and phytochemicals fall under this category. These two terms are typically used to refer not to primary metabolites (amino acids, sugars, and other chemicals directly responsible for life) but to secondary metabolites (produced as an adaptation to the ecosystem). Natural products share several important characteristics which make them extremely important for consideration in drug discovery efforts. Natural products inherently fall into regions of the biologically relevant chemical space, which refers to all chemicals that are biologically active *(4-7)*. This in fact makes sense, since the secondary metabolites produced by plants and other organisms have evolved in the context of surrounding organisms on which they act. Natural products exhibit a high tendency to be metabolite-like, and so they are largely compatible with cellular transport systems to gain entry into tissue *(8)*. On top of this, natural products possess massive chemical and structural diversity unmatched by synthetic small molecules, providing endless possibilities for drug scaffolds and pharmacophores *(9)*. For example, it has been demonstrated that 83% of natural product core ring scaffolds were not present in commercially available screening libraries and molecules *(10)*. Additionally, a retrospective analysis of one company's high throughput screening (HTS) campaigns showed that inclusion of natural products would have significantly improved hit rates *(11)*. And with all this, approximately 60% of the >126,000 compounds in *The Dictionary of Natural Products (12)* satisfied Lipinski's rule of five and are drug-like *(7)*. On the whole, natural products and derivatives thereof make up more than half of all the drugs in clinical use across the world, with at least one quarter of the total being contributions from plants *(13)*.

Advantages of phytochemicals over other natural products

While it is important to explore all types of natural products in drug discovery efforts, phytochemicals, or the chemicals plants produce, present key advantages. First and foremost is the advantage of traditional medicine, which enables a targeted, ethnobotanical drug discovery methodology (Figure 1). Traditional medicinal knowledge has played an important role in human history across the world and ethnobotanists have used this body of knowledge to identify plants and parts thereof with traditional medicinal uses against specific diseases. Because of this, a study that aims to discover hits against fungal infections, for example, could narrow the screening library down to extracts of or chemicals produced by plants that are documented to have been traditionally used against such infections. In this way, the drug discovery approach is targeted as opposed to being a random screening of plant species.

Another advantage is that plant extracts are relatively simple to make in large quantities, especially for those species that are abundant in the wild or amenable to cultivation. There are numerous ways to obtain an extract of a plant or plant part; examples include steeping plant material in an organic solvent such as methanol or ethanol or performing a decoction by boiling in water. More advanced methods include ultrasound-assisted extraction, accelerated solvent extraction, and more *(14)*. Once the extracting solvent has been removed by evaporation and freeze-drying steps, what remains is the large portion of the plant part's chemical library that was soluble in the extracting solvent.

Plant extracts represent an exciting source of new chemical entities in drug screening due to the potential presence of multiple active chemicals and active chemicals that act synergistically. Indeed, vincristine and vinblastine are two alkaloids present in the Madagascar periwinkle, *Catharanthus roseus*, which exhibit potent anti-cancer activity and are approved by the United States Food and Drug Administration (US FDA). Additionally, some very intriguing results have been reported on the therapeutic use of the whole plant of sweet wormwood, *Artemisia annua*, the source of hugely successful anti-malarial, artemisinin. A study of a rodent model of malarial infection showed that oral delivery of the dried leaves of whole plant *A. annua* reduces parasitemia more effectively than a dose of pure artemisinin matching the whole plant content *(15)*. The administration of artemisinin in this whole plant form was documented to result in a 40-fold increase in the drug's bioavailability. From extracts of whole plants, single chemicals that contribute to bioactivity are discovered through the process of bioassay-guided fraction. In this framework, crude plant extracts are fractionated, with highly active fractions identified in bioassays subject to further iterations of fractionation until a highly enriched fraction or chemical that is active is isolated.

Overcoming challenges and new opportunities

Despite the past success and great promise of phytochemicals, they have experienced diminished representation in drug discovery efforts in the past three decades. As explained in numerous review papers *(9, 16-18)*, this lack of representation is not associated with poor promise but rather a combination of factors: embracing of combinatorial chemistry as sufficient to provide all the needed chemical diversity, perception that phytochemicals and natural products in general are incompatible with HTS, re-isolation of known chemicals, difficulty of performing chemical modifications on more complex structures, isolation of individual compounds from complex plant mixtures, and difficulty of acquiring foreign plants.

In fact, over the years these perceptions and difficulties

have been overcome. Combinatorial chemistry has provided disappointing output in practice *(19)*, and now high throughput screens of similar synthetic chemicals often suffer from low hit rates *(20)*. With this have come two assessments:

- For a screening library, the characteristic of diversity within the biologically relevant chemical space is of greater importance than library size *(8)*; and
- Biologically relevant chemical space is better covered by natural products than by synthetic compounds *(4-7)*.

In order to increase the hit rate of plant extracts in HTS, methods such as pre-fractionation have been used *(21-23)*. These methods aim to remove groups of chemicals such as very hydrophilic and hydrophobic chemicals from extracts before screening since they have a very low likelihood of being biologically active. In fact, from nine screens of a microbial natural product library comprised of 1,882 active cultures, 79.9% of the activities were observed in the fractions while only 12.5% was found in the crude culture extracts *(24)*. Also established are dereplication strategies to prevent re-discovery of known chemicals *(25-27)*. Such strategies make use of a combination of analytical methods including ultraviolet spectroscopy, tandem mass spectrometry (MS), and nuclear magnetic resonance (NMR) in order to ensure correct basic structures determination. In terms of medicinal chemistry, the field has advanced to where modifying complex structures is no longer as difficult *(18)*. Finally, acquiring foreign plants can be done through established international procedures and best practices. Through the United Nations Convention on Biological Diversity, a treaty signed in 1992 by more than 150 governments, and the Nagoya Protocol, nations hold sovereign rights over their traditional medicines and should receive equitable benefits in exchange for sharing them and for the successes that result from their utilization *(28)*.

The realm of anti-infective drug discovery, then, is set for a re-emergence of phytochemicals and natural products in general. Not only are old challenges falling, but new technologies have opened the doors to innovation. One of the aims of metabolomics is to analyze the total metabolites contained in an organism under specific conditions at a specific time. This technology is aided by instrumentation such as MS and NMR that allow for masses and structures of chemicals in a sample to be elucidated. Combining this with genomics approaches allows for the identification of genes and their contributions to metabolite production. Taken together, these two technologies can inform scientists who seek to genetically engineer plants with an optimized biosynthetic pathway for the production of a particular metabolite *(29-31)*. Indeed, the use of plant biotechnology to "improve or enhance the inherent economic or culturally valuable traits of plants as described and influenced by ethnobotany" falls under the domain of the newly expanding field of ethnophytotechnology *(32)*.

Metabolomic analysis of botanical fractions can aid in identifying fractions most likely to contain bioactive constituents *(33)*. Such analyses can be paired with rapidly-improving information technologies to utilize online databases, allowing for deduction of potential bioactivities based on unique features of compounds. Metabolomics has also allowed for the study of the complex chemical mixtures of various plants prescribed in combination under traditional Chinese medicine and their effects on complex biological systems *(34-36)*.

Phytochemicals as a promising source of anti-infectives

The above discussion speaks to the potential of phytochemicals for drug discovery in general. Upon this foundation, an understanding can be built concerning their potential not just for the discovery of novel anti-infectives but for the circumvention of antimicrobial resistance. Keeping all the above in mind, a perplexing statistic remains: While 69% of all US FDA-approved antibacterials are natural products or derivatives thereof, 97% of these come from microbes while only 3% come from plants *(37)*. In fact, this statistic reflects not the potential of phytochemicals for the development of novel anti-infectives but rather a combination of three phenomena:

- The actual aforementioned neglect of phytochemicals as drug sources due to perceived and real challenges;
- The tiny portion of total plants studied to date for anti-infective drug discovery; and
- The challenges faced by laboratories across the world, particularly academic, that have identified anti-infective activity in plant extracts and need to progress to chemical isolation and lead optimization.

Over time, not only can the latter two challenges be expected to be resolved, but phytochemicals can be expected to regain the attention of scientists involved in anti-infective drug discovery. In general, consideration for phytochemicals is beginning to increase, with approximately 15% of the drug interventions in 2013 in the ClinicalTrials.gov database being plant-related, 60% of which coming from just 10 taxonomic families *(38)*.

Innovation is needed in order to slow down or circumvent the development of antimicrobial resistance, and this involves developing anti-infectives with different mechanisms of action capable of attenuating microbial pathogenicity. To this extent, a number of plant extracts have been identified. For example, an enriched extract of the Elmleaf blackberry, *Rubus ulmifolius*, demonstrated a potent ability to improve antibiotic efficacy

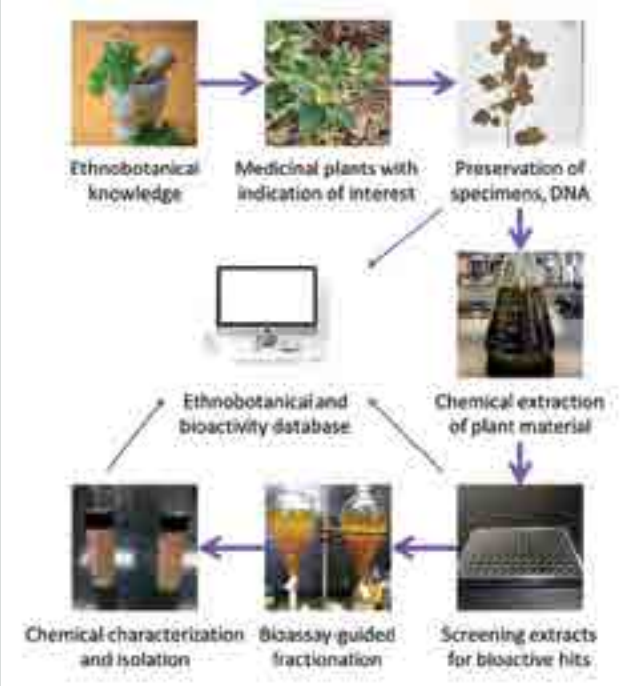
against staphylococcal biofilms *(39, 40)* and to eradicate pneumococcal *(41)* biofilms. Current research on this extract aims to develop it as a medical device coating and antibiotic adjuvant. Another example is an enriched extract of the European Chestnut, *Castanea sativa*. This extract demonstrated a potent ability to inhibit the quorum sensing system of cell-to-cell communication in methicillin-resistant *Staphylococcus aureus* (MRSA) *(42)*. This system of communication between cells is the chief modulator of pathogenicity in *S. aureus*; consequently, treatment with this *C. sativa* extract severely impaired MRSA pathogenesis in a mouse skin infection model without manifesting local or systemic toxicity *(43)*. Importantly, both of the plants mentioned here were included in preliminary screenings of plant extracts for anti-infective activity due to their reported use in traditional medicinal practices in the Mediterranean for the treatment of infections *(40, 42)*.

Perhaps the most important innovation of all is translating the following phenomenon from traditional medicine into the clinic: while antimicrobial resistance has always developed to single chemicals used in monotherapy, it has not emerged detectably where traditional healers have treated patients with whole plants. One example of this is artemisinin and its parent plant, *A. annua*. It is established for numerous diseases, including malaria, that resistance to two or more drugs administered in combination will develop more slowly. This is because instead of requiring mutations to yield resistance to one mechanism of action, now the pathogen would need to simultaneously develop more mutations to occlude yet other mechanisms of action. For this reason, artemisinin is commonly co-administered with other anti-malarials *(44)*. A recent study showed that oral delivery of the dried leaves of whole plant *A. annua* overcame existing resistance to artemisinin in a rodent model of malarial infection *(45)*. Moreover, stable resistance to the whole plant took three times longer to develop than stable resistance to artemisinin alone. It may very well be that treatment with whole plants or extracts thereof, which contain hundreds of unique secondary metabolites, represents the most advanced form of combination therapy. Perhaps whole plant or crude extract treatment utilizes the plant's intrinsic multicomponent defense system to make the development of enough resistance mutations statistically unfeasible. Such observations provide compelling rationale to further explore crude plant extracts for the minimal components responsible for yielding the full multi-pronged defence. To this extent, the US FDA has a botanical drug track which accommodates botanical compositions that are well-defined *(46)*.

Conclusions

It is clear that phytochemicals represent a promising source of novel anti-infectives and agents for possibly circumventing antimicrobial resistance. What is more, as a drug discovery resource, phytochemicals remain largely untapped. A recent report analyzing drugs approved by the US FDA has concluded that natural products in general and derivatives thereof have to date contributed much to drug discovery efforts, are likely to continue contributing in the future, and that public and private investment into natural product drug discovery is highly justified *(37)*. There exists much opportunity for innovation based on an understanding of phytochemicals. For instance, a current paradigm in drug discovery is to begin with drug-like synthetic chemicals and sift through them in search of bioactivities. However, considering that phytochemicals represent one of the riches sources of biologically-relevant chemicals, an alternative paradigm to explore is to begin with bioactive plant secondary metabolites and then apply filters of drug-likeness, pharmacokinetics, and so on. With attention now increasingly directed at phytochemicals as a promising source anti-infectives, their re-emergence as a major contributor to this field is but imminent. ■

Figure 1: The ethnobotanical approach to drug discovery. Knowledge of traditional medicinal uses for plants is consulted to identify plants with potential therapeutic phytochemicals. These plants are then collected, their identities are verified, and a specimen of each plant is preserved in an herbarium. Bulk plant material is prepared for chemical extraction, and the extracts are employed in bioactivity screens. Bioactive extracts then go through the process of bioassay-guided fractionation, eventually leading to the isolation of single bioactive phytochemicals. Throughout this process, data is recorded in a database



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PHAGES AS ANTIBACTERIAL AGENTS: LABORATORY TRAINING IN DEVELOPING COUNTRIES

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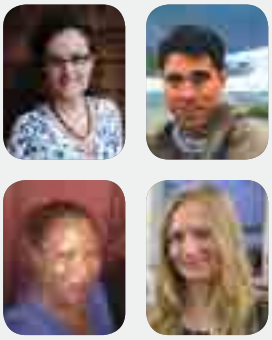


By 2050 an estimated 10 million people will die each year from antibiotic-resistant infections — almost 90% of those in the developing world *(1)*. Thus, alternatives to conventional antibiotics are particularly important for the developing world, with the added criteria that they must also be inexpensive, given resource limitations in low- and middle-income countries. Bacteriophage (phages) are promising antimicrobials that are not only effective against antibiotic-resistant bacteria and inexpensive to develop, they are also relatively easy to isolate from contaminated environments. We describe here an educational programme through which we are bringing phage expertise to public health scientists in developing countries.

Using phages to address antimicrobial resistance in the developing world

Phages are bacteria-killing viruses that are found wherever bacteria are present. Since they are highly specific, they can be selected to target only certain bacteria while leaving other, helpful bacteria as well as human and animal cells unharmed *(2)*. Numerous organizations, including the Gates Foundation, the Wellcome Trust and the US National Institutes of Health, have identified phages as an important technology to help overcome the antibiotic resistance crisis. Indeed, phage products could be developed and used to kill antibiotic-resistant, as well as antibiotic-sensitive, bacteria in food, water, livestock and people, potentially saving thousands of lives – if not millions *(3)*. Phages are also safe, having been used for more than 100 years in the former Soviet Union *(4)*. In addition, the US Department of Agriculture as well as the Food and Drug Administration have approved phage products in the United States *(5)*. However, no phage products are available yet in Africa or Asia, and only a small number of academic groups in the developing world have conducted any phage research.

Phages for Global Health is a non-profit organization whose mission is to facilitate the application of phage technology in developing countries. We accomplish this in two general ways:

- Delivering short-term laboratory training workshops through which we teach scientists in developing countries how to isolate and characterize phages locally.
- Partnering with developing world researchers to co-develop phage products for specific applications in their countries.

Our overall goal is to empower these scientists to develop phage products that will be both technically effective and socially accepted within their local cultural contexts.

The purpose of this article is to describe our laboratory training workshops in more detail. The pilot workshop was hosted during July 2017 in East Africa at Makerere University (Uganda). Additional partner universities included the University of Nairobi (Kenya), Sokoine Agricultural University (Tanzania) and Kampala International University (Uganda). During the two-week workshop, 25 scientists from Ethiopia, Kenya, Tanzania and Uganda gathered to learn the key essentials of phage biology as well as to receive hands-on laboratory training. Plans are underway for a repeat workshop in East Africa for a new cohort of scientists (hosted in Kenya), and also for future workshops in West Africa (hosted in Nigeria), northern Africa (in Egypt), southern Africa (in Botswana), as well as our first workshop in Asia (in Indonesia). We describe here the logistical considerations for delivering the workshop, the key topics covered, and also early impact data from the initial East African cohort.

Planning for the workshop

Preliminary discussions began more than a year before the actual workshop, and many of our early planning efforts were

focused on determining the location, budget, instructional content, and participant requirements. Our African partners, which included a panel of infectious disease scientists from leading universities across East Africa, played integral roles in the decision-making processes, providing local technical and cultural guidance.

Workshop location: We first needed to establish a host location for the workshop. Holding it at an academic institution in the United States or Europe would make reagent and material acquisition trivial and efficient, but could greatly increase the cost, since participants would require support for international travel and expensive lodging at the workshop venue. On the other hand, the training would be more realistic if it were conducted in a typical laboratory on location in East Africa, rather than in state-of-the-art facilities overseas. After some consultation, we decided that Makerere University in Kampala, Uganda, was the best location, having the requisite facilities and being centrally located in the region. In addition, a small team of researchers at Makerere University had already begun conducting basic phage isolation experiments, so they would be able to provide onsite technical support before and during the workshop (e.g., growing up batches of bacteria and phages for use during the workshop).

Budgetary needs: Next we needed to determine an appropriate budget based on the location. This included working out the logistics involved in transporting, housing, feeding, and providing laboratory supplies and networking opportunities for the participants throughout the two-week workshop. Having local support from partner institutions made this process much easier, though required substantial communication and time. Once the budget was set, fundraising was accomplished through formal grant applications to non-governmental organizations as well as through crowdfunding. Ultimately, support came from the Bill & Melinda Gates Foundation, the Conservation, Food & Health Foundation, and also many individuals who donated through the online GlobalGiving platform (https://goto.gg/25810). Materials and equipment were also donated by companies and research organizations (EpiBiome and the University of Leicester) interested in fostering workshops such as this.

Instructional content: Our team, which included the workshop instructors (Drs Chan, Nale and Clokie) and project manager (Dr Nagel), drafted the syllabus and laboratory manual for the technical components of the workshop and outlined the laboratory supplies that would be needed. In addition, a public engagement specialist from the University of Nairobi, Dr Erastus Kang'ethe, agreed to teach a session on how African scientists might dialogue with and educate stakeholders regarding the potential use of phages as antibacterial agents in their countries. This was a critical part of the workshop, since public understanding and buy-in will be essential as local scientists work to develop and apply phage products in Africa.

Participant selection: We decided that the maximum number of workshop participants we could accommodate would be 25, taking into account not only on the selected laboratory space, but also the optimal instructor-to-participant ratio. Approximately four months before the workshop, we announced the call for applications. Our East African partners publicized this through existing university communication channels (email lists, department posting boards) and professional networks (medical and veterinary associations and boards). Applicants from throughout East Africa were invited, including scientists at a variety of professional levels, such as faculty members, lecturers, students, lab technicians, university administrators and government scientists. Our intention was to incorporate both senior scientists in positions to influence how resources at their institutions would be used for future phage research, as well as junior scientists who would work in the laboratories on a daily basis.

Each candidate was required to submit a prepared application and provide two letters of recommendation. The final participants were selected based on three criteria: 1) possessing appropriate laboratory skills; 2) demonstrated enthusiasm for learning phage biology and 3) an indication that their institution would provide ongoing support for future phage teaching and research. In total there were 81 applicants from four countries (Ethiopia, Kenya, Tanzania, and Uganda) and from a variety of institutions, including universities, national reference laboratories, and ministries of health, agriculture, livestock and fisheries. The final 25 participants came from all four countries and represented 14 different institutions. The result of this selection process was an energetic, enthusiastic and diverse group of students, veterinarians, clinicians, faculty members and administrators who formed strong relationships through the course of the workshop.

Workshop lectures

There were two broad goals for the workshop:

- Learn phage biology, experimental techniques and potential applications.
- Develop a network of phage researchers that spanned East Africa as well as Europe and the United States.

These objectives were achieved through a daily schedule that included morning lectures and afternoon laboratory sessions, with significant interactions amongst all participants and instructors. The lectures were designed to cover key areas of phage biology and to provide the theory necessary to fully understand the content of the laboratory sessions.

This included general topics such as an introduction to phage biology, structure, ecology, genomics, applications, bioinformatics, and also public engagement strategies. As appropriate, the instructors also presented case studies from work in their own laboratories.

Specific learning goals included participants gaining a working knowledge of: 1) the fundamentals of phage research, particularly the lytic, temperate and pseudolysogenic lifestyles and the biological consequences of each cycle; 2) phage recognition and adsorption to host receptors, the process of genetic material penetration and production and release of new phage progeny; 3) phage structure and proteins involved in infection, replication and bacterial lysis; 4) techniques used to image/enumerate phages; 5) molecular and genome characterization of phages and the application of this to further phage research; 6) the use of model phages to study molecular mechanisms of phage interactions with their host bacteria; 7) phage ecology, particularly how they infect and modulate bacterial biology in environmental and medical settings; 8) phages as potential novel therapeutics (using whole phages or phage-based products) or as diagnostic tools (exploiting phages or phage proteins as selective tests for rapid and cheap diagnostics); 9) phage discovery and history, diverse applications of phages as therapeutic and diagnostic agents; 10) current phage research, particularly those that relate to problems of interest to our cohort; 11) in vitro and in vivo models appropriate for studying phage-bacterial interactions, including a range of "realistic" models demonstrating the importance of using "real life" conditions in experimental studies; 12) strategies to develop phage mixtures that sensitize bacteria to antibiotics or reduce probability of bacteria developing resistance against the phages; 13) how to detect toxin genes in phages so that they may be avoided in therapeutic products, and 14) methods to facilitate community awareness and cultural acceptance of phage products in Africa. In addition to lectures presented by the instructors, participants were given a set of pre-reading materials (research articles and reviews), which they discussed amongst themselves and presented to the group.

Laboratory training

For the laboratory sessions, participants were divided into groups of three, with each group comprised of scientists from different countries and professional levels, to the extent possible. The overall learning goals were to gain hands-on experience of how to work with model phages and bacterial isolates, as well as how to isolate and characterize new ones from the environment. We used phages that infect *Escherichia coli* and *Pseudomonas aeruginosa* because they are relatively easy to isolate and manipulate. Specific topics and activities included: 1) sample collection from sewage, soil and water; 2) direct and enrichment procedures for isolating phages; 3) isolation of bacteria using specific media for *Escherichia coli* and *Pseudomonas aeruginosa*; 4) how to make serial dilutions, quantify phages and purify plaques; 5) how to make clonal preparations of newly isolated phages, including isolating isogenic phages to ensure that downstream work is carried out on one phage; 6) phage and bacterial viability assays using PFU and CFU enumeration; 7) host range analysis using quantitative approaches and calculations of multiplicity of infection and efficiency of plaquing, and 8) how to work with phages in biofilms.

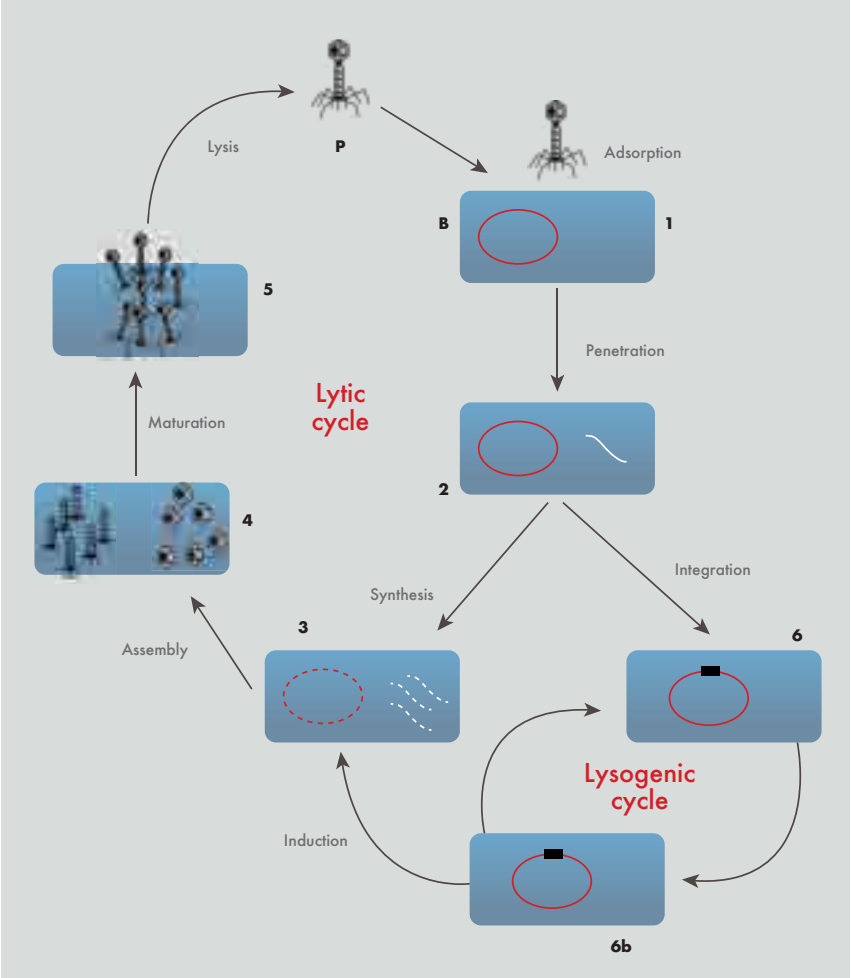
In addition to studying the physical characteristics of phages, participants also learned how to determine the genomic properties of phages using simple molecular approaches (DNA extraction and PCR) and bioinformatic tools. To illustrate these, sample DNA data and open source tools were used to teach basic genome annotation approaches and visualization techniques. The programmes discussed included Rapid Annotations using Subsystems Technology (RAST), Artemis, and Molecular Evolutionary Genetics Analysis (MEGA). Specific and degenerate primers were designed using Primer3, and primer stats and prophage prediction were conducted using PHAge Search Tool (PHAST). By the end of the workshop, all the participants had successfully isolated phages and purified them through several rounds of plaque assay.

Outcomes and impact

At the end of the workshop, we surveyed the participants to assess which aspects had been most useful. They universally reported that the workshop was extremely informative and significantly improved both their theoretical and practical knowledge about phages. They particularly appreciated the many opportunities to interact with the instructors, and they found the emphasis on practical and bioinformatic aspects very valuable.

Regional network development: During the course of the workshop the participants developed a set of resolutions, led by the senior African representatives who have experience working at governmental levels and influencing policy. These resolutions are focused on ways to impact phage research within the East African context. The specific plans include 1) incorporating phage biology into university curricula; 2) initiating new phage projects and grant proposals; 3) publishing a collective paper on the novel phages identified during the workshop; 4) establishing a regional shared phage bank, and 5) engaging with stakeholders, especially regulatory authorities, in order to raise awareness about the benefits of phages for addressing AMR. The participants also established a WhatsApp group for sharing ideas, and this group communicates quite

Figure 1: Diagram showing lytic and lysogenic life cycles of phages



regularly and actively.

International connections: Fortuitously, our pilot workshop took place just a few weeks before the Evergreen International Phage Meeting in Olympia, Washington, and six of the participants from the workshop attended the conference, with special funding provided by the Bill & Melinda Gates Foundation. This conference is arguably the most cutting edge phage meeting worldwide and consisted of presentations on the fundamentals of phage biology, applications and therapy. Special sessions on phage commercialization were included for our workshop participants, who also attended all the main conference sessions. They reported that participating in the East Africa workshop made the conference accessible and that they would not have been able to fully understand the presentations without first attending the workshop.

Measuring impacts: Three months after the pilot workshop, we again surveyed the participants to evaluate any new activities that had been initiated as a result of the workshop. Notably, many of the newly formed resolutions have begun to be realized. Faculty members and students have initiated five new phage projects, incorporated phage biology into teaching curricula at four institutions, and have submitted two grant proposals to fund phage research, including one multi-university consortium grant. These outcomes are an indication that the initial goals of the workshop have been achieved, namely to teach key aspects of phage biology and to develop a network of scientists who can work together to further phage applications in the region. Clearly this is just a start, and further resources will be required. Nonetheless, we are confident that this effort is transformative and a major first step to improve capacity and infrastructure, not only in East Africa, but eventually in other regions of the developing world as well.

Phages (P) are viruses that specifically infect bacteria (B). Phages adsorb to specific receptors of susceptible bacteria, release DNA (1), which penetrate (2) and synthesis new particles (3). The particles assemble (4), form new phages and destroy the host bacteria (5) during the lytic cycle. Lytic phages can be developed for therapeutic purposes. Temperate phages integrate into the bacterial chromosome (6) and replicate (6b) in the in a stable fashion within the host during the lysogenic cycle, but can be induced to enter into the lytic pathway. Temperate phages can affect the properties of bacteria by contributing to their diversity, evolution and pathogenicity. ■

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Dr Tobi Nagel, PhD, is Founder and President of Phages for Global Health, a non-profit organization that facilitates the application of phage technology for underserved populations. She is also a member of the Fulbright Specialist programme, focusing on building scientific infrastructure in developing countries. Prior to founding Phages for Global Health, Tobi worked in the pharmaceutical industry for 15 years. She holds a PhD in Medical Engineering from the Harvard-MIT Division of Health Sciences and Technology.

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Dr Janet Nale, PhD, is a Postdoctoral Research Associate at the University of Leicester in the Department of Infection, Immunity and Inflammation. Her expertise is in the development of phages as alternative therapeutics for pathogenic bacteria, utilizing in vitro and in vivo model systems. She optimized the first phage cocktail to eradicate Clostridium difficile. Janet is originally from and educated in Nigeria and obtained her MSc and PhD from University of Leicester.

Professor Martha Clokie, PhD, is Professor of Microbiology at the University of Leicester. Her laboratory focuses on phage research, and she has published 56 papers and edited three books on phage biology. Over the last 15 years, she has pioneered studies of developing phages for therapeutic purposes for humans and animals. She has a track record of translating fundamental science to applied settings for human and animal health. She obtained her PhD from the University of Leicester.

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COMPLEX BONE AND JOINT INFECTIONS: TREATMENT WITH BACTERIOPHAGES AS SALVAGE THERAPY

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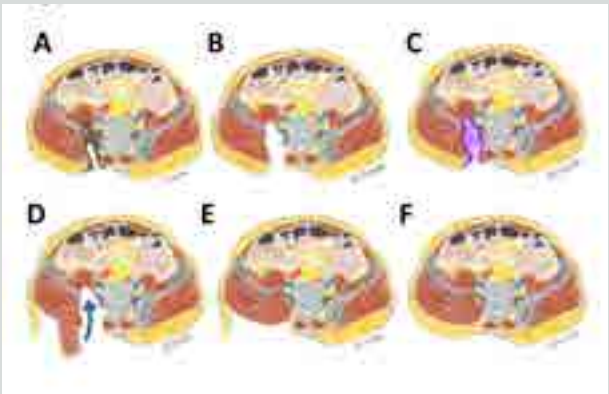
The treatment of bone and joint infection (BJI) is challenging, as the recurrence rate remains high despite conventional strategies based on surgery and prolonged antibiotherapy. We report on the use of bacteriophages produced in France (according to European good manufacturing practice) as salvage therapy in patients with complex BJI. A personalized bacteriophage cocktail was produced and applied locally during surgery. We think that this unique experience of innovative personalized medicine with bacteriophages is the first step to better identify eligibility criteria for clinical trials involving patients with more common BJI. Personalized phage therapy would be an excellent adjuvant treatment to improve the prognosis of BJI.

Background and burden of BJI

Different kinds of bone and joint infection (BJI) have been described and are associated with different therapeutic strategies and prognoses *(1)*. Some of them, such as uncomplicated childhood osteomyelitis, are easy to treat, requiring short-course antimicrobial therapy without surgery. Others, such as implant-associated BJI, which represent a very heterogeneous group, are more complex to treat and eradication of the pathogen is challenging. Indeed, pathogens develop various strategies to persist in *vivo* in such patients at the site of infection. Most bacteria, but especially staphylococci and *P. aeruginosa* are able to produce biofilm on the material surface or in a dead bone segment, so-called sequestrum *(1)*. Currently, the only way to eradicate biofilm is to remove it mechanically, i.e. to clean remove the implant and/or to resect all sequestrum. Biofilm is not the only way for bacteria to persist, they are able to invade bone cells then to persist by reducing aggressive virulent behaviour and form an intracellular sanctuary (especially *S. aureus*). Among implant-associated infections, it is important to distinguish prosthetic-joint infection from long-bone implant associated infection, also called osteomyelitis. Most prosthetic-joint infections are located at the hip or the knee in the elderly. These infections constantly need surgery and prolonged antibiotherapy. In the case of acute prosthetic joint infection (inoculation <1 month), the surgery consists in a debridement and a surgical lavage, with implant retention and the exchange of the mobile part only of the prosthesis (i.e., polyethylene articular inert element that allows mobility between the implants). In patients with chronic infections, one-stage (explantation and preimplantation during the same surgery) or two-stage (explantation, then reimplantation several weeks later) exchange procedure is mandatory, but these surgeries are significantly more invasive, with risk for peroperative hemorrhage and for more anesthetic complications, with a putative loss/reduction of motor function *(2)*. In patients with chronic long-bone implant associated infection, the surgical strategy depends on the local spread of the disease that may be limited to the cortical bone, or expanded to the medullary bone with instability (this is called septic pseudarthrosis), requiring

Figure1: **Patients with a right sacro-iliac osteomyelitis with bone exposition (panel A) requiring a two-step surgery with bone debridement (panel B), local application of negative pressure therapy (panel C), and then particular additional surgery with muscle and skin and soft tissue flap to cover the defect (panel D, E and F)**



large bone resection followed by complex reconstruction *(3)*. Some patients also have skin and soft tissue defects with bone exposition, that requires a particular additional surgery with a skin and soft tissue flap to cover the defect (Figure 1). In such patients, it is difficult to imagine a cure if the skin and soft tissue reconstruction is not considered. All these situations require a prolonged antimicrobial therapy from six weeks to three months targeting the pathogen(s) involved, using intravenous and/or oral antibiotics, depending on drug susceptibilities (antibiogram). The success rate reaches 60 – 80% in acute prosthetic joint infection, 80 – 90% in chronic prosthetic joint infection and varies from 30 to 90% in patients with chronic long bone implant associated infection, depending on the stage of the disease, and if a bo ne and/or skin and soft tissue reconstruction is required *(1-3)*. In all of these patients, especially those with the most complex disease form, team-work is required to personalize disease management, determine an optimal medico-surgical strategy, and limit treatment failure, motor disability and amputation risk. Concerning the burden of BJI, a national study in France based on the national health administration database demonstrated that BJIs have a major clinical and economic impact. The overall prevalence was 54 cases per 100,000 inhabitants, which agrees with other studies performed in Europe and the United States. BJI prevalence is age- and sex-dependent, with a six-fold increase in patients between 50 and 70 years old. Most patients have underlying diseases, especially diabetes, and related comorbidities, including ulcer sores and vascular disorders. In 2008, for France, only for the total direct cost of BJI-related care, the estimates reach €259 million (€7,178 per hospital stay); one of the main contributors to this cost being the rate of hospital readmission (19%) *(4)*. However, these cost estimates did not take into account indirect costs such as those associated with long-term care or rehabilitation. In fact, the long-term bone and joint infections-associated morbidity, which is estimated to involve 30 – 40% of bone and joint infection patients, mainly explains the massive individual and societal impact of bone and joint infections, including long-term or definitive incapacity for work, partial or total disability, amputation, reconstruction and the high inpatient and outpatient costs.

As a consequence, the French Health Ministry founded a network of hospital regional centres called CRIOAc (Centres de Référence des Infections Ostéoarticulaires complexes), with dedicated funding. Their mission was to facilitate the management of complex BJI, to provide an access for patients to experienced clinical teams, to benefit patients from adapted techniques for complex BJI and finally to promote clinical, translational and fundamental studies and researches. At the present time, nine CRIOAcs are approved in France, including the regional reference centre of the Auvergne-Rhône-Alpes Region: the CRIOAc Lyon (http://www.crioac-lyon.fr).

BJI is more and more associated with antimicrobial resistance

As BJI frequently occur after trauma and surgery, most of them are healthcare-associated infections. BJI are classically associated with staphylococci, streptococci, enterococci enterobacteriaceae, *Pseudomonas aeruginosa* and/or anaerobes. Staphylococci may be resistant to methicillin, and potentially to the most important drug combinations for the treatment of staphylococcal BJI: rifampin and fluoroquinolone. Some Enterococci are resistant to amoxicillin. Enterobacteriaceae occasionnaly produce extended spectrum betalactamases or carbapenemases and are frequently resistant to fluoroquinolone. *P. aeruginosa* are sometimes multi-resistant, with the emergence of pan drug-resistant strains. The impact of antibiotic resistance on the outcome of BJI is not well established, but is likely significant, as suboptimal antimicrobial therapy is associated with a higher risk of relapse. Furthermore, the bone penetration of most antibiotics is limited, especially for beta-lactams and glycopeptides, with only about 20% of the administered drug able to penetrate into bone. Finally, new antibiotics approved by FDA and/or EMA in the last five years (large spectrum beta-lactams such as ceftolozane/tazobactam and ceftazidime/avibactam; lipoglycopeptides such as dalbavancin; new oxazolidinones such as tedizolid) are not expected to be evaluated in patients with BJI.

In this context, therapeutic alternatives are much needed and very welcome to circumvent multi-resistance and therapeutic deadlocks because of clinical or physiological reasons.

Phage therapy and the Eastern European experience

Bacteriophages or phages are one of the most abundant organisms in the biosphere. A bacteriophage is a virus able to infect a bacterium. Using lytic bacteriophages as

antibacterial treatment is a very interesting approach to treat bacterial infections. Antibiotics need several intravenous or oral administrations in a day to reach significant concentrations and remain above the bacterial microbial inhibitory concentration (MIC) at the site of infection. Lytic phages act differently as they infect and rapidly kill the targeted bacteria by taking over its cellular machinery to produce new phagic components to ultimately assemble and release numerous new phage particles, that can infect gain bacteria from the same strain that are locally present. This latter phenomenon, in comparison with antibiotics, is exponential and self-sustained after a single or a few administrations. Lytic phages penetrate into tissues and remain present as long as multiplication in a susceptible bacterium is possible at the site of infection. Then, they are eliminated by the body when all susceptible bacteria are eradicated. No effect of phages on healthy tissue and cells has been reported because of their high specificity towards bacteria *(5)*.

The clinical practice of phage therapy is common in Eastern Europe, and in particular in the Republic of Georgia (Eliava Institute) and in Poland (Hirszfeld Institute of Immunology and Experimental Therapy) *(6-8)*. Historically, George Eliava was a collaborator with the French microbiologist Felix d'Hérelle from the Pasteur Institute, who discovered phage therapy in 1917. George Eliava exported the clinical practice of phages to Tbilisi in the early 1920s by starting to use a mix of phages (a "cocktail") named "Pyophage". That product targeted *Staphylococcus aureus*, *E. coli*, *Pseudomonas aeruginosa*, *Proteus spp*., and *Streptococcus spp*. It was produced commercially in France until 1978. Following private investment, members of Eliava institute developed in the late 1990s a new phage company, Biochimpharm, that produces (but without following the European good manufacturing practice (GMP)) its own licensed versions of Pyophage. This "fixed" cocktail is currently available in public pharmacies throughout the country *(6, 7)*. In Poland, the approach is different, as it is based on selection of active phages from a bank against the individual bacteria that infects the patient, to adapt the treatment (personal medicine) and to ensure the antibacterial activity of phages used *(6, 8)*. Polish phages are also not produced according to European GMP standards.

In western Europe and the United States, a few patients have been occasionally treated with imported non-GMP phages, especially for patients with recurrent bacterial infectious diseases potentially associated with an extreme condition (Figure 2) *(6-10)*. In such countries, medical health authorities consider that it is of a crucial importance to respect GMP standards when producing phages for conducting clinical trials and targeting market authorizations, as manufacturing of bacteriophage drugs requires the elimination of bacterial components that are generated during the production process

Figure 2: Map of the Europe with the inventory of places where phagotherapy for BJI is used

such as toxins, in order to limit pyrogenicity and adverse events that may arise during phage administration/use.

Chronic osteomyelitis is currently one of the indications of phage therapy in Eastern Europe, especially in patients infected with multidrug-resistant isolates *(6-8)*. Indeed, there is no correlation between antibiotic resistance and phage efficacy as bacterial killing differs between antibiotics and phages. In this clinical situation, phages that are produced in a liquid form are used alone most of the time, without surgery, in patients with fistula or bone exposition. Phages are inoculated directly throughout the fistula or directly applied on an exposed bone using nebulization or direct local applications (Figure 3). In such patients, it is believed that phages go to and penetrate into infected bone in a step-by-step manner, by infecting the pathogen that liberates new phages that then penetrate themselves into bone and bacterial biofilm.

Manufacturing of bacteriophages by Pherecydes in France

Pherecydes owns a library with the ability to produce various bacteriophages targeting *P. aeruginosa* and *S. aureus*, belonging to Pherecydes Pharma library. Indeed, a specific bacteriophage targeting for instance *P. aeruginosa*, could be not always be fully active on all *P. aeruginosa* strains, that's why, as antibiotics, an in vitro evaluation of the phage activity, as it is currently performed for antibiotics (antibiogram) could be particularly relevant. The activity of phages are tested on the patient's strain by performing a phagogram (identification of the strain's susceptibility to the bacteriophage, on the model of antibiogram used for antibiotics) using two different in vitro methods to be able to prepare a cocktail of the most active bacteriophages on a particular clinical strain (Figure 4).

The CRIOAc network in France and the selection of patients for the use of bacteriophages in CRIOAc Lyon

The CRIOAc network aims to facilitate the management

Figure 3: **Patient with a tibia chronic osteomyelitis with bone exposition, for whom bone debridement with antibiotherapy followed by skin and soft tissue reconstruction is considered as essential to obtain a cure (panel A). Patient with femoral chronic osteomyelitis with purulent discharge from a fistula. Bone debridement is here also required, but not skin and soft tissue reconstruction (panel B). Chronic long bone osteomyelitis could be managed with only phagotherapy Eastern counties, by inoculated directly the phage in conta ct with the bone defect or throughout the fistula (panel C; from Kutateladze *M. Trends Biotechnol.* 2010)**

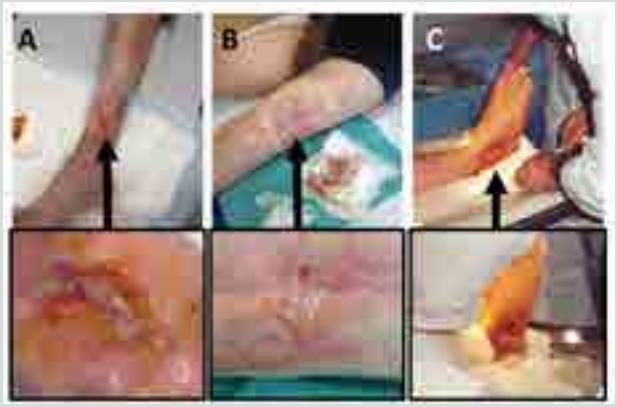


Figure 4: **Phagograms were based on a plaque assay (panel A) and a killing assay (panel B). Three out the four phages tested on the patient's strain led to the formation of plaque forming units (panel A, upper picture, red arrow heads) in the bacterial layer on the agar plate. The EOP score calculated with the phage titer derived from the dilution series on the patient strain (panel A, upper picture) and the dilution series on the reference strain (panel B, lower picture) was high for these three phages. These phages were considered as active and efficient. By contrast, although Phage D led to a partial lysis of the bacterial layer no PFU were visible, this phage was considered as inactive. In the killing assay (panel B), three out of the four phages showed a complete inhibition of the patient's strain growth (PN1777, PN1797, PN1658), while one phage (PN1658) had no impact on the growth PN1658**

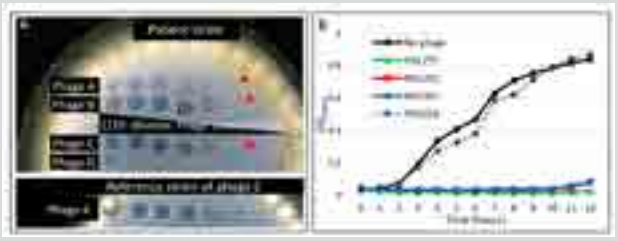
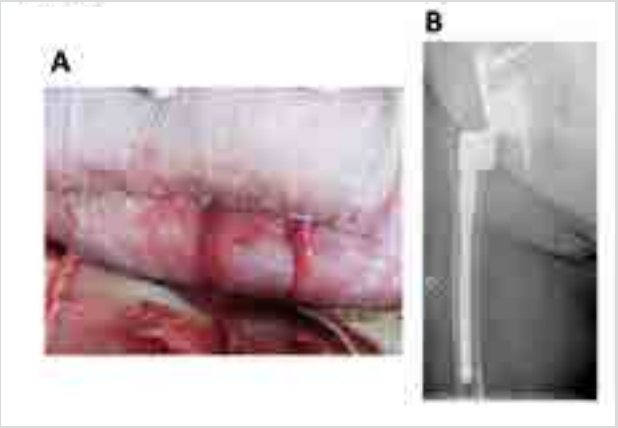


Figure 5: **Eighty-year-old patient with purulent discharge (panel A) during a relapsing polymicrobial prosthetic-joint infection. The prosthesis was previously already change four times in the past for infections. As there was no prosthesis loosening at X-Ray, it was difficult to imagine an explantation without serious bone damage (fracture) and peroperative risk of complications (bleeding) or death**



of complex BJI and to provide an access for patients to experienced clinical teams. Among the nine CRIOAc approved in France, the CRIOAc Lyon (http://www.crioac-lyon.fr) particularly aims to facilitate access to innovation for patients, from different approaches that include rapid and molecular diagnosis of BJI, use of local antibiotics, new devices such as silver-coated implants or bone substitutes with antimicrobial effects, and phagotherapy. The CRIOAc Lyon and Pherecydes are partners in a programme called PHOSA (http://www.phosa.eu) whose the final objective is to assemble and use cocktails of bacteriophages for patients with BJI.

CRIOAc Lyon recruits about 500 new patients each year, with heterogenous forms of BJI, including 100–150 prosthetic-joint infections, and 100–150 long-bone chronic osteomyelitis. Other forms of osteomyelitis, such as pelvic or mandibular osteomyelitis, are less prevalent. All cases are discussed in multidisciplinary meetings involving orthopedic surgeons, infectiologists and microbiologists, to personalize and optimize the complex management of the disease, taking into account the patient's general condition, medical history of BJI, antimicrobial susceptibilities, as well as the motor function and mechanical aspect of the bone and/or joint involved. Some patients present with complex BJI, defined by the presence of at least one specific criterion such as: (i) patient with severe comorbidity limiting treatment options and/or with severe allergy; (ii) patient infected with difficult-to-treat micro-organism(s) especially with multidrug resistance; (iii) BJI requiring bone resection and bone and/or soft-tissue reconstruction; (iv) relapsing BJI. Some patients present with particularly severe clinical situation with a poor prognosis, i.e. ageing patients with chronic infected large prosthetic joint for whom explantation is not feasible (Figure 5), or patients infected with pan drug-resistant pathogens. In 2017, among 1,132 cases discussed during multidisciplinary meetings (including 531 patients managed in our centre), we considered phagotherapy as salvage therapy in seven patients (case selection phase; Figure 6). In four patients, the phagotherapy was finally not performed: three had *S. epidermidis* chronic prosthetic joint, a pathogen for which no phage active on *S. epidermidis* was available in the Pherecydes library), and one had *P. aeruginosa* chronic prosthetic joint that finally required a debridement in emergency. Two other patients had *S. aureus* chronic prosthetic joint with productive fistula and for whom explantation was considered as impossible, and one patient with pelvic osteomyelitis who was infected with a pan drug-resistant *P. aeruginosa*. After the identification of each eligible patient, we discussed the indication with the ANSM (French National Agency for the Safety of Medicines and Health Products) and its dedicated committee called "Specialized Temporary Scientific

Committee in Phagotherapy".

Discussion with health authorities, performance of the phagogram, current process of preparation and administration of the bacteriophage cocktail

Finally, after discussion with health authorities and the specialized committee, we decided to propose personalized phagotherapy to the three latter patients as compassionate salvage therapy. The bacterial isolates were sent to pherecydes to perform the phagogram. Pherecydes has a library with the ability to produce various bacteriophages targeting *P. aeruginosa* and *S. aureus*, belonging to Pherecydes Pharma library. Phages could be tested on the patient's strain using two different in vitro methods i.e. plaque assay and killing assay (Figure 4). In the plaque assay 10µl of serial dilutions of each phage were spotted on the patient's strain as well as on their own reference strain. The appearance of plaque forming unit (PFU) on the bacterial layer indicated that the phage was active on the patient's strain. Moreover, the efficiency of plating (EOP) score, defined as the ratio of the phage titer on the patient's strain / phage titer on its reference strain, could be determined with the plaque assay and was informative about the active phage dose. In the killing assay (Figure 4), the patient's strain was inoculated at 107 CFU/ml in a 96-well plate in the presence or absence of one phage at three different doses. The bacterial concentration was recorded over time by optical density at 600 nm (Thermo Scientific Multiscan GC). The absence or decrease of bacterial growth in the presence of a phage compared to the culture without phage revealed the phage activity. The potentially selected phages were amplified on their own host in 1l of animal free Lysogeny broth culture medium. After centrifugation, the supernatant was vacuum filtered through 0.22 µm filters and then concentrated through a tangential flow filtration system to a volume of 100 ml in DPBS. Host DNA and endotoxins is eliminated through the purification process and their concentration measured to check they remained below the approved levels. Lastly, each phage type could be individually packaged at a concentration of 1.1010 PFU/ml in pharmaceutical grade glass vials containing 1 ml of each phage solution and then submitted to the following quality controls: sterility, phage identity, phage purity (level of residual bacterial DNA and proteins, level of residual reagents added during the purification process and level of residual endotoxins), phage titer and pH. Among these controls the level of endotoxins is critical: it is evaluated using the LAL assay (Thermo Scientific, 88282) according to the manufacturer. For each patient, three to six active bacteriophages were sent to our pharmacy. Our pharmacist (GL) prepared each cocktail in a volume of 30-50mL under sterile condition just before the administration. During each surgical procedure that consisted in arthrotomy-synovectomy in the two patients with *S. aureus*

Figure 6: Process in France to obtain the use of bacteriophages as compassionate use in patient presenting a bone and joint infection requiring a salvage therapy

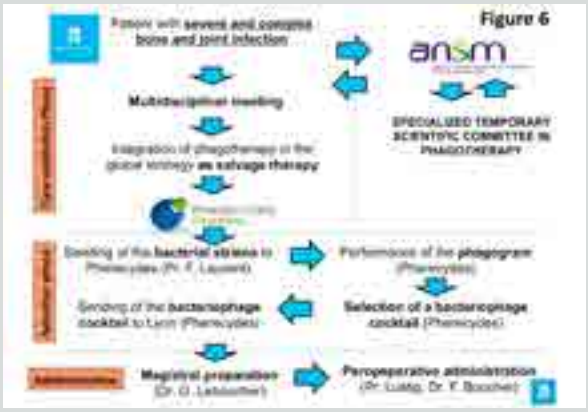
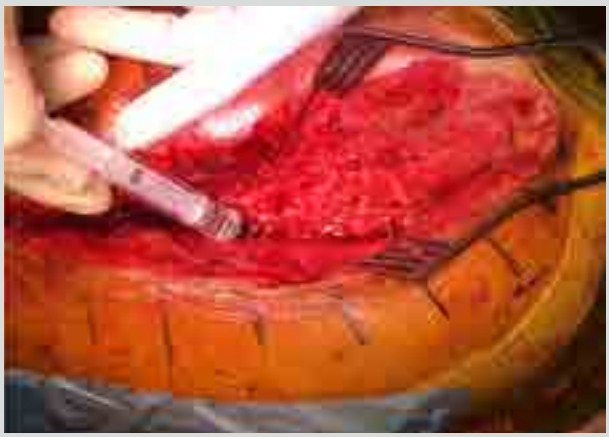


Figure 7: Peroperative administration of a cocktail of bacteriophages, after joint debridement and arthrotomy-lavage, just before joint closing in a patient with relapsing prosthetic joint infection



prosthetic joint and debridement and bone resection in the patient with pelvic osteomyelitis, the surgeon directly applied the phage solution at the site of infection. For patients with prosthetic joint infection, after arthrotomy-synovectomy and reduction of the bacterial inoculum, the joint was surgically closed tightly, just before the phage administration in the joint (Figure 7). For the patient with pelvic osteomyelitis, the phage solution was locally administered after bone debridement. In this latter patient, four local applications were performed before performing the skin and soft tissue reconstruction.

Future directions for phagotherapy in the field of BJI

There are a number of factors favourable to the use of bacteriophages in France: (i) the production of bacteriophages with a high level of purity, according to European GMP; (ii) agreement of the French National Agency for the Safety of Medicines and Health Products (ANSM) for the use of bacteriophages as compassionate therapy; (iii) motivation of infectiologists and orthopaedic surgeons from a reference centre that recruits a large cohort of patients, including more

complex cases that required salvage therapy and (iv) motivation of pharmacists that agree to take responsibility to combine the bacteriophages and to manufacture a magistral preparation (cocktail of bacteriophages) just before the peroperative administration. From our point of view, eligible patients for phagotherapy as salvage therapy are only patients evaluated in reference centre, and each case as to be discussed with the ANSM and its dedicated committee. It seems reasonable to limit this treatment to (i) patients with prosthetic joint infection at high risk of complications in the case of explantation, and for whom suppressive oral antimicrobial therapy is not an option and (ii) patients with chronic osteomyelitis due to multidrug-resistant pathogens (such as pan drug-resistant *P. aeruginosa/S. aureus/ Enterobacteriaceae*) with limited therapeutic options and for whom a skin and soft-tissue reconstruction is required. However, it is now time to consider phagotherapy in patients with less severe BJI, in adjunction to the conventional therapies (surgery and antimicrobials), to increase the success rate of this difficult-to-treat disease, especially in patients with *S. aureus* prosthetic joint infection, long bone osteomyelitis and diabetic foot osteomyelitis. Some previous data indicated that bacteriophages can penetrate biofilm, and could be nice candidates for such patients *(11-15)*. Crucial preclinical data as part of the PHOSA consortium (www.phosa.eu) will be available in 2018–2019. We will determine the bacteriophages activity in a large collection of *S. aureus* isolates responsible for BJI. We will also evaluate the in vitro activity of bacteriophages in bacteria embedded in biofilm, and in animal models of implant-associated osteomyelitis. Finally, clinical academic studies including patients with *S. aureus* prosthetic joint infection requiring prosthesis exchange and in patients with S. aureus diabetic foot will start at the end of 2018. Finally, it would be of interest to have available bacteriophages that are active on enterobacteriaceae and coagulase-negative staphylococci (such as *S. epidermidis*), as these pathogens are frequently involved in patients with BJI and are more and more resistant to conventional antibiotics.

Conclusion

Phagotherapy is an emerging option for patients with bone and joint infections. The compassionate use of bacteriophages manufactured in France according to European GMP has just been used as salvage therapy in selected patients with complex BJI due to *S. aureus* or *P. aeruginosa*. Preclinical data and data from clinical trials will help to expand the use of bacteriophages in this difficult-to-treat disease. ■

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Professor Tristan Ferry has been full Professor in Infectious Disease at the University of Lyon, France, since 2014. He is the co-chair of the Infection department in Lyon North University Hospital, and the coordinator of CRIOAc Lyon, that has managed 500 new patients each year. He has a special interest in access to innovation for patients with BJI, especially concerning the optimization of off-label use of antibiotics and alternative treatments such as local antibiotherapy and phagotherapy.

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Dr Guy-Charles Fanneau de La Horie has over 20 years of experience in the pharmaceutical and biotechnology industries. Before joining Pherecydes Pharma, he held a number of international management roles, including posts at Schering-Plough, Biogen and IDM, in both Europe and the United States. More recently, he was managing director of PathoQuest, a company developing a NGS-based infectious disease diagnostic technology. Between 2006 and 2013 he was the CEO of Neovacs and coordinated the 2010 IPO. Prior to that, he spent eight years with Biogen, where he set up and ran the subsidiaries in France and Benelux. During his time with Biogen he managed the US$ 700 million salesforce in the United States and held Europe-wide responsibilities for marketing, regulatory and medical affairs. A graduate of the National Veterinary School in Lyon, France (1982), Dr Fanneau de La Horie also holds an MBA from INSEAD, awarded in 1988.

Dr Jérome Gabard joined Pherecydes Pharma in September 2009 to build the Company's expertise in preparing bacteriophages for therapeutic applications. He has been the architect of its first phage therapy clinical trial: PhagoBurn (2015–2017). Today he focuses on developing personalized medicinal treatments with phages. Since his research and development work in biotechnologies at DuPont de Nemours (1989–2000), Dr Gabard has been Life Sciences Director in The MarkeTech Group, where he developed sales and conducted strategic and operational marketing studies.

Professor Frédéric Laurent is full Professor in Clinical Microbiology at the University of Lyon. He is the chair of bacteriology department – Institut for Infectious Agents in Lyon North University Hospital, and co-director of the French National Reference Centre for Staphylococci. He is in charge of the diagnosis of Bone and Joint Infections in Hospices Civils de Lyon and is a member of the board of the CRIOAc Lyon (Regional Reference Centre for Complex Bone and Joint Infections). As co-PI of the team "Staphylococcal pathogenesis" in the International Centre for Infectiology Research (INSERM U1111 - CNRS UMR5308 – ENS Lyon – University of Lyon), he has a special interest in the understanding of the switch from acute to chronic BJI, in the prevention and treatment chronic forms and in the development and implantation of innovative technologies for BJI diagnosis.

Cindy Fevre, a microbiologist and expert in bacteriology, is the R&D manager at Pherecydes Pharma. She is in charge of leading the phage development effort of the Company. Her international experience (UMC Utrecht, the Netherlands) led her to manage R&D collaborations with an industrial perspective through multidisciplinary and multicultural research team. Her PhD carried out at Pasteur Institute (Paris) was on the antibiotic resistance, virulence and genetic diversity of Klebsiella. She has been working on other major human pathogens (listeria, Staphylococcus aureus, *etc.) and acquired a solid knowledge of the biology and genomics of bacteriophages.*

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INVESTMENT AND SOCIETY

AMR CONTROL IN DISCUSSION WITH...

DR ENIS BARIŞ, PRACTICE MANAGER, EUROPE AND CENTRAL ASIA HEALTH, NUTRITION AND POPULATION GLOBAL PRACTICE, WORLD BANK

On the eve of the 71st World Health Assembly, WAAAR Vice-Present Garance Upham interviewed World Bank's Dr Enis Barış to obtain the latest views of the Bank on AMR and related issues tabled by the WHO at the WHA, especially at a time when WHO DG Dr Tedros and the Bank's Director Dr Jim Yong Kim concluded an understanding on the launch of a Global Preparedness Monitoring Board which showed the closeness of the two institutions. We asked for an update on the Bank's investments decision one year after the Bank's first report on AMR (an issue covered by Dr Tim Evans and Enis Barış in *AMR Control 2017* and the French edition).

Q: The WHO GPW (Global Program of Work) is focusing on universal health coverage (UHC), placing AMR within the broader UHC framework and from the report of the World Bank on AMR, the World Bank Group team (WBG) is thinking along the same lines. Could you please explain?

Dr Enis Barış: I think it is very important to think of AMR as a health system challenge, sustainable solutions to which can only be found in strengthening health systems. Weaknesses in health system stewardship in general – and AMR stewardship in particular, in relation to infection control, are often cited. There also are issues pertaining to incentives, be they prescribing behaviour or payment modalities on the supply side, and on the demand side those related to healthcare seeking behaviour and health literacy. That said, a comprehensive set of remedial actions for AMR containment would require agreement on a sensible mix of both AMR-sensitive and AMR-specific solutions.

Q: The WHO plans for one billion people covered by Universal Health Coverage (UHC) has been met with some cynicism, yet I remember when Dr Jim Yong Kim, then in charge of HIV at WHO, initiated the "3 by 5", which was also met with disbelief. Twelve years later, we see the three million people living with AIDS under the antiretroviral treatment objective surpassed expectations and Dr Kim is now President of the World Bank. Does that mean the health sector, which you are from, will support WHO to achieve this?

Dr Enis Barış: The World Bank has always valued its partnership with WHO in advocating for UHC globally as a means to improve health, a desideratum in its own right, but also as a means to increase human capital and productivity to help eradicate poverty which is also closely linked to financial protection from the impoverishing consequences of ill-health. We believe that what gets measured is managed more effectively and that requires setting benchmarks and ambitious but achievable targets. We will continue working with WHO towards the achievement of UHC goals globally.

Q: Infection prevention and control (IPC) is first on the list of priorities in the global action plan on AMR adopted in the World Health Assembly in 2015, because health structures are conveyor belts for transmission and dissemination of AMR infections. Yet it is one area where countries are moving the least. Only five countries mentioned IPC in the United Nations General Assembly in 2016, out of more than 100 making statements. Over a year ago, a WHO study showed 23 European countries had no IPC system. Worldwide, we see some progress, like the recent Indian national IPC plan, but it will take a lot more political clout and investment to implement. Is the World Bank going to spur investments in this domain?

Dr Enis Barış: We at the WBG are very much engaged in infection prevention and control, both through our investment and advisory services in several sectors, including Water and Agriculture and of course Health, Nutrition and Population (HNP). We have been providing financial and technical assistance to strengthen preparedness and response capacity of countries both at the regional and national levels, not only to outbreaks and epidemics, but also for more routine surveillance and laboratory services. In addition, the HNP Practice is

engaged in several activities that are instrumental in mitigating and containing AMR. Of note is our engagement in the AMRH – African Medicines Regulatory Harmonization initiative – to improve faster access to quality pharmaceuticals, including antimicrobials, by lowering costs and therefore increasing affordability. Finally, in numerous operations that we provide funds for, we support development, piloting and scaling-up of standard treatment protocols in primary care and inpatient care, and in-service training of healthcare workers, which all are key AMR-sensitive measures.

Q: There is a shortage of older antibiotics and older vaccines affecting most regions of the world; there is a national report on this in France, for example. In part, this is due to the low return on investments of old generics, even though many would be useful for today's AMR infections and would spare later-generation antibiotics which need to be dispensed sparingly to decrease resistance risks. Your views on this? Would you favour public investments?

Dr Enis Barış: I am very much in favour of reverting back to some of the older, cheaper and yet efficacious antibiotics, many of which are no longer produced, or produced in sufficient quantity because of pricing disincentives. I made this point explicitly last year at an event on medicine quality in the margins of the World Health Assembly. As for public investment, I believe it is worthy of further investigation.

Q: What are your views on vaccines as preventatives? Shouldn't there be more emphasis on these?

Dr Enis Barış: Definitely. Think of the pneumococcal conjugate vaccine which after its introduction has brought about significant reduction in drug-resistant *Streptococcus pneumoniae* (DRSP) in vaccinated individuals, but also in the unvaccinated through herd immunity, by reducing occurrence of childhood pneumonia. *Haemophilus influenzae* type b vaccine is another example which is deemed to have reduced the burden of antibiotic resistance for the very same reasons.

Q: As co-author of the WBG's 2017 report on AMR, what do you see as the World Bank's priorities for AMR in 2018? Was your report effective in spurring countries to act on AMR?

Dr Enis Barış: We are very proud of our report which was the first one that forecast the global impact of AMR on economic growth, trade, productivity and poverty. The elimination of the latter, as you know, is one of our twin corporate goals, the other one being boosting shared prosperity in the world. The report has been received very favourably by the global AMR community, but, by the same token, has imparted us with new responsibilities as a prime development finance institution with a global remit and reach to explore novel solutions to multisectoral One Health policy challenges, such as antibiotic use for growth promotion in the animal sector. Therefore we are now working on defining the scope of the much neglected One Health research agenda that goes beyond advocating for research for new antibiotics. This is a necessary R&D area, but not sufficient by any stretch, especially in low- and middle-income countries where the main issue is more about having access to antibiotics and stewarding their proper use in both human and animal sectors.

Q: Many, including in the WHO leadership, see health ministries as "Cinderellas" in national budgets, and, at least until Ebola struck, health emergencies were not taken as matters of national security. Is this changing now? Is your argument on the great economic costs of AMR spurring better budgeting, or will it, since there don't seem to be major changes today?

Dr Enis Barış: I am not sure I'd use the term "Cinderella" to characterize ministries of health. Having spent my entire career engaging with ministers of health and finance, I have an acute understanding of the fiscal space constraints in the public sphere and the multiple demands that ministers of finance are facing from all sectors. What is key, though, and we at the World Bank are working a lot to make it happen, is to engage with all concerned parties in an evidence-based dialogue to document the return on investment in health emergencies preparedness and response, very much making the point that an ounce of prevention is better than a pound of cure.

Q: What do you think of Peter Sands, new head of the Global Fund to Fight Aids, Tuberculosis and Malaria, saying that to address AMR and global health security, the world needs to solve existing infectious diseases with better systems?

Dr Enis Barış: I'd agree entirely. We may not preempt or prevent outbreaks, but we can and must prevent epidemics through better preparedness and response of resilient health systems. ■

Enis Barış is a medical doctor with degrees in Public Health (MSc) and Epidemiology (PhD) and experience as Director, Manager and Technical Expert in over 30 countries. Dr Barış is currently the Practice Manager in the Health, Nutrition and Population Global Practice for the Europe and Central Asia Region at the World Bank. Previously, he was the Practice Manager for the Middle East & North Africa and the Caribbean Regions. He also worked for the WHO as the Director of the Division of Country Health Systems, and for the International Development Research Centre of Canada as Chief Scientist and Senior Scientific Advisor.

ANTHROPOLOGY'S CONTRIBUTION TO AMR CONTROL

LAURIE DENYER WILLIS (LEFT) AND **CLARE I R CHANDLER** (RIGHT), DEPARTMENT OF GLOBAL HEALTH AND DEVELOPMENT, LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE, UK

This article will introduce emerging anthropological approaches to antimicrobials and AMR control across four broad themes: care, pharmaceuticals and markets, knowledge and ecologies. These themes echo calls for a One Health approach to AMR that connects disciplines, sectors and continents in its approach, constructing interventions that operate at the level of global systems as well as shaping possibilities in the local contours of care, life and livelihoods, engaging an important balance of social liveability with good governance.

Anthropology is interested in the everyday realities of people's lives and livelihoods, and how this reflects wider social, economic and political forms, asking, "what makes common sense here, and why?" Anthropologists concerned with antimicrobial resistance (AMR), then, are interested in how antimicrobial use makes sense in different contexts, as well as the science and practices around AMR emergence and transmission. Anthropological study of antimicrobial use around the globe dates back to the 1980s and has repeatedly demonstrated how use is shaped by cultural, political and economic systems, as much as by individual beliefs. Anthropologists have made important contributions to the study of infectious diseases over many decades too that can inform studies of AMR emergence and transmission, highlighting structural factors that affect the likelihood of contracting diseases, including structural violence and the notion of syndemics *(1, 2, 3)*. The work of anthropologists to understand the ways global health crises are constructed and responded to are also instructive for interpreting AMR *(4, 5, 6)*. Together, these accounts have illustrated the complex stories behind our relations with microbes and antimicrobial medicines across the world today and help us to study and anticipate consequences – intended or not – of both AMR and AMR control strategies globally.

Anthropological accounts bring to the fore the rich social-material worlds that microbes and antimicrobials are situated in, and in doing so offer policy-makers, scientists, and funders new ways to conceptualize and act upon AMR. For example, anthropologists might propose that antibiotics are so deeply embedded in the way our societies, politics, and economies work, that they have become are a kind of infrastructure that enables life as we know it *(7)*. If antimicrobials are infrastructure, it is important to understand the extent and nature of the way we have become intertwined with these medicines in order to anticipate the consequences of resistance and the best ways to control it. While a "rational use" framework has informed many AMR policy undertakings over the past few decades *(8)*, and anthropologists have provided evidence of consumers' own rationalities for use of medicines, it is valuable to go beyond the rational-irrational dichotomy if we are to understand and address our collective dependencies on antibiotics and the ways we have come to relate to and control microbes today *(7)*.

This article will introduce emerging anthropological approaches to antimicrobials and AMR control across four broad themes: care, pharmaceuticals and markets, knowledge and ecologies. These themes echo calls for a One Health approach to AMR that connects disciplines, sectors and continents in its approach, constructing interventions that operate at the level of global systems as well as shaping possibilities in the local contours of care, life and livelihoods, engaging an important balance of social liveability with good governance.

Care

Antibiotics often take the form of care in contemporary life. They are objects that "care" for our sick and vulnerable. Giving antibiotics, then, is often a central way that caregivers perform their care. From a physician with limited time for a patient, to a parent with a sick child running out the door to work, or even the humanitarian necessity of bestowing affordable pharmaceuticals on the developing world, antibiotics are a central part of how we give and receive what we think of as "good care". This complicates, of course, many approaches to AMR control. In the Philippines, for example, Mark Nichter's *(9)* ethnographic work explores how and why the use of antibiotics

as prophylaxis has emerged as the main way that sex workers and their clients believe they can protect themselves from Sexually Transmitted Infections (STIs). Here, sex workers and their clients used antibiotics as a preventative care strategy. They made decisions to take antibiotics before sex, after sex, occasionally or routinely, depending upon their own situations and familiarity with particular sex workers or clients. Antibiotics, in this case, are imagined as a kind of care that can be self-administered in a context where sex workers, and those who have sex with them, routinely encounter stigma and vulnerability within healthcare systems. Self-administering antibiotics as prophylactic is a way to diminish potential harm within the (healthcare) system.

In anthropology, we say then that care is situated and contextual *(10, 11, 12, 13)*. This means that we cannot take for granted that practice is based on the exercise of reason, but instead see that practice is emergent in a wider picture. What are the particularities, immediate details, socioeconomic or cultural expectations behind a certain care decision that shapes antibiotic use? It is easy to fall into the trap of casting behaviour as "misguided", but by highlighting the institutional, ethical, and everyday forms of care that hinge on antimicrobial use (and vice versa), we open a space to think differently about care and its contexts.

Pharmaceuticals and markets

Anthropological research aims to situate medicines as they are prescribed, sold, and traded within local and global networks of relations embedded in particular histories, legacies and political economies. On a global scale, antimicrobials operate within the business models of the multinational pharmaceutical industry. Anthropologists have written extensively on the ways in which the operationalization of these models of pharmaceutical distribution has shaped approaches to disease and health. For example, on the global scale, one of the unintended consequences of scaling up international action on health – from malaria to HIV/AIDS treatment – has been observed as "the consolidation of a model of public health centred on pharmaceutical distribution" (14, p.84) rather than prevention and/or clinical care. For many in the Global South, while pharmaceuticals are becoming more widely available, it can still be impossible to actually see a physician when visiting a public health clinic. Many social scientists now refer to this shift in health delivery as the "pharmaceuticalization" of public health *(14, 15, 16, 17)*. Pharamaceuticalization, here, is a term used to capture the prevailing pharmaceutical-centric approach to health and care, leading to the neglect of other health necessities, such as healthy living conditions, preventative care and/or ease of access to physicians, nurses or community health workers.

More locally, "pharmaceuticalization" can play out in complex ways. Our own research in Uganda suggests that people often turn to "informal" providers of antibiotics when they cannot get to a health clinic *(18)*. The reasons for being unable to access a healthcare unit are varied, including day wage labour work, parenting responsibilities, lack of transportation to out of reach clinics, and severe understaffing in available clinics. Our research found that these providers operate on the boundaries of legitimacy, echoing what others have found elsewhere in the Global South. Sarah Pinto *(19)*, for example, suggests that the way informal providers fill the gaps where legitimate public health institutions have been too weakened to operate means they are informally sanctioned by the state. In policy and development debates about "informal providers" and their clients, these informal providers are often characterized as "irrational" and exploitative. On the other hand, "formal" institutions are understood as decidedly rational actors and purveyors of legitimate biomedical knowledge *(19)*. The danger here is formal and informal providers get defined in opposition to each other, and we fail to understand the knot of reasons why informal providers are trusted and called-on in the everyday lives of those who seek healthcare in environments with limited "formal" options.

When considering AMR control measures in these contexts we need to be attuned to potential unintended consequences of further limiting access to medicines or uncritically delegitimizing the informal vendors many access medicines from. Medicines are not just material things, they are social things too, that are ascribed specific social and cultural meaning *(20, 21)*. For example, globally, "poor women" are consistently understood as the "target" of public health interventions *(22, 23, 24)*. Played out on the local level, control policies and programmes often get funneled through public healthcare systems towards poor communities, sharpening a perception among these communities that medical technologies and best-care practices – which at times is equated with provision of antibiotics – are not being safeguarded generally, but specifically for the rich and well connected *(25, 26)*.

Knowledge

Public health practitioners are increasingly observing that knowledge does not always equate to practice. From smoking to obesity, researchers have observed that having more knowledge rarely results in behaviour change. And yet, most of our AMR strategies start at this point; with the assumption that if patients or doctors were simply better informed, they would act differently, and thus energy and funds are directed to knowledge assessment and awareness raising activities *(27, 28)*. What anthropological research has widely demonstrated, however, is that knowledge about "rational" antimicrobial

use does not always equate to following recommendations in practice for patients or clinicians *(29, 30)*. What people deem "rational" tends to be what makes sense in their own particular context, and top-down "rational" guidelines can seem out of sync with local needs and desires. This prompts anthropologists to ask what other ways are there to think about AMR and antimicrobial use? And to question why we so often start with individual cognition.

Anthropologists have increasingly drawn attention to the complex set of beliefs embedded in biomedical science and practice, pointing out the ways in which science and technologies are culturally made and shaped *(31, 32, 33)*. Duana Fullwiley (34), for example, has written on the ways that the science of sickle cell disease is a product of postcolonial genetic science, structural adjustment policies, and patient activism in West Africa. She argues that how we have come to know the African sickle-cell is a product of ethnic, national and global relations of power.

Taking the perspective of biomedical science-as-culture can be informative for understanding how AMR has become conceptualized as both an urgent problem and a kind of scientific object that can be studied. Anthropologists of Science often focus on the networks, language, and actors that come together in order to practice and produce science, illustrating the dependence of the sciences on society and politics, rather than its independence and pure objectivity *(35)*. Science is always partly shaped by cultural ideas about the body, mind, gender and race, among other factors *(36, 37, 38, 39)*. For example, we know that policy-guidelines and scientific studies often attribute the rise in AMR to individual behaviour of doctors, patients, drug sellers and their customers. This makes sense within models that locate individual human action at the centre. However, how well these models map on to the materialities of microbial, genetic and antimicrobial ecosystems is still unclear. One approach to understanding how we have ended up with these particular models of biology is tracing the social history of biology and locating dominant narratives within their wider context. For example, we learn in Roberto Esposito's *(40)* Immunitas how entwined our visions of microbial life are with our political histories in Europe, and how this has shaped what we have seen as possible anti-microbial measures.

Another approach is to delve further into the details of processes through which AMR has written a "biology of history" as Hannah Landecker *(41)* has pointed out. Landecker depicts how mass consumer culture, differences in access and regulation of antimicrobials, and neoliberal market politics have all been inscribed into the biology of AMR. These examples demonstrate how understanding the co-construction of science and policy of AMR can open up new spaces for knowledge production. Indeed, Landecker's work on antibiotics explores how the meanings associated with terms such as "antibiotic resistance" or "microbes" shifts both historically, but also in different contexts, demonstrating the effects of scientific knowledge on the world, its potential limitations, and the way alternatives can be side-lined or ignored. When such anthropological works are combined with historical analysis, this allows us to reveal the contingency of networks and practices, and the role of shifting biological and social ideas, in determining particular scientific understanding and technologies (For other historical work that have explored entanglements between science, politics, companies and publics in relation to AMR, see for example *(42)*, *(8)*, and *(43)*.

Ecologies

The concept and policy mandate of One Health requires an opening up of the research agenda to think about the ways human life coexists with microbes, animals, plants and the environment. We are asked to decentre the human in our understanding of health and disease and to instead consider human life within complex ecologies. Our relationships, for example, with animals – from pets to livestock – bring us into contact with the microbial worlds inside these animals. Seemingly mundane questions about how we care for animals, where they sleep, whether we consider them family or food (or both), and what we choose to inject them with, are all components that shape our entanglement with the microbial world and the conditions of AMR today.

In anthropology, we refer to this approach of "decentering" human life as Multi-species Ethnography *(44)*. In other words, we must take the lives of other species besides humans seriously. In doing so, multi-species ethnography seeks to contribute to a better understanding of how we live with and against other species, such as mammals, insects, fungi and even microbes themselves *(45, 46, 47, 48, 49)*. Multi-species ethnography offers a way to empirically explore the contingency of human-nonhuman-antibiotic-microbe relations in the production and movement of AMR, the specificity of contexts where it arises, and the different responses mobilized.

Heather Paxson's *(48)* ethnographic work among artisanal cheese makers and their relationships with microbial life is one interesting way to consider the dynamic ways we think about bacteria and its place in human life. Paxson outlines how artisanal cheese producers must compete with prevailing Pasteurian conceptions of microbial life that takes all microscopic organisms to be inherently "risky" to consumers. These cheesemakers, however, take a "post-Pasteurian" point of view, one that attributes different bacterial and fungal strains to unique tastes and meanings. Here, microscopic life is not a potential danger, but instead a form of potential value.

Steve Hinchliffe and Kim Ward *(50)* provide another excellent

example of this entanglement of microbials and human life and health through their ethnographic work on piggeries in the United Kingdom. They outline the ways that farmers actively work with, rather than against, complex microbial environments in the "making of safe life" for pigs and humans. They explain how vets, breeders and farmers have situated knowledge and practices that are "obscured and even endangered when biosecurity is reduced to the simple protection of disease-free livestock" (50, p. 136). Raising and keeping healthy pigs – that are healthy for humans and the environments alike – is a complex dance that is more than just keeping microbes out. In fact, the relations and interactions of animals, microbes and people are conceptualised by farmers as key to ensuring health. When AMR control policies attempt to reduce these complex relations into universal categories called "disease-free" or "biosecure" these framings risk becoming part of the problem, not the solution.

Conclusion

Antimicrobial usage and AMR control are social, political and economic in nature. Anthropologists, and other social scientists can help to inform courses of action to address these complex interactions. Without a collaborative and interdisciplinary approach, effective ways to address AMR may be missed, and the global community will risk implementing programmes with potentially adverse and unintended consequences. By highlighting how antimicrobials form key infrastructures within our societies, anthropological work can elucidate why behaviour change or knowledge-focused initiatives may be useful if well informed, but ultimately will be insufficient to address widespread antimicrobial use. Control programmes and policies that understand antimicrobials as key infrastructures – part and parcel of modern life as we know it – will take measures to address AMR at the level of global systems as well as attending to local contours of antimicrobial use, balancing social liveability with good governance. As well as drawing attention to context, anthropologists can inspire new research and policy avenues by highlighting the ways that our frameworks of science and action are culturally constructed, offering alternative lenses through which to construct the problem and generate action to address this major public health issue. ■

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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 multi-professional structure including veterinary medicine, strong involvement of consumers, participation of several parliamentarians (deputies), global programmes including antibiotic stewardship, infection control, use of old and recent diagnostic tools, research, and upgrades of vaccination programmes, official support from many professional societies, from many different countries or various bodies."

DR JEAN CARLET, PRESIDENT, WWW.WAAAR.ORG

The non-governmental organization ACdeBMR (*L'Alliance contre le Développement des Bactéries Multirésistantes aux Antibiotiques*) was constituted on 2 December 2011. Subsequently, its internationally adopted name in English became: "The World Alliance Against Antibiotic Resistance" (WAAAR).

Actions in 2015–2017

WAAAR has joined the network of international not-for-profit civil society organizations initiated by CDDEP (Center for Disease Dynamics, Economics, and Policy) and which was launched on the occasion of the United Nations General Assembly, 21 September 2016 in New York City, United States.

WAAAR President Dr Jean Carlet attended, as well as Garance Upham, Deputy Executive Secretary of WAAAR and member of Medicus Mundi International, and Tim Probart, CEO of Global Health Dynamics.

WAAAR in France

Founded in Paris, ACdeBMR/WAAAR is the major player in France itself and in the French speaking world on antibiotic resistance issues.

Dr Carlet and the WAAAR team campaigned for decisive action, and in early 2015 Dr Carlet was selected to put together and chair France's National Task Force on the Preservation of Antibiotics for 2015 relying on the many experts who are members of the WAAAR in the field of human and animal health, diagnostics and economics, patient safety and hospital-acquired infections prevention.

WAAAR internationally

WAAAR has many members and collaborators in French speaking Africa who lead actions on AMR, such as Dr Frank Mansour Adéoty in the Ivory Coast, former Minister of Health of Bénin, Dr Dorothée Kinde Gazard, or retired (but ever active) Senegalese Colonel physician Babacar N'Doye whose top level international and national expertise in infection control was found very pertinent during the recent Ebola epidemic in Guinea Conakry.

WAAAR international seminars

Patient safety and HIV in the era of AMR

March 2016: WAAAR sponsored and organized a satellite event during ICAAP12 (International Conference on AIDS in Asia-Pacific) with Partners in Population and Development, on 21 March 2016.

Garance Upham was joined by USAID Assist, India's desk Nigel Livesley (see article in *AMR Control 2016*) in presenting how HIV care is intimately concerned with AMR for three basic reasons: the rise in drug-resistant opportunistic infections, the risks of contracting drug-resistant pathogens in health systems, and, of course, the rise in ARV resistant HIV cases.

From Ebola to AMR: The urgency of infection control

May 2015: World Health Assembly WAAAR Geneva branch organized a satellite seminar at the United Nations Palais in

coordination with South Africa, sponsored by Nigeria, Sierra Leone and the United States of America.

Co-chaired by Mrs Precious Matsoso, DG Health Systems in the RSA and Garance Upham, Vice-President of WAAAR, the seminar was graced by WHO DG Margaret Chan, and heard high level country representatives such as the DG Health for Sierra Leone, Dr Brima Kargbo and Deputy Assistant Secretary, Office of Global Affairs. Department of Health and Human Services, United States Dr Mitchell Wolfe.

Among the keynote speakers on the topic was Dr Edward T Kelley, WHO Director for the Department of Health delivery and Security. High level representatives attending the World Health Assembly from many countries participated in the event. In February 2017, WAAAR entered the European Union (EU) World Competition for NGO involvement on AMR and won Third Prize.

WAAAR publications

After *AMR Control 2015* and *AMR Control 2016*, with participation from well known experts such as Lord Jim O'Neill from the United Kingdom Review on AMR, one of the major think tanks on AMR, *AMR Control 2017* brought you another round of expert opinions on AMR from around the world.

AMR Control 2015 and *AMR Control 2016*, published by Global Health Dynamics, have had a huge success. The books has been widely disseminated, in particular to agencies, like WHO, ECDC, CDC, the European Commission. A pre- 2016 edition has also been presented to high-level Ministers and DGS at the WHO Executive Board in January 2016 and at the United Nations World Health Assembly in May 2016.

AMR Control 2018 has enjoyed the scientific expertise of our new International Advisory Scientific Committee (IASC) which was formed in the Spring of 2017.

The AMR-Times Newsletter, Le Temps de la Résistance aux Antimicrobiens, is a new monthly email newsletter available in French and in English, with a less frequent edition in Arabic. And, it is expected, soon in Spanish and Portuguese. It has over 3,000 direct subscribers and an estimated reach approaching 12,000 via scientific and professional networks who are re-distributing the newsletter among their own network.

A mostly volunteer and doctoral students young team manages this project with offshoots in Algeria, China, Egypt, Italy, Lebanon, The Netherlands, France, United Kingdom and Switzerland where it is based.

AMR-Times reports on leading scientific news on AMR, conferences and events. An e-Journal is under construction.

WAAAR interventions in scientific conferences

Dr Carlet, and other prominent members of WAAAR, present scientific papers in conferences around the world, too numerous to be listed here. These included high-level seminars and conferences during 2015–2017: Oslo, Norwegian Institute of Public Health, Amsterdam's DRIVE-AB, French Foreign Ministry and WHO "Climate Change and Health", Wilton Park Conference on AMR in LMICs, and multiple United Nations Member States meetings in the field of health, trade, economic development and investment.

We have intensified our relationships with official bodies and agencies (EU, CDC, ECDC, EMA, WHO...) All request copies of *AMR Control* and our input.

Dr Jean Carlet, MD, has published in many scientific journals for more than 20 years, specializing in acute care, on Sepsis, ARDS, issues in infection control and antibiotic resistance. As president of WAAAR and Chair of the French Task Force, the demand for publications and interventions in scientific congress has increased greatly.

WAAAR Board, membership and collaborations

The 800 members of WAAAR are physicians, hospital managers, scientific researchers, hygiene nurses, patients and patient organizations, economists and concerned persons, from over 55 countries.

In June 2014, the WAAAR initiated the Paris Declaration which enlisted the support of over 100 persons and, up to 145 societies or institutes.

WAAAR is among the largest networks, along with REACT or APUA, of people actively working to make the world safe for human beings in the "post-antibiotic era", a partner of the World Sepsis Day and a collaborator of COMBACTE.

At the time of the United Nations General Assembly on AMR in September 2017, WAAAR participated in the founding of CARA, The Conscience of Antimicrobial Resistance Accountability.

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Teresa Zurberg
Survivor, *C. difficile* canine scent detection team
and antimicrobial resistance fighter

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